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ORIGINAL ARTICLE

Post-therapeutic response evaluation by a combination of endoscopy and CT scan in esophagogastric adenocarcinoma after chemotherapy: better than its reputation

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Abstract
Background Neoadjuvant chemotherapy is an accepted standard of care for locally advanced esophagogastric cancer. As only a subgroup benefits, a response-based tailored treatment would be of interest. The aim of our study was the evaluation of the prognostic and predictive value of clinical response in esophagogastric adenocarcinomas.
Methods Clinical response based on a combination of endoscopy and computed tomography (CT) scan was evaluated retrospectively within a prospective database in center A and then transferred to center B. A total of 686/740 (A) and 184/210 (B) patients, staged cT3/4, cN0/1 underwent neoadjuvant chemotherapy and were then re-staged by endoscopy and CT before undergoing tumor resection. Of 184 patients, 118 (B) additionally had an interim response assessment 4–6 weeks after the start of chemotherapy.
Results In A, 479 patients (70 %) were defined as clinical nonresponders, 207 (30 %) as responders. Median survival was 38 months (nonresponders: 27 months, responders: 108 months, log-rank, $p < 0.001$). Clinical and histopathological response correlated significantly ($p < 0.001$). In multivariate analysis, clinical response was an independent prognostic factor (HR for death 1.4, 95 %CI 1.0–1.8, $p = 0.032$). In B, 140 patients (76 %) were nonresponders and 44 (24 %) responded. Median survival was 33 months, (nonresponders: 27 months, responders: not reached,

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$p = 0.003$). Interim clinical response evaluation (118 patients) also had prognostic impact ($p = 0.008$). Interim, preoperative clinical response and histopathological response correlated strongly ($p < 0.001$).

Conclusion Preoperative clinical response was an independent prognostic factor in center A, while in center B its prognostic value could only be confirmed in univariate analysis. The accordance with histopathological response was good in both centers, and interim clinical response evaluation showed comparable results to preoperative evaluation.

Keywords Esophagogastric adenocarcinoma · Chemotherapy · Clinical response · Histopathological response · Response evaluation

Introduction

The standard treatment for locally advanced esophagogastric adenocarcinoma in Europe is either preoperative chemotherapy or chemoradiotherapy [1–3]. However, the majority of patients are nonresponsive [4]. Based on this information, response-based treatment stratification would be of utmost interest.

Despite an enormous number of studies about predictors of response and prognosis in esophagogastric adenocarcinomas, no molecular marker can be used in clinical routine to tailor treatment apart from HER2 expression in the palliative setting [5]. Three different types of response evaluation have been studied: morphological response evaluation by histopathology, metabolic response evaluation by functional imaging, and clinical response evaluation by conventional imaging modalities. Histopathological response is regarded as a reference method according to recent studies [6]. A clear disadvantage is that information about histopathological regression can only be achieved after resection, and thus can only be used as a prognostic marker. The use of the early metabolic response evaluation by FDG-PET is restricted as well, due to limitations of FDG-avidity in gastric cancer, the limited availability, and the missing validation in multicenter trials [7].

Clinical response evaluation was used to describe the effects of neoadjuvant treatment for more than 10 years; however, it is still not widely accepted as it is judged to be investigator dependent. Indeed, the data on clinical response assessment are conflicting: judgments range from calling it an important prognostic factor to regarding it as senseless information [8, 9]. One of the reasons for this uncertainty is that the association of clinical response with histopathological response is not well studied. Furthermore, clinical response evaluation can be performed at different time points with different criteria for response and after different treatment regimens (chemotherapy/chemoradiotherapy). Especially after chemoradiotherapy, the value of a restaging with computed tomography (CT) scan and/or endoscopic ultrasound seems to be limited, because discrimination between residual tumor and post-therapeutic changes (edema, scar) is difficult [8, 9,].

To dissolve some of the controversies in this field our exploratory study was aimed at evaluating clinical response in a large patient cohort with respect to later histopathological response and prognosis, with emphasis on the question of whether nonresponding patients can be identified by clinical response defined by a combination of CT scan and endoscopy.

The same clinical response assessment was sequentially applied in a second independent patient population. Additionally, in the second population, an interim response evaluation after 4–6 weeks of chemotherapy was performed and tested for its correlation with subsequent histopathological response, preoperative clinical response and prognosis.

Patients and methods

Out of 954 patients with esophagogastric adenocarcinomas (esophagus, gastroesophageal (GE) junction, stomach) treated with neoadjuvant chemotherapy, 860 patients with pretherapeutic and post-therapeutic CT scan and endoscopy followed by resection were included in this study. The initial tumor categories were cT3/4 and cN0/+. Data were documented in a prospective database.

We retrospectively analyzed 686 patients from the Klinikum Rechts-der-Isar, Technische Universität München, Germany between 1987 and 2007 (cohort A). For validation, we analyzed the data of corresponding patients ($n = 184$) of the Surgical Department, University of Heidelberg, Germany from 2007 to 2011 (cohort B). Additionally, in 118 patients of cohort B, an interim evaluation of clinical response after 4–6 weeks of chemotherapy was performed (Fig. 1).

Preoperative staging

Preoperative staging consisted of a CT scan as well as upper gastrointestinal endoscopy in all patients. Endoscopy and CT scan were repeated after the end of chemotherapy. In a subgroup of patients, an additional staging was done after 4–6 weeks of chemotherapy within study protocols (interim assessment).

Clinical response assessment

Clinical response was evaluated and standardized after chemotherapy, before surgery, by the respective interdisciplinary tumor boards.

