Gastric Cancer (2015) 18:11–22
DOI 10.1007/s10120-014-0388-5

REVIEW ARTICLE

A systematic review and meta-analysis of gastric cancer treatment in patients with positive peritoneal cytology

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Received: 13 November 2013 / Accepted: 2 May 2014 / Published online: 3 June 2014

Abstract Gastric cancer patients with positive peritoneal cytology as the only marker of metastatic disease have poor prognoses. There is no universal consensus on the most appropriate treatment regimen for this particular patient group. We reviewed and analyzed published data to determine the optimal treatment regimen for patients with peritoneal cytology-positive gastric adenocarcinomas. Six electronic databases were explored [PubMed, Cochrane (Systematic Reviews and Controlled Trials), PROSPERO, DARE, and EMBASE]. The primary outcome was overall survival with secondary outcomes including patterns of recurrence and treatment-related morbidity. Six studies were included for data extraction. There was no significant heterogeneity between studies. The use of S1 monotherapy was associated with a significant survival benefit (HR 0.48; 95 % CI 0.32–0.70; $p = 0.0002$). Intraoperative intraperitoneal chemotherapy (IIPC) with adjuvant chemotherapy showed a trend toward improvement in overall survival (HR 0.70; 95 % CI 0.47–1.04; $p = 0.08$). A recent randomized controlled trial examining extensive intraperitoneal lavage (EIPL) with IIPC showed a significant improvement in overall survival (5-year overall survival, 43.8 % for EIPL-IPC group compared with 4.6 % for IPC group). However, these promising results need to be validated in larger prospective randomized trials.

Keywords Peritoneal cytology · Gastric cancer · Intraperitoneal chemotherapy · Extensive intraperitoneal lavage

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Introduction

Gastric adenocarcinoma is the fourth most common cancer and the second leading cause of cancer death worldwide [1]. Apart from countries with national screening programs such as Japan and Korea, most gastric cancer patients present with advanced disease because early-stage tumors are usually asymptomatic. Routine staging of gastric adenocarcinomas consists of esophagogastroscopy and computerized tomography (CT) of the chest, abdomen, and pelvis. Endoscopic ultrasound (EUS) is used selectively in patients with early-stage tumors to determine if endoscopic resection is feasible or whether neoadjuvant therapy is warranted. Laparoscopy and peritoneal cytology have been shown to detect occult metastatic disease not seen on conventional imaging [1–4].

Gastric cancer patients with evidence of macroscopic peritoneal carcinomatosis have very poor prognoses, with a median overall survival of 3–6 months [5]. Those with only microscopic metastatic peritoneal disease, detected by the presence of malignant cells in peritoneal washout, also have dismal long-term outcomes, with 5-year survival rates ranging from 0 % to 18 %, with the majority succumbing to peritoneal recurrence within 2 years [2].

Currently, there is no established consensus to direct treatment for patients with positive peritoneal cytology (PPC) as the only marker of metastatic gastric adenocarcinoma. The aim of this systematic review is to investigate the following four modalities of treatment (and their possible additional benefit to standard treatment) as well as their role in the management of patients with PPC-only disease: (1) extensive intraperitoneal lavage (EIPL); (2) intraoperative intraperitoneal chemotherapy (IIPC); (3) oral S-1 chemotherapy; and (4) neoadjuvant chemotherapy with curative resection.

Methods

Database search

An electronic search of PubMed was conducted from January 1, 1990 to January 31, 2014 using the search strategy as outlined in the Appendix. Our search strategy consisted of combining the medical subject headings (MeSH) terms as well as using the standard PubMed syntax: "stomach neoplasm/" AND ("peritoneal lavage/" OR "positive peritoneal cytology.tw" OR "intraperitoneal free cancer cells.tw") NOT [(gastrointestinal stromal tum$).tw OR GIST.tw]. We included only those studies in relationship to "humans" and limited to the English, Mandarin, and Japanese languages. Additionally, a separate search of the following databases was performed: Cochrane Database of Systematic Reviews, Cochrane Register of Controlled Trials, Embase, International Prospective Register of Systematic Reviews (PROSPERO), and Database of Abstracts of Reviews of Effectiveness (DARE).

Selection criteria

The inclusion criteria for the studies were as follows: (1) patients with histologically proven gastric adenocarcinoma who underwent staging laparoscopy and peritoneal cytology; and (2) of those patients who underwent peritoneal washouts, we reviewed overall survival of those patients who had positive peritoneal cytology as the only marker of advanced disease and their treatment regimens. We excluded any studies from our search based on the following criteria: (1) we were unable to extract the overall survival of those patients exclusively with positive peritoneal cytology; or (2) patients with gastrointestinal stromal tumors (GIST) or patients with synchronous cancer; or (3) investigators did not provide baseline characteristics and the overall survival of a control or comparison group. Additionally, we did not impose restrictions on gender, age, or ethnicity. The studies examined were limited to the English, Japanese, and Mandarin languages and used only if the full text was available for analysis. We perused the reference lists of pertinent review articles, presentations, or congress proceedings for other articles that fulfill the inclusion criteria.

Analysis of studies

The primary investigator of this study (C.C.) reviewed each of the included articles in English independently from the other two investigators (S.C. and C.D.). The second investigator (Y.K.) reviewed selected Japanese studies and articles for inclusion in this study. A third-party Mandarin translator in conjunction with S.C. perused articles in Mandarin that were initially deemed to be pertinent from the PubMed search. Each included study was analyzed for methodological rigor according to the guidelines and standards as stipulated by the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) [6] and the Consolidated Standards of Reporting Trials (CONSORT) [7] guidelines for reporting randomized controlled trials. As some studies had omissions in design as per these guidelines, advice on whether to include the study was sought from the other two senior investigators (S.C. and C.D.). If a study did not include enough information in regard to the outcome of the treatment and control groups, no attempt was made to contact the authors, and these studies were excluded from the analysis.

Data extraction and statistical analysis

Within each study, we isolated the patient cohort of interest, defined as those patients with positive peritoneal cytology without peritoneal carcinomatosis. Based on the included articles, we divided the analysis of patients into two main groups according to treatment modality: (1) intraoperative intraperitoneal chemotherapy (IIPC) and adjuvant chemotherapy; and (2) S-1 oral monotherapy. Data were extracted from each study according to each treatment modality; however, data for systemic chemotherapy were insufficient to be included as part of the meta-analysis, so a descriptive analysis was undertaken instead.

Only a number of studies were identified for meta-analysis, and funnel plots were created according to treatment modality (refer to Figs. 1, 2) to illustrate the spread of effect estimates from individual studies.

