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Prognostic value of pretreatment serum lactate dehydrogenase level in patients with solid tumors: a systematic review and meta-analysis

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Although most studies have reported that high serum lactate dehydrogenase (LDH) levels are associated with poor prognosis in several malignancies, the consistency and magnitude of the impact of LDH are unclear. We conducted the first comprehensive meta-analysis of the prognostic relevance of LDH in solid tumors. Overall survival (OS) was the primary outcome; progression-free survival (PFS) and disease-free survival (DFS) were secondary outcomes. We identified a total of 68 eligible studies that included 31,857 patients. High LDH was associated with a HR for OS of 1.48 (95% CI = 1.43 to 1.53; P < 0.00001; I² = 93%), an effect observed in all disease subgroups, sites, stages and cutoff of LDH. HRs for PFS and DFS were 1.70 (95% CI = 1.44 to 2.01; P < 0.00001; I² = 13%) and 1.86(95% CI = 1.15 to 3.01; P = 0.01; I² = 88%), respectively. Analysis of LDH as a continuous variable showed poorer OS with increasing LDH (HR 2.11; 95% CI = 1.35 to 3.28). Sensitivity analyses showed there was no association between LDH cutoff and reported HR for OS. High LDH is associated with an adverse prognosis in many solid tumors and its additional prognostic and predictive value for clinical decision-making warrants further investigation.

ancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries¹. In the United States, a total of 1,660,290 new cancer cases and 580,350 cancer deaths were projected to occur in 2013². In Europe, there were an estimated 3.45 million new cases of cancer (excluding non-melanoma skin cancer) and 1.75 million deaths from cancer in 2012³. Furthermore, the global burden of cancer continues to increase, largely because of population growth and increased life-expectancy³. Invasion and metastasis are two important hallmarks of cancer and are responsible for the majority of cancer deaths⁴. Although much effort has been devoted to the diagnosis and therapy of cancers, the overall prognosis is still unsatisfactory. A lack of knowledge of molecular biomarkers in cancer has limited the development of personalized therapies and improvements in survival. Therefore, there is an urgent need for universal, effective, readily available and inexpensive biomarkers in solid tumors to identify patients with a poor prognosis so that novel treatments can be initiated earlier.

The metabolism of cancer cells differs from that of normal cells. This is largely because cancer cells exhibit metabolic alterations that are frequently associated with reprogramming. Unlike normal cells, cancer cells preferentially metabolize glucose by glycolysis to generate sufficient energy for the demands of rapid proliferation, even in the presence of adequate $oxygen^5$. This phenomenon is known as the Warburg effect and is one of the predominant metabolicalterations that occur during malignant transformation. In this process, transcriptional programs regulated by oncogenes stabilize hypoxia-inducible factor 1 alpha (HIF-1 α). HIF-1 α contributes to the upregulation of most enzymes involved in the glycolytic pathway, including lactate dehydrogenase (LDH). In the final step of aerobic glycolysis, LDH converts pyruvate tolactate, which is coupled with the oxidation of NADH to NAD+. These metabolic changes are reflected by an elevated serum LDH level⁶(hereinafter LDH).

Elevated LDH has been recognized as a poor prognostic indicator in cancer for many years⁷⁻¹⁰. LDH has also been incorporated in prognostic scores for several types of cancer¹¹. However, the consistency and magnitude of

the prognostic impact of LDH are unclear¹²⁻¹⁴. The aim of this study was to review published studies and use standard meta-analytic techniques to quantify the prognostic value of LDH in various solid tumors.

Methods

Data sources and searches. This analysis was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines¹⁵. PubMed was searched for studies evaluating the LDH and survival in solid tumors from 1978 to 2014. We used various medical subject heading terms, including "I-lactate dehydrogenase", "prognosis", "multivariate analysis" and "proportional hazard model". Title/abstract words included "lactate dehydrogenase", "prognose", "prognostic", "multivariate analysis", "proportional hazard model". Title/abstract words included "lactate dehydrogenase", "proportional hazard model", "COX proportional hazard model" and "COX models". The full search strategy is described in the Supplementary Methods (available online).

Study selection. Inclusion criteria for the primary analysis were as follows: 1) studies of people with solid tumors reporting on the prognostic impact of LDH; 2) prospective or retrospective cohort design with a clearly defined source population and justifications for all excluded eligible cases; 3) sample size greater than 200; 4) statistical analysis using multivariate proportional hazards modeling that adjusted for clinical prognostic factors; and 5) reporting of the resultant adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) or a P value for overall survival (OS). For the secondary analyses, studies providing a HR for cancer-specific survival (CSS), progression-free survival (PFS), disease-free survival (DFS), or recurrence-free survival (RFS) were included as well.

Data extraction. OS was the primary outcome of interest. CSS, PFS, and DFS were secondary outcomes. Two authors (J.Z. and H.W.) independently extracted information using predefined data abstraction forms. The following details were extracted: name of first author, year of publication, number of patients included in analysis, disease site, disease stage (non-metastatic, metastatic, mixed [both non-metastatic and metastatic]), study type (prospective or retrospective), cutoff defining high LDH, and HRs and associated 95% confidence intervals for OS, PFS, DFS, or RFS as applicable. HRs were extracted preferentially from multivariate analyses where available. Where several HR values were given in an article, the value adjusted for most confounders was used.

Data synthesis. The meta-analysis was conducted initially for all included studies for each of the endpoints of interest. Subgroup analyses were conducted for predefined parameters such as disease site, disease stage and LDH cutoff, and all data were limited to multivariate analyses. Disease site subgroups were generated if at least three studies on that site were available; the remaining studies were pooled in a subgroup termed "other." LDH cutoff subgroups were < 250 U/L, 250–300 U/L, 301–400 U/L, and >400 U/L. In three studies, the effect of LDH was reported as a continuous variable; we pooled those studies separately. Univariate meta-regression model analysis was performed to evaluate the relationship between covariates (LDH cutoff) and the HR for OS.

Statistical analyses. The meta-analysis was performed with RevMan 5.2 analysis software (Cochrane Collaboration, Copenhagen, Denmark). Estimates of HRs were weighted and pooled using the generic inverse-variance and random-effect model¹⁶. Analyses were conducted for all studies, and differences between the subgroups were assessed using methods described by Deeks et al.¹⁷. Publication bias was assessed by visual inspection of the funnel plot. Heterogeneity was assessed using Cochran Q and I² statistics. Meta-regression analysis was conducted using Stata12.0 software. All statistical tests were two-sided, and statistical significance was defined as P less than 0.05. No correction was made for multiple testing.

Results

Description of studies. Sixty-eight studies were included in the meta-analysis. The selection process for the systematic review is shown in Figure S1 and the characteristics of the included studies are shown in Table 1. A total of 31,857 patients were included and the median trial sample size was 363.

Overall survival. Sixty-three studies comprising 29,620 patients reported HRs for OS. All studies analyzed LDH as a dichotomous variable. The studies have clearly shown that upper limit of normal (ULN) remains common for high LDH. The median cutoff for high LDH was 250U/L (range = 200-1000).

Two of the 63 eligible studies (3.2%) reported a non-statistically significant HR. A forest plot of all studies is presented in Figure 1. Overall, LDH greater than the cutoff was associated with a HR for OS of 1.48 (95% CI = 1.43 to 1.53; P < 0.00001). As the heterogeneity among studies was significant (P < 0.00001; I² = 93%),

a random-effects model was applied. To explore potential sources of heterogeneity, we performed subgroup analysis in the following subgroups: disease site, tumor stage, and LDH subdivided by predefined cutoffs.

The effect of LDH on OS among disease subgroups is shown in Figure 2. The prognostic effect of LDH was highest in renal cell carcinoma (HR = 1.84, 95% CI = 1.35 to 2.51), followed by naso-pharyngeal carcinoma (HR = 1.82, 95% CI = 1.48 to 2.24), sarcoma (HR = 1.79, 95% CI = 1.30 to 2.47), melanoma (HR = 1.76, 95% CI = 1.56 to 1.98), prostate cancer (HR = 1.55, 95% CI = 1.06 to 2.26), colorectal cancer (HR = 1.52, 95% CI = 1.29 to 1.79), and lung cancer (HR = 1.50, 95% CI = 1.27 to 1.78). The HR for the subgroup of other unselected solid tumors was 1.69 (95% CI = 1.44 to 2.00). For the eight disease-site subgroups analyzed, there was statistically significant heterogeneity between disease sites (P < 0.00001), but no significant differences in the prognostic values of LDH between the subgroups (P for subgroup difference = 0.68).

The effect of LDH on OS among different disease stages is shown in Figure 3. The HRs were 1.54 (95% CI = 1.32 to 1.80) for nonmetastatic disease, 1.70 (95% CI = 1.59 to 1.82) for metastatic disease, and 1.20 (95% CI = 1.16 to 1.24) for a mixed group consisting of studies that included both metastatic and non-metastatic patients. There was statistically significant heterogeneity between disease stages (P < 0.00001). The prognostic value of LDH also varied significantly between different disease stages (P for subgroup difference < 0.00001).

The effect of LDH on OS among different cutoffs for LDH is shown in Figure 4. The HRs were 1.71 (95% CI = 1.38 to 2.12) for LDH cutoff < 250 U/L, 1.67(95% CI = 1.52 to 1.84) for LDH cutoff 250 to 300U/L, 1.69 (95% CI = 1.27 to 2.24) for LDH cutoff 301 to 400U/L, and 1.72(95% CI = 1.45 to 2.05) for LDH cutoff > 400 U/L. There was no statistically significant heterogeneity between the different cutoffs for LDH (P for subgroup difference = 0.99).

The scatter plot for the univariate meta-regression analysis is shown in Figure 5.A total of 63 studies was included in the metaregression analysis. Overall, there was no statistically significant association between LDH cutoff and the HR for OS (P = 0.614).

There was evidence of publication bias, with fewer small studies reporting negative results than would be expected (Supplementary Figure S2).

Three studies, comprising 1,766 patients, analyzed LDH as a continuous variable and reported HRs for OS. The pooled summary HR of these studies was 2.11 (95% CI, 1.35–3.28; P = 0.0003; $I^2 = 84\%$) per incremental LDH unit (Supplementary Figure S5).

Progression-free survival. Six studies, comprising 2,451 patients, reported HRs for PFS. Overall, LDH greater than the cutoff was associated with a HR for PFS of 1.70 (95% CI = 1.44 to 2.01; P < 0.00001; $I^2 = 13\%$). A forest plot is presented as Figure S3.

Disease-free (Recurrence-free) survival. A total of five trials, comprising 1,992 patients, reported HRs for DFS. Overall, LDH greater than the cutoff was associated with a HR for the endpoints of 1.86 (95% CI = 1.15 to 3.01; P = 0.01; $I^2 = 88\%$). A forest plot is presented in Figure S4.

Discussion

This is the first comprehensive meta-analysis of the prognostic relevance of LDH in solid tumors and it is based on a large pool of clinical studies (31,857 patients). We found a consistent effect of an elevated LDH on OS (HR = 1.48, 95%CI = 1.43 to 1.53) across all disease subgroups and stages. In addition, there is a trend toward a stronger prognostic value of LDH in metastatic disease compared with non-metastatic disease, which may reflect greater tumor burden. The prognostic impact of LDH on PFS and DFS (or RFS) is also robust. Interestingly, different cutoffs of LDH for different disease

Tak	Table 1 Baseline Characteristics of Included Studies	haracteris	stics of Incl	luded Studies								
Р	Fist Author	Year	Sample Size	LDH (High/Low)	Site	Stage	Cutoff (UI/L)	Outcome	Study type	Follow-up Time(mo)	Risk of Bias	Adjusted Variable
7 -	Laurie ⁴¹ Motzer ⁷	2007 2013	210 1059	109/47 NA	sclc Rcc	z₹	ULN 1.5ULN	OS PFS/OS	ዋ ሌ	A N N		Gender, ECOG PS, Anemia grade Ethnic origin, ECOG PS, Time from diagnosis to treatment, Bone metastases, Hb, Ca, Neutrophils, CAAking
ო	Polee ³²	2003	350	296/54	Esophageal	Z + X	NIN	OS	Я	ΝA	_	WHO Performance, Extent of disease, Paclitaxel
4	Han ³¹	2003	383	232/151	Many kinds of cancer	× × ×	NIN	OS	Я	ΝA	т	PS(WHO), White blood count, Hb, Number of sites of
2	Atzpodien ³⁰	2003	425	330/95	RCC	٤	220	SO	R	20 +	-	Neutrophil counts, CRP, Time from diagnosis of tumour to metastatic disease, Number of metastatic sites, Bone
\$	Bidard ⁵⁶	2012	267	121/99	Breast cancer	۲	NIN	PFS	ط	14.9	_	merasrases Triple negative, PS, Number of metastatic sites, CTC, A1 5.3 CVEPA 21.1 CEA AIP CINDEY
N	Culp ⁴⁷	2010	566	107/366	RCC	٤	618	SO	۵.	20	-	Albumin, ALP, Wb, Metastasectomy at any time, Liver metastasis, Clinical tumor classification, Fuhrman nuclear grade, No. of metastatic sites at CN, Sarcomatoid dedifferentiation, Clear cell histology,
œ	Pierga ²⁸	2001	1336	1039/ 297	Breast cance	٤	NIN	OS	٩	۸A		rreament Karnofsky index, Disease free interval, No. of metastatic sites, Liver involvement, Adjuvant
6	Cook³7	2006	635	566/69	HRPC	٤	454	OS	Я	٨A	_	die Nord Albumin, Analgesics, ECOG, NTx, Age, PSA, Hb, Albumin, Analgesics, ECOG, NTx,
10	Wan ⁸	2013	400	367/33	Nasopharyngeal	z	245	DFS/OS	Я	٩N	_	bar Age, Tumor stage, Node stage
1	Mekenkamp°	2012	1010	637/365	Colorectal cancer	٤	NIN	SO	R	ΝA	-	Diameter, Invasion depth, Lymph node status, Number Jymph nodes, Number positive Jymph nodes, MMR
12	Sougioultzis ⁵⁴	2011	311	137/173	Gastric carcinoma	٤	225	SO	ъ	ЧИ	-	status, hava matation status, bavar matation status Palliative gastrectomy, Chemotherapy, Liver metastasis, Abdominal/Peritoneal metastasis, Histobagical grade, CA72–4, Weight Ioss, Blood
13	Zhou ⁶¹	2012	465	424/31	Nasopharyngeal	Z + ¥	245	DFS/OS	Я	44.7	_	rransusions N category, T category, Age
14	Lagerwaard ²³	1999	1292	1081/ 211	carcinoma Many kinds of cancer	z	NIN	SO	ĸ	ЧИ	_	PS, Number and distribution of brain metastases, Site of primary tumor, Histology, Interval between primary tumor and brain metastases, Systemic tumor activity,
15	Aoe ³⁵	2005	309	448/157	Lung cancer	Z + X	450	SO	Я	AN	т	response to steroid treatment, treatment modality Anemia, TNM stage ECOG PS, Sex, Histologic type,
16	Bacci ³⁸	2007	742	464/278	Ewing's sarcoma	Z + X	NIN	SO	Я	ΝA	_	Age Pelvis, Other sites, Interval symptoms to diagnosis,
∠l	Armstrong ⁵⁵	2012	404	264/140	RCC	٤	NIN	OS	R	٨A	т	Treatment, Interaction term, KPS, Prior nephrectomy, No. 24 metantic sites: Corrected actions. Hb.
18	Gripp ⁴⁰	2007	205	130/75	Many kinds	Ν 4 Μ	240	OS	ط	٩N	_	WBC, Dyspnea, Morphine, KPS, Brain metastasis, Coloradal Braza,
19	Giaccone ³⁶	2005	216	NA	or curicer SCLC	z	NIN	SO	ط	AN	т	connectat, preas Sex, Chest radiotherapy, PCI, Platelets



3

Table 1 | Continued

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Adjusted Variable	Karnofsky PS, Hb, Calcium, Time from initial RCC	alagnosis to start or interteron-alpha merapy Sex, Age, Fever, Anemia, Axial location, Radiation therapy only for local control, Type of chemotherapy	regimen, crientoiner apyritatee inectosis KPS, Hb, Ca, Prior nephrectomy. ECOG PS, TTD, Albumin, Lymphocytes	No 50% decline within 12 wk, Hb, Age ECOG PS, Number of metastatic sites, Time from	Paprifectomy to metastanc alsease, ALY, Ca PS, Stage, ALP, CEA, Sex Age, Sex, PS, No.sites, Liver involvement, Primitive	rumor, rume to metastasis, Aajuvant C.I., ALr, CEA ECOG PS, Skin rash Recurrence vs. metastasis, KPS, Liver metastasis,	Perironeal metastasis, ALP, CKP RPS, Pleural fluid glucose level, CRP, Pleural effusion, provent uticheries of Action of plantastastastastastastastastastastastastast	Platelet count, TNM stage, ECOG PS, Sex, Histologic	ype, Age Number of treatment lines, PS, Surgery, Maintenance	riterapy, time to trist progression of tumour Anorexis, Resting dyspnea, ECOG, Leukocytosis,	Dimution, creatinine Other sites, Interval symptoms to diagnosis, Treatment	Age, performance status, clinical presentation, disease localization, pathologic findings, PSA, PSA/	Par railo, CEA, Aur,CKr Erythrocyte sedimentation rate, Hb, ALP, GGT, Contrained Alternation	MYCN oncogene amplification, Abdominal tumor, Stage, VanillyImandelic (VMA) urinary excretion,	Ferritin, Neuron-specific enolase (NSÉ) AJCC T category, AJCC N category, Age	Sex, Age, Metastasis at presentation, Lung metastasis, Post-treatment S-LDH level, Drug number of chemotherapy, Number of involved sites, Liver	metastasis, Bone metastasis Age, T classification, N classification	Age, Sex, PS, Histopathology, smoking status, Response after 1-line CT, First-line CT, PFS after 1-line	CT, Second-line CT ECOG-PS, Extensive disease, NLR
	Karnofsky PS, I	Sex, Age, Feve therapy only fo	KPS, Hb, Ca, F ECOG PS, TTD	No 50% declir ECOG PS, Nur	PS, Stage, ALP, CEA, Sex Age, Sex, PS, No.sites, Liv	tumor, 11me to metas ECOG PS, Skin rash Recurrence vs. metas	KPS, Pleural flu	Platelet count,	type, Age Number of trec	Anorexia, Rest Bitizubia, Czazi	Other sites, Interval s	Age, performa disease localiz	FAF ratio, CEA, ALP, CKF Erythrocyte sedimentation	MYCN oncogene am Stage, Vanillylmande	Ferritin, Neuro AJCCT catego	Sex, Age, Metr Post-treatment { chemotherapy,	metastasis, Bone metastasis Age, T classification, N clas	Age, Sex, PS, I Response after	CT, Second-line CT ECOG-PS, Extensiv
Risk of Bias	-	_	I	т –	т –	ΤТ	Т	т	т	т	_	_	т	_	т	-	_	_	
Follow-up Time(mo)	46	126	33 NA	A A N A	A A N A	A A N A	NA	٩N	AA	NA	AA	31	NA	AN	AN	NA	51.5	AN	AA
Study type	Я	2	<u>ک</u> م	~ ~	~~~	~~~	ъ	Я	Я	Я	Я	2	Я	R	2	R	ъ	2	Я
Outcome	OS	OS	S S S	OS OS	OS OS	S S S	OS	SO	SO	SO	SO	OS	OS	SO	SO	SO	DFS/OS	SO	SO
Cutoff (UI/L)	1.5 ULN	NIN	1.5ULN NA	230 1.5ULN	N N N	ULN 220	500	450	500	502	240	400	400	1000	240	245	225	NIN	240
Stage	× ×	z	Z Z + + S S	Z + ₹ ₹	Z + ₹ ₹	Z Z + + S S	× ×	N + M	X + X	× + ×	Ν + Χ	٤	× ×	X + X	X + X	٤	z	Υ + ¥	× N N
Site	RCC	Ewing's sarcoma	RCC Many kinds	or cancer CRPC RCC	SCLC Colorectal	Cancer NSCLC Pancreatic cancer	Pleural	Lung Cancer	NSCLC	Many kinds	or cancer Osteosarcoma	Prostate Cancer	Bladder Cancer	Neuroblastoma	Nasopharyngeal	carcinoma carcinoma	Nasopharyngeal	NSCIC	SCLC
LDH (High/Low)	NA	238/121	A A A Z	164/90 222/52	1 <i>47/</i> 137 283/252	A A A A	AA	AA	177/45	94/115	1116/ 305	NAN	AA	162/106	AA	379/310	AN	154/175	75/39
Sample Size	463	357	670 406	254 300	284 535	257 326	363	611	245	209	1421	241	202	246	533	689	601	329	499
Year	2002	2000	1999 2011	1999 2007	1997 2011	2010 2009	2010	2004	2012	2010	2004	2007	1993	1997	2012	2013	2014	2013	2014
Fist Author	Motzer ²⁹	Bacci ²⁶	Motzer ²⁴ Feliu	Scher ²⁵ Escudier ³⁹	Kawahara ¹⁹ Chibaudel ⁵²	Kim ⁴⁸ Hashimoto ⁴⁶	Tanrikulu ⁵⁰	Aoe ³³	Giroux ¹⁰	Suh ⁴⁹	Bacci ³⁴	Saito ⁴²	Hannisdal ¹⁸	Tonini ²⁰	Li58	Jin ⁶⁵	Wei ⁷⁵	Sau ¹⁴	Wang ⁷⁴
ź	20	21	22 23	24 25	26 27	28 29	30	31	32	33	34	35	36	37	38	39	40	41	42



		+line		lson	Hb,	mor	CRP,		PS	ases,		۲P	уdr		± ^	5	,9-9,	put	mber	nostic		on of	sdent
	Adjusted Variable	Age, Sex, PS, Primary site, Liver metastasis, First-line chemotherapy, Prior surgery	site, Opioid analgesic use, MP	Age, ECOG PS, Number of comorbidities, Gleason sum score, Lymph node metastatic only, Bone	metastasis, Visceral metastasis, Liver metastasis, Hb, Albumin, ALP, PSA, PSA-doubling time, NLR	Fibrinogen, Hb, Ca, T stage, Fuhrman grade, Tumor	sıze Time from initial diagnosis to metastasis, Hb, Ca, CRP, Liver metretreis Rone metretreis Lvmmh node	ie ilieidaidaid, Eyliipii ilode	Time from diagnosis to TKI, Neutrophils, ECOG PS	Age, ir row score Gender, Age, Number of first line cycles, Metastases,	Resection prim. Tumour, Study-arm, Response	curegory Liver-limited disease, N-stage of primary, KPS, ALP	Cerebral metastases, First systemic therapy		Gender, ALP, Histological subtype, Metastasis at discussis Survised marcins Tumor nerrosis rate	Postoperative chemotherapy, Surgery after	recurrence, Chemotherapy after recurrence,, Age, Gender, Lines of chemotherapy,CEA,CA19-9,	GGI,ALP S1008 Time interval between initial diagnosis and	stage IV diagnosis, Site of distant metastasis, Number	ot involved distant sites Fime from initial diagnosis to treatment, Hb, Prognostic	ateaory. Mutation	Age, Chemoresponse, Albumin, M-stage, Location of	primary melanoma Sex, Age at diagnosis of stage IV disease, Antecedent
	Ac	Age, Sex, PS, Primary site, L chemotherapy, Prior surgery	ECOG PS, Disease site, Alhumin Hh PSA AIP	Age, ECOG PS, Nu sum score, Lymph no	metastasis, Visceral Albumin, ALP, PSA,	Fibrinogen, Hb, Ca,	sıze Time from initial diaç Livar matastasis Bor	metastasis	Time from diagnosis	Gender, Age, Numk	Resection prim. Tum	Liver-limited disease	S100B, Cerebral me	Brain metastasis	Gender, ALP, Histold	Postoperative chemo	recurrence, Chemoth Age, Gender, Lines	GGL,ALP S1008 Time intervo	stage IV diagnosis, S	ot involved distant sites Time from initial diagno	metastatic group Aae. Gender. M1 Cateaorv. Mutation	Age, Chemorespons	primary melanoma Sex, Age at diagnos
	Risk of Bias	т	_	т		_	-		3			-	_		_		Т	_	I	-		_	
	Follow-up Time(mo)	AA	٩N	ΝA		AN	NA		15	¥ Z		55.4	27	46	51		AA	NA		21.5	12	AN	AN
	Study type	ъ	Я	ĸ		2	R		2	~ ~		Я	Ж	R	R		R	2	:	Я	2	R	۵.
	Outcome	SO	SO	SO		DFS/OS	SO		PFS/OS	SO		SO	SO		RFS/OS		PFS/OS	SO)	SO	SO	SO	SO
	Cutoff (UI/L)	NIN	NIN	1.2 ULN		1.5 ULN	1.5 ULN		1.5 ULN			250	ULN	ULN	ULN		NIN	Z		1.5ULN	ULN	NIN	200
	Stage	× ×	٤	٤		Z + ¥	٤		z Z	Z + ≷ ≥		٤	٤	Z	Z + ¥		۶	z		٤	٤	٤	Z
	Site	Neuroendocrine carcinoma of the digestive system	CRPC	CRPC		RCC	RCC		RCC	Colorectal	Cancer	Colorectal Cancer	Melanoma	Melanoma	Osteosarcoma		Colorectal	Cancer Melanoma	5	RCC	Melanoma	Melanoma	Melanoma
	LDH (High/Low)	AA	565/482	AN		197/89	388/34		285/34 52 /55	152/138		270/201	263/175	131/63	101/81		154/82	502 /228		299/23	263/97	430/275	246/125
	Sample Size	206	1050	357		286	473		319	290 290		215	372	215	240		239	8.5.5		361	677	740	589
	Year	2014	2014	2014		2013	2013		2014	2013		2013	2013	2014	2013		2013	2012	 - 	2012	2012	2011	2008
Table 1 Continued	Fist Author	Yamaguchi ⁷⁶	Halabi ^{zo}	Templeton ⁷³		Du ⁶²	Shinoharaó7		Poprach ⁷²	rowies van Kessel ⁶⁸		Giessen ⁶⁴	Weide ⁶⁹	Meckbach ⁷¹	Durnali ⁶³		He ¹³	Weide ⁶⁰		Shinohara ⁵⁹	Jakob ⁵⁷	Bedikian ⁵¹	Neuman ⁴⁵
Table	Ž	43	44	45		46	47		48	50		51	52	53	54		55	56)	57	58	59	60