A decrease of the maximal transversal primary tumor diameter of > 50 % measured on CT and a decrease of the

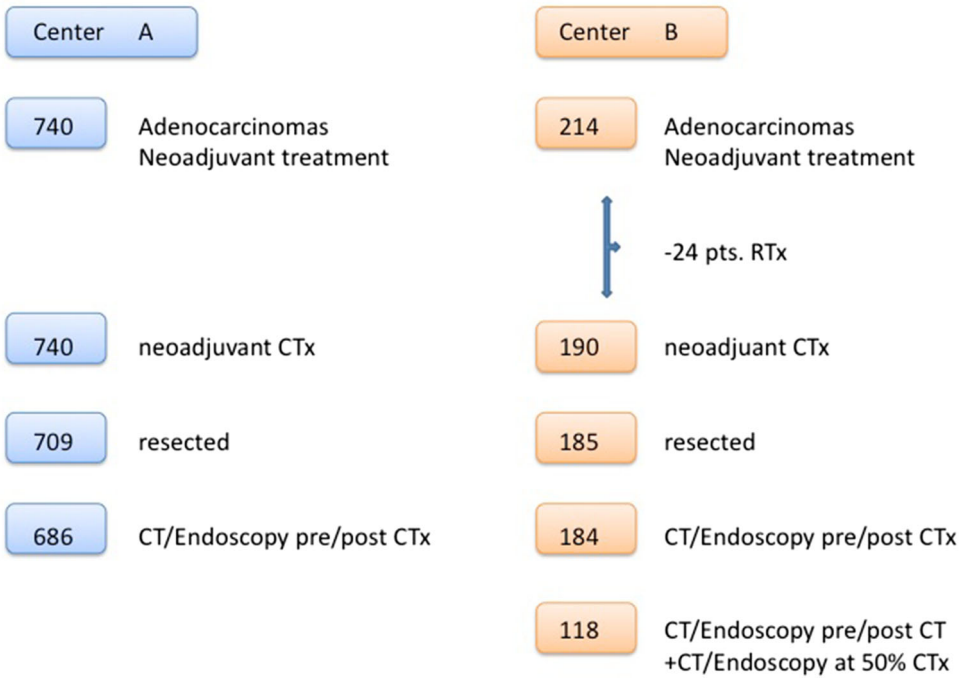

Fig. 1 Flow chart

endoluminal tumor size of >75 % as visualized by endoscopy were classified as clinical response [10]. Both criteria had to be fulfilled for being categorized as a clinical responder. These criteria have been used in previous studies. A detailed description of clinical response evaluation is presented in Supplemental Table 1.

Chemotherapy

Chemotherapy was performed with one of the following chemotherapy regimes: OLF/PLF, consisting of at least 6 weeks of either oxaliplatin 85 mg/m^2 or cisplatin 50 mg/m^2 on days 1, 15, 29 (1 h infusion time) and folinic acid (500 mg/m^2 over 2 h) plus fluorouracil (2000 mg/m^2 over 24 h) on days 1, 8, 15, 22, 29 and 36, all repeated on day 49. Patients aged 60 years or younger with a good health status were additionally given paclitaxel (80 mg/m^2 over 3 h) on days 0, 14 and 28.

In Heidelberg, most patients (63 %) were treated with EOX: epirubicin 50 mg/m^2 (day 1), oxaliplatin 130 mg/m^2 (day 1), and capecitabin 1,250 mg/m^2 (days 1–21), all repeated on day 22. Other delivered regimens were PLF (see above) and FLOT: oxaliplatin 85 mg/m^2 (day 1), docetaxel 50 mg/m^2 (day 1), folinacid 200 mg/m^2 (day 1), and 5-fluoruracil 2,600 mg/m^2 (day 1), all repeated on day 15.

Surgery

In patients with esophageal cancer, either an abdominothoracic approach with intrathoracic anastomosis including a two-field lymphadenectomy, or a transhiatal esophagectomy with cervical anastomosis was performed. In patients with carcinoma of the esophagogastric junction, we did a transhiatal extended gastrectomy and a D2-lymphadenectomy. For patients with tumor localization in the middle or distal third of the stomach, we performed a total gastrectomy with D2-lymphadenectomy, and for distal gastric tumors, a subtotal gastrectomy including a D2-lymphadenectomy.

Histopathological workup and regression analysis

Histopathological workup was done by pathologists experienced in upper gastrointestinal cancer. Tumors were classified according to the TNM classification 6th edition (Munich) and according to the TNM classification, 7th edition (Heidelberg). Regression was classified using the Becker regression score [11]: tumor regression grade (TRG) 1a (complete regression) and 1b (< 10 % residual tumor) are classified as histopathological response.

Follow-up

Most patients were followed on an outpatient basis of the Surgical Department, Klinikum Rechts der Isar, Munich or the National Center for Tumor Diseases, Heidelberg. Patients who were not followed in one of these departments were contacted by phone to obtain follow-up data.