Hazards ratios were used as the summative statistical measure to determine the effects, if any, on overall survival between the various treatment regimens. None of the selected studies explicitly specified the exact hazards ratio for the different population arms; hence, we had to manually extrapolate this from the Kaplan–Meier survival curves using a method described by Parmar et al. [8]. To do this, the primary investigator manually determined the

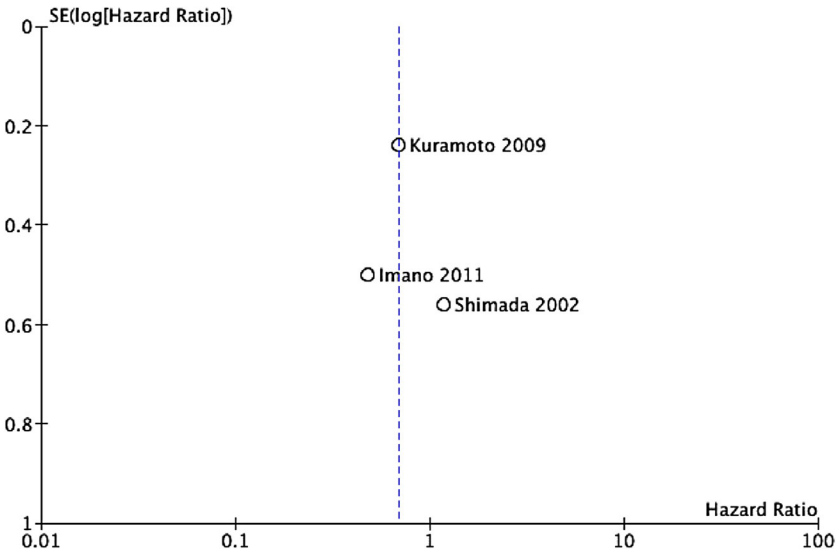

Fig. 1 Funnel plot for intraoperative intraperitoneal chemotherapy (IIPC) and adjuvant chemotherapy

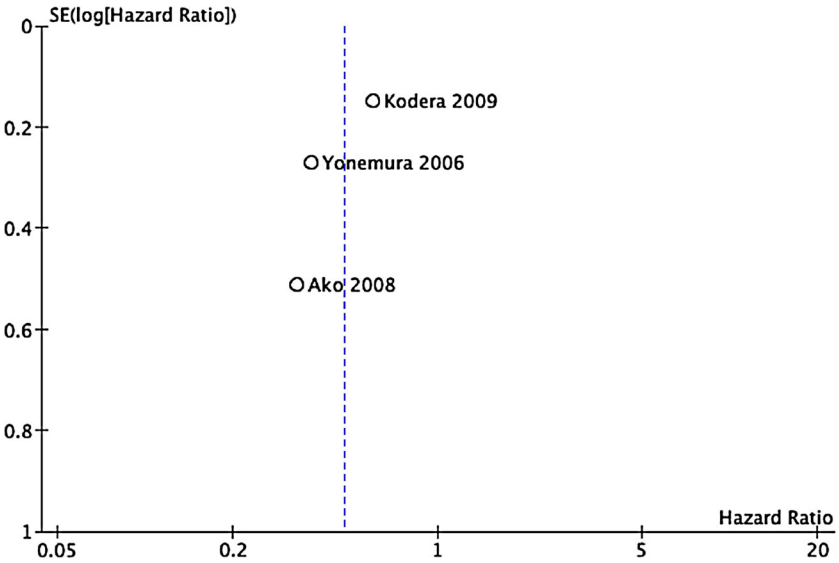

Fig. 2 Funnel plot for S-1 monotherapy

estimate of the survival rate at specific time points on the Kaplan–Meier survival curve of interest from each of the studies. The data were then inserted into a spreadsheet to calculate the hazards ratio, the natural logarithm of the hazards ratio, and standard error and confidence intervals to create the forest plots. We used the software Revman 5 [Review Manager (RevMan) Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011] for the creation of forest plots and statistical analyses.

For the purposes of our meta-analysis, we used the random effects model to be conservative in our estimates because studies varied greatly in their sample sizes and a number of studies were not explicit in their methodology of obtaining peritoneal washouts. The I-squared statistical measure was used to estimate any variance between studies. A value of I^2 >50 % was considered substantial heterogeneity.

Results

Selected studies

Of the 244 articles that were identified by electronic searching, 154 were excluded based upon reviewing the title and abstract. A total of 90 articles were selected for full-text review and 81 full-text articles were excluded, the major reasons being (1) we were not able to isolate those patients with only positive peritoneal cytology; or (2) no control group was specified in the study or a historical control group was provided with no survival data (Fig. 3).

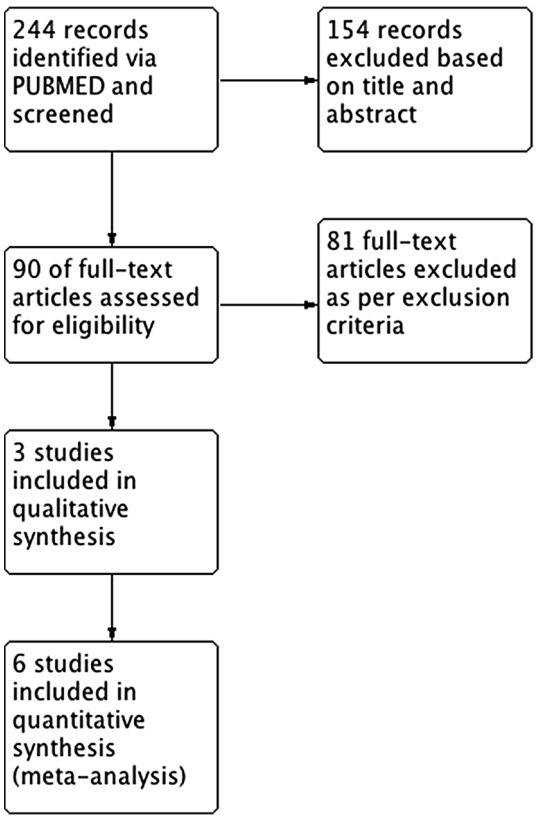

Fig. 3 PRISMA flow diagram on selection of studies

Nine studies in total were included in this study: one randomized controlled trial (RCT) investigating the utility of EIPL with IIPC compared to surgery alone; three studies examining the role of neoadjuvant chemotherapy to be discussed and appraised qualitatively; and five additional studies included for data extraction and the purposes of this meta-analysis. We pooled the results of six studies into two distinct arms according to the treatment of interest: (1) intraperitoneal chemotherapy with adjuvant chemotherapy; and (2) S-1 oral monotherapy.

Quality of studies

The total of six studies used in the meta-analysis included one multicenter randomized controlled study by Kuramoto et al. [9]. In addition, there were four prospective cohort studies [10–13] with one remaining retrospective cohort study [14].

The only randomized controlled trial in this study was appraised in accordance with the CONSORT guidelines. The process of randomization was performed in the operating room by sealed envelope, and although this study did not explicitly mention the procedures involved in randomization, it did reference another study adopting the same method [15]. Because of the nature of the study, double blinding was not possible; however, the surgeon was informed of the selected treatment after definitive curative surgery. Additionally, baseline clinicopathological features between the trial arms were similar, with the authors explicitly stating the use of the 'Japanese Classification of Gastric Carcinoma' (1999) for staging purposes.

All nonrandomized cohort studies explicitly stated the inclusion criteria for population sampling. A number of nonrandomized cohort studies had inadequacies in population recruitment, and one study utilized a historical control group [13]. This study, by Kodera et al., lacks any information on baseline characteristics of the control group, and there were limited outcome data for this group. Moreover, one prospective cohort study [11] provided no information on the baseline characteristics of the intervention and control arms. Concerning harm, most studies reviewed the complications of therapy, with the exception of three studies [9–11].