Sex, Site, ECOG PS, Leukocytes, Neutrophils ECOG PS, Disease stage, Metastatic sites, Visceral

_ _

50.4 NA

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PFS/OS OS

2ULN 618

Σ٤

Melanoma Melanoma

317/46 358/258

363 616

2007 2008

Bedikian<sup>44</sup>

61 62

Schmidt<sup>43</sup>

\_

₹

2

SO

618

N + N

Many kinds

142/85

227

2000

Viganó<sup>27</sup>

63

of cancer

No. of metastases

metastasis, Albumin, Response to treatment

Primary tumor, Liver metastasis, Comorbidity, Weight loss, ECOG PS, Nausea, Clinical estimation of survival, Albumin, Lymphocyte count



| Tab                              | Table 1   Continued                                                                                                |                                                                   |                                                                         |                                                                                                   |                                                                                                                               |                                                                       |                                                                                |                                                                               |                                                                                     |                                                                                        |                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|--------------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|-----------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ²                                | Fist Author                                                                                                        | Year                                                              | Sample<br>Size                                                          | LDH<br>(High/Low)                                                                                 | Site                                                                                                                          | Stage                                                                 | Cutoff<br>(UI/L)                                                               | Outcome                                                                       | Outcome Study type                                                                  | Follow-up<br>Time(mo)                                                                  | Risk of<br>Bias                                                 | Adjusted Variable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 64                               | 64 Tamura <sup>22</sup>                                                                                            | 1998 253                                                          | 253                                                                     | NA                                                                                                | SCLC                                                                                                                          | M + N ULN                                                             | NIN                                                                            | SO                                                                            | R                                                                                   | AN                                                                                     | т                                                               | Extent of disease, Number of metastatic sites, Albumin,<br>Weicht loss                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 65                               | Eton O <sup>2 1</sup>                                                                                              | 1998                                                              | 318                                                                     | Ч                                                                                                 | Melanoma                                                                                                                      | ٤                                                                     | 225                                                                            | OS                                                                            | 2                                                                                   | ΥA                                                                                     | т                                                               | Albumin, Soft fissue and/or single visceral organ<br>metastases (especially lung), Sex, Enrollment late in the<br>decade                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 66                               | D'AMICO <sup>77</sup>                                                                                              | 2005 494                                                          | 494                                                                     | AN                                                                                                | HRPC                                                                                                                          | ٤                                                                     | 74-<br>2077                                                                    | SO                                                                            | 2                                                                                   | 15.6-<br>16.8                                                                          | _                                                               | Hb, Age, ECOG PS, ALP, Treatment, PSA response<br>duration, PSA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 67                               | Halabi <sup>z8</sup>                                                                                               | 2003                                                              | 760                                                                     | ٩N                                                                                                | HRPC                                                                                                                          | ٤                                                                     | 173-<br>437                                                                    | OS                                                                            | ĸ                                                                                   | ΑN                                                                                     | т                                                               | PS, Gleason, ALP, PSA, Visceral disease, Hb                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 68                               | Schellhammer <sup>79</sup> 2013 512                                                                                | 2013                                                              | 512                                                                     | AN                                                                                                | CRPC                                                                                                                          | ٤                                                                     | 84-<br>1662                                                                    | OS                                                                            | <u>م</u>                                                                            | AN                                                                                     |                                                                 | PSA, Hb, ECOG, ALP, Gleason score                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| Abbr<br>disea<br>Lactic<br>lymph | eviations: SCLC: small-cell<br>se-free survival; RFS: recu<br>dehydrogenas; ALP: alka<br>ocytes; CRP: C-reaction p | lung cancer;<br>rrence-free su<br>line phosphal<br>rrotein; IPFSG | NSCLC: non-sn<br>rvival; M: meta<br>tase; PSA: pros<br>i: International | mall-cell lung cancer,<br>astatic; N: non-metas<br>state specific antiger<br>Prognostic Factors ; | ;;RCC: renal cell carcinoma; H<br>static; M + N. mixed (non-me<br>n; Hb: hemoglobin; Ca: calcii<br>Study Group; CA19-9: carbc | HRPC: hormone<br>stastatic and m<br>um; PS: Perforr<br>shydrate antig | erefractory pros<br>etastatic); R: reti<br>nance Status; E(<br>en 19-9; CEA: c | state cancer; CRP<br>rospective; P: prc<br>COG PS: Eastern<br>aarcinoembryoni | C: castration refro<br>sspective; L: low r<br>1 Cooperative On<br>c antigen; GGT: g | actory prostate can<br>risk; High: high risl<br>cology Group Perf<br>gamma-glutamyl tr | icer; ULN: upp<br>k; NA: not av<br>ormance Stat<br>anspeptidase | Abbreviations: SCLC: small-cell lung cancer; NSCLC: non-small-cell lung cancer; RCC: rend cell carcinoma; HRPC: hormone-refractory prostate cancer; CRPC: castration refractory prostate cancer; ULN: upper limit of normal; OS: overall survival; PFS: progression-free survival; DFS: dispersion-free survival; PFS: progression-free survival; DFS: end cell carcinoma; MRPC: hormone-refractory prostate cancer; CRPC: castration refractory prostate cancer; ULN: upper limit of normal; OS: overall survival; PFS: progression-free survival; DFS: dispersion-free survival; PFS: progression-free survival; PFS: reaction-prostate cancer; CRP: Castratic survival; PFS: progression-free survival; PFS: progression-free survival; PFS: reaction-prostate cancer; MRS: Karnofsky performance score; LDH : lactific advalues; PSA: prostate specific antigen; Hb: hormance store; LDH : lactific advalues; PSA: prostate specific antigen; HS: Ferformance score; SFS: Ferformance score; LDH : lactific advalues; PSA: prostate specific advalues; PSA: prostate ad |

sites were reported in the included studies. However, the result of subgroups analysis for LDH cutoff showed that there was no association between LDH cutoff and reported HR for OS. This result was confirmed by meta-regression of LDH cutoff and HR for OS. Moreover, LDH was also related to poor prognosis in solid tumors when analyzed as a continuous variable. Our conclusions are supported by the fact that our selected studies were confined to those that used proportional hazards modeling to adjust for clinical prognostic factors and where the sample size was greater than 200.

There is a good biologic rationale for the use of LDH as a prognostic marker for cancer patients; however, the exact mechanism is not understood. One potential mechanism may be an association between LDH and the well-established phenomenon of oncogenicanaerobic glycolysis, or the Warburg effect<sup>5</sup>. This metabolic reprogramming is regulated by HIF-1 $\alpha$ , as well as myc, through the transcriptional activation of key genes encoding metabolic enzymes; these include LDH, which converts pyruvate to lactate. This process is closely associated with an increased risk of invasion, metastasis, and patient death<sup>77</sup>.

These analyses have several important implications. First, they show that a high LDH is associated with worse outcome, which suggests that LDH may be a useful biomarker to direct therapeutic selection<sup>78,79</sup>. This is because LDH is under the translational control of HIF-1 $\alpha$ , as well as myc, and thus is regulated by key oncogenic processes, such as the phosphatidylinositol 3-kinase/Akt/TORC1/ hypoxia-inducible factor (PI3K/Akt/TORC1/HIF) pathway<sup>80-82</sup>. A recent study has demonstrated that the TORC1 inhibitor, temsirolimus, could provide therapeutic benefit in patients with RCC and high LDH<sup>79</sup>. Further work to investigate the predictive value of pretreatment LDH in other solid tumors may provide a more general insight into which patients derive benefit from TORC1 inhibition. Second, they show that increased LDH may be interpreted as reflecting high tumor burden or tumor aggressiveness. This suggests that dynamic changes of LDH level may be useful for predicting the prognosis in cancer patients after a primary operation, adjuvant chemotherapy, hormonal therapy, or radiotherapy<sup>65</sup>. Third, LDH allows the identification of a subgroup of tumors with a worse outcome. It is essential in the treatment of cancer to distinguish between low- and high-risk patients, thereby allowing stratification for standard or intensified treatment protocols. It has been shown that LDH can be used as an effective biomarker to guide the selection of regorafenib in patients with colorectal cancer; patients with high LDH may not be optimal candidates for regorafenib<sup>83</sup>.To adequately address these issues and dissect the complex relationship between LDH and cancer, future studies should be conducted within tumor- and stagespecific cohorts.

The strengths of this meta-analysis include the large sample size, estimation of HR using multivariate proportional hazards modeling that adjusted for clinical prognostic factors, and analysis of a massive dataset comprising a large pool of clinical studies. LDH is also likely to be a cancer-specific biomarker, given that it is rarely increased in patients without cancer<sup>84</sup>. Thus, LDH may be a universal prognostic marker in cancer. To improve research in this area, studies with a more specific focus, such as those that address the impact of an individual LDH level on the prognosis of a homogeneous population of cancer patients (i.e., patients with the same cancer stage and sub-type), would likely be more informative.

These analyses have limitations. One of the main limitations is the significant heterogeneity between studies, although we used randomeffects models when pooling subgroup data. The heterogeneity in these studies could be explained by different patient characteristics or study designs. To facilitate interpretation, we grouped the patients by tumor type and tumor stage. Another limitation is that this is a literature-based analysis. It is compromised by the potential for publication bias, in which there is a tendency for predominantly positive results to have been published, thus inflating our estimate for the