Table 1 Patients' characteristics and prognostic factors (cohorts A and B)

Characteristics	*n*	%	Median (months)	3-Y-S (%)	5-Y-S (%)	*p*
(a) Cohort A						
Sex						
Male	548	80	39	52	42	0.118
Female	138	20	33	49	37	
Localization						
AEG I	221	32	44	54	43	0.207
AEG II	199	29	39	54	42	
AEG III	92	13	36	51	45	
Stomach	174	25	28	46	35	
Laurén						
Intestinal	348	51	55	59	50	<0.001
Non-int	318	47	28	44	32	
Grading						
Low grade	176	26	108	67	60	<0.001
High grade	496	72	31	46	34	
Clinical response						
No	479	70	27	43	33	<0.001
Yes	207	30	108	71	59	
Clinical response						
CR	0					<0.001
PR	206	30	108	71	59	
MR	240	35	27	43	35	
NC	219	32	32	45	32	
PD	21	3	9	5	0	
ypT						
ypT0	37	5	n.r.	80	76	<0.001
ypT1	56	8	n.r.	83	80	
ypT2	328	48	47	59	45	
ypT3	229	33	23	36	24	
ypT4	36	5	7	0	0	
ypN						
ypN0	263	38	108	72	62	<0.001
ypN1	271	40	32	46	33	
ypN2	90	13	23	34	22	
ypN3	62	9	12	11	11	
Lymphangiosis						
Yes	359	52	21	34	24	<0.001
No	326	48	102	67	57	
R-category						
R0	517	75	54	61	49	<0.001
R1	120	18	17	22	16	
R2	26	4	9	0	0	
Rx	23	3	27	49	37	
Histopathological response						
No	501	73	27	43	33	<0.001
Yes	177	26	n.r.	75	61	
TRG						
1a	36	5	n.r.	80	76	<0.001
1b	142	21	79	74	57	
2	170	25	40	54	40	
3	330	48	25	37	30	
(b) Cohort B						
Sex						
Male	150	82	31	47	43	0.829
Female	34	19	39	51	27	
Localization						
AEG I	49	26	29	43	34	0.987
AEG II	53	29	31	48	48	
AEG III	21	11	n.r.	57	57	
Stomach	61	33	30	49	35	
Laurén						
Intestinal	104	57	34	49	42	0.803
Non-int	73	40	39	51	39	
Grading						
Low grade	54	29	24	45	39	0.159
High grade	128	70	34	49	40	
Clinical response						
No	140	76	27	38	33	0.003
Yes	44	24	n.r.	74	58	
Clinical response						
CR	0					0.003
PR	44	24	n.r.	74	58	
MR	75	41	33	48	36	
NC	60	33	20	28	28	
PD	4	2	24	25	0	
Interim response						
No	88	72	27	40	33	0.008
Yes	30	28	n.r.	74	62	
ypT						
ypT0	20	11	44	71	42	0.004
ypT1	11	6	30	42	0	
ypT2	21	11	n.r.	69	69	
ypT3	110	60	29	44	40	
ypT4	22	12	16	21	21	
ypN						
ypN0	72	39	n.r.	67	65	<0.001
ypN1	37	20	24	35	29	
ypN2	36	20	25	39	26	
ypN3	23	13	24	28	28	
R-category						
R0	141	77	44	55	44	0.002
R1	37	20	19	28	28	
R2	6	3	24	20	20	

Table 1 continued

Characteristics	*n*	%	Median (months)	3-Y-S (%)	5-Y-S (%)	*p*
Regression						
1a	19	10	44	69	40	0.312
1b	14	8	31	49	49	
2	44	24	n.r.	55	55	
3	107	58	26	42	36	

3-Y-S 3-year-survival, *5-Y-S* 5-year-survival, *non-int* non-intestinal, *low grade* G1/2, *high grade* G3/4, *CR* complete response, *PR* partial response, *MR* minor response, *NC* no change, *PD* progressive disease, *TRG* tumor regression grade, *n.r.* not reached

Statistical analysis

SPSS 17.0 (IBM, Inc. Chicago) was used for statistical analysis. Median survival times were calculated using the Kaplan–Meier method. Survival times are counted in months from time of diagnosis to death, differences were determined with the log-rank test. Univariate and multivariate analysis was done by Cox stepwise proportional hazard model. To determine the correlation between different parameters, we used the Chi square-test, and Spearman correlation coefficients were calculated to quantify bivariate correlations. For diagnostic value of clinical response with respect to histopathological response and R0-resection, we calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV). A p value of less than 0.05 was considered as statistically significant.

Results

A total of 860 patients from two centers were included in the study.

Cohort A (Munich)

686 patients (548 male, 138 female) were included, with a median follow-up of the surviving patients of 51 months (5–204); 356 patients (52 %) died during follow-up. Median survival of the overall population was 40 months.

Clinical response was present in 207 patients (30 %). Median survival of this subgroup was 108 months with a 3-year and 5-year survival of 71 % and 59 %, respectively. In contrast, patients without clinical response to chemotherapy ($n = 479$, 70 %) had a median survival of 27 months (3-year and 5-year survival, 43 and 33 %, respectively) (Table 1a) (Fig. 2). One hundred and seventy-seven patients (26 %) were histopathological responders. The median survival of responders is not reached, in contrast to a median survival of 27 months of histopathologically nonresponding patients ($p < 0.001$).

All patients' characteristics of cohort A, including survival times and 3-year and 5-year survival rates, are summarized in Table 1a.

Association of clinical response with histopathological response and R-category

The accuracy between clinical response and histopathological tumor regression was 85 % for nonresponders and 52 % for responders (Chi square, $p < 0.001$). Sensitivity for predicting a histopathological response was 60.5 %, specificity 80.2 %, PPV 51.9 % and NPV 85.2 %. Clinical response also correlated significantly with an R0 resection status (Chi square, $p < 0.001$), Sensitivity 35.7 %, Specificity 87.0 %, PPV 89.4, NPV 30.7 % (Table 2).

Impact of tumor localization on response evaluation

Clinical response was statistically significant for prognosis in all localizations, whereas histopathological regression was only significant in AEG I and II. Response rates and prognostic impact decreased from proximal to distal (Table 3).