Table 1 Clinicopathological characteristics of extensive intraperitoneal lavage (EIPL) + intraperitoneal chemotherapy (IPC) group

	Kuramoto et al. [9]
Study period	1995–2005
Follow-up [median (range)]	5 years (5 years)
Sample size (control:exp)	29:30
Study type	Multicenter randomized controlled trial
Depth of tumour invasion	ss: 40 % (12/30)
	se: 50 % (15/30)
	si: 10 % (3/30)
Lymph node metastasis	N1: 43.3 % (13/30)
	N2: 43.3 % (13/30)
	N3: 13.3 % (4/30)
Histological classification	Tub2: 10 % (3/30)
	Por2: 43.3 % (13/30)
	Sig: 46.7 % (14/30)
Cytological detection method	Conventional Papanicolaou
Adjuvant chemotherapy	5-FU derivatives
EIPL-IPC technique	1 l normal saline ×10
IPC regimen	Cisplatin 100 mg/body for 1 h
Overall survival	5-year survival rate: 43.8 %
Recurrence pattern	Peritoneum: 40 % (12/30)
	Lymph node: 6.7 % (2/30)
	Liver: 6.7 % (2/30)
	Lung: 3.3 % (1/30)

ss subserosa, *se* serosa-exposed, *si* serosa-infiltrating, *RT-PCR* reverse transcriptase-polymerase chain reaction, *CEA* carcinoembryonic antigen, *EIPL* extensive intraperitoneal lavage, *IPC* intraperitoneal chemotherapy, *tub2* moderately differentiated type tubular adenocarcinoma, *por2* nonsolid type of poorly differentiated adenocarcinoma, *sig* signet ring-cell carcinoma, *NS* not stated

Intraoperative intraperitoneal chemotherapy (IIPC) with extensive intraperitoneal lavage (EIPL)

The randomized controlled study by Kuramoto et al. [9]. randomized 88 patients into three treatment groups: EIPL and IIPC, IIPC, and surgery alone (Table 1). A previous nonrandomized cohort study by Shimada et al. [11] that acted as a preliminary study to that of Kuramoto et al. utilized the same study population; hence, this study was omitted from our analysis (Table 1). Nevertheless, the Shimada et al. study established the role of EIPL in reducing the number of malignant cells in the peritoneal cavity. To prove this, in the EIPL-IIPC arm of Shimada's study, all the lavage fluid was sent for reverse transcriptase-polymerase chain reaction (RT-PCR) of the oncoprotein carcinoembryonic antigen (CEA). The study essentially established that optimal EIPL consisted of washing the intraperitoneal cavity with 1,000 ml physiological saline, repeated ten times to achieve the dilutional effect.

It is of importance to note that all patients received adjuvant chemotherapy in the form of 5-fluorouracil derivatives for 2 years after surgical treatment in the Kuramoto et al. study; however, the author did not specify whether some patients received S1. A significant proportion of patients had advanced tumors, with 50 % invading up to the serosal layer and 10 % infiltrating through the serosa. In addition, the majority of patients had either poorly differentiated tumors or signet ring cell-type tumors. However, those patients who underwent EIPL with IIPC had a significantly improved 5-year overall survival of 43.8 % compared with 4.6 % and 0 % for those patients who had IIPC with surgery and surgery alone, respectively.

Intraoperative intraperitoneal chemotherapy (IIPC) with adjuvant chemotherapy (or S-1)

Three studies focused on the effects of IIPC with adjuvant chemotherapy on positive peritoneal cytology (Table 2). Two studies [9, 11] utilized the same chemotherapeutic regimen of cisplatin 100 mg per patient, whereas an additional study by Imano et al. [10] administered paclitaxel at a dose of 80 mg/m^2, with eight out of ten of their patients receiving adjuvant S-1 chemotherapy. The largest study, by Kuramoto et al., was characterized by a small percentage (6.9 %) of patients having advanced serosa-infiltrating disease. In contrast, the smaller study of Imano et al. ($n = 10$) noted the majority (80 %) of patients had serosa-infiltrating disease accompanied with more advanced staging on lymph node metastasis (40% N3a and 30 % N3b). Peritoneal disease remains a large contributor to the pattern of recurrence, accounting for 79.3 % and 85.7 %, respectively, in both the Kuramoto and Shimada cohorts. The only study that documented the harmful effects of IIPC was that by Imano et al., with 30 % (3/10) of their cohort sustaining a hematological grade 3 or 4 reaction.

Survival data from all three studies were pooled to summarize the effects of IIPC and adjuvant chemotherapy on overall survival (Fig. 4a). There appeared to be a trend that IIPC improved overall survival, although the summative hazards ratio did not reach statistical significance (HR 0.70; 95 % CI 0.47–1.04; $p = 0.08$). This finding can be attributed to the wide confidence interval of the estimate in the hazard ratio from the Shimada et al. study (HR 1.19; 95 % CI 0.40–3.55). There was no significant interstudy variance ($\tau^2 = 0$; $I^2 = 0$ %).

S1 monotherapy

There were three individual studies investigating the effects of S1 monotherapy on overall survival (Table 3). All trials instituted an identical S1 chemotherapy regimens, consisting of a twice-daily regimen of S-1 (dosing based on body surface area measurements) in a 6-week cycle consisting of 4 weeks of therapy and a 2-week break. Baseline clinicopathological characteristics among the three trials were similar in that the majority of patients had T3N2 disease with undifferentiated or poorly differentiated type adenocarcinoma. There was also a difference in the method of detection for free cancer cells, with the study by Yonemura et al. [12] utilizing immunohistochemistry in addition to the conventional Papanicolaou method. Monoclonal antibodies to human carcinoembryonic antigen and epithelial antigen were used and the immunohistochemical findings were evaluated separately; however, the results of this analysis were not mentioned in their paper.

The 2-year overall survival for patients who underwent S1 chemotherapy ranged from 47 % to 71.6 %. Patients in the study by Ako et al. [14] had the highest rate of overall survival among the three trials, with a significant difference in the 3-year overall survival rates between patients treated with S1 and the control group (71.6 % and 17.1 %, respectively). Recurrence patterns were similar among the three studies, with peritoneal disease and lymphatic nodes being the two most common sites of recurrence. In the study by Kodera et al. [13], the number of adverse events was noticeably higher when compared to the other trials. Hematological toxicities greater than or equal to grade 3 occurred in 21.3 % (10/47) of the cohort, with neutropenia and anemia being the most common. Additionally, 42.6 % (20/47) of the cohort experienced other toxicities greater than or equal to grade 3, the most common being anorexia and nausea.