| Hazard Relio         Hazard Relio         Hazard Relio           Ace 2005         0.3436         0.0185         1.9%         1.41         1.14         1.7.4           Ace 2005         0.3436         0.0170         0.9%         2.21         1.3.9         1.7.           Amstrong 2012         1.0322         0.700         0.9%         2.21         1.3.9         1.7.           Bacci 2000         0.2239         0.022         2.5%         1.3.9         1.1.6         1.67           Bacci 2000         0.4741         0.026         2.4%         1.52         1.96         1.83         1.7.           Becikas 2006         0.4727         0.158         1.56         1.56         1.56         1.57         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         1.56         <                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                          |                      |        |            |                    |     |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|----------------------|--------|------------|--------------------|-----|-------------------|
| Ace 2004         0.3436         0.1085         1.9%         1.44         1.14.1         1.14.1                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Study or Subgroup        | Ion[Hazard Ratio]    | SE     | Weight     | Hazard Ratio       |     |                   |
| Ace 2005       0.3148       0.1074       2.0%       1.37 [1:11, 163]         Arabong 2003       0.2624       0.1339       1.4%       1.30 [1:00, 169]         Bacci 2004       0.5878       0.2659       0.1391       1.4%       1.30 [1:00, 169]         Bacci 2007       0.6471       0.257       1.39 [1:49, 2.45]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                          | •• •                 |        | -          |                    |     |                   |
| Atzpodeni 2003       0.2624       0.1339       1.4%       1.30 [1.0, 1.69]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                          |                      |        |            |                    | -   | -                 |
| Bacc 2020 0 0.228 0.0023 2.5% 1.39 [1.6, 1.67]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Armstrong 2012           |                      |        | 0.9%       | 2.81 [2.01, 3.93]  |     |                   |
| Bacci 2004 0.5878 0.2068 0.6% 1.80 [1 20, 270]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                      |        |            |                    |     | _                 |
| Bacci 2007 0.647 1.1267 1.5% 1.91 1.94.2.45]<br>Bedikin 2010 0.4457 0.1225 1.6% 1.55 1.22 1.97<br>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                          |                      |        |            |                    | -   |                   |
| Bedkina 2008 0.4149 0.0940 2.4% 1.52 [12.6 1.83]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                          |                      |        |            |                    |     |                   |
| Bedfkan 2011 0.4357 0.1225 1.6%, 1.65 [1.22, 1.97]<br>Cook 2006 0.7372 0.1558 1.1%, 2.09 [1.54, 2.44]<br>T<br>Cook 2006 0.0727 0.1558 1.1%, 2.09 [1.54, 2.44]<br>T<br>Du 2013 0.060 0.0025 9.1%, 1.01 [1.00, 1.01]<br>Du 2013 0.060 0.0025 9.1%, 1.01 [1.00, 1.01]<br>Du 2013 0.0587 0.166 0.9%, 1.80 [1.30, 2.49]<br>Feliu 2011 0.1190 0.0522 6.6%, 1.03 [1.30, 2.49]<br>Feliu 2011 0.1190 0.0522 6.6%, 1.03 [1.30, 2.49]<br>Feliu 2011 0.1190 0.0526 0.0%, 1.00 [1.35, 2.66]<br>T<br>Feliu 2013 0.030 0.0190 2.1%, 1.27 [1.04, 1.55]<br>Giaccone 2005 0.0536 0.1390 1.3%, 1.17 [1.30, 2.25]<br>T<br>Feliu 2013 0.033 0.0191 2.1%, 1.27 [1.04, 1.55]<br>Giaccone 2005 0.0536 0.1390 1.3%, 1.04 [1.6, 1.69]<br>T<br>Habbi 2014 0.0356 0.0592 1.3%, 1.04 [1.6, 1.69]<br>T<br>Habbi 2014 0.0530 0.2491 0.057<br>Habbi 2014 0.0530 0.2107 0.67 [1.00, 1.00, 1.00]<br>T<br>Habbi 2013 0.0455 0.1592 1.3%, 1.40 [1.6, 1.69]<br>T<br>Hamisdal 1903 0.4418 0.1599 1.3%, 1.54 [1.8, 2.01]<br>T<br>Hamisdal 1903 0.4418 0.1599 1.3%, 1.54 [1.8, 2.01]<br>T<br>Hamisdal 1903 0.4480 0.0600 0.0% 1.60 [1.00, 1.05]<br>T<br>Habbi 2012 1.0118 0.18%, 1.82 [1.27, 2.60]<br>T<br>Habbi 2013 0.0530 0.2169 0.7% 2.275 [1.86, 4.07]<br>T<br>Kawahara 1997 0.6729 0.23%, 2.49 [1.24, 3.89]<br>T<br>Kawahara 1997 0.6729 0.23% 1.49 [1.24, 2.60]<br>T<br>Habbi 2012 1.0118 0.196 0.7% 2.275 [1.86, 4.07]<br>T<br>Kawahara 1997 0.6729 0.23% 1.66 [1.02, 2.69]<br>T<br>Habbi 2012 0.0130 0.4480 0.0600 2.03% 1.60 [1.36, 1.87]<br>T<br>Kawahara 1997 0.6729 0.22% 1.55 [1.32, 1.82]<br>T<br>Habbi 2014 0.5767 0.22 0.3% 2.219 [1.24, 3.89]<br>T<br>Habbi 2014 0.5767 0.22 0.3% 2.219 [1.24, 3.89]<br>T<br>Habbi 2014 0.5767 0.22 0.3% 2.219 [1.24, 3.89]<br>T<br>Habbi 2014 0.5769 0.126 0.136 [1.22, 2.61]<br>T<br>Habbi 2014 0.568 0.1269 0.15% 1.56 [1.20, 2.61]<br>T<br>Habbi 2014 0.568 0.1269 0.15% 1.56 [1.20, 2.61]<br>T<br>Habbi 2014 0.5420 0.126 0.15% 1.55 [1.22, 2.13]<br>T<br>Habbi 2017 0.568 0.1269 0.15% 1.55 [1.22, 2.13]<br>T<br>Habbi 2017 0.568 0.1269 0.15% 0.15% 0.161 0.0231<br>T<br>Habbi 2014 0.5420 0.1269 0.58% 0.260 1.50 0.331<br>T<br>Habbi 2014 0.5420 0.1269 0.5% 0.25% 0.5% 0.160 0.130 0.77<br>T<br>Habbi 2014 0.5420 0.1269 0.5% 0.25% 0.160 0.130 0.77 |                          |                      |        |            |                    |     | -                 |
| Chibaudel 2011 0.5676 0.1103 1.9% 1.80 14.5 2.23                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                          |                      |        |            |                    | -   | -                 |
| Cook 2006 0.7372 0.1558 1.1% 2.09 [1.54, 2.44]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                      |        |            |                    |     | <del>.</del>      |
| Du 2013       0.005       0.0025       9.1%       1.01 [100, 1.01]         Escudior 2007       0.5194       0.188       0.7%       1.68 [116, 2.43]         Escudior 2007       0.5194       0.188       0.7%       1.68 [116, 2.43]         Feliu 2011       0.196       0.3322       6.3%       1.13 [106, 1.20]         Giaccone 2005       0.6385       0.1399       1.3%       1.27 [104, 1.55]         Giaccone 2013       0.2395       0.2111       0.6%       2.00 [1.35, 2.96]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Cook 2006                | 0.7372               | 0.1558 |            |                    |     |                   |
| Dumail 2013         2.1988         0.71%         9.01 [21, 8, 37, 22]           Eton. 1998         0.5574         0.168         0.75%         1.66 [1, 16, 2, 43]           Eton. 1998         0.5578         0.166         0.9%         1.80 [1, 13, 2, 44]           Film 2011         0.1198         0.0322         6.9%         1.13 [1, 06, 1, 12, 14]           Giascone 2005         0.0338         0.0055         0.7%         2.20 [1, 15, 2.96]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Culp 2010                | 0.5068               | 0.1407 | 1.3%       | 1.66 [1.26, 2.19]  | -   | -                 |
| Escudier 2007 0.5194 0.188 0.7% 1.68 0.17.6.243 Feliu 2011 0.5878 0.168 0.3% 1.18 0.130 2.44 Feliu 2011 0.587 0.108 0.322 0.49% 1.37 110.6.120 Feliu 201 0.585 0.1399 1.3% 1.71 11.30 2.25 Feliu 201 0.682 0.49 1.3% 1.71 11.30 2.25 Feliu 201 0.68 1.3% 0.1019 2.1% 1.71 11.30 2.25 Feliu 201 0.68 1.3% 0.1019 2.1% 1.71 11.30 2.25 Feliu 201 0.68 1.3% 0.179 1.71 1.75 1.71 1.30 2.75 Feliu 201 0.68 1.38 1.3% 1.71 1.30 2.75 1.40 1.55 1.40 1.45 1.45 1.45 1.45 1.45 1.45 1.45 1.45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          |                      |        |            | 1.01 [1.00, 1.01]  | 1   |                   |
| Ebon 1998 0.6878 0.166 0.9% 1.80 [ 30, 2.49<br>Felia 2011 0.1196 0.0322 6.9% 1.131 [ 1.06, 1.20<br>Giascano 2005 0.5365 0.1399 1.3% 1.71 [ 1.30, 2.25<br>Giroux 2012 0.6981 0.2005 0.7% 2.00 [ 1.35, 2.98<br>Giroux 2012 0.6981 0.2005 0.7% 2.00 [ 1.35, 2.98<br>Giroux 2012 0.6981 0.2005 0.7% 2.00 [ 1.35, 2.98<br>Han 2003 0.4318 0.1399 1.3% 1.44 [ 1.16, 1.66 ] T<br>Han 2003 0.4318 0.1399 1.3% 1.44 [ 1.16, 1.66 ] T<br>Hansibal 1993 0.4055 0.1582 1.0% 1.50 [ 1.10, 2.05 ] T<br>Hansibal 1993 0.4055 0.1582 1.0% 1.50 [ 1.10, 2.05 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.27, 2.60 ] T<br>Hashimoto 2009 0.9977 0.1818 0.9% 1.32 [ 1.24, 3.69 ] T<br>Kawahara 1997 0.729 0.1433 1.2% 1.96 [ 1.48, 2.60 ] T<br>Hashimoto 2009 0.4383 0.082 2.9% 1.55 [ 1.32, 1.82 ] T<br>Hashimoto 2010 0.7687 0.292 0.3% 2.19 [ 1.24, 3.69 ] T<br>Hashimoto 2012 0.6068 0.2465 0.5% 1.66 [ 1.02, 2.69 ] T<br>Hashimoto 2012 0.6068 0.2465 0.5% 2.46 [ 1.83, 3.14 ] T<br>Mekenkamp 2012 0.6068 0.2465 0.5% 2.46 [ 1.83, 3.14 ] T<br>Mekenkamp 2012 0.6068 0.2465 0.5% 2.46 [ 1.83, 3.14 ] T<br>Mekenkamp 2012 0.6168 0.1139 1.8% 1.65 [ 1.42, 2.13 ] T<br>Mekenkamp 2012 0.6169 0.1266 1.5% 1.61 [ 1.02, 2.69 ] T<br>Hashimoto 2014 0.4329 0.1269 1.5% 1.72 [ 1.17, 1.22 ] T<br>Hashimoto 2015 0.1562 1.0% 1.22 [ 1.61, 3.56 ] T<br>Hashimoto 2014 0.4329 0.1269 1.5% 1.22 [ 1.61, 3.56 ] T<br>Hashimoto 2014 0.4329 0.1269 1.5% 1.22 [ 1.61, 3.56 ] T<br>Hashimoto 2013 0.446 0.176 0.5% 1.60 [ 1.00, 1.00 ] T<br>Hashimoto 2013 0.447 0.169 2.9% 2.24 [ 1.46, 3.56 ] T<br>Hashimoto 2014 0.4348 0.149 1.1% 1.40 [ 1.41, 1.82 ] T<br>Hashimoto 2014 0.4348 0.149 1.1% 1.41 [ 1.45, 2.24 ] T<br>Hashimoto 2014 0.4348 0.149 1.1% 1                                                                                                       |                          |                      |        |            |                    |     | _                 |
| Fellu 2011       0.1196       0.0322       6.9%       1.13 [1 0.6, 1.20]         Glascone 2005       0.5385       0.1399       1.3%       1.27 [1 0.4, 1.55]         Girsunz 2012       0.6931       0.2005       0.7%       2.00 [1.35, 2.96]         Girsunz 2012       0.6931       0.2005       0.7%       2.00 [1.35, 2.96]         Halabi 2014       0.3855       0.0599       2.3%       1.40 [1.16, 1.69]         Hansibiotid 2009       0.5977       0.1818       0.8%       1.50 [1 1.0, 2.05]         Hashimoto 2009       0.5977       0.1818       0.8%       0.97 [0.63, 1.48]         Jakob 2012       0.1168       0.78%       2.10 [1 3.6, 1.87]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                          |                      |        |            |                    |     |                   |
| Glascon 2005 Glassen 2013 Glassen 2014 Glassen 2017 Glass                                                                                                                                           |                          |                      |        |            |                    |     |                   |
| Glessen 2013       0.239       0.1019       2.1%       1.27       1.43       2.96         Girux 2012       0.6835       0.2005       0.7%       2.00       1.35, 2.96         Halab 2014       0.3855       0.2101       0.6%       2.40       1.59, 3.62         Hansibul 1993       0.4055       0.1582       1.0%       1.50       1.10       2.05         Hashinoto 2009       0.5977       0.1818       0.8%       0.97       10.63, 1.48       1.72       1.66         Jakob 2012       0.1160       0.996       0.7%       2.76       1.68, 4.07                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                      |        |            |                    |     | -                 |
| Giroux 2012         0.6331         0.2005         0.7%         2.00         1.35, 2.96           Gripp 2007         0.8755         0.2011         0.6%         2.40         [15.9, 3.62]           Han 2003         0.4318         0.1339         1.3%         1.44         [1.16, 1.69]           Han 2003         0.4318         0.1339         1.3%         1.44         [1.10, 2.05]           Hashimoto 2009         0.5977         0.1818         0.8%         1.82         [1.27, 2.60]           Jakob 2012         1.0116         0.1995         0.7%         2.75         [1.86, 4.07]           Jakob 2012         1.0116         0.1995         0.7%         2.75         [1.86, 4.07]           Lagenwaard 1997         0.6729         0.1433         1.60 [1.48, 1.87]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                          |                      |        |            |                    | -   | -                 |
| Gripp 2007       0.8755       0.2101       0.6%       2.40       [1.50, 3.62]         Halabi 2014       0.3365       0.0595       2.3%       1.40       [1.16, 1.69]         Han 2003       0.4055       0.1582       1.0%       1.50       1.10, 2.05]         Hanisdal 1993       0.4055       0.1582       1.0%       1.50       1.10, 2.05]         He 2013       -0.0336       0.2162       0.6%       0.97       0.63, 1.48]         Jin 2013       0.4669       0.680       3.0%       1.60       1.8, 6.407         Kim 2010       0.7857       0.292       0.3%       2.19       1.24, 3.89]         Lagerward 1997       0.4333       0.0462       0.9%       1.55       1.32         Lagier 2007       0.3075       0.0991       2.2%       1.55       1.32       -         Lagier 2007       0.3075       0.0991       2.2%       1.36       1.21, 6.5]       -         Mickenkamp 2012       0.5162       0.5%       1.66       1.02, 2.69]       -       -         Motzer 1999       0.9002       0.1265       1.5%       2.46       1.93, 3.41       -         Motzer 1999       0.9002       0.1267       1.5% <t< td=""><td></td><td></td><td></td><td></td><td></td><td>· ·</td><td></td></t<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                          |                      |        |            |                    | · · |                   |
| Han 2003 0.4318 0.1369 1.3% 1.54 [1.18, 2.01]<br>Hannisdal 1993 0.4055 0.1582 1.0% 1.50 [1.10, 2.05]<br>He 2013 0.0336 0.2162 0.6% 0.97 [0.63, 1.48]<br>He 2013 0.0336 0.2162 0.6% 0.97 [0.63, 1.48]<br>Kawahara 1997 0.6729 0.1433 1.2% 1.96 [1.48, 2.60]<br>Kawahara 1997 0.6729 0.1433 1.2% 1.96 [1.48, 2.60]<br>Lagerward 1999 0.4383 0.082 2.9% 1.55 [1.32, 1.82]<br>Lagerward 1999 0.4383 0.082 2.9% 1.36 [1.12, 1.65]<br>He cold 2.045 0.0566 0.2465 0.5% 1.66 [1.02, 2.69]<br>He cold 2.045 0.0566 0.2465 0.5% 1.66 [1.02, 2.69]<br>He cold 2.045 0.1286 1.4% 1.65 [1.28, 2.13]<br>Mekenkamp 2012 0.5006 0.1286 1.5% 1.42 [1.11, 1.85]<br>Herego 0.1245 1.5% 2.46 [1.93, 3.14]<br>Motzer 1999 0.9002 0.1245 1.5% 2.46 [1.93, 3.14]<br>Meter 1999 0.9002 0.1245 1.5% 1.42 [1.11, 1.82]<br>Pierga 2001 0.6931 0.0829 2.9% 2.20 [1.70, 2.35]<br>Pierga 2001 0.6931 0.0829 2.9% 2.20 [1.70, 2.35]<br>Porch 2014 0.8242 0.2274 0.5% 2.28 [1.46, 3.56]<br>Porch 2014 0.8242 0.2274 0.5% 2.28 [1.46, 3.56]<br>Tamura 1998 0.003 0.001 9.1% 1.00 [1.00, 1.00]<br>Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00]<br>Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 2.67]<br>Sul 2007 0.4818 0.2367 0.5% 1.62 [1.02, 2.57]<br>Sul 2013 0.4625 0.1289 1.5% 0.81 [0.64, 1.64]<br>Tamura 1998 0.0365 0.1765 0.8% 2.22 [1.46, 3.56]<br>Tamura 1998 0.0365 0.1765 0.8% 2.22 [1.46, 3.63]<br>Tamura 1998 0.0365 0.1765 0.8% 2.24 [1.56, 3.33]<br>Tamina 1997 1.4061 0.6316 0.1% 4.08 [1.16, 1.43]<br>Tamina 1997 1.4061 0.6316 0.1% 4.08 [1.16, 1.43]<br>Tamina 1998 0.0365 0.1765 0.8% 2.24 [1.56, 3.33]<br>Tamina 1997 1.4061 0.6316 0.1% 4.08 [1.16, 1.43]<br>Tamina 1998 0.0365 0.1765 0.8% 2.24 [1.56, 3.33]<br>Tamina 1997 1.4061 0.6316 0.1% 4.08 [1.18, 1.407]<br>Tamina 1998 0.0365 0.1765 0.8% 2.24 [1.56, 3.33]<br>Tamina 1997 1.4061 0.6316 0.1% 4.08 [1.16, 1.33]<br>Tamina                                                          | Gripp 2007               | 0.8755               | 0.2101 | 0.6%       | 2.40 [1.59, 3.62]  |     |                   |
| Hamiadal 1993 0.4655 0.1582 1.0% 1.50 [1.10, 2.05]<br>Hashimoto 2009 0.5977 0.1818 0.8% 1.82 [1.27, 2.60]<br>Hashimoto 2012 1.0116 0.1995 0.7% 2.75 [1.86, 4.07]<br>Jakob 2012 1.0116 0.1995 0.7% 2.75 [1.86, 4.07]<br>Kawahara 1997 0.6729 0.1433 1.2% 1.96 [1.48, 2.60]<br>Lagerwaard 1999 0.4383 0.082 2.9% 1.55 [1.32, 1.82]<br>Lagerwaard 1999 0.4383 0.082 2.9% 1.55 [1.32, 1.82]<br>Lagerwaard 1999 0.4383 0.082 2.9% 1.55 [1.32, 1.82]<br>Laute 2007 0.3075 0.0991 2.2% 1.36 [1.12, 1.65]<br>Meckenkamp 2012 0.5068 0.2465 0.5% 1.66 [1.02, 2.69]<br>Meckenkamp 2012 0.5008 0.1296 1.4% 1.65 [1.28, 2.13]<br>Motzer 1999 0.9002 0.1245 1.5% 2.46 [1.98, 3.14]<br>Motzer 1999 0.9002 0.1245 1.5% 2.46 [1.98, 3.14]<br>Motzer 2002 1.1725 0.1726 0.9% 3.23 [2.30, 4.53]<br>Motzer 2013 0.4517 0.1805 0.8% 1.57 [1.10, 2.24]<br>Pierga 2001 0.6331 0.0229 2.9% 2.20 [1.70, 2.35]<br>Polea 2003 0.40455 0.1582 1.0% 1.55 [1.32, 1.82]<br>Salto 2007 0.4818 0.2357 0.5% 1.42 [1.11, 1.82]<br>Pierga 2011 0.6931 0.0229 2.9% 2.20 [1.70, 2.35]<br>Salto 2007 0.4818 0.2357 0.5% 1.42 [1.11, 1.82]<br>Schmidt 2017 0.7865 0.1259 1.5% 0.81 [0.64, 1.04]<br>Scher 1999 0.0003 0.001 9.1% 1.00 [1.00, 1.00]<br>Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00]<br>Tamura 1998 0.3036 0.1259 1.5% 0.81 [0.64, 1.04]<br>Tamura 1998 0.3036 0.1765 0.8% 2.22 [1.46, 3.66]<br>Tamura 1998 0.3036 0.1765 0.8% 2.24 [1.58, 3.17]<br>Tamura 1998 0.3036 0.1765 0.8% 2.24 [1.56, 3.83]<br>Tamura 1998 0.3036 0.1765 0.8% 2.24 [1.58, 3.17]<br>Tamura 1998 0.3036 0.1765 0.8% 2.24 [1.56, 3.83]<br>Tamura 1998 0.3056 0.2769 0.6% 1.80 [1.20, 2.70]<br>Tamura 1998 0.3056 0.3058 0.30% 2.65 [1.64, 1.93]<br>Tamura 1998 0.3056 0.3059 0.30% 2.65 [1.64, 3.13]<br>Tamura 1998 0.3056 0.3059                                                           | Halabi 2014              | 0.3365               | 0.0959 | 2.3%       | 1.40 [1.16, 1.69]  | 7   | F                 |
| Hashinoto 2009       0.5977       0.1818       0.8%       1.82 [1.27, 2.60]         He 2013       -0.036       0.2162       0.6%       0.97 [0.63, 1.48]         Jin 2013       0.4669       0.0806       3.0%       1.60 [1.36, 1.87]         Kawahara 1997       0.6729       0.133       1.2%       1.96 [1.48, 2.60]         Lagerwaard 1999       0.4333       0.082       2.9%       1.55 [1.32, 1.82]         Lagerwaard 1999       0.4333       0.082       2.9%       1.55 [1.32, 1.82]         Lagerwaard 1999       0.4333       0.082       2.9%       1.55 [1.32, 1.82]         Layerwaard 1999       0.4333       0.082       2.9%       1.55 [1.32, 1.82]         U2012       0.5068       0.2465       0.5%       1.66 [1.02, 2.69]         Meekhakamp 2012       0.5088       0.236       1.36 [1.48, 2.31]       T         Mekenkamp 2012       0.5008       0.1296       1.4%       1.66 [1.02, 2.69]         Motzer 1999       0.9002       0.1245       1.5%       2.46 [1.93, 3.14]         Motzer 2002       1.1725       0.1296       1.4%       1.66 [1.02, 2.57]         Polee 2003       0.4550       0.1582       1.0%       1.20 [1.0, 2.35]         Polee 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                          |                      |        |            |                    | -   | -                 |
| He 2013 -0.0336 0.2162 0.6% 0.97 [0.63, 1.48]<br>Jakob 2012 1.0116 0.1995 0.7% 2.75 [1.86, 4.07]<br>Kawabara 1997 0.6729 0.1433 1.2% 1.96 [1.48, 2.60]<br>Kawabara 1997 0.6729 0.1433 1.2% 1.96 [1.48, 2.60]<br>Lagerward 1999 0.4383 0.022 2.9% 1.55 [1.32, 1.82]<br>Laurie 2007 0.375 0.0991 2.2% 1.36 [1.22, 1.82]<br>Laurie 2007 0.375 0.0991 2.2% 1.66 [1.02, 2.69]<br>Meskbach 2014 0.8329 0.1852 0.8% 2.30 [1.60, 3.31]<br>Mekenkamp 2012 0.6152 0.1139 1.8% 1.86 [1.28, 2.13]<br>Motzer 1999 0.9002 0.1246 1.5% 2.46 [1.93, 3.14]<br>Motzer 1999 0.9002 0.1246 1.5% 2.46 [1.93, 3.14]<br>Motzer 2013 0.4517 0.1805 0.8% 1.57 [1.10, 2.24]<br>Pierga 2001 0.6931 0.0829 2.9% 2.00 [1.70, 2.35]<br>Pierga 2001 0.6931 0.0829 2.9% 2.00 [1.70, 2.35]<br>Pierga 2001 0.6931 0.0829 2.9% 2.00 [1.70, 2.35]<br>Pierga 2001 0.6418 0.2377 0.5% 1.42 [1.02, 2.57]<br>Sau 2013 0.2058 0.1259 1.5% 0.24 [1.46, 3.56]<br>Saito 2007 0.7885 0.1259 1.5% 0.22 [1.64, 3.36]<br>Saito 2007 0.7885 0.1259 1.5% 0.22 [1.64, 3.56]<br>Saito 2007 0.7885 0.1259 1.5% 0.22 [1.64, 3.56]<br>Saito 2007 0.7885 0.1259 1.5% 0.22 [1.60, 3.03]<br>Tarrivul 2010 0.5439 0.1269 1.7% 1.60 [1.10, 2.05]<br>Pierga 2013 0.0459 0.1778 0.8% 1.77 [1.10, 2.24]<br>Tarrivul 2010 0.5439 0.1786 0.156 0.8% 1.72 [1.32, 2.44]<br>Tarrivul 2010 0.5439 0.1259 1.5% 0.22 [1.60, 3.03]<br>Tarrivul 2007 0.7885 0.1625 1.0% 2.20 [1.60, 3.03]<br>Tarrivul 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.46]<br>Tarrivul 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.43]<br>Wang 2014 0.5446 0.176 0.8% 1.72 [1.22, 2.43]<br>Tarrivul 2010 0.5499 0.1778 0.8% 1.73 [1.22, 2.43]<br>Tarrivul 2010 0.5446 0.176 0.8% 1.72 [1.22, 2.43]<br>Tarrivul 2010 0.5446 0.176 0.8% 1.72 [1.22, 2.43]<br>Tarrivul 2010 0.5446 0.176 0.8% 1.72 [1.22, 2.43]<br>Tarrivul 2010                                                            |                          |                      |        |            |                    |     |                   |
| Jakob 2012       10116       0.1969       0.7%       2.75 [1.86, 4.07]         Jin 2013       0.4669       0.0806       3.0%       1.60 [1.36, 1.87]         Kim 2010       0.7857       0.292       0.3%       2.19 [1.24, 3.89]         Lagerwaard 1999       0.4333       0.082       2.9%       1.55 [1.32, 1.82]         Lagerwaard 1999       0.4333       0.082       2.9%       1.55 [1.2, 1.65]         Li 2012       0.5068       0.2465       0.5%       1.36 [1.42, 1.65]         Li 2012       0.5068       0.2465       0.5%       2.30 [1.60, 3.31]         Meeknakamp 2012       0.6152       0.139       1.8%       1.85 [1.48, 2.31]         Motzer 1999       9.9002       0.1266       1.4%       1.66 [1.02, 2.69]         Notzer 2002       1.172       0.1726       0.5%       3.23 [2.30, 4.53]         Motzer 2002       1.172       0.1726       1.5%       1.42 [1.11, 1.82]         Pelerga 2011       0.6829       0.29%       2.00 [1.70, 2.35]       -         Pelerga 2014       0.8242       0.2274       0.5%       2.28 [1.46, 3.56]       -         Sala 2007       0.4818       0.2357       0.5%       1.62 [1.02, 2.57]       -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          |                      |        |            |                    |     |                   |
| Jin 2013       0.4669       0.0806       3.0%       1.60       [1.48, 2.60]         Kawahara 1997       0.6729       0.1433       1.2%       1.96       [1.24, 3.89]         Lagereward 1999       0.4383       0.082       2.9%       1.55       [1.2, 1.82]       -         Laurie 2007       0.3075       0.0991       2.2%       1.36       [1.12, 1.65]       -         Li 2012       0.5068       0.2465       0.5%       1.66       [1.02, 2.69]       -         Mekenkamp 2012       0.6152       0.18%       1.85       [1.42, 1.65]       -         Motzer 1999       0.9002       0.1245       1.5%       2.46       [1.93, 3.14]       -         Motzer 2013       0.4517       0.1726       0.5%       2.46       [1.93, 3.14]       -         Neuman 2008       0.3607       0.1257       1.5%       1.42       -       -         Poleg 2003       0.4055       0.1582       1.0%       1.50       [1.0, 2.26]       -         Saiu 2013       0.4055       0.1582       1.0%       1.50       [1.0, 2.25]       -         Solid 2014       0.8242       0.2274       0.5%       2.28       [1.66]       -       -     <                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          |                      |        |            |                    |     | <u> </u>          |
| Kawahara 1997       0.6729       0.1433       1.2%       1.96 [1.48, 2.60]         Kim 2010       0.7857       0.292       0.3%       2.19 [1.24, 3.89]         Lagerwaard 1999       0.4383       0.082       2.9%       1.55 [1.32, 1.82]         Laure 2007       0.3075       0.0991       2.2%       1.36 [1.12, 1.65]         Li 2012       0.5068       0.2465       0.5%       1.66 [1.02, 2.69]         Meckbach 2014       0.6329       0.1852       0.189       1.38 [1.48, 2.31]         Mekenkamp 2012       0.6152       0.1245       1.5%       2.46 [1.93, 3.14]         Motzer 1999       0.9002       0.1245       1.5%       2.46 [1.93, 3.14]         Motzer 2003       0.4655       0.1582       1.08%       1.57 [1.10, 2.24]         Neuman 2008       0.3507       0.1257       1.5%       1.42 [1.11, 1.82]         Pierg 2001       0.6931       0.0829       2.9%       2.00 [1.70, 2.35]         Porach 2014       0.8242       0.2274       0.5%       1.62 [1.02, 2.57]         Salo 2007       0.4818       0.2357       0.5%       1.62 [1.02, 2.57]         Salo 2013       0.003       0.001       9.1%       1.00 [1.00, 1.00]         Shinohara 2013 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td><b>.</b></td>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                          |                      |        |            |                    |     | <b>.</b>          |
| Kim 2010       0.7857       0.292       0.3%       2.19       [1.24]       3.89         Lagerevaard 1999       0.4383       0.082       2.9%       1.55       [1.32, 1.82]       -         Laurie 2007       0.3075       0.0991       2.2%       1.36       -       -         Mekchach 2014       0.8562       0.4862       0.5%       1.66       [1.02, 1.65]       -         Mekenkamp 2012       0.6152       0.1139       1.8%       1.85       [1.48, 2.31]       -         Motzer 1999       0.9002       0.1246       1.5%       2.46       [1.93, 3.14]       -         Motzer 2002       1.1725       0.726       0.9%       3.23       [2.30, 4.53]       -         Motzer 2013       0.4517       0.1805       0.8%       1.57       [1.0, 2.24]       -         Neuman 2008       0.3307       0.1257       1.5%       1.42       -       -         Polea 2003       0.4055       0.5%       1.28       [1.46, 3.66]       -       -         Salu 2013       -0.2258       0.159       1.0%       1.60       [1.00, 2.35]       -       -         Subinobrar 2012       0.6329       0.2519       0.5%       2.28 <td></td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                          |                      |        |            |                    |     |                   |
| $ \begin{array}{c c c c c c c c c c c c c c c c c c c $                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                      |        |            |                    | -   |                   |
| Li 2012 0.5068 0.2465 0.5% 1.66 [1.02, 2.69]<br>Meckbach 2014 0.8329 0.1852 0.8% 2.30 [1.60, 3.31]<br>Mekenkamp 2012 0.5008 0.1296 1.4% 1.65 [1.28, 2.31]<br>Motzer 1999 0.9002 0.1245 1.5% 2.46 [1.93, 3.14]<br>Motzer 2013 0.4517 0.1805 0.8% 1.57 [1.10, 2.24]<br>Neuman 2008 0.3507 0.1257 1.5% 1.42 [1.11, 1.82]<br>Peleg 2001 0.6831 0.0829 2.9% 2.00 [1.70, 2.35]<br>Peleg 2001 0.6831 0.0829 2.9% 2.00 [1.70, 2.35]<br>Peleg 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05]<br>Peleg 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05]<br>Peleg 2003 0.4055 0.1582 1.0% 1.50 [1.10, 2.05]<br>Saito 2007 0.4818 0.2357 0.5% 1.62 [1.02, 2.57]<br>Sai 2013 0.4055 0.1259 1.5% 0.81 [0.64, 1.04]<br>Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00]<br>Schmidt 2007 0.7885 0.1625 1.0% 2.20 [1.60, 3.03]<br>Shinohara 2013 0.47 0.1289 1.5% 1.72 [1.34, 2.21]<br>Sub 2010 0.5439 0.1778 0.8% 1.73 [1.22, 246]<br>Tamura 1998 0.3365 0.1761 1.1% 1.40 [1.04, 1.88]<br>Tamura 1998 0.3365 0.1761 1.1% 1.40 [1.04, 1.88]<br>Tamura 1998 0.3365 0.1765 0.8% 2.24 [1.66, 3.83]<br>Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.16, 1.91]<br>Van Kessel 2013 0.447 0.1912 0.6% 2.52 [1.66, 3.83]<br>Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.18, 14.07]<br>Van 2013 0.9658 0.3053 0.3% 2.63 [1.44, 4.78]<br>Weide 2013 0.447 0.1059 2.0% 1.60 [1.10, 2.70]<br>Wan 2013 0.9658 0.3053 0.3% 2.63 [1.44, 4.78]<br>Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.18, 14.07]<br>Van 2013 0.9658 0.3053 0.3% 2.63 [1.44, 4.78]<br>Weide 2012 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Weide 2013 0.477 0.1059 2.0% 1.60 [1.30, 1.97]<br>Weide 2014 0.5448 0.176 0.8% 1.72 [1.22, 2.43]<br>Tamura 1988 0.3365 0.53 0.3% 2.63 [1.44, 4.78]<br>Tamura 198 0.43 0.278 0.20% 1.60 [1.30, 1.97]<br>Tamura 198 0.3458 0.439 0.4178 0.489 1.50 [1.16, 1.93]<br>Tamura 198 0.43 0.278 0.400 0.56 0.5% 1.60 [1.30, 1.97]<br>Tamura 198 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Tamura 198 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Tamura 2.24 0.07 0.50 2.0% 1.60 [1.                                                          | Lagerwaard 1999          | 0.4383               | 0.082  | 2.9%       | 1.55 [1.32, 1.82]  | ·   | •                 |