Impact of the respective time periods on response evaluation

Clinical and histopathological responses were both stable prognostic factors over the different time periods (Table 4).

Multivariate analysis

Multivariate analysis (forward conditional hazard model) included grading, Laurén's subtype, clinical response, ypT-category, ypN-category, R-category, lymphangiosis and TRG. Clinical response was an independent prognostic factor (Nonresponse: HR for death 1.4, 95 % CI 1.0–1.8, $p = 0.032$). Other independent factors were R-category, lymphangiosis carcinomatosa, ypT-category and ypN-category (each $p < 0.001$) (Table 5).

Chemotherapy regimens

447 patients (65.2 %) of the patients were treated with a platinum containing chemotherapy, 137 patients (20.0 %) received additionally taxanes, 54 patients (7.9 %) received additionally epirubicine and 48 patients (6.9 %) received various regimen. Taxanes-containing regimens had the longest survival (median 108.0 months), followed by platinum based regimens (37.2 months) and others (34.0 months). The shortest survival could be observed

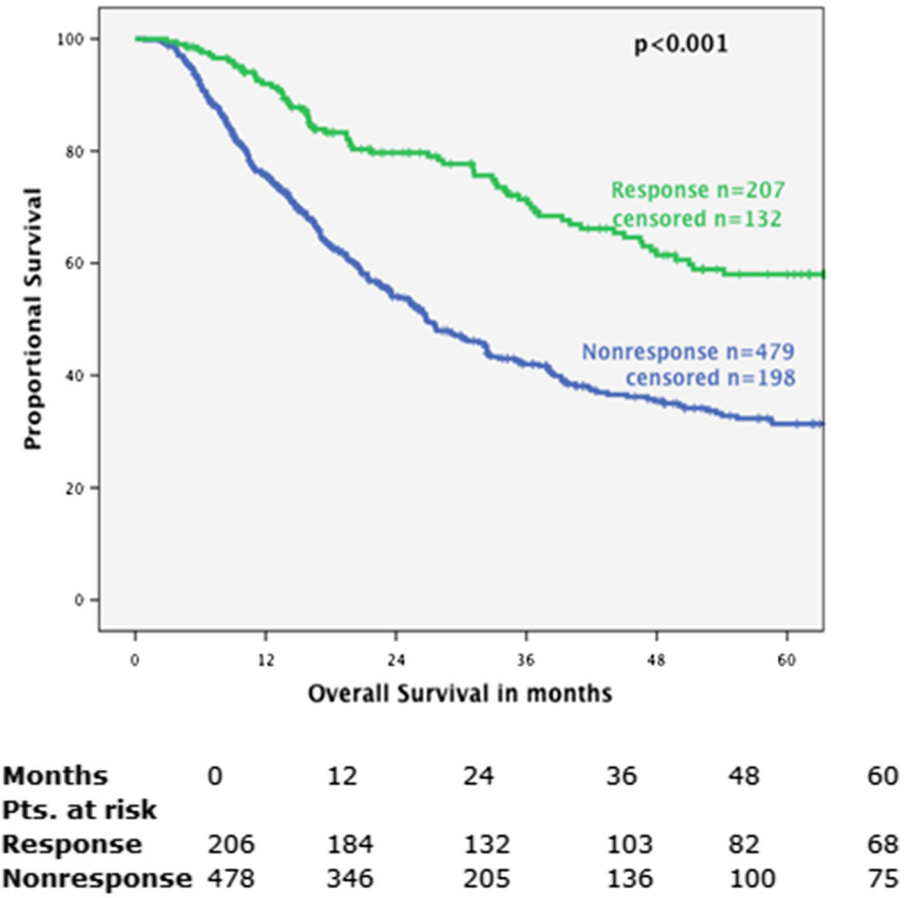

Fig. 2 Clinical response and survival in center A

Table 2 Correlation between clinical response and histopathological tumor regression, correlation between clinical response and R-category (cohort A)

Histopathological regression	Clinical response		*p*	Spearman
	No ($n = 472$)	Yes ($n = 206$)		
No ($n = 501$)	402 (85 %)	99 (48 %)	<0.001	0.389
Yes ($n = 177$)	70 (15 %)	107 (52 %)		
R-category	Clinical response		*p*	Spearman
	No ($n = 479$)	Yes ($n = 207$)		
R0 ($n = 517$)	332 (69 %)	185 (89 %)	<0.001	−0.214
R1/2 ($n = 169$)	147 (31 %)	22 (11 %)		

after treatment with epirubicin (19.5 months) ($p < 0.001$). The type of chemotherapy did not correlate with clinical or histopathological response.

Cohort B (Heidelberg)

One hundred and eighty-four patients (150 male, 34 female) were analyzed with a median follow-up of 29 months of the surviving patients. Eighty-two patients (45 %) died during follow-up, median survival was 33 months.

Clinical response was evident in 24 %. The median survival was not reached in clinical responders in contrast to 27 months in nonresponders ($p = 0.003$) (Fig. 3). In contrast to cohort A, TRG was not significantly associated with survival ($p = 0.312$) (Table 1b).