Survival data from these three studies were pooled to ascertain the effects of S1 chemotherapy on disease prognosis (Fig. 4b). There was a significant increase in the

Table 2 Clinicopathological characteristics of IIPC and adjuvant chemotherapy/S1 group

	Kuramoto et al. [9]	Shimada et al. [11]	Imano et al. [10]
Study period	1995–2005	1989–1999	2004–2009
Follow-up	5 years (5 years)	NS (2 years)	2.43 years (1.36–4 years)
Sample size	30:29	8:7	NS[c]:10
Study type	Multicenter RCT	Prospective cohort study	Prospective phase 2 study
Depth of tumor invasion	ss: 41.4 % (12/29)	NS	T3 (ss): 20 % (2/10)
	se: 51.7 % (15/29)		T4a (si): 80 % (8/10)
	si: 6.9 % (2/29)		
Lymph node metastasis	N1: 55.2 % (16/29)	NS	N1: 10 % (1/10)
			N2: 20 % (2/10)
	N2: 37.9 % (11/29)		N3a: 40 % (4/10)
	N3: 6.9 % (2/29)		N3b: 30 % (3/10)
Histological classification	Tub2: 13.8 % (4/29)	NS	Diffuse: 40 % (4/10)
	Por2: 37.9 % (11/29)		Intestinal: 60 % (6/10)
	Sig: 48.3 % (14/29)		
Cytological detection method	Conventional Papanicolaou	Conventional Papanicolaou	Conventional Papanicolaou
Adjuvant chemotherapy	5-FU derivatives	5-FU derivatives	S-1/paclitaxel[b]
IPC regimen	Cisplatin 100 mg/body for 1 h	Cisplatin 100 mg/body for 1 h	Paclitaxel 80 mg/m^2 for 24 h
Overall survival	5-year survival: 4.6 %	2-year survival: 14.3 %	3-year survival: 56 %
	3-year survival: 18 %[a]		
Recurrence pattern	Peritoneum: 79.3 % (23/29)	Peritoneum: 85.7 % (6/7)	NS
	Lymph node: 10.3 % (3/29)	Lung: 14.3 % (1/7)	
	Liver: 3.4 % (1/29)		
	Lung: 3.4 % (1/29)		
Complications	NS	NS	Grade 3/4 neutropenia: 10 % (1/10)
			Grade 3/4 anemia: 20 % (2/10)

ss subserosa, *se* serosa-exposed, *si* serosa-infiltrating, *CEA* carcinoembryonic antigen, *EIPL* extensive intraperitoneal lavage, *IPC* intraperitoneal chemotherapy, *tub2* moderately differentiated type tubular adenocarcinoma, *por2* nonsolid type of poorly differentiated adenocarcinoma, *sig* signet ring-cell carcinoma, *NS* not stated

[a] Estimated 3-year survival from Kaplan–Meier survival curve

[b] Eight patients had S-1; one patient paclitaxel; and one patient nil else

[c] Historical control group was used

overall survival rates of patients who were administered S1 chemotherapy compared to the control (HR 0.48; 95 % CI 0.32–0.70; $p = 0.0002$). There was moderate interstudy variance at I^2 equal to 39 % ($p = 0.19$).

Neoadjuvant chemotherapy with primary resection

Three studies evaluated the role of primary resection in combination with neoadjuvant chemotherapy. The first study, by Badgwell et al., retrospectively reviewed 39 patients with PPC who received neoadjuvant chemotherapy (exact regimen not stated) with or without external-beam radiation therapy. The 3-year overall survival rate for patients given neoadjuvant treatment was 12 % vs. 0 % ($p = 0.005$) for patients treated with a palliative approach [16]. Further analysis of the cohort that received neoadjuvant treatment revealed that surgical resection was associated with a better overall survival (HR 0.24; 95 % CI 0.17–0.35). Nevertheless, only 10 of 24 patients who had neoadjuvant treatment underwent surgery, with each case being selected based on a decision made at a multidisciplinary meeting. The study did not elaborate on the rationale for each case selection.

Mezhir et al. examined the outcome of 291 patients with positive peritoneal cytology treated at the Memorial Sloan Kettering Cancer Center. In their subgroup analyses, patients who received cisplatin-based chemotherapy had a better median overall survival than those who underwent an immediate gastrectomy (1.7 vs. 1.1 years) [17]. Patients who achieved negative peritoneal cytology on completion of chemotherapy had the best long-term outcome, regardless of whether tumor resection had been performed.

A retrospective review by Lorenzen et al. examined the effects of cisplatin, folinic acid plus fluorouracil, as part of

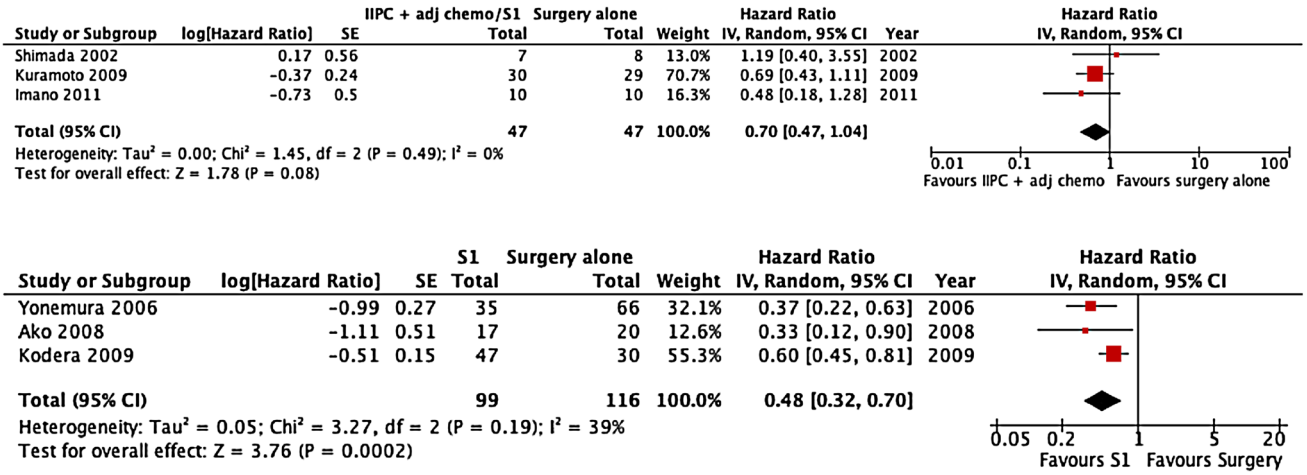

Fig. 4 **a**, **b** Forest plot of hazards ratio (HR) of overall survival (OS) at 2 years with intraoperative intraperitoneal chemotherapy (IIPC) with adjuvant chemotherapy versus surgery alone (**a**) and S1 monotherapy versus surgery alone (**b**). Estimate of the hazards ratio of each individual study corresponds to each shape with the *horizontal line* estimating the 95 % confidence interval (CI)

neoadjuvant treatment in a cohort of patients with PPC-only disease. Patients in this study received a mean of 1.8 cycles of chemotherapy followed by radical tumor resection with a D2 lymphadenectomy [18]. On completion of neoadjuvant chemotherapy, patients whose peritoneal cytology status converted from positive to negative had improved survival compared to those who had persistent peritoneal disease (median survival of 36.1 vs. 9.2 months; 2-year survival rates of 71.4 % vs. 25 %). Nevertheless, the change in cytology status from positive to negative conferred only short-term survival, as the overall 5-year survival rates were not significantly different compared to those who did not respond to chemotherapy.