| Meckbach 2014       0.8329       0.1852       0.8%       2.30       1.60, 3.31         Mekenkamp 2012       0.6152       0.1139       1.8%       1.86       1.48, 2.31         Mekenkamp 2012       0.5008       0.1296       1.4%       1.65       1.28, 2.13         Motzer 1999       0.9002       0.1245       1.5%       2.46       1.93, 3.14         Motzer 2013       0.4517       0.100       0.8%       1.57       1.0, 2.24         Neuman 2008       0.3507       0.1257       1.5%       1.42       1.11, 1.82         Pierga 2001       0.6831       0.0629       2.9%       2.00       1.70, 2.05         Polee 2003       0.4055       0.1582       1.0%       1.50       1.10, 2.05         Poprach 2014       0.8242       0.2274       0.5%       2.28       1.46, 3.56         Salu 2007       0.4818       0.2357       0.5%       1.62       1.02, 2.57         Salu 2013       -0.2058       0.1259       1.0%       2.20       1.60, 1.00         Scher 1999       0.003       0.001       9.1%       1.00       1.00         Scher 1999       0.03365       0.1577       1.60       1.10, 2.33         Sougioultzis                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                          |                      |        |            |                    |     | -                 |
| Mekenkamp 2012       0.6152       0.1139       1.8%       1.85       1.48, 2.31         Mekenkamp2 2012       0.5008       0.1296       1.4%       1.65       [1.28, 2.13]         Motzer 1999       0.9002       0.1245       1.5%       2.46       [1.39, 3.14]         Motzer 2013       0.4517       0.1805       0.8%       1.57       [1.10, 2.24]         Neuman 2008       0.3507       0.157       1.5%       1.42       [1.11, 1.82]         Pierga 2001       0.6931       0.0829       2.9%       2.00       [1.70, 2.35]         Poprach 2014       0.8242       0.2274       0.5%       2.28       [1.46, 3.56]         Salto 2007       0.4618       0.2257       0.5%       2.28       [1.46, 3.56]         Scher 1999       0.003       0.001       9.1%       1.00       [1.00, 1.00]         Schmidt 2007       0.7885       0.1625       1.0%       2.20       [1.60, 3.03]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                          |                      |        |            |                    |     |                   |
| Mekenkamp 2 2012       0.5008       0.1296       1.4%       1.65       1.28, 2.13]         Motzer 1999       0.9002       0.1245       1.5%       2.46       1.33, 3.14]         Motzer 2013       0.4517       0.1805       0.8%       1.57       1.10, 2.24]         Neuman 2008       0.3507       0.1257       1.5%       1.42       1.11, 1.82]         Pierga 2001       0.6831       0.0829       2.9%       2.00 [1.70, 2.35]         Polee 2003       0.4055       0.1582       1.0%       1.50 [1.10, 2.05]         Polee 2003       0.4055       0.1582       1.0%       1.62 [1.02, 2.57]         Saito 2007       0.4418       0.2327       0.5%       0.22 [1.46, 3.56]         Schridt 2007       0.7885       0.1625       1.0%       2.20 [1.60, 3.03]         Schridt 2007       0.7885       0.1625       1.0%       2.20 [1.60, 3.03]         Shinohara 2012       0.6329       0.2519       0.4%       1.88 [1.15, 3.09]         Shinohara 2013       0.47       0.1912       0.7%       1.60 [1.10, 2.33]         Sub 2010       0.5499       0.1778       0.8%       1.73 [1.22, 2.46]         Tamikulu 2010       0.8650       0.1676       0.8%       2                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                          |                      |        |            |                    |     | -<br>-            |
| Motzer 1999       0.9002       0.1245       1.5%       2.46 [1.93, 3.14]         Motzer 2002       1.1725       0.1726       0.9%       3.23 [2.30, 4.53]         Motzer 2013       0.4517       0.1805       0.8%       1.57 [1.10, 2.24]         Neuman 2008       0.3507       0.1257       1.5%       1.42 [1.11, 1.82]         Pierga 2001       0.6831       0.0829       2.9%       2.00 [1.70, 2.35]         Polee 2003       0.4055       0.1582       1.0%       1.50 [1.10, 2.05]         Polee 2003       0.4055       0.1582       1.0%       1.50 [1.10, 2.05]         Saito 2007       0.4418       0.2327       0.5%       1.62 [1.02, 2.57]         Sau 2013       -0.2058       0.1259       1.5%       0.81 [0.64, 1.04]         Scher 1999       0.003       0.001       9.1%       1.00 [1.00, 1.00]         Schmidt 2007       0.7885       0.1625       1.0%       2.20 [1.60, 3.03]         Suipolara 2012       0.6329       0.2519       0.4%       1.88 [1.15, 3.09]         Sougioultzis 2011       0.5423       0.1289       1.77 [1.34, 2.21]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                          |                      |        |            |                    |     |                   |
| Motzer 2002       1.1725       0.1726       0.9%       3.23       2.30       4.53         Motzer 2013       0.4517       0.1805       0.8%       1.57       [1.10, 2.24]         Neuman 2008       0.3607       0.1257       1.5%       1.42       [1.11, 1.82]         Pierga 2001       0.6829       2.9%       2.00       [1.70, 2.35]         Polee 2003       0.4055       0.1582       1.0%       1.50       [1.10, 2.2,57]         Saito 2007       0.4818       0.2357       0.5%       1.62       [1.02, 2.57]         Sau 2013       -0.2058       0.1259       1.5%       0.81       [0.64, 1.04]         Scher 1999       0.003       0.001       9.1%       1.00       [1.00, 2.30]         Shinohara 2012       0.6329       0.2519       0.4%       1.88       [1.15, 3.09]         Shinohara 2013       0.47       0.1912       0.7%       1.60       [1.10, 2.33]         Sougioultiz 2011       0.5423       0.1289       1.5%       1.72       [1.34, 2.21]         Tamura 1998       0.3365       0.157       1.1%       1.40       [1.04, 1.88]       1.73         Tamura 1998       0.365       0.1765       0.8%       2.22                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                          |                      |        |            |                    |     | -                 |
| Motzer 2013 $0.4517$ $0.1805$ $0.8\%$ $1.57$ $1.10, 2.24$ Neuman 2008 $0.3507$ $0.1257$ $1.5\%$ $1.42$ $11.11, 1.62$ Pierga 2001 $0.6931$ $0.0829$ $2.9\%$ $2.00$ $1.70, 2.35$ Polee 2003 $0.4055$ $0.1582$ $1.0\%$ $1.50$ $1.10, 2.05$ Poprach 2014 $0.8242$ $0.2274$ $0.5\%$ $2.28$ $1.46, 3.56$ Saito 2007 $0.4818$ $0.2357$ $0.5\%$ $1.62$ $1.02, 2.57$ Sau 2013 $-0.2058$ $0.1255$ $1.5\%$ $0.81$ $0.64, 1.04$ Scher 1999 $0.003$ $0.001$ $9.1\%$ $1.00$ $1.00$ $1.00$ Scher 1999 $0.003$ $0.001$ $9.1\%$ $1.00$ $1.00, 1.00$ $1.5\%$ Shinohara 2012 $0.6329$ $0.259$ $0.4\%$ $1.88$ $1.73$ $1.72$ $1.34, 2.21$ $1.233$ Sougioultizis 2011 $0.5423$ $0.128$ $1.5\%$ $1.72$ $1.48, 1.77$ $1.362$ $1.4\%$ Sub 2010 $0.5423$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                      |        |            |                    |     |                   |
| Pierga 2001 $0.6931$ $0.0829$ $2.9\%$ $2.00$ $[1.70, 2.35]$ Polee 2003 $0.4055$ $0.1582$ $1.0\%$ $1.50$ $[1.10, 2.05]$ Poprach 2014 $0.8242$ $0.2274$ $0.5\%$ $2.28$ $[1.46, 3.56]$ Saito 2007 $0.4818$ $0.2357$ $0.5\%$ $1.62$ $[1.02, 2.57]$ Sau 2013 $-0.2058$ $0.1259$ $1.5\%$ $0.81$ $[0.64, 1.04]$ Scher 1999 $0.003$ $0.001$ $9.1\%$ $1.00$ $[1.00, 2.33]$ Shinohara 2012 $0.6329$ $0.2519$ $0.4\%$ $1.88$ $[1.53, .09]$ Shinohara 2013 $0.47$ $0.1912$ $0.7\%$ $1.60$ $[1.02, 2.33]$ Sougioultzis 2011 $0.5423$ $0.1289$ $1.5\%$ $1.72$ $[1.34, 2.21]$ Tamirkul 2010 $0.5499$ $0.1778$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Tamirkul 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.83]$ Torini 1997 $1.4061$ $0.6316$ $0.1\%$ $1.02, 2.70$ $0.273$ $0.276$ <td></td> <td></td> <td></td> <td></td> <td></td> <td> -</td> <td></td>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                          |                      |        |            |                    | -   |                   |
| Polee 2003 $0.4055$ $0.1582$ $1.0\%$ $1.50$ $11.10$ , $2.05$ ]         Poprach 2014 $0.8242$ $0.2274$ $0.5\%$ $2.28$ $1.46$ , $3.56$ ]         Saito 2007 $0.4818$ $0.2357$ $0.5\%$ $1.62$ $1.02$ , $2.57$ ]         Sau 2013 $-0.2058$ $0.1259$ $1.5\%$ $0.81$ $0.64$ , $1.04$ ]         Scher 1999 $0.003$ $0.001$ $9.1\%$ $1.00$ $1.00$ $1.00$ Schmidt 2007 $0.7885$ $0.1625$ $1.0\%$ $2.20$ $1.60$ , $3.03$ ]         Shinohara 2012 $0.6329$ $0.2519$ $0.4\%$ $1.88$ $(1.15, 3.09]$ Shinohara 2013 $0.47$ $0.1912$ $0.7\%$ $1.60$ $(1.10, 2.33]$ Sougioultzis 2011 $0.5423$ $0.1292$ $1.73$ $1.22, 2.46$ ]         Tamira 1998 $0.3655$ $0.1575$ $0.8\%$ $1.73$ $1.22, 2.46$ ]         Tamira 1998 $0.3655$ $0.1765$ $0.8\%$ $2.52$ $1.63, 3.817$ ]         Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $1.50$ $1.16, 1.93$ ] $1.050$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Neuman 2008              | 0.3507               | 0.1257 | 1.5%       | 1.42 [1.11, 1.82]  | -   | -                 |
| Poprach 2014 $0.8242$ $0.2274$ $0.5\%$ $2.28$ $1.46, 3.56$ Saito 2007 $0.4818$ $0.2357$ $0.5\%$ $1.62$ $1.02, 2.57$ Sau 2013 $-0.2058$ $0.1259$ $1.5\%$ $0.81$ $[0.64, 1.04]$ Scher 1999 $0.003$ $0.001$ $9.1\%$ $1.00$ $[1.00, 1.00]$ Schmidt 2007 $0.7885$ $0.1625$ $1.0\%$ $2.20$ $[1.60, 3.03]$ Shinohara 2012 $0.6329$ $0.2519$ $0.4\%$ $1.88$ $[1.15, 3.09]$ Shinohara 2013 $0.47$ $0.912$ $0.7\%$ $1.60$ $[1.02, 2.3]$ Sougioultzis 2011 $0.5423$ $0.1289$ $1.5\%$ $1.72$ $[1.34, 2.21]$ Suh 2010 $0.5439$ $0.1778$ $0.8\%$ $1.72$ $[1.34, 2.21]$ Tamura 1998 $0.3365$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ $-0.014$ $0.9243$ $0.219$ $0.1\%$ $0.2070$ Wan 2013 $0.468$ $0.$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                          |                      |        |            |                    |     | -                 |
| Saito 2007 0.4818 0.2357 0.5% 1.62 [1.02, 2.57]<br>Sau 2013 -0.2058 0.1259 1.5% 0.81 [0.64, 1.04]<br>Scher 1999 0.003 0.001 9.1% 1.00 [1.00, 1.00]<br>Schmidt 2007 0.7885 0.1625 1.0% 2.20 [1.60, 3.03]<br>Shinohara 2012 0.6329 0.2519 0.4% 1.88 [1.15, 3.09]<br>Shinohara 2013 0.47 0.1912 0.7% 1.60 [1.10, 2.33]<br>Sougioultzis 2011 0.5423 0.1289 1.5% 1.72 [1.34, 2.21]<br>Sub 2010 0.5449 0.1778 0.8% 1.73 [1.22, 2.46]<br>Tamura 1998 0.3365 0.1517 1.1% 1.40 [1.40, 1.88]<br>Tanrikulu 2010 0.8065 0.1765 0.8% 2.24 [1.58, 3.17]<br>Templeton 2014 0.9243 0.213 0.6% 2.52 [1.66, 3.83]<br>Tonini 1997 1.4061 0.6316 0.1% 4.08 [1.18, 14.07]<br>van Kessel 2013 0.4028 0.1298 1.4% 1.50 [1.16, 1.93]<br>Viganó 2000 0.5678 0.2069 0.6% 1.80 [1.20, 2.70]<br>Wan 2013 0.9658 0.3053 0.3% 2.63 [1.44, 4.78]<br>Wang 2014 0.5939 0.1138 1.8% 1.81 [1.45, 2.26]<br>Weide 2013 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Weide 2013 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Weide 2013 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Weide 2013 0.47 0.1059 2.0% 1.60 [1.30, 1.97]<br>Yamaguchi 2014 0.4318 0.149 1.1% 1.54 [1.15, 2.06]<br>Zhou 2012 1.1112 0.317 0.3% 3.04 [1.63, 5.65]<br>Total (95% Cl) 1000% 1.48 [1.43, 1.53]<br>Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); P <sup>2</sup> = 93%<br>0.01 0.1 1 10 100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                          |                      |        |            |                    |     |                   |
| Sau 2013-0.20580.12591.5%0.81[0.64, 1.04]Scher 19990.0030.0019.1%1.00[1.00, 1.00]Schmidt 20070.78850.16251.0%2.20[1.60, 3.03]Shinohara 20120.63290.25190.4%1.88[1.15, 3.09]Shinohara 20130.470.19120.7%1.60[1.10, 2.33]Sougioultzis 20110.54230.12891.5%1.72[1.34, 2.21]Sub 20100.54990.17780.8%1.73[1.22, 2.46]Tamikulu 20100.80650.17650.8%2.24[1.58, 3.17]Templeton 20140.92430.2130.6%2.52[1.66, 3.83]Tonini 19971.40610.63160.1%4.08[1.18, 14.07]van Kessel 20130.40280.12981.4%1.50[1.16, 1.93]Vigao 20000.58780.20690.6%1.80[1.20, 2.70]Wan 20130.96580.30530.3%2.63[1.44, 4.78]Wang 20140.54460.1760.8%1.72[1.22, 2.43]Weide 20120.470.10592.0%1.60[1.30, 1.97]Yamaguchi 20140.43180.1491.1%1.54[1.15, 2.06]Zhou 20121.11120.3170.3%3.04[1.63, 5.65]Total (95% Cl)100.0%1.48[1.43, 1.53]Hetergeneilty: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); I <sup>2</sup> = 93%0.010.110100 <td>•</td> <td></td> <td></td> <td></td> <td></td> <td></td> <td></td>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | •                        |                      |        |            |                    |     |                   |
| Scher 1999       0.003       0.001       9.1%       1.00 [1.00, 1.00]         Schmidt 2007       0.7885       0.1625       1.0%       2.20 [1.60, 3.03]         Shinohara 2012       0.6329       0.2519       0.4%       1.88 [1.15, 3.09]         Shinohara 2013       0.47       0.1912       0.7%       1.60 [1.00, 2.33]         Sougioultzis 2011       0.5423       0.1289       1.5%       1.72 [1.34, 2.21]         Suh 2010       0.5499       0.1776       0.8%       1.73 [1.22, 2.46]         Tamura 1998       0.3365       0.1765       0.8%       2.24 [1.58, 3.17]         Templeton 2014       0.9243       0.213       0.6%       2.52 [1.66, 3.83]         Tonini 1997       1.4061       0.6316       0.1%       4.08 [1.18, 14.07]         van Kessel 2013       0.4028       0.1298       1.4%       1.50 [1.16, 1.93]         Viganó 2000       0.5878       0.2069       0.6%       1.80 [1.20, 2.70]         Wan 2013       0.9658       0.3053       0.3%       2.63 [1.44, 4.78]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                          |                      |        |            |                    | -   |                   |
| Schmidt 2007 $0.7885$ $0.1625$ $1.0\%$ $2.20$ [1.60, 3.03]         Shinohara 2012 $0.6329$ $0.2519$ $0.4\%$ $1.88$ [1.15, 3.09]         Shinohara 2013 $0.47$ $0.1912$ $0.7\%$ $1.60$ [1.10, 2.33]         Sougioultzis 2011 $0.5423$ $0.1289$ $1.5\%$ $1.72$ [1.34, 2.21]         Suh 2010 $0.5429$ $0.1778$ $0.8\%$ $1.73$ [1.22, 2.46]         Tamura 1998 $0.3365$ $0.1517$ $1.1\%$ $1.40$ [1.04, 1.88]         Tamura 1998 $0.3365$ $0.1765$ $0.8\%$ $2.24$ [1.58, 3.17]         Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ [1.66, 3.83]         Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ [1.18, 14.07]         van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ [1.20, 2.70]         Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ [1.45, 2.26]         Weig 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ [1.30, 1.97]         Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ [1.30, 1.97]         Yamaguchi 2014 $0.4318$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                      |        |            |                    | +   |                   |
| Shinohara 2012 $0.6329$ $0.2519$ $0.4\%$ $1.88$ $[1.15, 3.09]$ Shinohara 2013 $0.47$ $0.1912$ $0.7\%$ $1.60$ $[1.10, 2.33]$ Sougioultzis 2011 $0.5423$ $0.1289$ $1.5\%$ $1.72$ $[1.34, 2.21]$ Sub 2010 $0.5499$ $0.1778$ $0.8\%$ $1.73$ $[1.22, 2.46]$ Tamura 1998 $0.3365$ $0.1517$ $1.1\%$ $1.40$ $1.04$ , $1.88]$ Tanrikulu 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ $[1.18, 14.07]$ van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.16, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ $-7$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                          |                      |        |            |                    |     | <b></b>           |
| Sougioultzis 2011 $0.5423$ $0.1289$ $1.5\%$ $1.72$ $[1.34, 2.21]$ Suh 2010 $0.5499$ $0.1778$ $0.8\%$ $1.73$ $[1.22, 2.46]$ Tamura 1998 $0.3365$ $0.1517$ $1.1\%$ $1.40$ $[1.04, 1.88]$ Tanrikulu 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ $[1.18, 14.07]$ van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.6, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $[1.44, 4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ $-$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $1.30, 1.97$ $-$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $1.52$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Shinohara 2012           | 0.6329               | 0.2519 | 0.4%       |                    | -   | -                 |
| Suh 2010 $0.5499$ $0.1778$ $0.8\%$ $1.73$ $[1.22, 2.46]$ Tamura 1998 $0.3365$ $0.1517$ $1.1\%$ $1.40$ $[1.04, 1.88]$ Tanrikulu 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ $[1.18, 14.07]$ van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.6, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $[1.44, 4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ $-$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.63, 5.65]$ -                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | Shinohara 2013           | 0.47                 | 0.1912 | 0.7%       | 1.60 [1.10, 2.33]  | -   | -                 |
| Tamura 1998 $0.3365$ $0.1517$ $1.1\%$ $1.40$ $[1.04, 1.88]$ Tanrikulu 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ $[1.18, 14.07]$ van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.16, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $1.44$ , $4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $1.45$ , $2.26$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $1.30$ , $1.97$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $1.30$ , $1.97$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $1.52, 2.06$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $1.63, 5.65$ Tot                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | •                        |                      |        |            |                    |     |                   |
| Tanrikulu 2010 $0.8065$ $0.1765$ $0.8\%$ $2.24$ $[1.58, 3.17]$ Templeton 2014 $0.9243$ $0.213$ $0.6\%$ $2.52$ $[1.66, 3.83]$ Tonini 1997 $1.4061$ $0.6316$ $0.1\%$ $4.08$ $[1.18, 14.07]$ van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.16, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $[1.44, 4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Weid 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.63, 5.65]$ Total (95% CI)       100.0% $1.48$ $[1.43, 1.53]$ $1.00$ $1.00$ Heterogeneity: Tau <sup>2</sup> = $0.00$ ; Chi <sup>2</sup> = $962.78$ , df = $63$ (P < $0.00001$ ); l <sup>2</sup> = $93\%$ $0.01$ $0.1$ $1$ <td< td=""><td></td><td></td><td></td><td></td><td></td><td></td><td>-</td></td<>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                          |                      |        |            |                    |     | -                 |
| Templeton 2014       0.9243       0.213       0.6%       2.52 [1.66, 3.83]         Tonini 1997       1.4061       0.6316       0.1%       4.08 [1.18, 14.07]         van Kessel 2013       0.4028       0.1298       1.4%       1.50 [1.16, 1.93]         Viganó 2000       0.5878       0.2069       0.6%       1.80 [1.20, 2.70]         Wan 2013       0.9658       0.3053       0.3%       2.63 [1.44, 4.78]         Wang 2014       0.5939       0.1138       1.8%       1.81 [1.45, 2.26]         Weid 2012       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Weide 2013       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Yamaguchi 2014       0.4318       0.149       1.1%       1.54 [1.15, 2.06]         Zhou 2012       1.1112       0.317       0.3%       3.04 [1.63, 5.65]         Total (95% CI)       100.0%       1.48 [1.43, 1.53]       1.01         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       1.00                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                          |                      |        |            |                    |     |                   |
| Tonini 1997       1.4061       0.6316       0.1%       4.08 [1.18, 14.07]         van Kessel 2013       0.4028       0.1298       1.4%       1.50 [1.16, 1.93]         Viganó 2000       0.5878       0.2069       0.6%       1.80 [1.20, 2.70]         Wan 2013       0.9658       0.3053       0.3%       2.63 [1.44, 4.78]         Wang 2014       0.5939       0.1138       1.8%       1.81 [1.45, 2.26]         Weide 2014       0.5446       0.176       0.8%       1.72 [1.22, 2.43]         Weide 2012       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Weide 2013       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Yamaguchi 2014       0.4318       0.149       1.1%       1.54 [1.15, 2.06]         Zhou 2012       1.1112       0.317       0.3%       3.04 [1.63, 5.65]         Total (95% CI)       100.0%       1.48 [1.43, 1.53]       1         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                          |                      |        |            |                    |     |                   |
| van Kessel 2013 $0.4028$ $0.1298$ $1.4\%$ $1.50$ $[1.16, 1.93]$ Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $[1.44, 4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Weide 2014 $0.5446$ $0.176$ $0.8\%$ $1.72$ $[1.22, 2.43]$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.5, 2.06]$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $[1.63, 5.65]$ Total (95% CI)       100.0% $1.48$ $[1.43, 1.53]$ $1.00$ Heterogeneity: Tau <sup>2</sup> = $0.00;$ Chi <sup>2</sup> = $962.78,$ df = $63$ (P < $0.00001$ ); l <sup>2</sup> = $93\%$ $0.01$ $0.1$ $100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                      |        |            |                    | -   |                   |
| Viganó 2000 $0.5878$ $0.2069$ $0.6\%$ $1.80$ $[1.20, 2.70]$ Wan 2013 $0.9658$ $0.3053$ $0.3\%$ $2.63$ $[1.44, 4.78]$ Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Wei 2014 $0.5446$ $0.176$ $0.8\%$ $1.72$ $[1.22, 2.43]$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.5, 2.06]$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $[1.63, 5.65]$ Total (95% CI)       100.0% $1.48$ $[1.43, 1.53]$ $1.10$ $100$ Heterogeneity: Tau <sup>2</sup> = $0.00;$ Chi <sup>2</sup> = $962.78,$ df = $63$ (P < $0.00001$ ); l <sup>2</sup> = $93\%$ $0.01$ $0.1$ $100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                          |                      |        |            |                    | -   | -                 |
| Wang 2014 $0.5939$ $0.1138$ $1.8\%$ $1.81$ $[1.45, 2.26]$ Wei 2014 $0.5446$ $0.176$ $0.8\%$ $1.72$ $[1.22, 2.43]$ Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.15, 2.06]$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $[1.63, 5.65]$ Total (95% Cl)       100.0% $1.48$ $[1.43, 1.53]$ $4$ Heterogeneity: Tau <sup>2</sup> = $0.00;$ Chi <sup>2</sup> = $962.78,$ df = $63$ (P < $0.00001$ ); l <sup>2</sup> = $93\%$ $0.01$ $0.1$ $100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          |                      |        |            |                    | -   | -                 |
| Waig 2014       0.5939 0.1138       1.6%       1.01 [1.49, 2.26]         Weid 2014       0.5446       0.176       0.8%       1.72 [1.22, 2.43]         Weide 2012       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Weide 2013       0.47       0.1059       2.0%       1.60 [1.30, 1.97]         Yamaguchi 2014       0.4318       0.149       1.1%       1.54 [1.15, 2.06]         Zhou 2012       1.1112       0.317       0.3%       3.04 [1.63, 5.65]         Total (95% CI)       100.0%       1.48 [1.43, 1.53]       1         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       1       100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                          |                      |        |            |                    |     |                   |
| Weide 2012 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.15, 2.06]$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $[1.63, 5.65]$ Total (95% Cl)       100.0% $1.48$ $[1.43, 1.53]$ $1.00$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93% $0.01$ $0.1$ $10$ $100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                          |                      |        |            |                    |     | -                 |
| Weide 2013 $0.47$ $0.1059$ $2.0\%$ $1.60$ $[1.30, 1.97]$ Yamaguchi 2014 $0.4318$ $0.149$ $1.1\%$ $1.54$ $[1.15, 2.06]$ Zhou 2012 $1.1112$ $0.317$ $0.3\%$ $3.04$ $[1.63, 5.65]$ Total (95% Cl)       100.0% $1.48$ $[1.43, 1.53]$ $1.112$ $1.0200$ Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93% $0.01$ $0.1$ $100$ $100$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                          |                      |        |            |                    | -   | •<br><del>•</del> |
| Yamaguchi 2014       0.4318       0.149       1.1%       1.54 [1.15, 2.06]         Zhou 2012       1.1112       0.317       0.3%       3.04 [1.63, 5.65]         Total (95% Cl)       100.0%       1.48 [1.43, 1.53]       1         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       1       10       100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                          |                      |        |            |                    | .   | <b>-</b>          |
| Zhou 2012       1.1112       0.317       0.3% $3.04$ [1.63, 5.65]         Total (95% Cl)       100.0%       1.48 [1.43, 1.53]       1         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       1       10       100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                          |                      |        |            |                    | _   | -                 |
| Total (95% Cl)       100.0%       1.48 [1.43, 1.53]         Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%       0.01       0.1       1       10       100         Test for overall effect: $T = 22.95$ ( $P < 0.00001$ )       0.00001); l <sup>2</sup> = 93%       0.01       0.1       1       100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                          |                      |        |            |                    |     |                   |
| Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 962.78, df = 63 (P < 0.00001); l <sup>2</sup> = 93%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                          | 1.1112               | 5.617  | 5.070      | 5.5 , [1.55, 5.55] |     |                   |
| Test for overall effect: $Z = 22.95$ ( $B < 0.00001$ ) 0.01 0.1 1 10 100                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Total (95% CI)           |                      |        | 100.0%     | 1.48 [1.43, 1.53]  |     |                   |
| Test for overall effect: $7 = 22.95$ (P < 0.00001)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | • •                      |                      |        | P < 0.0000 | 01); I² = 93%      |     | 10 100            |
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Figure 1 | Forest plots showing HR for OS for LDH greater than or less than the cutoff. HRs for each study are represented by the squares, the size of the square represents the weight of the study in the meta-analysis, and the horizontal linecrossing the square represents the 95% confidence interval (CI). All statistical tests were two-sided.