Association of standard preoperative and interim clinical response evaluation

An interim response evaluation was performed in 118 patients. 72 % were classified as nonresponders, 27 % as

Table 3 Prognostic impact of clinical response with respect to tumor localization

	n	Median	3-Y-S (%)	5-Y-S (%)	*p*
Clinical response					
AEG I					
No	143	27	44	34	0.001
Yes	78	108	69	57	
AEGII					
No	123	32	42	33	<0.001
Yes	76	102	75	59	
AEGIII					
No	66	26	42	36	0.005
Yes	26	88	75	67	
Stomach					
No	147	25	43	31	0.028
Yes	27	78	63	58	
Histopathologicalresponse					
AEG I					
No	157	30	47	35	<0.001
Yes	57	n.r.	76	66	
AEGII					
No	136	28	40	27	<0.001
Yes	63	n.r.	81	72	
AEGIII					
No	69	31	47	42	0.173
Yes	23	n.r.	65	52	
Stomach					
No	139	24	39	33	0.11
Yes	34	44	70	40	

3-Y-S 3-year-survival, *5-Y-S* 5-year-survival, *n.r.* not reached

responders. The percentage of concordant cases as determined by interim and standard preoperative evaluation was 94 % for responders and 93 % for nonresponders ($p < 0.001$). Two patients were first classified as responders and later as nonresponders (2 %), five patients were first classified as nonresponders, and later as responders (4 %) (Table 6). Sensitivity of interim response evaluation with respect to preoperative evaluation was 84.4 %, Specificity 97.6 %, PPV 93.3 %, and NPV was 94.3 %. Interim response was also significantly associated with survival ($p = 0.008$) (Table 1b).

Association of clinical response with histopathological response and R-category

Correct prediction of histopathological response was 92 % for nonresponding patients and 50 % for responding patients ($p < 0.001$), Sensitivity with respect to histopathological response was 66.7 %, Specificity 85.4 %, PPV 50 %, and NPV was 92.1 %.

98 % of clinical responders had a R0-resection compared to only 70 % of nonresponders ($p < 0.001$), Sensitivity with respect to R0-resection was 30.5 %, Specificity 85.4 %, PPV 97.8 %, and NPV was 30.0 % (Table 6).

Multivariate Analysis

Significant factors (included factors: clinical response, ypT-category, ypN-category, R-category) were ypT- ($p = 0.015$) and ypN-category ($p < 0.001$). Clinical response failed to reach statistical significance ($p = 0.536$).

Chemotherapy regimen

In the Heidelberg cohort, 25 patients (17.1 %) had platinum-based regimens, 112 patients (76.6 %) additionally had epirubicin, and eight (5.5 %) additionally had taxanes, while one patient received a different chemotherapy. The type of chemotherapy did not influence survival ($p = 0.360$), but patients having been treated with platinum containing chemotherapy had a significantly higher clinical response rate (48 versus 37.5 % with taxanes and 19.6 % with epirubicine, $p = 0.022$), and no association was found for histopathological response.

Table 4 Prognostic impact of clinical and histopathological responses with respect to the different time periods

	n	Median	3-Y-S (%)	5-Y-S (%)	*p*
Clinical response					
1987–1991					
No	27	16	15	10	0.002
Yes	8	n.r.	88	63	
1992–1996					
No	71	22	34	27	<0.001
Yes	31	n.r.	71	61	
1997–2002					
No	168	25	39	30	<0.001
Yes	78	102	73	57	
2003–2007					
No	213	48	56	40	0.032
Yes	90	n.r.	68	68	
Histopathological response					
1987–1991					
No	19	15	11	5	0.003
Yes	13	41	62	44	
1992–1996					
No	74	23	38	31	0.032
Yes	25	78	68	56	
1997–2002					
No	182	26	41	31	<0.001
Yes	63	n.r.	76	61	
2003–2007					
No	226	39	51	41	<0.001
Yes	76	n.r.	82	66	

3-Y-S 3-year-survival, *5-Y-S* 5-year-sruvival, *n.r.* not reached

Table 5 Multivariate analysis (forward conditional hazard model)

Variable	Category	HR for death	95 % CI	*p*
Clinical response	Response	Reference		0.032
	Nonresponse	1.4	1.02–1.8	
ypT	ypT0	0.2	0.07–0.43	<0.001
	ypT1	0.1	0.05–0.29	
	ypT2	0.3	0.2–0.47	
	ypT3	0.5	0.3–0.67	
	ypT4	Reference		
ypN	ypN0	0.4	0.25–0.56	
	ypN1	0.5	0.38–0.75	
	ypN2	0.5	0.34–0.72	
	ypN3	Reference		
Lymphangiosis	No	0.7	0.5–0.9	<0.001
	Yes	Reference		
R-category	R0	Reference		
	R1	1.5	1.14–1.98	<0.001
	R2	2.8	1.7–4.7	
	Rx	1.2	0.61–2.18	