Quantitative data from the aforementioned studies examining the utility of systemic chemotherapy were not pooled to conduct a meta-analysis for the following reasons: (1) differences in chemotherapeutic regimens including (but not limited to) the drugs utilized, the timing of administration, and the dosage; (2) a paucity of information from the studies on the method of selecting patients who were deemed suitable for surgical resection.

Patterns of recurrence and toxicity profile

The peritoneum is the most common site of recurrence for all modalities of treatment, followed closely by locoregional lymphatic and hepatic recurrence. Metastatic disease to extraperitoneal organs such as the lung and bone is infrequent in all the studies, with less than 7 % of patients affected.

Toxicities related to IIPC and S1 chemotherapy are recorded in Tables 2 and 3, respectively. In regard to IIPC with S1 chemotherapy, Imano et al. recorded the incidence of adverse reactions. In this cohort, two patients had grade 3 anemia and 1 patient grade 3 neutropenia, all of whom did not require any additional treatment. In addition, only one patient developed a surgical site infection, and there were no other operative complications (data not shown).

In relation to S1 monotherapy, leukopenia and anemia were the most common hematological reactions, with grade 3 nausea, vomiting, and malaise being the most common nonhematological reaction. There were no treatment-related deaths in all studies with S1.

The studies relating to the use of systemic chemotherapy did not report any adverse effects on the use of chemotherapy.

Discussion

The optimal management of gastric adenocarcinoma patients with positive peritoneal cytology as the only marker of metastatic disease remains unclear. Most of these patients have a poor prognosis, with a substantially high risk for peritoneal recurrence, even in the absence of overt peritoneal carcinomatosis [3, 17, 19–24]. Nath et al. demonstrated no significant difference in median survival between patients with only positive malignant cytology (13 months) versus those with macroscopic peritoneal disease (9 months) [25]. In the study by Bando et al., all 296 patients (24 % of cohort) with positive peritoneal cytology died within 3 years despite radical tumor resection [19]. Data from Memorial Sloan Kettering Cancer Center showed that although the overall prognosis for gastric cancer patients with microscopic metastatic peritoneal disease remains poor (median disease-specific survival of 1.3 years), systemic chemotherapy with tumor resection can lead to improved survival in a subgroup of patients [17].

Table 3 Clinicopathological characteristics of S1 group

	Yonemura et al. [12]	Ako et al. [14]	Kodera et al. [13]
Study period	2000–2005	1986–2005	2002–2006
Follow-up	NS (2.8 years[b])	2.2 years (5.2 years[b])	6.4 years (6.84 years[b])
Sample size	66:35	20:17	30:47
Study type	Prospective cohort study	Retrospective cohort study	Prospective cohort study
Depth of tumor invasion	T1: 0	T2: 5.9 % (1/17)	T1: 4.3 % (2/47)
	T2: 14.3 % (5/35)	T3: 88.2 % (15/17)	T2: 4.3 % (2/47)
	T3: 77.1 % (27/35)	T4: 5.9 % (1/17)	T3: 78.7 % (37/47)
	T4: 8.6 % (3/35)		T4: 12.8 % (6/47)
Lymph node metastasis	N0: 20 % (7/35)	N0: 5.9 % (1/17)	N0: 10.6 % (5/47)
	N1: 28.6 % (10/35)	N1: 23.5 % (4/17)	N1: 23.4 % (11/47)
	N2: 42.9 % (15/35)	N2: 64.7 % (11/17)	N2: 53.2 % (25/47)
	N3: 8.6 % (3/35)	N3: 5.9 % (1/17)	N3: 12.8 % (6/47)
Histological classification	Differentiated: 25.7 % (9/35)	Differentiated: 35.3 % (6/17)	Differentiated: 38.3 % (18/47)
	Poorly diff.: 74.3 % (26/35)	Undiff.: 64.7 % (11/17)	Undiff/mucin: 61.7 % (29/47)
Cytological detection method	Papanicolaou + IHC	Papanicolaou	Papanicolaou
Adjuvant chemotherapy	No	No	No
S-1 regimen	BSA <1.25 m^2 40 mg, <1.5 m^2 50 mg, >1.5 m^2 60 mg	BSA <1.25 m^2 40 mg, <1.5 m^2 50 mg, >1.5 m^2 60 mg	BSA <1.25 m^2 40 mg, <1.5 m^2 50 mg, >1.5 m^2 60 mg
	BD 28 days + 2-week rest/6 weeks until recurrence, toxicity, refusal	BD 28 days + 2-week rest/6 weeks until recurrence, toxicity, refusal	BD 28 days + 2-week rest/6 weeks until recurrence, toxicity, refusal
Overall survival	2-year survival: 53 %	2-year survival: 71.6 %	2-year survival: 47 %
Recurrence pattern	Peritoneum: 31.4 % (11/35)	Peritoneum: 29.4 % (5/17)	Peritoneum: 55.3 % (26/47)
	Lymph nodes: 14.3 % (5/35)	Lymph nodes: 23.5 % (4/17)	Lymph nodes: 8.5 % (4/47)
	Bone: 5.7 % (2/35)		Bone: 2.1 % (1/47)
	Liver: 2.9 % (1/35)		Liver: 8.5 % (4/47)
Complications	Grade 3/4 malaise: 9 % (3/35)	Grade 3/4 LP: 5.9 % (1/17)	Grade 3/4 hem: 21.3 % (10/47)
	Grade 3/4 LP: 6 % (2/35)	Grade 3/4 HB: 5.9 % (1/17)	Grade 3/4 other[a]: 42.6 % (20/47)

IHC immunohistochemistry, *BSA* body surface area, *LP* leukopenia, *hem* hematological reaction, *HB* hyperbilirubinemia, *Undiff* undifferentiated, *mucin* mucinous type, *RT-PCR* reverse transcriptase-polymerase chain reaction, *BD* twice daily, *NS* not stated

[a] Kodera et al. grade 3/4 other: most common other toxicity was anorexia and nausea followed by increases in laboratory values of liver enzymes aspartate aminotransferase/alkaline phosphatase, bilirubin, as well as general malaise

[b] Actual range of follow-up not specified; value represented is the last patient who died/was followed-up as estimated from the Kaplan–Meier survival curve

The utilization of systemic chemotherapy in Western gastric cancer patients is variable with the option of single or combination regimens. In this review, the study by Badgwell et al. did not state the chemotherapeutic regimen whereas the studies by Mezhir et al. and Lorenzen et al. utilized mostly cisplatin-based regimens. Despite recent advances in the development of novel chemotherapeutic drugs, overall survival still remains poor, and we present here a number of hypotheses. First, the majority of Western patients with gastric cancer present late in the disease process with more advanced tumors. Systemically administered chemotherapy may not reach therapeutic tumoricidal concentrations, especially with serosal-invading tumors and peritoneal disease. A seminal study by Los et al. [26] demonstrated that in a rodent model of colorectal adenocarcinoma with peritoneal metastasis, the concentration of platinum in the periphery of the tumor is higher with intraperitoneal compared with intravenous administration. Second, there are a number of adverse effects related to systemic chemotherapy that have a significant impact on

the patient's quality of life, and very few studies have measured quality of life-adjusted survival as a major outcome [27].