| 1.7.1 Renal<br>Armstrong 2012<br>Atzpodien 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.18, 37.32]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Gava Kessel 2013<br>Subtotal (95% CI)<br>Heterogeneity-<br>Bacci 2000<br>Bacci 2007<br>Durnali 2013<br>Subtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.18, 37.32]<br>1.79 [1.30, 2.47]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp2 2012<br>Mekenkamp2 2012<br>Unit (95% C)<br>Heterogeneity: Chi<br>Heterogeneity: Chi<br>Bacci 2000<br>Bacci 2000<br>Bacci 2007<br>Dumail 2013<br>Subtotal (95% C)<br>Heterogeneity: Tau <sup>2</sup> =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.010)<br>0.5878<br>0.239<br>-0.0356<br>0.6152<br>0.5008<br>0.4028<br>0.032<br>0.0306<br>0.4028<br>0.032<br>0.4028<br>0.032<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4 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1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.18, 37.32]<br>1.79 [1.30, 2.47]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp2 2012<br>Mekenkamp2 2012<br>Underspanely: Colorectal<br>Baci 2000<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Dumail 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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0.010)<br>0.5878<br>0.239<br>-0.0356<br>0.6152<br>0.5008<br>0.4028<br>0.032<br>0.0306<br>0.4028<br>0.032<br>0.4028<br>0.032<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4028<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4048<br>0.4 | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2.1%<br>0.6%<br>1.8%<br>1.4%<br>9.3%<br>0.02); I <sup>2</sup> =<br>2.5%<br>0.6%<br>1.5%<br>0.1%<br>4.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.18, 37.32]<br>1.79 [1.30, 2.47]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Meterogeneity: Call<br>Heterogeneity: Call<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Dumail 2013<br>Subtotal (95% CI)<br>Heterogeneity: Call<br>Test for overall effect:<br>1.7.8 Other<br>Felia 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Z = 2.58 (P = 0.010)<br>0.5878<br>0.239<br>-0.0336<br>0.6152<br>0.000<br>0.4028<br>0.032 Chi <sup>2</sup> = 13.14, d<br>Z = 4.98 (P < 0.0000<br>0.3293<br>0.6877<br>0.6471<br>2.1988<br>0.06; Chi <sup>2</sup> = 10.29, d<br>Z = 3.60 (P = 0.0003<br>0.1196                                                                                                                                                                                                                                                                                                                                  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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.2069<br>0.7249<br>f = 3 (P =<br>)<br>0.0322                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 2.1%<br>0.6%<br>1.8%<br>1.4%<br>9.3%<br>0.02); l <sup>2</sup> =<br>2.5%<br>0.6%<br>1.5%<br>0.1%<br>4.7%<br>2.002); l <sup>2</sup> =                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         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1.67)<br>1.91 (1.49, 2.45)<br>9.01 (1.20, 2.70)<br>1.91 (1.49, 2.45)<br>9.01 (1.20, 2.70)<br>1.79 (1.30, 2.47)<br>7.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | •<br>•                                |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Van Kassel 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P =<br>)<br>0.0322<br>0.2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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2.70]<br>1.91 [1.40, 2.45]<br>9.01 [2.16, 37.32]<br>1.73 [1.06, 1.20]<br>2.40 [1.59, 3.62]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giassen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>2012<br>Mekenkamp 2012<br>2012<br>Metengenetic, 2013<br>Subtotal (85% CI)<br>Heterogenetic, 7ax <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Felix 2011<br>Gripp 2007<br>Han 2003<br>Baci 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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                                                                                                                                                                                                                                                         | *<br>•<br>•                           |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Van Kessel 2013<br>Subtotal (8% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1993                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 7.32]<br>1.73 [1.06, 1.20]<br>2.40 [1.59, 3.62]<br>1.51 [1.10, 2.65]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Metenkamp2 2012<br>Subtotal (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2000<br>Dumai 2013<br>Subtotal (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Han 2003<br>Hannibal 1993<br>Hanshinoto 2099                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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1.79)<br>1.62 (1.29, 1.79)<br>1.62 (1.29, 1.79)<br>1.62 (1.29, 1.72)<br>1.79 (1.20, 2.70)<br>1.79 (1.30, 2.47)<br>1.79 (1.30, 2.47)<br>2.40 (1.59, 3.62)<br>1.54 (1.18, 2.01)<br>1.54 (1.12, 2.56)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>(Abbadde 2011<br>Glessen 2013<br>He 2013<br>Mekenkamp 2012<br>Van Kessel 2013<br>Subtotal (85% CI)<br>Heterogeneily: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sercome<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2007<br>Dumail 2007<br>Bacci 2004<br>Bacci 2004<br>Heterogeneily: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1993<br>Hashinoto 2009<br>Lagerward 1999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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=<br>6.9%<br>0.6%<br>1.3%<br>1.0%<br>0.8%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.27 [1.04, 1.55]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>= 62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 37.32]<br>1.73 [1.06, 1.20]<br>2.40 [1.59, 3.62]<br>1.52 [1.30, 2.47]<br>1.51 [1.10, 2.05]<br>1.52 [1.27, 2.60]<br>1.52 [1.27, 2.52]<br>1.52 [1.27, 2.52]<br>1.52 [1.27, 2.52]<br>1.52                                                                                                                                |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>Hekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Meterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2000<br>Durnali 2013<br>Subtotal (6%, CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Han 2003<br>Hannidad 1993<br>Hanshimoto 2006<br>Lagerward 1999<br>Herga 2001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P =<br>0.0322<br>0.2101<br>0.1359<br>0.13582<br>0.1382<br>0.1382<br>0.1382<br>0.1382                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2.1%<br>0.6%<br>1.8%<br>1.4%<br>9.3%<br>0.02); I <sup>2</sup> =<br>2.5%<br>0.6%<br>1.5%<br>0.1%<br>4.7%<br>0.02); I <sup>2</sup> =<br>6.9%<br>0.6%<br>1.3%<br>1.0%<br>0.8%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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1.79)<br>5.62 (1.29, 1.79)<br>5.62 (1.29, 1.79)<br>5.71 (1.10, 1.20)<br>1.91 (1.49, 2.45)<br>9.01 (1.20, 2.70)<br>1.91 (1.40, 1.20)<br>1.93 (1.59, 3.62)<br>1.54 (1.16, 2.01)<br>1.50 (1.10, 2.55)<br>1.82 (1.27, 2.60)<br>1.56 (1.32, 1.82)<br>2.00 (1.70, 2.35)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudal 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Van Kessel 2013<br>Subtotal (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2013<br>Subtotal (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1903<br>Hashimoto 2008<br>Lagerward 1599<br>Pierga 2001<br>Poise 2003                                                                                                                                                                                                                                                                                                                                                                                                                                  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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.2269<br>0.2269<br>0.1267<br>0.7249<br>f = 3 (P =<br>0.0322<br>0.2169<br>0.1359<br>0.1582<br>0.01582                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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1.79]\\ 1.52[1.29, 1.79]\\ 1.62[1.29, 1.79]\\ 1.63[1.61, 0.2, 270]\\ 1.61[1.40, 2.42]\\ 1.79[1.40, 2.47]\\ 1.71[1.40, 2.47]\\ 2.40[1.59, 3.62]\\ 1.13[1.06, 1.20]\\ 2.40[1.59, 3.62]\\ 1.54[1.18, 2.01]\\ 1.54[1.10, 2.05]\\ 1.54[1.10, 2.05]\\ 1.54[1.22, 1.82]\\ 2.00[1.70, 2.35]\\ 1.52[1.22, 1.82]\\ 2.00[1.70, 2.35]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 1.50[1.10, 2.05]\\ 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                                                                                                                                                                                                                                                     |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Waterkamp 2012<br>2012<br>Subtota (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Dumai 2013<br>Subtota (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feilus 2011<br>Gripp 2007<br>Han 2003<br>Hannisda 1993<br>Hanshimoto 2009<br>Lagerward 1999<br>Pierga 2001<br>Poles 2001<br>Poles 2001<br>Poles 2001                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>= 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P =<br>0.0322<br>0.1359<br>0.1359<br>0.1359<br>0.1818<br>0.0822<br>0.1818                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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2.13]<br>1.52 [1.29, 1.79]<br>2.62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [1.20, 2.70]<br>1.71 [1.60, 1.20]<br>2.40 [1.59, 3.62]<br>1.54 [1.18, 2.01]<br>1.50 [1.10, 2.55]<br>1.62 [1.27, 2.60]<br>1.62 [ |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>(Abbacude 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Van Kessel 2013<br>Subtotal (85% CI)<br>Heterogeneily: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sercoma<br>Bacci 2004<br>Bacci 2004<br>Bacci 2004<br>Bacci 2007<br>Dumail 2001<br>Bacci 2004<br>Bacci 2004<br>Heterogeneily: Tau <sup>2</sup> =<br>Test for overall effect<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1993<br>Hashinoto 2009<br>Lagerward 1999<br>Pirega 2001<br>Polee 2003<br>Sougioultzis 2011<br>Sougioultzis 2011<br>Sougioultzis 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | $Z = 2.58 (P = 0.010)$ $0.5878$ $0.239$ $-0.036$ $0.0152$ $0.00162$ $0.0028$ $0.032 Chi^2 = 13.14, d$ $Z = 4.98 (P < 0.0000$ $0.3293$ $0.6471$ $Z = 3.60 (P = 0.0003$ $0.1196$ $0.4718$ $0.06471$ $Z = 3.60 (P = 0.0003$ $0.1196$ $0.4758$ $0.4718$ $0.4755$ $0.4711$ $0.4383$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ $0.4955$ $0.4423$ 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=<br>)<br>0.0322<br>0.2101<br>0.1552<br>0.11582<br>0.01552<br>0.11582<br>0.01552<br>0.11582<br>0.0159                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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=<br>2.5%<br>0.6%<br>1.5%<br>0.6%<br>1.5%<br>0.02); I <sup>2</sup> =<br>6.9%<br>0.6%<br>1.3%<br>1.0%<br>1.0%<br>1.0%<br>1.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 1.27 [1.04, 1.55]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.48, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>62%<br>1.39 [1.16, 1.67]<br>1.61 [1.49, 2.45]<br>9.01 [2.10, 2.70]<br>9.01 [2.10, 2.70]<br>9.01 [2.10, 2.72]<br>1.79 [1.30, 2.47]<br>2.40 [1.59, 3.62]<br>1.51 [1.00, 1.20]<br>2.40 [1.59, 3.62]<br>1.52 [1.27, 2.60]<br>1.52 [1.27, 2.60]<br>1.52 [1.27, 2.60]<br>1.52 [1.27, 2.60]<br>1.52 [1.27, 2.60]<br>1.55 [1.22, 1.82]<br>2.00 [1.70, 2.35]<br>1.50 [1.10, 2.05]<br>1.52 [1.22, 2.46]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Waterkamp 2012<br>2012<br>Subtota (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Dumail 2013<br>Subtota (85% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feilus 2011<br>Gripp 2007<br>Han 2003<br>Hannisda 1993<br>Hanshimoto 2009<br>Lagerward 1999<br>Pierga 2001<br>Poles 2001<br>Poles 2001<br>Poles 2001                                                                                                                                                                                                                                                                                                                                                                                                                                                                       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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>= 5 (P = 1)<br>0.0923<br>0.2069<br>0.1207<br>0.7249<br>= 3 (P = 1)<br>0.0322<br>0.2101<br>0.1582<br>0.0188<br>0.0188<br>0.01882<br>0.01882<br>0.01882<br>0.01882<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.01582<br>0.0159<br>0.0159<br>0.0159<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0129<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0129<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.0209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.01209<br>0.0000000000000000000000000000000000 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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Watkamp 2012<br>Van Kassel 2012<br>Van Kassel 2012<br>Van Kassel 2012<br>Van Kassel 2014<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Durnali 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Felius 2011<br>Gripp 2007<br>Hansidal 1983<br>Hannisdal 1983<br>Hannisdal 1983<br>Hannisdal 1983<br>Hansimotol 2003<br>Porega 2001<br>Polee 2003<br>Sougioultzs 2011<br>Sub 2010<br>Tannikula 2010                                                                                                                                                                                                                                                                                                                                                                                                                                             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0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P =<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P =<br>)<br>0.0322<br>0.2101<br>0.1552<br>0.11582<br>0.01552<br>0.11582<br>0.01552<br>0.11582<br>0.0159                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             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1.79]\\ 1.52[1.29, 1.79]\\ 1.52[1.29, 1.79]\\ 1.61[1.49, 2.42]\\ 0.01[2.10, 2.70]\\ 9.01[2.10, 2.70]\\ 9.01[2.10, 2.70]\\ 9.01[2.10, 2.71]\\ 1.61[1.49, 2.42]\\ 1.79[1.30, 2.47]\\ 2.40[1.59, 3.62]\\ 1.13[1.06, 1.20]\\ 2.40[1.59, 3.62]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.16, 2.01]\\ 1.54[1.12, 2.44]\\ 1.54[1.16, 2.01]\\ 1.54[1.12, 2.44]\\ 1.54[1.10, 2.05]\\ 1.52[1.22, 2.46]\\ 1.52[1.22, 2.46]\\ 1.52[1.22, 2.46]\\ 1.54[1.58, 3.17]\\ 1.54[1.54, 2.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 1.54[1.54, 3.17]\\ 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                                                                                                                                                                                                                                                         | · · · · · · · · · · · · · · · · · · · |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Subtotal (95% CI)<br>Heterogeneity: Car<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Durnali 2013<br>Subtotal (95% CI)<br>Heterogeneity: Car<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Han 2003<br>Hannisdal 1993<br>Hansimoto 2009<br>Lagerward 1999<br>Polerg 2001<br>Polerg 200<br>Polerg 200<br>Polerg 2                                                                              | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $-0.0358$ $0.0452$ $0.5026$ $0.0328$ $0.0328$ $0.0328$ $0.0428$ $0.0328$ $0.0328$ $0.0421$ $0.3293$ $0.5878$ $0.6471$ $2.1988$ $0.061 ChiP = 10.29, d$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.4196$ $0.423$ $0.6421$ $0.4423$ $0.6421$ $0.4425$ $0.6423$ $0.6499$ $0.8065$ $1.4061$ $0.5878$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P = 1)<br>0.0223<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P = 0)<br>0.0322<br>0.2101<br>0.1359<br>0.1359<br>0.1359<br>0.13582<br>0.0629<br>0.13582<br>0.0629<br>0.1289<br>0.1289<br>0.1289<br>0.1289<br>0.1289<br>0.1289<br>0.1280<br>0.0222<br>0.139<br>0.1280<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.129<br>0.022<br>0.129<br>0.022<br>0.129<br>0.022<br>0.129<br>0.022<br>0.129<br>0.022<br>0.129<br>0.022<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.032<br>0.0 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=<br>5.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,<br>0.002,002,002,002,002,002,002,002,002,00 | $\begin{array}{c} 1.27 \ [1.04, 1.55 \\ 0.97 \ [0.53, 1.48] \\ 1.65 \ [1.48, 2.31] \\ 1.65 \ [1.48, 2.13] \\ 1.65 \ [1.28, 2.13] \\ 1.52 \ [1.28, 1.73] \\ 1.52 \ [1.29, 1.79] \\ 1.52 \ [1.29, 1.79] \\ 1.52 \ [1.29, 1.79] \\ 1.51 \ [1.49, 2.45] \\ 0.01 \ [2.18, 0.723] \\ 1.79 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.71 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.72 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.73 \ [1.40, 2.47] \\ 1.74 \ [1.40, 1.40, 1.40] \\ 1.74 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] \\ 1.75 \ [1.40, 1.40] 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| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mark Kasel 2012<br>Mark Kasel 2012<br>Mark Kasel 2012<br>Mark Kasel 2013<br>Bacci 2000<br>Bacci 2000<br>Bacci 2007<br>Durnali 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tat <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1903<br>Haanimota 2003<br>Haanimota 2003<br>Haanimota 2001<br>Parena 2001<br>Pare                                                                      | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $0.0358$ $0.0452$ $0.5028$ $0.0328$ $0.0428$ $0.0328$ $0.0428$ $0.0328$ $0.0428$ $0.03293$ $0.6878$ $0.6471$ $2.1988$ $0.061 Chi2 = 10.29, d$ $2.3.60 (P = 0.0003$ $0.4718$ $0.4755$ $0.4755$ $0.4378$ $0.4755$ $0.4378$ $0.4755$ $0.4378$ $0.4755$ $0.4318$ $0.4689$ $0.06831$ $0.4623$ $0.4699$ $0.06828$ $0.4378$ $0.4378$ $0.4378$ $0.4378$ $0.4388$ $0.4388$ $0.4388$ 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>0.1298<br>f = 5 (P = 1<br>1)<br>0.0923<br>0.2069<br>0.1267<br>0.7249<br>f = 3 (P = 1<br>0.0322<br>0.2101<br>0.1352<br>0.2010<br>0.1582<br>0.1582<br>0.1818<br>0.0829<br>0.1582<br>0.1289<br>0.1582<br>0.1289<br>0.1582<br>0.1289<br>0.1788<br>0.0829<br>0.1788<br>0.0829<br>0.1788<br>0.0829<br>0.1788<br>0.0829<br>0.1788<br>0.0829<br>0.1818<br>0.0829<br>0.1819<br>0.0829<br>0.1819<br>0.0829<br>0.1819<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0.1297<br>0                                                                                                                               | 2.1%, 0.6%, 1.8%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%,                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.27 [1.04, 1.52]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.28, 2.13]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>2.62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 37.32]<br>1.79 [1.30, 2.47]<br>2.40 [159, 3.62]<br>1.43 [1.66, 1.20]<br>2.40 [159, 3.62]<br>1.59 [1.20, 2.70]<br>1.59 [1.22, 1.23]<br>2.00 [1.70, 2.55]<br>1.52 [1.32, 1.82]<br>2.00 [1.70, 2.55]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.48]<br>2.24 [1.58, 3.17]<br>4.08 [1.16, 1.02, 0.70]<br>1.59 [1.10, 2.57]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.48]<br>2.24 [1.58, 3.17]<br>4.08 [1.15, 2.06]<br>1.59 [1.20, 2.70]<br>1.50 [1.10, 2.57]<br>1.50 [1.10, 2.57]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.44]<br>1.73 [1.20, 2.40]<br>1.54 [1.15, 2.06]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Enterspenity:<br>1.7.7 Sarcoma<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Durnal 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Felia 2011<br>Gripp 2007<br>Han 2003<br>Hannisdal 1993<br>Hansimoto 2009<br>Daegerwand 1999<br>Pierga 2001<br>Pierga 2001<br>Sougioultzis 2011<br>Sub 2010<br>Tannikul                                                                                                    | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $-0.0356$ $0.6152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.028$ $0.0328$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.0471$ $2.1988$ $0.067$ $0.5477$ $0.0473$ $0.0471$ $2.1988$ $0.067$ $0.1196$ $0.0755$ $0.4718$ $0.0693$ $0.0493$ $0.0493$ $0.0493$ $0.0492$ $0.0492$ $0.0493$ $0.0492$ $0.0493$ $0.0492$ $0.0492$ $0.0492$ $0.0492$ $0.0492$ $0.0493$ $0.0492$ $0.0492$ $0.0492$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ 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                                                                                                                                                                                                            | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>f = 5 (P = 1)<br>0.0223<br>0.2069<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.02749<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0423<br>0.1359<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.5256<br>0.0429<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>1.525<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.5                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2.1%, 0.6%, 1.8%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%,                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.27 [1.04, 1.52]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.48, 2.13]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>= 62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 37.32]<br>1.79 [1.30, 2.47]<br>1.13 [1.06, 1.20]<br>1.13 [1.07, 1.20]<br>2.40 [1.59, 3.62]<br>1.50 [1.22, 1.23]<br>2.00 [1.70, 2.35]<br>1.50 [1.22, 1.23]<br>2.24 [1.58, 3.17]<br>4.08 [1.16, 1.20]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.48]<br>1.74 [1.34, 2.21]<br>1.73 [1.20, 2.40]<br>1.54 [1.15, 2.06]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mark Kasel 2012<br>Mark Kasel 2012<br>Mark Kasel 2012<br>Mark Kasel 2013<br>Bacci 2000<br>Bacci 2000<br>Bacci 2007<br>Durnali 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tat <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Hannisdal 1903<br>Haanimota 2003<br>Haanimota 2003<br>Haanimota 2001<br>Parena 2001<br>Pare                                                                      | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $-0.0356$ $0.6152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.028$ $0.0328$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.0471$ $2.1988$ $0.067$ $0.5477$ $0.0473$ $0.0471$ $2.1988$ $0.067$ $0.1196$ $0.0755$ $0.4718$ $0.0693$ $0.0493$ $0.0493$ $0.0493$ $0.0492$ 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                                                                                                                                                               | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>f = 5 (P = 1)<br>0.0223<br>0.2069<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.02749<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0423<br>0.1359<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.5256<br>0.0429<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>1.525<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.5                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2.1%, 0.6%, 1.8%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%,                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.27 [1.04, 1.52]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.48, 2.13]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>= 62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 37.32]<br>1.79 [1.30, 2.47]<br>1.13 [1.06, 1.20]<br>1.13 [1.07, 1.20]<br>2.40 [1.59, 3.62]<br>1.50 [1.22, 1.23]<br>2.00 [1.70, 2.35]<br>1.50 [1.22, 1.23]<br>2.24 [1.58, 3.17]<br>4.08 [1.16, 1.20]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.48]<br>1.74 [1.34, 2.21]<br>1.73 [1.20, 2.40]<br>1.54 [1.15, 2.06]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Enterspenity: Chiba<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Durnal 2013<br>Subtotal (95% C)<br>Heterogeneity: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Gripp 2007<br>Han 2003<br>Hannisdal 1993<br>Hanshimoto 2009<br>Lagerward 1999<br>Poles 2003<br>Sougioultzis 2011<br>Sin 2010<br>Tannikul 2010<br>Tonini 1997<br>Viganö 2000<br>Yamaguchi 2014<br>Subtotal (95% C)<br>Heterogeneity: 2014<br>Subtotal (95% C)<br>Heterogenei                                                                                                                                                    | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $-0.0356$ $0.6152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.0152$ $0.000$ $0.028$ $0.0328$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.028$ $0.0471$ $2.1988$ $0.067$ $0.5477$ $0.0473$ $0.0471$ $2.1988$ $0.067$ $0.1196$ $0.0755$ $0.4718$ $0.0693$ $0.0493$ $0.0493$ $0.0493$ $0.0492$ $0.0492$ $0.0493$ $0.0492$ $0.0493$ $0.0492$ $0.0492$ $0.0492$ $0.0492$ $0.0492$ $0.0493$ $0.0492$ $0.0492$ $0.0492$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0493$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ $0.0494$ 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                                                                                                                                                                                                                                                                                                                                                                     | 0.1019<br>0.2162<br>0.1139<br>0.1296<br>f = 5 (P = 1)<br>0.0223<br>0.2069<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.0269<br>0.02749<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0322<br>0.2101<br>0.1359<br>0.0423<br>0.1359<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.525<br>0.0429<br>1.5256<br>0.0429<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>0.0499<br>1.525<br>1.525<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.555<br>1.5                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2.1%, 0.6%, 1.8%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%, 1.4\%,                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.27 [1.04, 1.52]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.48, 2.13]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>= 62%<br>1.39 [1.16, 1.67]<br>1.80 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 37.32]<br>1.79 [1.30, 2.47]<br>1.13 [1.06, 1.20]<br>1.13 [1.07, 1.20]<br>2.40 [1.59, 3.62]<br>1.50 [1.22, 1.23]<br>2.00 [1.70, 2.35]<br>1.50 [1.22, 1.23]<br>2.24 [1.58, 3.17]<br>4.08 [1.16, 1.20]<br>1.72 [1.34, 2.21]<br>1.73 [1.22, 2.48]<br>1.74 [1.34, 2.21]<br>1.73 [1.20, 2.40]<br>1.54 [1.15, 2.06]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]<br>1.56 [1.44, 2.00]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                       |
| Test for overall effect:<br>1.7.6 Colorectal<br>Chibaudel 2011<br>Giessen 2013<br>He 2013<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Mekenkamp 2012<br>Metentagenety: Call<br>Heterogenety: Call<br>Heterogenety: Call<br>Bacci 2000<br>Bacci 2000<br>Bacci 2000<br>Durnal 2013<br>Subtotal (6%, C1)<br>Heterogenety: Tau <sup>2</sup> =<br>Test for overall effect:<br>1.7.8 Other<br>Feliu 2011<br>Grip 2007<br>Han 2003<br>Hennisdal 1993<br>Hanshinoto 2009<br>Lagerward 1999<br>Pierga 2001<br>Pore 2001<br>Pore 2001<br>Sub 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Viganó 2000<br>Viganó 2000<br>Viganó 2000<br>Viganó 2000<br>Viganó 2010<br>Sub 2010 | Z = 2.58 (P = 0.010) $0.5878$ $0.239$ $-0.0366$ $0.6152$ $0.0036$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0326$ $0.0471$ $2.1986$ $0.0617$ $0.1196$ $0.0755$ $0.0471$ $2.1988$ $0.061 Chip = 10.29, d$ $2.3.60 (P = 0.0003$ $0.1196$ $0.0755$ $0.04318$ $0.06931$ $0.0499$ $0.06931$ $0.0499$ $0.06931$ $0.0499$ $0.06931$ $0.0492$ $0.0499$ $0.06931$ $0.0416$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0587$ $0.0498$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.0000$ $0.00000$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.1019<br>0.2162<br>0.2162<br>0.1296<br>0.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.1296<br>d.                                                                                                                            | 2.1%<br>2.18%<br>0.6%<br>1.8%<br>1.4%<br>9.3%<br>9.3%<br>9.3%<br>0.02); F<br>4.7%<br>4.7%<br>6.9%<br>0.02); F<br>4.7%<br>6.9%<br>0.02); F<br>4.7%<br>4.7%<br>4.7%<br>4.7%<br>4.7%<br>4.7%<br>4.7%<br>4.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.27 [1.04, 1.55]<br>0.97 [0.63, 1.48]<br>1.65 [1.48, 2.31]<br>1.65 [1.48, 2.13]<br>1.65 [1.28, 2.13]<br>1.62 [1.28, 2.13]<br>1.52 [1.29, 1.79]<br>= 62%<br>1.39 [1.6, 1.67]<br>1.67 [1.20, 2.70]<br>1.91 [1.49, 2.45]<br>9.01 [2.16, 3.72]<br>1.71 [1.06, 1.20]<br>1.71 [1.06, 1.20]<br>2.40 [1.59, 3.62]<br>1.59 [1.30, 2.47]<br>1.59 [1.30, 2.47]<br>1.59 [1.30, 2.47]<br>1.59 [1.10, 2.05]<br>1.59 [1.10, 2.05]<br>1.59 [1.10, 2.05]<br>1.59 [1.10, 2.05]<br>1.52 [1.22, 2.46]<br>2.24 [1.58, 3.17]<br>4.06 [1.16, 1.47]<br>1.10 [2.02, 77]<br>1.60 [1.10, 2.07]<br>1.61 [1.12, 2.74]<br>1.61 [1.15, 2.46]<br>2.44 [1.53, 3.17]<br>4.06 [1.16, 1.47]<br>1.67 [1.44, 2.00]<br>1.68 [1.44, 2.01]<br>1.68 [1.44, 2.01]<br>1.68 [1.43, 1.53]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                       |