HR hazard ratio

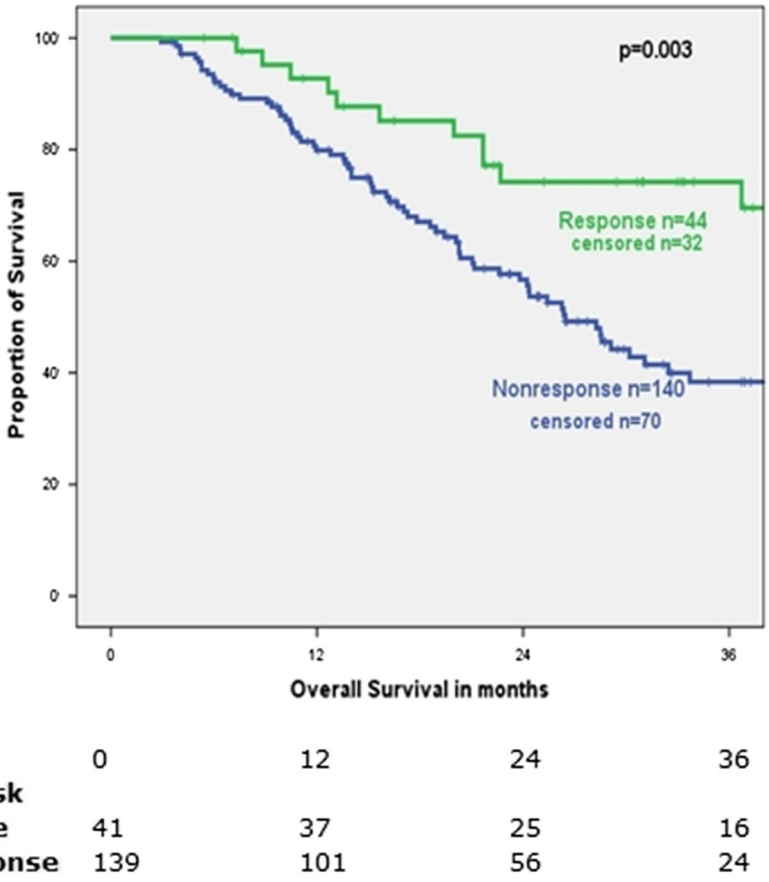

Fig. 3 Clinical response and survival in center B

Table 6 Correlation between interim clinial response and standard clinical response, correlation between clinical response and histopathological tumor regression, correlation between clinical response and R-category (cohort B)

Standard clinical response	Clinical response (interim)		*p*	Spearman
	No ($n = 88$)	Yes ($n = 30$)		
No ($n = 85$)	83 (94 %)	2 (7 %)	<0.001	0.85
Yes ($n = 33$)	5 (6 %)	28 (93 %)		
Histopathological regression	Clinical response (standard)		*p*	Spearman
	No ($n = 140$)	Yes ($n = 44$)		
No ($n = 151$)	129 (92 %)	22 (50 %)	<0.001	0.469
Yes ($n = 33$)	11 (8 %)	22 (50 %)		
R-category	Clinical response (standard)		*p*	Spearman
	No ($n = 140$)	Yes ($n = 44$)		
R0 ($n = 141$)	98 (70 %)	43 (98 %)	<0.001	−0.279
R1/2 ($n = 43$)	42 (30 %)	1 (2 %)		

Discussion

Clinical response to preoperative chemotherapy was assessed as a combination of endoscopy and CT scan in a large patient series in two academic centers. It was shown that clinical response assessment is feasible and that it has a strong correlation with histopathological response and survival. Even an interim response evaluation seems to have a significant prognostic impact.

Of note, the goal of this study was not mainly to correctly identify patients with a complete histopathological response, but instead to test the hypothesis that nonresponse and poor prognosis can be assessed by clinically available tools. A major limitation of our study is its retrospective exploratory design, despite the clinical response assessment being documented prospectively and preoperatively without knowledge of the final histopathological workup. Furthermore, no separate documentation of results of endoscopy and CT scan are available, so the accuracy of the different staging methods cannot be analyzed. Detailed data were documented only for subgroups [10]. Additionally, no interobserver variability can be reported, since clinical response was evaluated in an interdisciplinary tumor board. Another drawback is the limited number of patients who had interim clinical response evaluation. It could also be criticized that AEG I, II, III tumors and gastric cancer were analyzed together, as studies showed that these different subtypes may have a different prognosis [12]. Nevertheless, we think that an analysis within all patients with esophagogastric adenocarcinoma is justified. Like in the MAGIC trial, these different tumor localizations are often treated following the same principles [1, 2], and in most centers the treatment regimens do not differ at the moment, and patients with chemoradiotherapy were excluded [3].

Only in the Munich subgroup did chemotherapy regimens have influence on prognosis. Patients treated additionally with taxanes had the best prognosis, which is in line with literature [13–15]. However, in the neoadjuvant setting, no superiority could be shown for taxanes [16], and no randomized data are available so far. The association of merely platinum-based regimens with clinical response might be influenced by the small subgroups, because normally, higher response rates are expected for triple chemotherapy regimens, especially for taxane-containing regimens [17–21].

Our subgroup analysis showed a decreasing response rate and prognostic impact from proximal to distal, similar to recent published data [12]. However clinical response remained statistically significant in all localizations, in contrast to histopathological regression.

It was often assumed that clinical response assessment is too investigator dependent, and therefore results may not be reliable enough in unexperienced hands. We cannot rule out that this is true, as three experienced investigators (L.F., B.M., O.K.) were identical in both centers and their experience and methodology were transferred from center A to B in 2007. Nevertheless, the combined data from widely available diagnostic tools (CT and endoscopy) are very promising. The correct prediction of a histopathological response remains difficult, but the correct prediction of a histopathological nonresponse was high, with 85 % in center A and 92 % in center B. Furthermore, 94.3 % of the clinical nonresponders after interim assessment remained nonresponder after the end of the full chemotherapy. Consequently, a later response to chemotherapy seems to be rare and one may assume that identification of nonresponse by interim assessment is possible. Future studies should test the hypothesis that if ineffective chemotherapy is withdrawn early or modified, prognosis is not impaired.

Clinical response was strongly associated with prognosis in both centers. The prognosis of clinical responders despite low association with final histopathological response was excellent, with 108 months median in center A and not reached in center B, and the prognosis of nonresponders was nearly identical with 27 months and 27 months, respectively. This points out that histopathological response is only one of the potentially available surrogate parameters for prognosis [4, 22], despite that it is judged as the gold standard to date. However, up to 30 % of the histopathological responders die due to recurrence [4, 22]. The rate of clinical response was not high, but realistic with a percentage of 30 and 24 %, which reflects the data obtained for histopathological response after chemotherapy [6].