We surmise that these aforementioned reasons contribute to the paucity of studies examining the role of systemic chemotherapy in PPC-only disease. Currently, there is still some contention about the choice of systemic chemotherapy in advanced gastric cancer with positive cytology with or without peritoneal carcinomatosis. Three recent large randomized controlled trials have shown a survival benefit with adjuvant systemic chemotherapy over surgery alone [28]: the European MAGIC trial, the American INT 0116, and the Japanese ACTS-GC trial by Sakuramoto et al. [29], having shown that single agent S-1 chemotherapy was superior to surgery alone. All three studies utilized different chemotherapeutic regimens with highly variable methodologies and recruitment criteria.

The pooled results from our study show that S-1 may play a role in the treatment of micrometastatic disease. S-1 (Taiho Pharmaceuticals) is a combination of tegafur [a prodrug of 5-fluorouracil (5-FU)], gimeracil (CDHP, an inhibitor of enzymes that metabolize 5-FU), and oteracil (a drug that reduces gastrointestinal cytotoxicity from 5-FU). The advantage of S1 over other chemotherapeutic agents is its ability to attain higher concentrations intraperitoneally [30]. A recent Japanese retrospective study by Iwasaki et al. [31] compared the efficacy of S1 (monotherapy or with the addition of cisplatin) with non-S-1 adjuvant chemotherapy after gastrectomy. Five-year survival rates were 34.8 % and 0 % ($p = 0.019$), respectively, thus supporting the addition of S1 to the adjuvant chemotherapeutic regimen to maximize survival. We were unable to include this study in our analysis because patients in the S1 group had monotherapy either with or without the addition of cisplatin. Moreover, the specific chemotherapeutic regimen as well as their method to detect peritoneal cancer cells was not described. Another study by Ito and colleagues [32] utilized RT-PCR as a method for cytological detection of intraperitoneal free cancer cells (IFCCs). All patients (32) who received S1 monotherapy were positive for CEA and negative with conventional Papanicolaou staining in their peritoneal lavage. The 2-year survival rate of 93.5 % for this cohort is alarmingly different from the other studies considering S-1 monotherapy (Yonemura et al., Kodera et al., Ako et al.). The lower tumor volume of this patient cohort, thus needing detection with more sensitive molecular methods such as RT-PCR, is a plausible explanation of the higher survival rate. We decided not to include the study by Ito et al. in the meta-analysis because of the markedly different method of detection of IFCCs. The use of RT-PCR to detect micrometastatic disease is currently not widely accepted because of its variation in technique, the choice of detection of different tumor-derived antigens, and the possibility of false-positive results. In fact, a recent systematic review incorporating a number of studies that examined the utility of RT-PCR showed wide confidence intervals in diagnostic performance, including an accuracy of 61–89.7 %, sensitivity of 31–100 %, and specificity of 58.8–95 % [2].

The evidence behind the use of S1 monotherapy as standard postoperative adjuvant chemotherapy was predominantly based upon studies that included patients of Asian ethnicity, and the applicability of these results to the Western setting must be approached with caution. Quite recently, the study by Ajani and colleagues published in 2010 reported that the combination of S-1/cisplatin did not significantly improve overall survival over the conventional regimen of 5-FU/cisplatin [33]. Despite the finding of a null hypothesis, the safety profile of S-1/cisplatin was far superior than that of 5-FU/cisplatin in terms of grade 3 or 4 neutropenia, stomatitis, hypokalemia, and treatment-related deaths. The results of the Ajani et al. [34] trial can be explained by the different pharmacokinetics of S-1 in the Caucasian population, whereby the maximum tolerated dose of S-1 is lower in Caucasians as a result of polymorphic differences in the CYP2A6 enzyme responsible for the metabolism of the drug. As a consequence, S-1 is not readily utilized in the Western world.

Intraoperative intraperitoneal chemotherapy has been proposed as an alternate option to eradicate IFCCs. The rationale behind the use of IIPC is the ability to maintain higher drug concentrations intraperitoneally for a longer period of time compared to systemic therapy alone while also minimizing systemic adverse effects. The advantages of IIPC in prolonging survival have been demonstrated in ovarian and colorectal cancers. With gastric cancer, numerous studies during the past two decades have shown that IIPC may play an adjunctive role in prolonging survival [35]. Our results for the role of IIPC alone in cytology-positive disease did not reach statistical significance although there was a trend toward improving survival. This finding may be attributed to the myriad of chemotherapeutic regimens available: Imano and colleagues utilized paclitaxel with the addition of S1 adjuvant chemotherapy whereas the other two studies used cisplatin. Both cisplatin and paclitaxel have been shown to have therapeutic effects intraperitoneally [36, 37]; however, we believe that the addition of adjuvant S-1 chemotherapy in the majority of Imano's cohort may have contributed to the 3-year survival rate of 56 %. Moreover, another difference with Imano's cohort was that patients were subjected to 24 h of intraperitoneal chemotherapy postoperatively by clamping the abdominal drainage tubes. Thus, one could presume that the increased duration of exposure may have had a greater therapeutic effect.

In addition to IIPC, the additional modality of hyperthermia with chemotherapy was shown to increase overall survival in a recent meta-analysis conducted by Yan and colleagues [35]. This meta-analysis appraised 13 randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer (without overt distal or peritoneal metastasis). Unfortunately, the trials did not include a subgroup analysis for patients with PPC-only disease. However, a review article by Kaibara [38] retrospectively investigated the effect of continuous hyperthermic peritoneal perfusion (CHPP) on patients with PPC-only disease. The 5-year overall survival for patients treated with CHPP was 33.3 % compared to only 4.2 % in the control group. Despite the survival advantage gained with hyperthermic chemotherapy, complications arising from intraabdominal abscesses and neutropenia are significantly increased [35]. Comparatively, the use of EIPL is relatively harmless with no reported adverse effects.

The theory behind the use of EIPL in positive lavage cytology is that free cancer cells have not achieved implantation on the peritoneal surface and thus can be washed out of the peritoneal cavity with a repetitive number of lavages. The concept of peritoneal lavage is not new and has been used in colorectal cancer [39]. The aforementioned studies of EIPL in gastric cancer have shown significant improvements in overall survival of up to 47 % overall survival at 5 years [9, 40]. Nevertheless, an important point to address is that these studies utilized normal physiological saline as the medium for lavage. Conversely, a recent experimental laboratory study has shown that repetitive intraperitoneal normal saline lavage may actually exacerbate free cancer cell dissemination by promoting exfoliation from serosal surfaces and/or insecure lymphatic vessels [41]. Within the limitations of an animal model, Ito and colleagues explored the use of distilled water as a medium for peritoneal lavage in mice. The main premise for using water is that it acts as an osmotic stressor and as a diluting factor. Their findings suggest that the use of distilled water is associated with significantly increased rates of tumor lysis in mice models of colorectal cancer cell intraperitoneal spillage. Moreover, the results of a recent innovative study by Han and colleagues suggested that inappropriate surgical technique during radical gastrectomy and lymph node dissection may be the causative factor in spilling malignant cells into the peritoneal cavity via the gastric lumen or poorly sealed lymphovascular pedicles [42]. Following this, the only ongoing randomized phase III trial to evaluate the prognostic value of EIPL in addition to standard treatment in gastric cancer is the Japanese CCOG 1102 study by Misawa et al. [43], whereby this multi-institutional study aims to recruit 300 patients with resectable gastric cancer (including cytology positive-only disease). These findings and ongoing projects incite the need for more clinical studies to establish the utility of peritoneal lavage in PPC-only disease, not only as a part of staging but after any definitive surgery to minimize the degree of malignant cell spillage.