Figure 2 | Forest plots showing HRs by disease subgroups.

association between LDH and outcome. Our strict inclusion criteria (study size greater than 200, the requirement for HRs, and a requirement for a 95% CI or P value) may have introduced selection bias. Most of the included studies were retrospective, which may have introduced reporting bias. Finally, different cutoffs used to assess high LDH level in these studies might also have contributed to the

heterogeneity because it is possible that more false-positive cases were obtained with a cutoff of < 300 U/L than with a cutoff of >300 U/L. However, there is no accepted and validated absolute LDH level above which high LDH can be assigned. Instead, we used a cutoff of ULN. This may have introduced substantial heterogeneity, which may not have been fully accounted for by our use of sensitive



| tudy or Subgroup log                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | a[Hazard Ratio] SE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Weight                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Hazard Ratio<br>IV, Random, 95% CI                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | Hazard Ratio<br>IV. Random, 95% CI |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| .5.1 Non metastatic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | weight                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 14, Nalidolli, 33/8 Cl                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | IV. Random, 93 % CI                |
| Bacci 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.3293 0.0923                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.39 [1.16, 1.67]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| Giaccone 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.5365 0.1399                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.3%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.71 [1.30, 2.25]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| aurie 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.3075 0.0991                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2.2%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.36 [1.12, 1.65]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| /an 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.9658 0.3053                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2.63 [1.44, 4.78]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| /ei 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.5446 0.176                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.72 [1.22, 2.43]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| ubtotal (95% CI)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 7.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.54 [1.32, 1.80]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | •                                  |
| leterogeneity: Tau <sup>2</sup> = 0.01<br>Test for overall effect: Z = 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 0.16); l <sup>2</sup> = 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    |
| .5.2 Mixed (Non metasta                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | tic and metastatic)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |
| loe 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3436 0.1085                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.41 [1.14, 1.74]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| oe 2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.3148 0.1074                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 2.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.37 [1.11, 1.69]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| Bacci 2004                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.5878 0.2069                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.80 [1.20, 2.70]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Bacci 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.6471 0.1267                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.91 [1.49, 2.45]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| Du 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.005 0.0025                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 9.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.01 [1.00, 1.01]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | +                                  |
| Durnali 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 2.1988 0.7249                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 9.01 [2.18, 37.32]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    |
| eliu 2011                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.1196 0.0322                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 6.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.13 [1.06, 1.20]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Giroux 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.6931 0.2005                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2.00 [1.35, 2.96]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Gripp 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.8755 0.2101                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2.40 [1.59, 3.62]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| lan 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.4318 0.1359                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.3%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.54 [1.18, 2.01]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
| lannisdal 1993                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.4055 0.1582                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.50 [1.10, 2.05]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| lashimoto 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.5977 0.1818                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.82 [1.27, 2.60]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Kawahara 1997                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.6729 0.1433                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.96 [1.48, 2.60]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| (im 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.7857 0.292                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2.19 [1.24, 3.89]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| .i 2012<br>Antzer 1000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.5068 0.2465                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.66 [1.02, 2.69]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <sup>1</sup>                       |
| Notzer 1999<br>Antzer 2002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.9002 0.1245                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 2.46 [1.93, 3.14]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Notzer 2002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.1725 0.1726<br>0.4055 0.1582                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 3.23 [2.30, 4.53]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Polee 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | -0.2058 0.1259                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.50 [1.10, 2.05]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Sau 2013<br>Scher 1999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.003 0.001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1.5%<br>9.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.81 [0.64, 1.04]<br>1.00 [1.00, 1.00]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 1                                  |
| Suh 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.003 0.001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.73 [1.22, 2.46]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| amura 1998                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.3365 0.1517                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.40 [1.04, 1.88]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| anrikulu 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.8065 0.1765                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 2.24 [1.58, 3.17]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| onini 1997                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.4061 0.6316                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 4.08 [1.18, 14.07]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    |
| /iganó 2000                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.5878 0.2069                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.80 [1.20, 2.70]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Vang 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.5939 0.1138                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.81 [1.45, 2.26]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | -                                  |
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.4318 0.149                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 1.54 [1.15, 2.06]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | <del>~</del>                       |
| amaguchi 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |
| ′amaguchi 2014<br>Ihou 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 3.04 [1.63, 5.65]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| ′amaguchi 2014<br>2hou 2012<br>Subtotal (95% CI)<br>leterogeneity: Tau <sup>2</sup> = 0.00<br>Γest for overall effect: Ζ = 5                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | 1.1112 0.317<br>; Chi² = 366.19, df = 27 (                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.3%<br><b>49.2%</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 3.04 [1.63, 5.65]<br><b>1.20 [1.16, 1.24]</b><br>); I <sup>2</sup> = 93%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |
| 2012<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0.00<br>Test for overall effect: Z = 9<br>.5.3 Metastatic                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1.1112 0.317<br>; Chi² = 366.19, df = 27 (<br>9.92 (P < 0.00001)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.3%<br><b>49.2%</b><br>P < 0.00001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.20 [1.16, 1.24]<br>); I <sup>2</sup> = 93%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                    |
| Zhou 2012<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0.00<br>Test for overall effect: Z = S                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 1.1112 0.317<br>; Chi² = 366.19, df = 27 (                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.20 [1.16, 1.24]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| (hou 2012<br>Subtotal (95% CI)<br>leterogeneity: Tau <sup>2</sup> = 0.00<br>rest for overall effect: Z = 9<br>.5.3 Metastatic<br>Armstrong 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.1112 0.317<br>; Chi <sup>2</sup> = 366.19, df = 27 (<br>9.92 (P < 0.00001)<br>1.0332 0.1709                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | <b>1.20</b> [1.16, 1.24]<br>);   <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |
| (hou 2012<br>Subtotal (95% Cl)<br>leterogeneity: Tau <sup>2</sup> = 0.00<br>cest for overall effect: Z = S<br>.5.3 Metastatic<br>Armstrong 2012<br>Atzpodien 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 1.1112 0.317<br>; Chi <sup>2</sup> = 366.19, df = 27 (<br>9.92 (P < 0.00001)<br>1.0332 0.1709<br>0.2624 0.1339                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | <b>1.20</b> [1.16, 1.24]<br>);   <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |
| <pre>/hou 2012<br/>Subtotal (95% Cl)<br/>leterogeneity: Tau<sup>2</sup> = 0.00<br/>rest for overall effect: Z = S<br/>.5.3 Metastatic<br/>xrmstrong 2012<br/>Atzpodien 2003<br/>Bedikian 2008</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | $\begin{array}{rl} 1.1112 & 0.317 \\ \text{; Chi}^2 = 366.19,  df = 27 \ (, 9.92 \ (P < 0.00001) \\ & & \\ 1.0332 & 0.1709 \\ & 0.2624 & 0.1339 \\ & 0.4194 & 0.0948 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    |
| <pre>thou 2012 subtotal (95% Cl) leterogeneity: Tau<sup>2</sup> = 0.00 "est for overall effect: Z = 9 .5.3 Metastatic trmstrong 2012 Atzpodien 2003 Bedikian 2008 Bedikian 2011</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \mbox{; Chi}^2 = 366.19, \mbox{ df } = 27 \mbox{ (} \\ 0.92 \mbox{ (P } < 0.00001) \\ \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |
| <pre>thou 2012 Subtotal (95% Cl) leterogeneity: Tau<sup>2</sup> = 0.00 Test for overall effect: Z = 9 .5.3 Metastatic Armstrong 2012 Atzpodien 2003 Sedikian 2008 Bedikian 2008 Bedikian 2011 Cook 2006 Culp 2010</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                    |
| <pre>thou 2012 subtotal (95% Cl) leterogeneity: Tau<sup>2</sup> = 0.00 "est for overall effect: Z = 9 .5.3 Metastatic trmstrong 2012 Atzpodien 2003 Bedikian 2008 Bedikian 2011 Chibaudel 2011 Cook 2006 Lulp 2010 Escudier 2007</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br><b>49.2%</b><br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.20 [1.16, 1.24]<br>);   <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                    |
| <pre>thou 2012 subtotal (95% Cl) eleterogeneity: Tau<sup>2</sup> = 0.00 cest for overall effect: Z = 6</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                    |
| <pre>thou 2012 subtotal (95% CI) eleterogeneity: Tau<sup>2</sup> = 0.00 est for overall effect: Z = S</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 \ 0.1339 \\ 0.4194 \ 0.0948 \\ 0.4357 \ 0.1225 \\ 0.5878 \ 0.1103 \\ 0.7372 \ 0.1558 \\ 0.5068 \ 0.1407 \\ 0.5194 \ 0.1888 \\ 0.5878 \ 0.166 \\ 0.239 \ 0.1019 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    |
| thou 2012 Subtotal (95% CI) Heterogeneity: Tau <sup>2</sup> = 0.00 Fest for overall effect: Z = S .5.3 Metastatic Armstrong 2012 Atzpodien 2003 Bedikian 2003 Bedikian 2011 Chibaudel 2011 Cook 2006 Sup 2010 Escudier 2007 Eton 1998 Biessen 2013 Halabi 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1868 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.3%<br>49.2%<br>P < 0.0001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.20 [1.16, 1.24]<br>); l <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |
| Zhou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 9           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Sedikian 2008           Bedikian 2001           Cook 2006           Julp 2010           Escudier 2007           Iction 1998           Siessen 2013           Halabi 2014           He 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br>49.2%<br>P < 0.0001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.20 [1.16, 1.24]<br>);   <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                    |
| <pre>thou 2012 subtotal (95% Cl) leterogeneity: Tau<sup>2</sup> = 0.00 "est for overall effect: Z = 6</pre>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | $\begin{array}{rrrr} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 1.20 [1.16, 1.24]<br>);   <sup>2</sup> = 93%<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]<br>2.75 [1.86, 4.07]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau² = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2008           Bedikian 2001           Chibaudel 2011           Cook 2006           Culp 2010           Siscudier 2007           Eton 1998           Siessen 2013           Halabi 2014           He 2013           Jakob 2012           in 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 \ 0.1339 \\ 0.4194 \ 0.0948 \\ 0.4357 \ 0.1225 \\ 0.5878 \ 0.1103 \\ 0.7372 \ 0.1558 \\ 0.5068 \ 0.1407 \\ 0.5194 \ 0.1888 \\ 0.5878 \ 0.166 \\ 0.239 \ 0.1019 \\ 0.3365 \ 0.0959 \\ -0.0336 \ 0.2162 \\ 1.0116 \ 0.1995 \\ 0.4669 \ 0.0806 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.62, 4.2] 1.68 [1.62, 4.3] 1.68 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                    |
| thou 2012<br><b>subtotal (95% CI)</b><br><b>leterogeneity:</b> Tau <sup>2</sup> = 0.00<br>'est for overall effect: Z = 6<br><b>.5.3 Metastatic</b><br>trmstrong 2012<br>stzpodien 2003<br>Jedikian 2008<br>Jedikian 2011<br>Chibaudel 2011<br>Chibaudel 2011<br>Chibaudel 2011<br>Sculp 2010<br>Sicculer 2007<br>tion 1998<br>Siessen 2013<br>talabi 2014<br>He 2013<br>akob 2012<br>in 2013<br>agerwaard 1999                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 \ 0.1339 \\ 0.4194 \ 0.0948 \\ 0.4357 \ 0.1225 \\ 0.5878 \ 0.1103 \\ 0.7372 \ 0.1558 \\ 0.5068 \ 0.1407 \\ 0.5194 \ 0.1888 \\ 0.5878 \ 0.166 \\ 0.239 \ 0.1019 \\ 0.3365 \ 0.0959 \\ -0.0336 \ 0.2162 \\ 1.0116 \ 0.1995 \\ 0.4669 \ 0.0806 \\ 0.4383 \ 0.082 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Zhou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 9           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2011           Chibaudel 2011           Cook 2006           Subje 2010           Escudier 2007           Italabi 2014           He 2013           Jakob 2012           Jin 2013           .agerwaard 1999           Aeckbach 2014                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |
| thou 2012           subtotal (95% CI)           leterogeneity: Tau <sup>2</sup> = 0.00           rest for overall effect: Z = 9           .5.3 Metastatic           urmstrong 2012           txtpzodien 2003           tedikian 2011           bribaudel 2011           broke           broke           sedikian 2006           bulp 2010           cscudier 2007           tton 1998           biesesen 2013           alalabi 2014           te 2013           akob 2012           in 2013           agerwaard 1999           Ackbach 2014           Aekbang 2012                                                                                                                                                                                                                                                                                                                                                                                                                                     | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0366 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.3%<br>49.2%<br>P < 0.00001<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>0.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]<br>2.75 [1.86, 4.07]<br>1.60 [1.36, 1.87]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.85 [1.48, 2.31]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                    |
| hou 2012<br><b>Jubtotal (95% CI)</b><br>leterogeneity: Tau <sup>2</sup> = 0.00<br>jest for overall effect: Z = 9<br><b>.5.3 Metastatic</b><br>trrmstrong 2012<br>ttzpodien 2003<br>ledikian 2008<br>ledikian 2011<br>thibaudel 2011<br>took 2006<br>2019 2010<br>iscoudier 2007<br>iton 1998<br>biessen 2013<br>lalabi 2014<br>le 2013<br>akob 2012<br>in 2013<br>agerwaard 1999<br>leckbach 2014<br>lekenkamp 2012<br>lekenkamp 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0866 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1822 \\ 0.8329 & 0.1822 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>0.8%<br>0.8%<br>1.8%<br>1.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]<br>2.75 [1.86, 4.07]<br>1.60 [1.36, 1.87]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.85 [1.48, 2.31]<br>1.85 [1.48, 2.31]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           vrmstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2011           Chibaudel 2011           Cook 2006           Culp 2010           Siscudier 2007           Eton 1998           Siessen 2013           Hakob 2012           in 2013           agerwaard 1999           Aekenkamp 2012           Aekenkamp 2012           Aekenkamp 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                             | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.1022 \\ 0.4194 \\ 0.0948 \\ 0.4357 \\ 0.1225 \\ 0.5878 \\ 0.1033 \\ 0.7372 \\ 0.1588 \\ 0.5068 \\ 0.1407 \\ 0.5194 \\ 0.1888 \\ 0.5878 \\ 0.166 \\ 0.239 \\ 0.1019 \\ 0.3365 \\ 0.0829 \\ -0.0336 \\ 0.2162 \\ 1.0116 \\ 0.1995 \\ 0.4669 \\ 0.0806 \\ 0.4383 \\ 0.082 \\ 0.8329 \\ 0.182 \\ 0.6152 \\ 0.1139 \\ 0.5008 \\ 0.1296 \\ 0.4517 \\ 0.1805 \\ \hline \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.65 [1.28, 2.13] 1.67 [1.20, 2.24]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    |
| Chou 2012           subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           rest for overall effect: Z = 9           .5.3 Metastatic           vrmstrong 2012           tzpodien 2003           Bedikian 2001           Chibaudel 2011           Cook 2006           Siessen 2013           Ialabi 2014           He 2013           akob 2012           agerwaard 1999           Aeckbach 2014           Aekenkamp 2012           Aekenkamp 2012           Aekenkamp 2013           Ieuman 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>1.8%<br>1.8%<br>1.8%                                                                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.57 [1.10, 2.24] 1.42 [1.11, 1.82]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    |
| Chou 2012           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           trmstrong 2012           Atzpodien 2003           Bedikian 2001           Sodok 2008           Bedikian 2001           Cook 2006           Culp 2010           Escudier 2007           Eton 1998           Biessen 2013           Halabi 2014           te 2013           Jakob 2012           in 2013           agerwaard 1999           Ackenakamp 2012           Akeenkamp 2012           Aleuman 2008           Pierga 2001                                                                                                                                                                                                                                                                                                                                                                                                     | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1403 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5688 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1257 \\ 0.8507 & 0.1257 \\ 0.6931 & 0.0829 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.7%<br>0.9%<br>2.1%<br>0.9%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.5%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.6, 2.49]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.36, 1.87]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.85 [1.48, 2.31]<br>1.85 [1.48, 2.31]<br>1.85 [1.48, 2.31]<br>1.85 [1.48, 2.31]<br>1.65 [1.28, 2.13]<br>1.57 [1.10, 2.24]<br>1.42 [1.11, 1.82]<br>2.00 [1.70, 2.35]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2011           Chibaudel 2011           Cook 2006           Julp 2010           Escudier 2007           Eton 1998           Biessen 2013           Halabi 2014           Heckbach 2012           In 2013           Lagerwaard 1999           Aeckbach 2014           Aekenkamp 2012           Alexenkamp 2012           Pierga 2001           Piorpach 2014                                                                                                                                                                                                                                                                                                                                                                                      | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.92 \ (P < 0.00001) \\ \hline 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.7%<br>0.9%<br>2.1%<br>0.9%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.5%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.57 [1.10, 2.24] 1.42 [1.11, 1.82]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           urmstrong 2012           tzpodien 2003           Jedikian 2008           Bedikian 2011           Choix 2006           Culp 2010           Siscudier 2007           Ston 1998           Siessen 2013           Halabi 2014           He 2013           akob 2012           in 2013           agerwaard 1999           Aeckbach 2014           Aekenkamp 2012           Mekenkamp 2012           Pierga 2001           Ooprach 2014           Saito 2007                                                                                                                                                                                                                                                                                                                                                                              | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0866 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.5%<br>0.5%                                                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.68 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]<br>2.75 [1.86, 4.07]<br>1.60 [1.36, 1.87]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.85 [1.48, 2.31]<br>1.65 [1.28, 2.13]<br>1.57 [1.10, 2.24]<br>1.42 [1.11, 1.82]<br>2.00 [1.70, 2.35]<br>2.28 [1.46, 3.56]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                    |