In a study by the Cologne group [8], 32 % of the patients were estimated as complete responders after chemoradiotherapy, and 35 % as partial responders. This seems to be overestimated and might explain the missing predictive value for histopathological response and prognosis within this particular study.

In the last two decades, the simple clinical response evaluation was almost abandoned and all efforts were put into molecular and metabolic response evaluation or prediction [7, 23–25]. Despite all efforts, no molecular marker gained relevance in the preoperative setting to tailor treatment. Only for FDG-PET in AEG I and II was a metabolic response based treatment algorithm shown to be feasible and meaningful in prospective studies [24–26]. However, the value of FDG-PET has not yet been reproduced in multicenter trials. Only few studies on clinical response evaluation exist so far. They were mostly retrospective, included small patient numbers and produced conflicting results. Most studies were designed to predict a complete histopathological response and failed [8]. They concluded that clinical response evaluation after preoperative chemoradiotherapy in esophageal cancer had no place in clinical practice, and no patient with complete response should be harmed by denying a surgical resection due to an accuracy of only 47 % for a subsequent histopathological complete response [8]. As mentioned, our intention was different, and for our purpose, clinical response seems to be feasible. Additionally, our evaluation was after chemotherapy only, which might minimize treatment-related changes like fibrosis or inflammation, and might render response evaluation more accurate. The interim clinical response evaluation may not be possible as early as by FDG-PET after 2 weeks [23–25], but seems to be realistic after 4–6 weeks.

To exclude a relevant bias caused by technical development over time, we analyzed the prognostic impact of response during the different time periods. We found clinical response to be a stable predictor of prognosis.

Our criteria for response may also be discussed, as they are mainly based on the former World Health Organization (WHO) classification, not on the Response Evaluation Criteria In Solid Tumors (RECIST) criteria. We aimed to keep the evaluation as simple as possible and continue with established criteria [7, 23, 27]. Overall, our criteria are in line with the published standard criteria [28]. The largest wall diameter in CT scan as a predictor for response after preoperative therapy has been proven to have prognostic relevance in other studies [29]. In contrast, more technically demanding volume-based evaluations by CT scan have rarely been studied and show conflicting results after 2 weeks of therapy [30, 31]. Admittedly, in endoscopy, despite our attempt of quantification, no exact measurement is possible and the results could be biased based on the experience of the endoscopist. However, endoscopic response has also shown to be of prognostic relevance in the literature [7, 23, 32].

Although clinical response evaluation has taken a back seat for more than two decades, our data based on a combination of endoscopy and CT scan are very promising. Clinical response has been shown to be significantly associated with histopathological response and with survival. Especially nonresponding patients can be identified with high accuracy. Additionally, an interim clinical response evaluation seems to be feasible, which might allow for a tailored preoperative treatment algorithm in the future for patients with esophagogastric adenocarcinomas.

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References

1. Cunningham D, Allum W, Stenning S, Thompson J, Van de Velde C, Nicolson M, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
2. Ychou M, Boige V, Pignon JP, Conroy T, Bouché O, Lebreton G, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715–21.
3. van Hagen P, Hulshof MC, van Lanschot JJ, Steyerberg EW, van Berge Henegouwen MI, Wijnhoven BP, et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. N Engl J Med. 2012;366(22):2074–84.
4. Fields RC, Strong VE, Gönen M, Goodman KA, Rizk NP, Kelsen DP, et al. Recurrence and survival after pathologic complete response to preoperative therapy followed by surgery for gastric or gastrooesophageal adenocarcinoma. Br J Cancer. 2011;104(12):1840–7.
5. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.
6. Becker K, Langer R, Reim D, Novotny A, Meyer zum Buschenfelde C, Engel J, et al. Significance of histopathological tumor regression after neoadjuvant chemotherapy in gastric adenocarcinomas a summary of 480 cases. Ann Surg. 2011;253(5):934–9.
7. Weber WA, Ott K, Becker K, Dittler HJ, Helmberger H, Avril NE, et al. Prediction of response to preoperative chemotherapy in adenocarcinomas of the esophagogastric junction by metabolic imaging. J Clin Oncol. 2001;19(12):3058–65.
8. Schneider PM, Metzger R, Schaefer H, Baumgarten F, Vallbohmer D, Brabender J, et al. Response evaluation by endoscopy, rebiopsy, and endoscopic ultrasound does not accurately predict histopathologic regression after neoadjuvant chemoradiation for esophageal cancer. Ann Surg. 2008;248(6):902–8.
9. Owaki T, Matsumoto M, Okumura H, Uchicado Y, Kita Y, Setoyama T, et al. Endoscopic ultrasonography is useful for monitoring the tumor response of neoadjuvant chemoradiation therapy in esophageal squamous cell carcinoma. Am J Surg. 2012;203(2):191–7.
10. Heger U, Bader F, Lordick F, Burian M, Langer R, Dobritz M, et al. Interim endoscopy results during neoadjuvant therapy for gastric cancer correlate with histopathological response and prognosis. Gastric Cancer2013 Sep.
11. Becker K, Mueller J, Schulmacher C, Ott K, Fink U, Busch R, et al. Histomorphology and grading of regression in gastric carcinoma treated with neoadjuvant chemotherapy. Cancer. 2003;98(7):1521–30.
12. Reim D, Gertler R, Novotny A, Becker K, Büschenfelde CM, Ebert M, et al. Adenocarcinomas of the esophagogastric junction are more likely to respond to preoperative chemotherapy than distal gastric cancer. Ann Surg Oncol. 2012;19(7):2108–18.
13. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, et al. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006;24(31):4991–7.
14. Al-Batran SE, Hartmann JT, Hofheinz R, Homann N, Rethwisch V, Probst S, et al. Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol. 2008;19(11):1882–7.
15. Homann N, Pauligk C, Luley K, Werner Kraus T, Bruch HP, Atmaca A, et al. Pathological complete remission in patients with oesophagogastric cancer receiving preoperative 5-fluorouracil, oxaliplatin and docetaxel. Int J Cancer. 2012;130(7):1706–13.
16. Bader FG, Lordick F, Fink U, Becker K, Hofler H, Busch R, et al. Paclitaxel in the neoadjuvant treatment for adeno carcinoma of the distal esophagus (AEG I). A comparison of two phase II trials with long-term follow-up. Onkologie. 2008;31(7):366–72.
17. Ott K, Sendler A, Becker K, Dittler H, Helmberger H, Busch R, et al. Neoadjuvant chemotherapy with cisplatin, 5-FU, and leucovorin (PLF) in locally advanced gastric cancer: a prospective phase II study. Gastric Cancer. 2003;6(3):159–67.