There are a limited number of studies exclusively investigating the treatment of gastric cancer with positive cytology alone. In this study, we broadened our search to Japanese and Chinese studies to limit the publication bias. Despite this, there is a lack of robust multicenter large randomized controlled trials to provide us with quality evidence, and we speculate that there are a number of reasons. First, a major reason is that not many patients receive appropriate preoperative staging with lavage cytology despite the overwhelming evidence that it is a strong predictor of recurrence and poor overall survival. Second, an additional complicating factor in the domain of preoperative staging is the advent of novel, more sensitive methods of detecting micrometastatic disease using immunohistochemical methods or RT-PCR [44], as alluded to earlier in this discussion. Papanicolaou staining remains the current 'gold standard' because of the various limitations in immunohistochemical and molecular methods including (but not limited to) the laborious processes required, the high costs involved, and the possibility of false-positive results with illegitimate transcription of noncancerous cells [45, 46]. These factors, and the differences between protocols and procedures between the 'East' and 'West,' prevent any possible adoption of these new techniques addressed by this study to any population. Future studies are needed whereby unified protocols for staging and treatment are utilized. Last, the findings from this review are limited because a small number of studies was available to us for analysis. Therefore, there is an inherent publication bias as depicted by the funnel plots (Figs. 1, 2) resulting from the mediocre methodological quality of included studies as well as the inherent esoteric nature of the population of interest.

Conclusion

Gastric cancer with cytology positive-only disease should be a target area of interest for future investigators as these patients have a lower tumor volume than patients with overt macroscopic peritoneal carcinomatosis and thus may benefit from aggressive treatment including, but not limited to: extensive intraperitoneal lavage with or without intraoperative intraperitoneal chemotherapy, neoadjuvant and postoperative chemotherapy in the form of S1 monotherapy. No definite conclusions can be made from this review as larger, multicentered randomized controlled trials are required to add to the limited body of evidence to compare the different treatment modalities in relationship to morbidity and improving overall survival.

Conflict of interest All named authors hereby declare that they have no conflict of interest to disclose. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Appendix

PubMed search strategy

Search	Add to builder	Query	Items found
#7	Add	Search (#6 AND #3)	244
#6	Add	Search (#5 OR #4)	4,049
#5	Add	Search ((peritoneal cytology).tw OR (intraperitoneal free cancer cells).tw)	79
#4	Add	Search peritoneal lavage/	3,977
#3	Add	Search (#1 NOT #2)	82,385
#2	Add	Search (gastrointestinal stromal tum$.tw OR GIST.tw)	6,886
#1	Add	Search stomach neoplasm/	83,677

References

1. Leake P-A, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. Gastric Cancer. 2011;15(S1):38–47. doi:10.1007/s10120-011-0047-z.
2. Leake P-A, Cardoso R, Seevaratnam R, et al. A systematic review of the accuracy and utility of peritoneal cytology in patients with gastric cancer. Gastric Cancer. 2011;15(S1):27–37. doi:10.1007/s10120-011-0071-z.
3. Bentrem D, Wilton A, Mazumdar M, Brennan M, Coit D. The value of peritoneal cytology as a preoperative predictor in patients with gastric carcinoma undergoing a curative resection. Ann Surg Oncol. 2005;12(5):1–7.
4. Chang L, Stefanidis D, Richardson WS, Earle DB, Fanelli RD. The role of staging laparoscopy for intraabdominal cancers: an evidence-based review. Surg Endosc. 2009;23(2):231–41. doi:10.1007/s00464-008-0099-2.
5. Yonemura Y, Endou Y, Sasaki T, et al. Surgical treatment for peritoneal carcinomatosis from gastric cancer. Eur J Surg Oncol (EJSO). 2010;36(12):1131–8. doi:10.1016/j.ejso.2010.09.006.
6. Jarlais Des DC, Lyles C, Crepaz N. Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement. Am J Public Health. 2004;94(3):361–6.
7. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. Int J Surg. 2012;10(1):28–55. doi:10.1016/j.ijsu.2011.10.001.
8. Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med. 1998;17(24):2815–34.
9. Kuramoto M, Shimada S, Ikeshima S, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009;250(2):242–6. doi:10.1097/SLA.0b013e3181b0c80e.
10. Imano M, Imamoto H, Itoh T, et al. Impact of intraperitoneal chemotherapy after gastrectomy with positive cytological findings in peritoneal washings. Eur Surg Res. 2011;47(4):254–9. doi:10.1159/000333803.
11. Shimada S, Tanaka E, Marutsuka T, et al. Short communication: extensive intraoperative peritoneal lavage and chemotherapy for gastric cancer patients with peritoneal free cancer cells. Gastric Cancer. 2002;5:168–72.
12. Yonemura Y, Endou Y, Bando E, et al. The usefulness of oral TS-1 treatment for potentially curable gastric cancer patients with intraperitoneal free cancer cells. Cancer Therapy. 2006;4:135–42.
13. Kodera Y, Ito S, Mochizuki Y, et al. A phase II study of radical surgery followed by postoperative chemotherapy with S-1 for gastric carcinoma with free cancer cells in the peritoneal cavity (CCOG0301 study). Eur J Surg Oncol (EJSO). 2009;35(11):1158–63. doi:10.1016/j.ejso.2009.03.003.
14. Ako E, Ohira M, Yamashita Y, et al. Efficacy of S-1 for gastric cancer patients with positive peritoneal lavage cytology. Hepatogastroenterology. 2008;55:1939–42.
15. Heslin M, Latkany L, Leung D. A prospective, randomized trial of early enteral feeding after resection of upper gastrointestinal malignancy. Ann Surg. 1997;226:567–80.
16. Badgwell B, Cormier JN, Krishnan S, et al. Does neoadjuvant treatment for gastric cancer patients with positive peritoneal cytology at staging laparoscopy improve survival? Ann Surg Oncol. 2008;15(10):2684–91. doi:10.1245/s10434-008-0055-3.
17. Mezhir JJ, Shah MA, Jacks LM, Brennan MF, Coit DG, Strong VE. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol. 2010;17(12):3173–80. doi:10.1245/s10434-010-1183-0.
18. Lorenzen S, Panzram B, Rosenberg R, et al. Prognostic significance of free peritoneal tumor cells in the peritoneal cavity before and after neoadjuvant chemotherapy in patients with gastric carcinoma undergoing potentially curative resection. Ann Surg Oncol. 2010;17(10):2733–9. doi:10.1245/s10434-010-1090-4.
19. Bando E, Yonemura Y, Takeshita Y, et al. Intraoperative lavage for cytological examination in 1,297 patients with gastric carcinoma. Am J Surg. 1999;178:256–62.
20. Oh CA, Bae JM, Oh SJ, et al. Long-term results and prognostic factors of gastric cancer patients with only positive peritoneal lavage cytology. J Surg Oncol. 2012;105(4):393–9. doi:10.1002/jso.22091.
21. Kodera Y, Nakanishi H, Ito S, et al. Prognostic significance of intraperitoneal cancer cells in gastric carcinoma: analysis of real time reverse transcriptase-polymerase chain reaction after 5 years of follow-up. J Am Coll Surg. 2006;202(2):231–6. doi:10.1016/j.jamcollsurg.2005.09.008.
22. Nakagawa S, Nashimoto A, Yabusaki H. Role of staging laparoscopy with peritoneal lavage cytology in the treatment of locally advanced gastric cancer. Gastric Cancer. 2007;10(1):29–34. doi:10.1007/s10120-006-0406-3.
23. Fukagawa T, Katai H, Saka M, et al. Significance of lavage cytology in advanced gastric cancer patients. World J Surg. 2010;34(3):563–8. doi:10.1007/s00268-009-0355-1.
24. Saito H, Kihara K, Kuroda H, Matsunaga T, Tatebe S, Ikeguchi M. Surgical outcomes for gastric cancer patients with intraperitoneal free cancer cell, but no macroscopic peritoneal metastasis. J Surg Oncol. 2011;104(5):534–7. doi:10.1002/jso.21983.
25. Nath J, Moorthy K, Taniere P, Hallissey M, Alderson D. Peritoneal lavage cytology in patients with oesophagogastric adenocarcinoma. Br J Surg. 2008;95(6):721–6. doi:10.1002/bjs.6107.
26. Los G, Mutsaers PH, van der Vijgh WJ. Direct diffusion of *cis*-diamminedichloroplatinum(II) in intraperitoneal rat tumors after intraperitoneal chemotherapy: a comparison with systemic chemotherapy. Cancer Res. 1989;49:3380–4.
27. Wagner AD. Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. J Clin Oncol. 2006;24(18):2903–9. doi:10.1200/JCO.2005.05.0245.