| Chou 2012           vibtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           rest for overall effect: Z = 9           .5.3 Metastatic           vrmstrong 2012           tzpodien 2003           Bedikian 2001           Chibadel 2011           Cook 2006           Siessen 2013           Ialabi 2014           He 2013           akob 2012           agerwaard 1999           Aeckbach 2014           Aekenkamp 2012           Alotzer 2013           Ieuman 2008           Pierga 2001           Poprach 2014           Solotzor 2017           Staito 2007           Schmidt 2007                                                                                                                                                                                                                                                                                                                                                                                              | $\begin{array}{c} 1.1112 & 0.317 \\ \hline 0.92 \ (P < 0.00001) \\ \hline 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.036 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.8%<br>1.8%<br>1.5%<br>2.9%<br>0.5%<br>0.5%<br>0.5%<br>1.0%                                                                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.66, 2.43] 1.66 [1.66, 2.43] 1.67 [1.60, 2.43] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.57 [1.10, 2.24] 1.42 [1.11, 1.82] 2.00 [1.70, 2.35] 2.28 [1.46, 3.56] 1.62 [1.02, 2.57]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           trymstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2001           Cook 2006           Colp 2010           Escudier 2007           Eton 1988           Bisessen 2013           Halabi 2014           He 2013           Jakob 2012           in 2013           agerwaard 1999           Ackback 2014           Aktzer 2013           Jeuman 2008           Pierga 2001           Ooprach 2014           Saito 2007           Schmidt 2007           Schmidt 2007                                                                                                                                                                                                                                                                                                                                     | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 (1) \\ 0.92 (P < 0.00001) \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>0.9%<br>2.1%<br>0.9%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>0.6%<br>0.7%<br>3.0%<br>0.8%<br>1.8%<br>1.8%<br>1.8%<br>1.4%<br>0.8%<br>1.5%<br>2.9%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.4%                                                                                                                                                                                                                                                                                                                                                        | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93] 1.30 [1.00, 1.69] 1.52 [1.26, 1.83] 1.55 [1.22, 1.97] 1.80 [1.45, 2.23] 2.09 [1.54, 2.84] 1.66 [1.26, 2.19] 1.68 [1.16, 2.43] 1.80 [1.30, 2.49] 1.27 [1.04, 1.55] 1.40 [1.16, 1.69] 0.97 [0.63, 1.48] 2.75 [1.86, 4.07] 1.60 [1.36, 1.87] 1.55 [1.32, 1.82] 2.30 [1.60, 3.31] 1.85 [1.48, 2.31] 1.65 [1.28, 2.13] 1.65 [1.28, 2.13] 1.67 [1.10, 2.24] 1.42 [1.11, 1.82] 2.00 [1.70, 2.35] 2.28 [1.46, 3.56] 1.62 [1.02, 2.57] 2.20 [1.60, 3.03]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                    |
| Chou 2012         Subtotal (95% CI)         Heterogeneity: Tau <sup>2</sup> = 0.00         rest for overall effect: Z = 0         .5.3 Metastatic         urmstrong 2012         tyzpodien 2003         Jedikian 2008         Bedikian 2011         Chou 2006         Julp 2010         Escudier 2007         Ston 1998         Biessen 2013         Jalabi 2014         Jeckbach 2014         Ackenkamp 2012         Ackenkamp 2012         Ackenkamp 2012         Metera 2013         Jeuman 2008         Pierga 2001         Porprach 2014         Schmidt 2007                                                                                      | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4848 & 0.237 \\ 0.7885 & 0.1625 \\ 0.6329 & 0.2519 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.5%<br>2.9%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.4%<br>0.4%                                                                                                                                                                                                                                                                                                                                                        | 1.20 [ $1.16$ , 1.24]<br>); $ ^2 = 93\%$<br>2.81 [2.01, 3.93]<br>1.30 [ $1.00$ , 1.69]<br>1.52 [ $1.22$ , 1.97]<br>1.80 [ $1.45$ , 2.23]<br>2.09 [ $1.54$ , 2.84]<br>1.66 [ $1.26$ , 2.19]<br>1.68 [ $1.16$ , 2.43]<br>1.60 [ $1.30$ , 2.49]<br>1.27 [ $1.04$ , 1.55]<br>1.40 [ $1.16$ , 2.43]<br>1.60 [ $1.30$ , 2.49]<br>1.27 [ $1.04$ , 1.55]<br>1.40 [ $1.16$ , 2.43]<br>1.65 [ $1.22$ , 2.81]<br>1.65 [ $1.32$ , 1.82]<br>2.30 [ $1.60$ , 3.31]<br>1.85 [ $1.48$ , 2.31]<br>1.65 [ $1.28$ , 2.13]<br>1.65 [ $1.28$ , 2.13]<br>1.65 [ $1.28$ , 2.13]<br>1.65 [ $1.28$ , 2.13]<br>1.65 [ $1.46$ , 3.56]<br>1.62 [ $1.02$ , 2.57]<br>2.28 [ $1.46$ , 3.56]<br>1.62 [ $1.02$ , 2.57]<br>2.20 [ $1.60$ , 3.03]<br>1.88 [ $1.15$ , 3.09]                                                                                                                                                                                                                                                              |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Bedikian 2008           Bedikian 2001           Chibaudel 2011           Cook 2006           Culp 2010           Siscudier 2007           Eton 1998           Siessen 2013           Halabi 2014           4e 2013           akob 2012           in 2013           agerwaard 1999           Aeckbach 2014           Aekenkamp 2012           Alexen 2001           Porprach 2014           Saito 2007           Schinohara 2012           Shinohara 2013           Sougioultzis 2011                                                                                                                                                                                                                                                                                              | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5687 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4483 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1266 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7885 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>2.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>0.7%<br>1.4%<br>0.0%<br>0.9%<br>1.4%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9 | 1.20 $[1.16, 1.24]$<br>); $ ^2 = 93\%$<br>2.81 $[2.01, 3.93]$<br>1.30 $[1.00, 1.69]$<br>1.52 $[1.26, 1.83]$<br>1.55 $[1.22, 1.97]$<br>1.80 $[1.45, 2.23]$<br>2.09 $[1.54, 2.84]$<br>1.66 $[1.26, 2.19]$<br>1.68 $[1.16, 2.43]$<br>1.80 $[1.30, 2.49]$<br>1.27 $[1.04, 1.55]$<br>1.40 $[1.36, 1.87]$<br>1.55 $[1.32, 1.82]$<br>2.30 $[1.60, 3.31]$<br>1.65 $[1.28, 2.13]$<br>1.65 $[1.28, 2.57]$<br>2.20 $[1.60, 3.03]$<br>1.88 $[1.15, 3.09]$<br>1.60 $[1.10, 2.33]$                                                                                                                                                                                                                                                                                                                  |                                    |
| Zhou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 9           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Sedikian 2008           Bedikian 2001           Cook 2006           Julp 2010           Escudier 2007           Iction 1998           Siessen 2013           Halabi 2014           He 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5678 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0866 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7885 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1289 \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>2.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.7%<br>3.0%<br>2.9%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>1.4%<br>0.8%<br>0.7%<br>1.4%<br>0.0%<br>0.9%<br>1.4%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>1.1%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9%<br>0.9 | $1.20 [1.16, 1.24]$ ); $ ^2 = 93\%$ 2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.62, 2.49]<br>1.68 [1.62, 2.49]<br>1.68 [1.62, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 1.69]<br>0.97 [0.63, 1.48]<br>2.75 [1.86, 4.07]<br>1.60 [1.36, 1.87]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.85 [1.48, 2.31]<br>1.65 [1.28, 2.13]<br>1.57 [1.10, 2.24]<br>1.42 [1.11, 1.82]<br>2.00 [1.70, 2.35]<br>2.28 [1.46, 3.56]<br>1.62 [1.02, 2.57]<br>2.20 [1.60, 3.03]<br>1.88 [1.15, 3.09]<br>1.60 [1.01, 2.33]<br>1.72 [1.34, 2.21]                                                                                                                                                                                                                                                                                                                                                                              |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           rest for overall effect: Z = 0           stor overall effect: Z = 0           .5.3 Metastatic           Armstrong 2012           Atzpodien 2003           Bedikian 2001           Chibaudel 2011           Cook 2006           Culp 2010           Sicesen 2013           Stalabi 2014           te 2013           akob 2012           in 2013           agerwaard 1999           Ackekanap 2012           Alotzer 2013           Verman 2008           Verga 2001           Poprach 2014           Saito 2007           Schmidt 2007           Schmidt 2007           Schmidt 2007           Schmidt 2013           Sougioultizs 2011                                                                                                                                                                                                                                                                 | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 (1) \\ 0.92 (P < 0.00001) \\ \hline \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5078 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.059 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1855 \\ 0.3607 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7885 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1289 \\ 0.9243 & 0.213 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>0.8%<br>1.8%<br>1.8%<br>1.8%<br>1.8%<br>1.5%<br>2.9%<br>0.5%<br>1.0%<br>0.4%<br>0.75%<br>1.5%<br>0.6%                                                                                                                                                                                                                                                                                                                                                                                               | 1.20 [ $1.16$ , 1.24]<br>); $ ^2 = 93\%$<br>2.81 [ $2.01$ , $3.93$ ]<br>1.30 ( $1.00$ , $1.69$ ]<br>1.52 [ $1.26$ , $1.83$ ]<br>1.55 [ $1.22$ , $1.97$ ]<br>1.80 [ $1.45$ , $2.23$ ]<br>2.09 [ $1.54$ , $2.84$ ]<br>1.66 [ $1.26$ , $2.19$ ]<br>1.68 [ $1.30$ , $2.49$ ]<br>1.27 [ $1.04$ , $1.55$ ]<br>1.40 ( $1.30$ , $2.49$ ]<br>1.27 [ $1.04$ , $1.55$ ]<br>1.40 ( $1.36$ , $1.48$ ]<br>2.75 [ $1.86$ , $4.07$ ]<br>1.65 [ $1.32$ , $1.82$ ]<br>2.30 [ $1.60$ , $3.31$ ]<br>1.85 [ $1.48$ , $2.31$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.67 [ $1.10$ , $2.24$ ]<br>1.42 [ $1.11$ , $1.82$ ]<br>2.00 [ $1.70$ , $2.35$ ]<br>2.28 [ $1.46$ , $3.56$ ]<br>1.62 [ $1.02$ , $2.57$ ]<br>2.20 [ $1.60$ , $3.03$ ]<br>1.88 [ $1.15$ , $3.09$ ]<br>1.67 [ $1.34$ , $2.21$ ]<br>2.52 [ $1.66$ , $3.83$ ]                                                                                                                                                                         |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 0           .5.3 Metastatic           vrmstrong 2012           Atzpodien 2003           Bedikian 2001           Stadikian 2001           Cook 2006           Julp 2010           Escudier 2007           Eton 1988           Siessen 2013           Halabi 2014           He 2013           Jakob 2012           Jung 2014           Je 2013           Jakob 2012           Jotzer 2013           Jakob 2012           Jotzer 2013           Jakob 2012           Jotzer 2013           Jeuman 2008           Pierga 2001           Oprach 2014           Saito 2007           Schmidt 2007           Shinohara 2012           Shinohara 2013           Sougioultzis 2011           Fempleton 2014           Sougioultzis 2011                                                                                                                                            | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 ( P < 0.00001 ) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5688 & 0.1607 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7865 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1298 \\ 0.9243 & 0.213 \\ 0.4028 & 0.1298 \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>0.6%<br>1.8%<br>1.8%<br>1.8%<br>1.8%<br>1.5%<br>2.9%<br>0.5%<br>1.0%<br>0.5%<br>1.0%<br>0.4%<br>0.7%<br>1.5%<br>2.9%                                                                                                                                                                                                                                                                                                                                                                | 1.20 [ $1.16$ , 1.24]<br>); $ ^2 = 93\%$<br>2.81 [2.01, 3.93]<br>1.30 [ $1.00$ , 1.69]<br>1.52 [ $1.26$ , 1.83]<br>1.55 [ $1.22$ , 1.97]<br>1.80 [ $1.45$ , 2.23]<br>2.09 [ $1.54$ , 2.84]<br>1.66 [ $1.26$ , 2.19]<br>1.68 [ $1.6$ , 2.43]<br>1.80 [ $1.30$ , 2.49]<br>1.27 [ $1.04$ , 1.55]<br>1.40 [ $1.16$ , 2.43]<br>1.80 [ $1.30$ , 2.49]<br>1.27 [ $1.84$ , 4.07]<br>1.60 [ $1.36$ , 1.87]<br>1.55 [ $1.32$ , 1.82]<br>2.30 [ $1.60$ , 3.31]<br>1.85 [ $1.48$ , 2.31]<br>1.65 [ $1.28$ , 2.13]<br>1.57 [ $1.10$ , 2.24]<br>1.62 [ $1.46$ , 3.66]<br>1.62 [ $1.02$ , 2.57]<br>2.20 [ $1.60$ , 3.03]<br>1.88 [ $1.15$ , 3.09]<br>1.60 [ $1.10$ , 2.33]<br>1.72 [ $1.34$ , 2.21]<br>2.52 [ $1.66$ , 3.83]<br>1.50 [ $1.16$ , 1.93]<br>1.60 [ $1.30$ , 1.97]                                                                                                                                                                                                                                      |                                    |
| Chou 2012           Subtotal (95% CI)           Heterogeneity: Tau <sup>2</sup> = 0.00           rest for overall effect: Z = 0           stor overall effect: Z = 0           stor overall effect: Z = 0           .5.3 Metastatic           vrmstrong 2012           Vtzpodien 2003           Bedikian 2001           Chibaudel 2011           Cook 2006           Culp 2010           Sicessen 2013           Sidaba 2014           te 2013           akob 2012           in 2013           agerwaard 1999           Ackbach 2014           Aekenkamp 2012           Alatain 2014           Poprach 2013           Jeauma 2008           Verga 2001           Poprach 2014           Saito 2007           Schmidt 2013           Veide 2013           Veide 2013           Sougioultzis 2011           Templeton 2014           Stubtotal (95% CI)         | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( ) \\ 9.92 (P < 0.00001) \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>0.9%<br>0.8%<br>1.8%<br>1.8%<br>1.8%<br>1.8%<br>1.5%<br>2.9%<br>0.5%<br>1.0%<br>0.4%<br>0.5%<br>1.0%<br>0.4%<br>0.5%<br>1.5%<br>0.6%<br>1.4%<br>2.0%<br>43.6%                                                                                                                                                                                                                                                                                                                                       | 1.20 [ $1.16$ , 1.24]<br>); $ ^2 = 93\%$<br>2.81 [ $2.01$ , $3.93$ ]<br>1.30 ( $1.00$ , $1.69$ ]<br>1.52 [ $1.26$ , $1.83$ ]<br>1.55 [ $1.22$ , $1.97$ ]<br>1.80 [ $1.45$ , $2.23$ ]<br>2.09 [ $1.54$ , $2.84$ ]<br>1.66 [ $1.26$ , $2.19$ ]<br>1.68 [ $1.30$ , $2.49$ ]<br>1.27 [ $1.04$ , $1.55$ ]<br>1.40 ( $1.16$ , $1.69$ ]<br>0.97 [ $0.63$ , $1.48$ ]<br>2.75 [ $1.86$ , $4.07$ ]<br>1.60 [ $1.36$ , $1.87$ ]<br>1.55 [ $1.32$ , $1.82$ ]<br>2.30 [ $1.60$ , $3.31$ ]<br>1.85 [ $1.48$ , $2.31$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.67 [ $1.10$ , $2.24$ ]<br>1.42 [ $1.11$ , $1.82$ ]<br>2.00 [ $1.70$ , $2.35$ ]<br>2.28 [ $1.46$ , $3.56$ ]<br>1.62 [ $1.02$ , $2.57$ ]<br>2.20 [ $1.60$ , $3.03$ ]<br>1.88 [ $1.15$ , $3.09$ ]<br>1.60 [ $1.10$ , $2.33$ ]<br>1.72 [ $1.34$ , $2.21$ ]<br>2.52 [ $1.66$ , $3.83$ ]<br>1.50 ( $1.16$ , $1.93$ ]<br>1.60 [ $1.30$ , $1.97$ ]<br>1.60 [ $1.30$ , $1.97$ ]<br>1.69 [ $1.58$ , $1.81$ ] |                                    |
| Chou 2012           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 9           .5.3 Metastatic           vrmstrong 2012           Vtzpodien 2003           Bedikian 2001           Saddikian 2011           Cook 2006           Julp 2010           Escudier 2007           Eton 1988           Siessen 2013           Halabi 2014           He 2013           Jakob 2012           Jung 2010           Escudier 2007           Eton 1988           Siessen 2013           Jalabi 2014           He 2013           Jakob 2012           Johzer 2013           Johzer 2013           Jeelman 2008           Pierga 2001           Optrach 2014           Saito 2007           Schmidt 2007           Sc | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5678 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7855 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1298 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.$ | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>0.9%<br>0.8%<br>1.8%<br>1.8%<br>1.8%<br>1.8%<br>1.5%<br>2.9%<br>0.5%<br>1.0%<br>0.4%<br>0.5%<br>1.0%<br>0.4%<br>0.5%<br>1.5%<br>0.6%<br>1.4%<br>2.0%<br>43.6%                                                                                                                                                                                                                                                                                                                                       | 1.20 [ $1.16$ , 1.24]<br>); $ ^2 = 93\%$<br>2.81 [ $2.01$ , $3.93$ ]<br>1.30 ( $1.00$ , $1.69$ ]<br>1.52 [ $1.26$ , $1.83$ ]<br>1.55 [ $1.22$ , $1.97$ ]<br>1.80 [ $1.45$ , $2.23$ ]<br>2.09 [ $1.54$ , $2.84$ ]<br>1.66 [ $1.26$ , $2.19$ ]<br>1.68 [ $1.30$ , $2.49$ ]<br>1.27 [ $1.04$ , $1.55$ ]<br>1.40 ( $1.16$ , $1.69$ ]<br>0.97 [ $0.63$ , $1.48$ ]<br>2.75 [ $1.86$ , $4.07$ ]<br>1.60 [ $1.36$ , $1.87$ ]<br>1.55 [ $1.32$ , $1.82$ ]<br>2.30 [ $1.60$ , $3.31$ ]<br>1.85 [ $1.48$ , $2.31$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.65 [ $1.28$ , $2.13$ ]<br>1.67 [ $1.10$ , $2.24$ ]<br>1.42 [ $1.11$ , $1.82$ ]<br>2.00 [ $1.70$ , $2.35$ ]<br>2.28 [ $1.46$ , $3.56$ ]<br>1.62 [ $1.02$ , $2.57$ ]<br>2.20 [ $1.60$ , $3.03$ ]<br>1.88 [ $1.15$ , $3.09$ ]<br>1.60 [ $1.10$ , $2.33$ ]<br>1.72 [ $1.34$ , $2.21$ ]<br>2.52 [ $1.66$ , $3.83$ ]<br>1.50 ( $1.16$ , $1.93$ ]<br>1.60 [ $1.30$ , $1.97$ ]<br>1.60 [ $1.30$ , $1.97$ ]<br>1.69 [ $1.58$ , $1.81$ ] |                                    |
| thou 2012<br><b>Subtotal (95% CI)</b><br><b>Heterogeneity:</b> Tau <sup>2</sup> = 0.00<br>Test for overall effect: Z = 6<br><b>.5.3 Metastatic</b><br>trrmstrong 2012<br>Atzpodien 2003<br>Bedikian 2008<br>Bedikian 2011<br>Chibaudel 2011<br>Cook 2006<br>Culp 2010<br>Escudier 2007<br>Eton 1998<br>Biessen 2013<br>Halabi 2014<br>He 2013<br>Lakob 2012<br>In 2013<br>Lakob 2012<br>In 2013<br>Lagerwaard 1999<br>Aeckbach 2014<br>Aekenkamp 2012<br>Aekenkamp 2012<br>Aekenkamp 2012<br>Adzer 2013<br>Neuman 2008<br>Pierga 2001<br>Poprach 2014<br>Schmidt 2007<br>Schmidt 2007<br>Schmidt 2007<br>Schmidt 2017<br>Veide 2013<br>Veide 2013<br>Veide 2013<br>Veide 2013<br>Veide 2014<br>Lam Kessel 2013<br>Veide 2014<br>Veide 2013<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = 0.02<br>Test for overall effect: Z = 1                                                                                                                                                             | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5678 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.0959 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.1139 \\ 0.507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7855 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1298 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.47 & 0.051 \\ 0.$ | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>1.1%<br>1.3%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>3.0%<br>2.9%<br>0.6%<br>0.8%<br>1.8%<br>1.4%<br>0.8%<br>1.8%<br>1.4%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.5                                                                                                                                                                                                                                                                                                                                                 | 1.20 [ $^{1}$ .16, 1.24]<br>); $ ^{2} = 93\%$<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [ $^{1}$ .45, 2.23]<br>2.09 [ $^{1}$ .54, 2.84]<br>1.66 [ $^{1}$ .66, 2.43]<br>1.80 [ $^{1}$ .60, 2.49]<br>1.27 [ $^{1}$ .04, 1.55]<br>1.40 [ $^{1}$ .61, 2.43]<br>1.80 [ $^{1}$ .30, 2.49]<br>1.27 [ $^{1}$ .04, 1.55]<br>1.40 [ $^{1}$ .61, 6.169]<br>0.97 [ $^{0}$ .63, 1.48]<br>2.75 [ $^{1}$ .86, 4.07]<br>1.60 [ $^{1}$ .36, 1.87]<br>1.55 [ $^{1}$ .32, 1.82]<br>2.30 [ $^{1}$ .60, 3.31]<br>1.65 [ $^{1}$ .28, 2.13]<br>1.57 [ $^{1}$ .10, 2.24]<br>1.42 [ $^{1}$ .11, 1.82]<br>2.20 [ $^{1}$ .60, 3.03]<br>1.85 [ $^{1}$ .48, 2.57]<br>2.20 [ $^{1}$ .60, 3.03]<br>1.85 [ $^{1}$ .46, 3.56]<br>1.62 [ $^{1}$ .02, 2.57]<br>2.20 [ $^{1}$ .60, 3.03]<br>1.88 [ $^{1}$ .15, 3.09]<br>1.60 [ $^{1}$ .30, 1.97]<br>1.60 [ $^{1}$ .30, 1.97]<br>1.60 [ $^{1}$ .30, 1.97]<br>1.60 [ $^{1}$ .30, 1.97]<br>1.69 [ $^{1}$ .58, 1.81]<br>] $^{2}$ = 51%     |                                    |
| Chou 2012           Subtotal (95% Cl)           Heterogeneity: Tau <sup>2</sup> = 0.00           Test for overall effect: Z = 9           .5.3 Metastatic           vrmstrong 2012           Vtzpodien 2003           Bedikian 2001           Saddikian 2011           Cook 2006           Julp 2010           Escudier 2007           Eton 1988           Siessen 2013           Halabi 2014           He 2013           Jakob 2012           Jung 2010           Escudier 2007           Eton 1988           Siessen 2013           Jalabi 2014           He 2013           Jakob 2012           Johzer 2013           Johzer 2013           Jeelman 2008           Pierga 2001           Poprach 2014           Saito 2007           Schmidt 2007           Sc | $\begin{array}{c} 1.1112 & 0.317 \\ (Chi^2 = 366.19, df = 27 ( 0.92 (P < 0.00001) \\ 1.0332 & 0.1709 \\ 0.2624 & 0.1339 \\ 0.4194 & 0.0948 \\ 0.4357 & 0.1225 \\ 0.5878 & 0.1103 \\ 0.7372 & 0.1558 \\ 0.5068 & 0.1407 \\ 0.5194 & 0.1888 \\ 0.5878 & 0.166 \\ 0.239 & 0.1019 \\ 0.3365 & 0.059 \\ -0.0336 & 0.2162 \\ 1.0116 & 0.1995 \\ 0.4669 & 0.0806 \\ 0.4383 & 0.082 \\ 0.8329 & 0.1852 \\ 0.6152 & 0.139 \\ 0.5008 & 0.1296 \\ 0.4517 & 0.1805 \\ 0.3507 & 0.1257 \\ 0.6931 & 0.0829 \\ 0.8242 & 0.2274 \\ 0.4818 & 0.2357 \\ 0.7885 & 0.1625 \\ 0.6329 & 0.2519 \\ 0.47 & 0.1912 \\ 0.5423 & 0.1288 \\ 0.47 & 0.1059 \\ 0.47 & 0.1059 \\ (Chi^2 = 61.37, df = 30 (P \\ 15.15 (P < 0.00001) \\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.3%<br>49.2%<br>P < 0.00001<br>0.9%<br>1.4%<br>2.4%<br>1.6%<br>1.9%<br>0.7%<br>0.9%<br>2.1%<br>2.3%<br>0.6%<br>0.7%<br>0.8%<br>1.4%<br>2.9%<br>0.8%<br>1.5%<br>2.9%<br>0.8%<br>1.5%<br>2.9%<br>0.5%<br>1.0%<br>0.4%<br>0.75%<br>1.5%<br>0.6%<br>1.4%<br>2.0%<br>43.6%<br>= 0.0006);<br>100.0%                                                                                                                                                                                                                                                                                                                              | 1.20 [1.16, 1.24]<br>); $ ^2 = 93\%$<br>2.81 [2.01, 3.93]<br>1.30 [1.00, 1.69]<br>1.52 [1.26, 1.83]<br>1.55 [1.22, 1.97]<br>1.80 [1.45, 2.23]<br>2.09 [1.54, 2.84]<br>1.66 [1.62, 2.49]<br>1.68 [1.62, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 2.43]<br>1.80 [1.30, 2.49]<br>1.27 [1.04, 1.55]<br>1.40 [1.16, 2.43]<br>1.55 [1.32, 1.82]<br>2.30 [1.60, 3.31]<br>1.65 [1.28, 2.13]<br>1.57 [1.10, 2.24]<br>1.42 [1.11, 1.82]<br>2.00 [1.70, 2.35]<br>2.28 [1.46, 3.56]<br>1.62 [1.02, 2.57]<br>2.20 [1.60, 3.03]<br>1.88 [1.45, 3.09]<br>1.60 [1.10, 2.33]<br>1.72 [1.34, 2.21]<br>2.52 [1.66, 3.83]<br>1.50 [1.16, 1.93]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.69 [1.58, 1.81]<br>$ ^2 = 51\%$                                                                                                                                                                                  |                                    |