18. Lorenzen S, Hentrich M, Haberl C, Heinemann V, Schuster T, Seroneit T, et al. Split-dose docetaxel, cisplatin and leucovorin/fluorouracil as first-line therapy in advanced gastric cancer and adenocarcinoma of the gastroesophageal junction: results of a phase II trial. Ann Oncol. 2007;18(10):1673–9.
19. Ajani JA, Fodor MB, Tjulandin SA, Moiseyenko VM, Chao Y, Cabral Filho S, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. J Clin Oncol. 2005;23(24):5660–7.
20. Roth AD, Fazio N, Stupp R, Falk S, Bernhard J, Saletti P, et al. Docetaxel, cisplatin, and fluorouracil; docetaxel and cisplatin; and epirubicin, cisplatin, and fluorouracil as systemic treatment for advanced gastric carcinoma: a randomized phase II trial of the Swiss Group for Clinical Cancer Research. J Clin Oncol. 2007;25(22):3217–23.
21. Thuss-Patience PC, Hofheinz RD, Arnold D, Florschütz A, Daum S, Kretzschmar A, et al. Perioperative chemotherapy with docetaxel, cisplatin and capecitabine (DCX) in gastro-oesophageal adenocarcinoma: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO){dagger}. Ann Oncol. 2012;23(11):2827–34.
22. Vallböhmer D, Hölscher AH, DeMeester S, DeMeester T, Salo J, Peters J, et al. A multicenter study of survival after neoadjuvant radiotherapy/chemotherapy and esophagectomy for ypT0N0M0R0 esophageal cancer. Ann Surg. 2010;252(5):744–9.
23. Ott K, Fink U, Becker K, Stahl A, Dittler H, Busch R, et al. Prediction of response to preoperative chemotherapy in gastric carcinoma by metabolic imaging: results of a prospective trial. J Clin Oncol. 2003;21(24):4604–10.
24. Ott K, Weber W, Lordick F, Becker K, Busch R, Herrmann K, et al. Metabolic imaging predicts response, survival, and recurrence in adenocarcinomas of the esophagogastric junction. J Clin Oncol. 2006;24(29):4692–8.
25. Lordick F, Ott K, Krause BJ, Weber WA, Becker K, Stein HJ, et al. PET to assess early metabolic response and to guide treatment of adenocarcinoma of the oesophagogastric junction: the MUNICON phase II trial. Lancet Oncol. 2007;8(9):797–805.
26. Zum Büschenfelde CM, Herrmann K, Schuster T, Geinitz H, Langer R, Becker K, et al. (18)F-FDG PET-guided salvage neoadjuvant radiochemotherapy of adenocarcinoma of the esophagogastric junction: the MUNICON II trial. J Nucl Med. 2011;52(8):1189–96.
27. Helmberger H, Baum U, Dittler HJ, Sendler A, Schulte B, Herter B, et al. Adenocarcinoma of the gastro-esophageal junction: CT for monitoring during neoadjuvant chemotherapy. Eur J Radiol. 1996;23(2):107–10.
28. Therasse P. Center EOfRaToCD. Evaluation of response: new and standard criteria. Ann Oncol. 2002;13(Suppl 4):127–9.
29. Swisher SG, Maish M, Erasmus JJ, Correa AM, Ajani JA, Bresalier R, et al. Utility of PET, CT, and EUS to identify pathologic responders in esophageal cancer. Ann Thorac Surg. 2004;78(4):1152–60 discussion-60.
30. Beer AJ, Wieder HA, Lordick F, Ott K, Fischer M, Becker K, et al. Adenocarcinomas of esophagogastric junction: multidetector row CT to evaluate early response to neoadjuvant chemotherapy. Radiology. 2006;239(2):472–80.
31. van Heijl M, Phoa SS, van Berge Henegouwen MI, Omloo JM, Mearadji BM, Sloof GW, et al. Accuracy and reproducibility of 3D-CT measurements for early response assessment of chemoradiotherapy in patients with oesophageal cancer. Eur J Surg Oncol. 2011;37(12):1064–71.
32. Lim JT, Truong PT, Berthelet E, Pai H, Joe H, Wai E, et al. Endoscopic response predicts for survival and organ preservation after primary chemoradiotherapy for esophageal cancer. Int J Radiat Oncol Biol Phys. 2003;57(5):1328–35.