28. Sano T. Adjuvant and neoadjuvant therapy of gastric cancer a comparison of three pivotal studies. Curr Oncol Rep. 2008;10:191–8.
29. Sano T. We have entered a new era of adjuvant/neoadjuvant therapy for gastric cancer. Gastrointest Cancer Res. 2008;1(4):156–7.
30. Oshima T, Yamada R, Hatori S, Kunisake C, Toshio I. Pharmacokinetics of S-1 in patients with peritoneal dissemination of gastric cancer. Oncol Rep. 2006;16:361–6.
31. Iwasaki Y, Ohashi M, Iwanaga T, et al. Therapeutic strategy for gastric cancer with positive peritoneal lavage cytology without peritoneal dissemination. Gan Kagaku Ryoho Cancer Chemother. 2012;39:2451–4.
32. Ito S, Kodera Y, Mochizuki Y, Kojima T, Nakanishi H, Yamamura Y. Phase II clinical trial of postoperative S-1 monotherapy for gastric cancer patients with free intraperitoneal cancer cells detected by real-time RT-PCR. World J Surg. 2010;34(9):2083–9. doi:10.1007/s00268-010-0573-6.
33. Ajani JA, Rodriguez W, Bodoky G, et al. Multicenter phase III comparison of cisplatin/S-1 with cisplatin/infusional fluorouracil in advanced gastric or gastroesophageal adenocarcinoma study: the FLAGS trial. J Clin Oncol. 2010;28(9):1547–53. doi:10.1200/JCO.2009.25.4706.
34. Ajani JA, Faust J, Ikeda K, Yao JC, Anbe H. Phase I pharmacokinetic study of S-1 plus cisplatin in patients with advanced gastric carcinoma. J Clin Oncol. 2005;23(28):6957–65. doi:10.1200/JCO.2005.01.917.
35. Yan TD, Black D, Sugarbaker PH, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007;14(10):2702–13. doi:10.1245/s10434-007-9487-4.
36. Takahashi I, Emi Y, Hasuda S, et al. Clinical application of hyperthermia combined with anticancer drugs for the treatment of solid tumors. Surgery (St. Louis). 2002;131(1):S78–84. doi:10.1067/msy.2002.119308.
37. Tsujitani S, Fukuda K, Saito H, et al. The administration of hypotonic intraperitoneal cisplatin during operation as a treatment for the peritoneal dissemination of gastric cancer. Surgery (St. Louis). 2002;131(1):S98–104. doi:10.1067/msy.2002.119359.
38. Kaibara N. Prophylaxis and treatment of peritoneal metastasis from gastric cancer. Nihon Geka Gakkai Zasshi. 1996;97(4):308–11.
39. Huguet EL, Keeling NJ. Distilled water peritoneal lavage after colorectal cancer surgery. Dis Colon Rectum. 2004;47(12):2114–9. doi:10.1007/s10350-004-0788-4.
40. Shimada S, Kuramoto M, Marutsuka T, Yagi Y, Baba H. Adopting extensive intra-operative peritoneal lavage (EIPL) as the standard prophylactic strategy for peritoneal recurrence. Rev Recent Clin Trials. 2011;6:266–70.
41. Ito F, Camoriano M, Seshadri M, Evans SS, Kane JM, Skitzki JJ. Water: a simple solution for tumor spillage. Ann Surg Oncol. 2011;18(8):2357–63. doi:10.1245/s10434-011-1588-4.
42. Han T-S, Kong S-H, Lee H-J, et al. Dissemination of free cancer cells from the gastric lumen and from perigastric lymphovascular pedicles during radical gastric cancer surgery. Ann Surg Oncol. 2011;18(10):2818–25. doi:10.1245/s10434-011-1620-8.
43. Misawa K, Mochizuki Y, Ohashi N, et al. A randomized phase III trial exploring the prognostic value of extensive intraoperative peritoneal lavage in addition to standard treatment for resectable advanced gastric cancer: CCOG 1102 study. Jpn J Clin Oncol. 2014;44(1):101–3. doi:10.1093/jjco/hyt157.
44. Marutsuka T, Shimada S, Shiomori K, et al. Mechanisms of peritoneal metastasis after operation for non-serosa-invasive gastric carcinoma: an ultrarapid detection system for intraperitoneal free cancer cells and a prophylactic strategy for peritoneal metastasis. Clin Cancer Res. 2003;9:678–85.
45. Ishii T, Fujiwara Y, Ohnaka S, et al. Rapid genetic diagnosis with the transcription? Reverse transcription concerted reaction system for cancer micrometastasis. Ann Surg Oncol. 2004;11(8):778–85. doi:10.1245/ASO.2004.12.043.
46. Mori T, Fujiwara Y, Sugita Y, et al. Application of molecular diagnosis for detection of peritoneal micrometastasis and evaluation of preoperative chemotherapy in advanced gastric carcinoma. Ann Surg Oncol. 2006;11(1):14–20. doi:10.1245/as0.2004.02.016.