Figure 3 | Forest plots showing HRs by stage subgroups.

| 1.11 |
|------|
|      |

| 1.4.1 <250                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | log[Hazard Ratio]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | IV, Random, 95% C                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | I IV, Random, 95% CI                  |
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| Atzpodien 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.2624                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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| Bacci 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.6471                                                                                                                                                                                                                                                                                                                                       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| Han 2003                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | 0.4318                                                                                                                                                                                                                                                                                                                                       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| Mekenkamp 2012                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 0.6152                                                                                                                                                                                                                                                                                                                                       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| Sau 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | -0.2058                                                                                                                                                                                                                                                                                                                                      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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.47 0<br>0.47 0<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, df<br>Z = 10.45 (P < 0.0000<br>0.005 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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0.0000<br>9.1%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.47<br>0.47<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, dt<br>Z = 10.45 (P < 0.0000<br>0.005<br>0.5194<br>0.4055                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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0.0000<br>9.1%<br>0.7%<br>1.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%<br>1.01 [1.00, 1.01]<br>1.68 [1.16, 2.43]<br>1.50 [1.10, 2.05]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.47<br>0.47<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, df<br>Z = 10.45 (P < 0.0000<br>0.5194<br>0.4055<br>1.1725                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%<br>1.01 [1.00, 1.01]<br>1.68 [1.16, 2.43]<br>1.50 [1.10, 2.05]<br>3.23 [2.30, 4.53]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013                                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.47 0<br>0.47 0<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, df<br>Z = 10.45 (P < 0.0000<br>0.5194 0<br>0.4055 0<br>1.1725 0<br>0.4517 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%<br>1.01 [1.00, 1.01]<br>1.68 [1.16, 2.43]<br>1.50 [1.10, 2.05]<br>3.23 [2.30, 4.53]<br>1.57 [1.10, 2.24]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.47<br>0.47<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, dl<br>Z = 10.45 (P < 0.0000<br>0.5194<br>0.4055<br>1.1725<br>0.4517<br>0.4517<br>0.4524                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%<br>0.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | $\begin{array}{c} 1.60 \left[ 1.30,  1.97 \right] \\ 1.60 \left[ 1.30,  1.97 \right] \\ 1.54 \left[ 1.15,  2.06 \right] \\ 1.67 \left[ 1.52,  1.84 \right] \\ 1); \ l^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014                                                                                                                                                                                                                                                                                                                                                                                                                                       | 0.47 0<br>0.47 0<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, df<br>Z = 10.45 (P < 0.0000<br>0.5194 0<br>0.4055 0<br>1.1725 0<br>0.4517 0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%<br>1.01 [1.00, 1.01]<br>1.68 [1.16, 2.43]<br>1.50 [1.10, 2.05]<br>3.23 [2.30, 4.53]<br>1.57 [1.10, 2.24]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007                                                                                                                                                                                                                                                                                                                                                                                                                         | 0.47<br>0.47<br>0.4318<br>0.05; Chi <sup>2</sup> = 106.95, dt<br>Z = 10.45 (P < 0.0000<br>0.005<br>0.5194<br>0.4055<br>1.1725<br>0.4517<br>0.8242<br>0.4818                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%<br>0.5%<br>0.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012                                                                                                                                                                                                                                                                                                                                                                                                       | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%<br>0.5%<br>0.5%<br>0.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.57 \left[ 1.52, 1.84 \right] \\ 1); \ l^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Templeton 2014<br>Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013                                                                                                                                                                                                                                                                                                                                                    | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 1.1725\\ 0.4818\\ 0.6329\\ 0.6329\\ 0.47\end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519<br>0.1912                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%<br>0.5%<br>0.4%<br>0.7%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 1.60 [1.30, 1.97]<br>1.60 [1.30, 1.97]<br>1.54 [1.15, 2.06]<br>1.67 [1.52, 1.84]<br>1); I <sup>2</sup> = 75%<br>1.01 [1.00, 1.01]<br>1.68 [1.16, 2.43]<br>1.50 [1.10, 2.05]<br>3.23 [2.30, 4.53]<br>1.57 [1.10, 2.24]<br>2.28 [1.46, 3.56]<br>1.62 [1.02, 2.57]<br>1.88 [1.15, 3.09]<br>1.60 [1.10, 2.33]                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% CI)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013                                                                                                                                                                                                                                                                                                                                                                                     | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519<br>0.1912                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.8%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.7%<br>1.4%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>van Kessel 2013<br>Subtotal (95% Cl)                                                                                                                                                                                                                                                                                                                                             | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ dt\\ Z=10.45\ (P<0.0000^{\circ})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | 0.1059<br>0.149<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519<br>0.2519<br>0.1912<br>0.1298                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (                                                                                                                                                                                                                                                                                                                         | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005 \\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.825\\ 0.18;\ Chi^2=104.15,\ di\\ 0.18;\ Chi^2=104.15,\ di\\ 0.418\\ 0.18;\ Chi^2=104.15,\ di\\ 0.18;\$                                                                                                                                                                                          | 0.1059<br>0.149<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519<br>0.2519<br>0.1912<br>0.1298                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      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\\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \ l^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2003<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2                                                                                                                                                                                                                                                                         | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000)\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.825\\ 0.18;\ Chi^2=104.15,\ di\\ 0.18;\ Chi^2=104.15,\ di\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2010<br>Motzer 2010<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2013<br>Van Kessel 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400                                                                                                                                                                                                                                                             | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.428\\ 0.522\\ 0.4028\\ 0.4028\\ 0.18;\ Chi^2=104.15,\ di\\ Z=3.62\ (P=0.0003)\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.00888<br>0.1582<br>0.1726<br>0.1805<br>0.2274<br>0.2357<br>0.2519<br>0.1912<br>0.1298<br>f = 9 (P                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2010<br>Motzer 2010<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2013<br>Van Kessel 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400                                                                                                                                                                                                                                                             | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000)\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.825\\ 0.18;\ 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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2004                                                                                                                                                                                                                                                  | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.428\\ 0.522\\ 0.4028\\ 0.4028\\ 0.18;\ Chi^2=104.15,\ di\\ Z=3.62\ (P=0.0003)\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2004<br>Aoe 2005                                                                                                                                                                                                                                                                    | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \end{array}$ $\begin{array}{c} 0.6329\\ 0.47\\ 0.4028\\ 0.18;\ Chi^2=104.15,\ di\\ Z=3.62\ (P=0.0003)\\ 0.3436\\ 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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2010<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008                                                                                                                                                                                                                              | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{\circ})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 0.4057\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \end{array}$ $\begin{array}{c} 0.18;\ Chi^2=104.15,\ di\\ Z=3.62\ (P=0.0003)\\ 0.3436\\ 0.3148\\ 0.4194\\ 0.4194\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | 0.1059<br>0.1059<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1888<br>0.1882<br>0.1882<br>0.1826<br>0.1805<br>0.2274<br>0.2519<br>0.2519<br>0.1912<br>0.1928<br>f = 9 (P<br>0.1085<br>0.1074<br>0.01074                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     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0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.8%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>16.2%<br>< 0.00001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                         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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2004<br>Ace 2005<br>Bedikian 2008<br>Cook 2006                                                                                                                                                                                                                       | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4513\\ 0.4514\\ 0.6329\\ 0.47\\ 0.4028\\ 0.418\\ 0.6329\\ 0.47\\ 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                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2004<br>Ace 2005<br>Bedikian 2008<br>Cook 2006                                                                                                                                                                                                                       | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{-1})\\ 0.055\\ 0.5194\\ 0.04055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.4517\\ 0.8242\\ 0.18;\ Chi^2=104.15,\ di\\ Z=3.62\ (P=0.0003)\\ 0.3436\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010                                                                                                                                                                                                                      | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4512\\ 0.4513\\ 0.4514\\ 0.6329\\ 0.47\\ 0.4028\\ 0.418\\ 0.6329\\ 0.47\\ 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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2007<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011                                                                                                                                                                                                        | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ dt\\ Z=10.45\ (P<0.0000\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.471\\ 0.4818\\ 0.6329\\ 0.471\\ 0.4228\\ \end{array}$ $\begin{array}{c} 0.18;\ Chi^2=104.15,\ dt\\ Z=3.62\ (P=0.003)\\ \end{array}$ $\begin{array}{c} 0.3436\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.1196\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2004<br>Ace 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012                                                                                                                                                                                               | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{\circ})\\ 0.005\\ 0.5194\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \end{array}$ $\begin{array}{c} 0.052\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ 0.4028\\ 0.4028\\ 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                                                                                                                                                                  | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2004<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007                                                                                                                                                             | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4055\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4517\\ 0.4512\\ 0.4517\\ 0.428\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4518\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.1196\\ 0.6931\\ 0.7885\\ 0.185\\ 0.7885\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.196\\ 0.785\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 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| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2004<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010                                                                                                                               | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ di\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005 \\ 0.5194 \\ 0.4055 \\ 1.1725 \\ 0.4517 \\ 0.8242 \\ 0.4517 \\ 0.8242 \\ 0.4517 \\ 0.8242 \\ 0.4517 \\ 0.8242 \\ 0.474 \\ 0.428 \\ 0.474 \\ 0.4028 \\ 0.132 \\ 0.474 \\ 0.4028 \\ 0.474 \\ 0.4028 \\ 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      |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2004<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010                                                                                                                               | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{-1})\\ 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.4055\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4512\\ 0.4517\\ 0.4512\\ 0.4517\\ 0.428\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4517\\ 0.4028\\ 0.4518\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.1196\\ 0.6931\\ 0.7885\\ 0.185\\ 0.7885\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.196\\ 0.785\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 0.185\\ 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0.185\\ 0.185\\ 0.185\\ 0.18$ | 0.1059<br>0.1059<br>0.149<br>0.149<br>f = 27 (F<br>1)<br>0.0025<br>0.1828<br>0.1828<br>0.1825<br>0.1828<br>0.1805<br>0.2237<br>0.2357<br>0.2357<br>0.2351<br>0.22519<br>0.1912<br>0.2357<br>0.22519<br>0.1912<br>0.1085<br>0.1074<br>0.0235<br>0.1074<br>0.0185<br>0.1074<br>0.0558<br>0.1074<br>0.0558<br>0.1074<br>0.0558<br>0.1074<br>0.0558<br>0.1074<br>0.0255<br>0.1726<br>0.0159<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1592<br>0.1575<br>0.1574<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.0055<br>0.00555<br>0.00555<br>0.00555<br>0.00555<br>0.005555<br>0.00 | 2.0%<br>2.0%<br>1.1%<br>41.3%<br>2 < 0.0000<br>9.1%<br>0.7%<br>0.9%<br>0.8%<br>0.5%<br>0.4%<br>0.7%<br>1.0%<br>2.4%<br>1.1%<br>1.3%<br>6.9%<br>0.7%<br>1.0%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \ l^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010                                                                                                                         | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ dl\\ Z=10.45\ (P<0.0000\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 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0.6329\\ 0.6329\\ 0.6329$        | 0.1059<br>0.1059<br>0.149<br>= 27 (F<br>0.0025<br>0.1888<br>0.0582<br>0.1582<br>0.1726<br>0.2357<br>0.2519<br>0.1912<br>0.2274<br>0.2357<br>0.2474<br>0.2357<br>0.1298<br>1 = 9 (P<br>0.1085<br>0.1074<br>0.0322<br>0.1074<br>0.0322<br>0.0322<br>0.1074<br>0.0322<br>0.0322<br>0.0322<br>0.1074<br>0.0322<br>0.0322<br>0.0322<br>0.0322<br>0.1074<br>0.0322<br>0.0322<br>0.0322<br>0.0322<br>0.0325<br>0.1074<br>0.0322<br>0.0322<br>0.0174<br>0.0322<br>0.0322<br>0.0174<br>0.0322<br>0.0075<br>0.0174<br>0.0322<br>0.0075<br>0.0174<br>0.0322<br>0.0075<br>0.0185<br>0.0184<br>0.0274<br>0.0275<br>0.0185<br>0.0185<br>0.0185<br>0.0185<br>0.0187<br>0.0174<br>0.0274<br>0.0275<br>0.0185<br>0.0187<br>0.0185<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0187<br>0.0174<br>0.0187<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0022<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.0174<br>0.01                                                                                                                                                                                                                                                                                                                                                                            | 2.0%<br>2.0%<br>2.0%<br>2.0%<br>2 < 0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>1.4%<br>16.2%<br>< 0.00001<br>1.9%<br>2.0%<br>2.4%<br>1.1%<br>1.9%<br>2.0%<br>0.7%<br>1.0%<br>0.9%<br>0.0%<br>0.0%<br>0.0%<br>0.0%<br>0.0%<br>0.0%<br>0                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2013<br>Van Kessel 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2004<br>Ace 2004<br>Ace 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tonini 1997                                                                                                   | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ df\\ Z=10.45\ (P<0.0000^{\circ})\\ 0.005\\ 0.5194\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4517\\ 0.4518\\ 0.418\\ 0.6329\\ 0.47\\ 0.4028\\ 0.18;\ Chi^2=104.15,\ df\\ Z=3.62\ (P=0.0003)\\ 0.3436\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.3148\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.5185\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5499\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5409\\ 0.8065\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5408\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 0.5608\\ 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                                                                                                                                                                                                                       | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000                                                                                                                            | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ dl\\ Z=10.45\ (P<0.0000\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 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                                                                                                                                                                                                                       | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.54 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \ l^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Subtotal (95% Cl)                                  | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05;\ Chi^2=106.95,\ dl\\ Z=10.45\ (P<0.0000\\ \end{array}$ $\begin{array}{c} 0.005\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.471\\ 0.4818\\ 0.6329\\ 0.471\\ 0.428\\ \end{array}$ $\begin{array}{c} 0.8242\\ 0.4818\\ 0.6329\\ 0.471\\ 0.428\\ \end{array}$ $\begin{array}{c} 0.18;\ Chi^2=104.15,\ dl\\ Z=3.62\ (P=0.003)\\ \end{array}$ $\begin{array}{c} 0.3436\\ 0.3436\\ 0.3448\\ 0.4194\\ 0.7372\\ 0.5068\\ 0.1196\\ 0.6331\\ 0.7885\\ 0.5499\\ 0.8065\\ 1.4061\\ \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | 0.1059<br>0.1059<br>0.149<br>0.149<br>= 27 (F<br>1)<br>0.0025<br>0.1682<br>0.1726<br>0.1808<br>0.1888<br>0.1726<br>0.2274<br>0.2357<br>0.2519<br>0.1912<br>0.0274<br>0.2274<br>0.2274<br>0.2274<br>0.2274<br>0.2274<br>0.2275<br>0.1695<br>0.1074<br>0.0298<br>0.1695<br>0.1675<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1607<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.2774<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1775<br>0.1                                                                                                                                                                                                                                                                                                                                                                          | 2.0%<br>2.0%<br>2.0%<br>2.0%<br>2<0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>1.4%<br>16.2%<br><0.00001<br>1.9%<br>2.0%<br>2.4%<br>1.1%<br>1.3%<br>6.9%<br>0.7%<br>1.0%<br>2.4%<br>1.1%<br>1.9%<br>2.0%<br>2.4%<br>1.1%<br>1.1%<br>1.1%<br>0.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (                                                                | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05; \ Chi^2 = 106.95, \ di\\ Z = 10.45 \ (P < 0.0000^{\circ})\\ \hline 0.005 \\ 0.5194\\ 0.4055\\ \hline 1.1725\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \hline 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.003\\ 0.8055\\ 0.5878\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 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                            | 0.1059<br>0.1059<br>0.149<br>0.149<br>1 = 27 (F<br>0.0025<br>0.1888<br>0.0582<br>0.1726<br>0.2357<br>0.2517<br>0.2519<br>0.1912<br>0.1025<br>1 = 9 (P<br>0.1085<br>0.1074<br>0.0027<br>0.1074<br>0.0227<br>0.1095<br>0.10174<br>0.0227<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10 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                                                                                                                                                                                                    | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2 | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05; \ Chi^2 = 106.95, \ di\\ Z = 10.45 \ (P < 0.0000^{\circ})\\ \hline 0.005 \\ 0.5194\\ 0.4055\\ \hline 1.1725\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \hline 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.003\\ 0.8055\\ 0.5878\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 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(P<br>0.1085<br>0.1074<br>0.0027<br>0.1074<br>0.0227<br>0.1095<br>0.10174<br>0.0227<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10                                                                                                                                                                                                                                                                                                                                                                                                                                | 2.0%<br>2.0%<br>2.0%<br>2.0%<br>2.0%<br>41.3%<br>2<0.0000<br>3.0%<br>0.7%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.5%<br>0.4%<br>0.7%<br>1.0%<br>2.4%<br>1.1%<br>6.9%<br>0.7%<br>1.3%<br>6.9%<br>0.7%<br>1.3%<br>6.9%<br>0.7%<br>1.3%<br>2.4%<br>1.1%<br>2.0%<br>2.4%<br>1.1%<br>2.0%<br>2.4%<br>1.1%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.0%<br>2.4%<br>2.4%<br>2.4%<br>2.4%<br>2.4%<br>2.4%<br>2.4%<br>2.4                                                                                                                                                                                                                                                                            | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$ $\begin{array}{c} 1.01 \left[ 1.00, 1.01 \right] \\ 1.68 \left[ 1.16, 2.43 \right] \\ 1.50 \left[ 1.10, 2.05 \right] \\ 3.23 \left[ 2.30, 4.53 \right] \\ 1.57 \left[ 1.10, 2.24 \right] \\ 2.28 \left[ 1.46, 3.56 \right] \\ 1.62 \left[ 1.02, 2.57 \right] \\ 1.88 \left[ 1.15, 3.09 \right] \\ 1.60 \left[ 1.10, 2.33 \right] \\ 1.50 \left[ 1.10, 2.33 \right] \\ 1.60 \left[ 1.10, 2.33 \right] \\ 1.69 \left[ 1.27, 2.24 \right] \\ 1.60 \left[ 1.26, 2.19 \right] \\ 1.13 \left[ 1.06, 1.20 \right] \\ 2.00 \left[ 1.35, 2.96 \right] \\ 2.20 \left[ 1.60, 3.03 \right] \\ 1.73 \left[ 1.22, 2.46 \right] \\ 2.24 \left[ 1.58, 3.17 \right] \\ 4.08 \left[ 1.18, 14.07 \right] \\ 1.80 \left[ 1.22, 2.70 \right] \\ 1.69 \left[ 1.42, 2.01 \right] \\ ); \  ^2 = 84\% \end{array}$ |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Aoe 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Subtotal (95% Cl)                                  | $\begin{array}{c} 0.47\\ 0.47\\ 0.47\\ 0.4318\\ \end{array}$ $\begin{array}{c} 0.05; \ Chi^2 = 106.95, \ di\\ Z = 10.45 \ (P < 0.0000^{\circ})\\ \hline 0.005 \\ 0.5194\\ 0.4055\\ \hline 1.1725\\ 0.4055\\ 0.4055\\ 0.4055\\ 0.4517\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4028\\ \hline 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.428\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.4028\\ 0.003\\ 0.8055\\ 0.5878\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.007; \ Chi^2 = 68.42, \ df = 0.0003\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 0.0005\\ 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                            | 0.1059<br>0.1059<br>0.149<br>0.149<br>1 = 27 (F<br>0.0025<br>0.1888<br>0.0582<br>0.1726<br>0.2357<br>0.2517<br>0.2519<br>0.1912<br>0.1025<br>1 = 9 (P<br>0.1085<br>0.1074<br>0.0027<br>0.1074<br>0.0227<br>0.1095<br>0.10174<br>0.0227<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10175<br>0.10                                                                                                                                                                                                                                                                                                                                                                                                                                | 2.0%<br>2.0%<br>2.0%<br>2.0%<br>2<0.0000<br>9.1%<br>0.7%<br>1.0%<br>0.9%<br>0.5%<br>0.4%<br>0.5%<br>0.4%<br>0.5%<br>1.4%<br>16.2%<br><0.00001<br>1.9%<br>2.0%<br>2.4%<br>1.1%<br>1.3%<br>6.9%<br>0.7%<br>1.0%<br>2.4%<br>1.1%<br>1.9%<br>2.0%<br>2.4%<br>1.1%<br>1.1%<br>1.1%<br>0.5%                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | $\begin{array}{c} 1.60 \left[ 1.30, 1.97 \right] \\ 1.60 \left[ 1.30, 1.97 \right] \\ 1.64 \left[ 1.15, 2.06 \right] \\ 1.67 \left[ 1.52, 1.84 \right] \\ 1); \  ^2 = 75\% \end{array}$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                       |
| Weide 2012<br>Weide 2013<br>Yamaguchi 2014<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.3 301-400<br>Du 2013<br>Escudier 2007<br>Hannisdal 1993<br>Motzer 2002<br>Motzer 2013<br>Poprach 2014<br>Saito 2007<br>Shinohara 2012<br>Shinohara 2012<br>Shinohara 2013<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2<br>1.4.4 >400<br>Ace 2005<br>Bedikian 2008<br>Cook 2006<br>Culp 2010<br>Feliu 2011<br>Giroux 2012<br>Schmidt 2007<br>Suh 2010<br>Tanrikulu 2010<br>Tonini 1997<br>Viganó 2000<br>Subtotal (95% Cl)<br>Heterogeneity: Tau <sup>2</sup> = (<br>Test for overall effect: 2 | $\begin{array}{c} 0.47\\ 0.47\\ 0.4318\\ 0.05; Chi^2 = 106.95, dt\\ Z = 10.45 (P < 0.0000\\ 0.5194\\ 0.4055\\ 1.1725\\ 0.4055\\ 1.1725\\ 0.4617\\ 0.8242\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.47\\ 0.4818\\ 0.6329\\ 0.4818\\ 0.6329\\ 0.4818\\ 0.6329\\ 0.4818\\ 0.6329\\ 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[1.46, 3.56]<br>2.28 [1.46, 3.56]<br>2.28 [1.46, 3.56]<br>1.60 [1.10, 2.33]<br>1.50 [1.10, 2.33]<br>1.60 [1.10, 2.33]<br>1.60 [1.10, 2.33]<br>1.60 [1.27, 2.24]<br>1.69 [1.27, 2.24]<br>1.69 [1.27, 2.24]<br>1.61 [1.26, 1.83]<br>2.09 [1.54, 2.84]<br>1.66 [1.26, 2.19]<br>1.13 [1.06, 1.20]<br>2.00 [1.35, 2.96]<br>2.20 [1.60, 3.03]<br>1.73 [1.22, 2.46]<br>2.24 [1.58, 3.17]<br>4.08 [1.18, 14.07]<br>1.80 [1.20, 2.70]<br>1.80 [1.20, 2.70]<br>1.80 [1.20, 2.70]<br>1.89 [1.42, 2.01]<br>); $ ^2 = 84\%$                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                       |

Figure 4 | Forest plots showing HRs by LDH cutoffs.

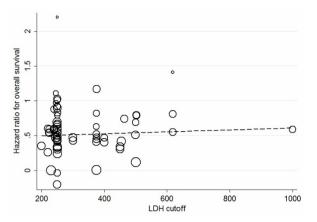


Figure 5 | Study-level (i.e., at the individual publication level) association of the cutoff used to define LDH and the HR for overall survival. Each study is represented by a circle, and the area of the circle proportional to the number of patients enrolled in each study. The gradient of the dashed line represents the results of the meta-regression ( $\beta = 1.000138$ ).

analyses. The use of ULN is less robust; however, this was the only feasible method with the data available. An internationally accepted and validated LDH cutoff is warranted.

In summary, our data suggest that pretreatment LDH is a simple, cost-effective prognostic factor that can be considered as a criterion to consider patients in different prognostic groups. LDH is also a potential predictive marker to guide individual therapy decisions in solid tumors. Further, adequate, multi-center prospective studies are required to explore the clinical utility of LDH in solid tumors.

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#### Author contributions

Conception and design: J.Z. and H.W. Collection and checking eligible studies included in the meta-analysis: J.Z. and Y.Y. Acquisition of data: J.Z. and Y.Y. Analysis of data: J.Z., Y.Y., B.L., Q.Y., P.Z. and H.W. Statistical analyses: J.Z., Y.Y. and B.L. Writing of manuscript: J.Z. and H.W. Preparation of tables and figures: B.L., Q.Y. and P.Z. All authors reviewed the manuscript.

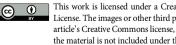
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