Original article

Prognostic significance of peritoneal lavage cytology in gastric cancer in Singapore

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Abstract

Background. Peritoneal lavage cytology has been included as part of the staging process in the 13th edition of the Japanese Classification of Gastric Cancer. However, this procedure has neither been studied nor established in our population. We aimed to evaluate its prognostic relevance among our patients with gastric cancer.

Methods. A total of 142 consecutive patients with gastric carcinoma were recruited prospectively. All had histologically proven gastric carcinomas and had undergone laparotomy and intraoperative peritoneal lavage for cytological examination at Singapore General Hospital. The fluid recovered was centrifuged and stained by the Papanicolaou method. All patients were followed up with endpoints of cancer recurrence and mortality.

Results. There were 91 men and 51 women; 36 patients (25.4%) had positive peritoneal lavage. Patients with advanced macroscopic features, presence of vascular invasion, nodal involvement, advanced depth of tumor invasion and metastatic disease tended to have positive lavage, by univariate logistic regression analysis. Despite curative resections, patients with positive cytology had a more dismal disease-free survival (mean, 27 months vs 53 months; $P < 0.0001$ by log rank test) and higher recurrence rate (54.5% vs 19.3%; $P = 0.007$ by log rank test). There was also a trend towards earlier recurrences (median, 8 months vs 11 months; $P = 0.37$). By multivariate Cox regression stepwise analysis, advanced depth of tumor invasion and positive lavage cytology were found to be independent poor prognostic factors for disease-free survival.

Conclusion. Positive peritoneal lavage cytology correlated well with advanced features of gastric cancer. It is an independent poor prognostic factor and the procedure should be routinely performed. Integration of lavage status into our current staging systems may serve as a guide for adjuvant therapeutic options to improve the survival of gastric cancer in our population.

Key word Peritoneal lavage cytology · Gastric cancer

Introduction

Peritoneal carcinomatosis represents one of the most common causes of failure after “curative” surgery for gastric cancer. This is believed to be due to the presence of malignant cells that have already seeded at the time of operation but cannot be detected using conventional diagnostic tools. Cytological examination using peritoneal washes obtained at the time of surgery has been used for assessing the presence of free cancer cells in the peritoneal cavity [1,2]. Data obtained by cytological examination of peritoneal washes have been included as one of the prognostic factors in the staging of gastric cancer by the Japanese Research Society for Gastric Cancer [3]. Recently, there has been a move towards combined-modality therapy to improve the outcome of advanced gastric cancer. Integration of lavage status into our current staging systems not only allows disease prognostication but also serves as a guide to adjuvant therapeutic options such as preoperative chemoradiation [4] or intraperitoneal chemotherapy [5]. However, the sensitivity of peritoneal lavage cytology has been reported to be relatively low, ranging from 22% to 30% in gastric carcinoma involving the serosa [6–8]. As up to 50% of patients with serosal invasion are known to develop peritoneal recurrence even when curative resections are performed [8], several investigators have recognized the need for more sensitive molecular methods of detecting peritoneal metastasis compared with conventional cytodiagnostic methods. In this article, we report our study of the prognostic relevance of free cancer cells in the peritoneal washings among our population with gastric cancer and its potential impact on our current management strategy.

Patients and methods

Between March 1998 and March 2002, a total of 142 consecutive patients receiving treatment from the upper gastrointestinal team at the Department of General Surgery, Singapore General Hospital, were prospectively recruited. All had histologically proven gastric carcinoma from endoscopic gastric biopsies and had undergone laparotomy and intraoperative peritoneal lavage for cytological examination. These patients had fulfilled the following criteria: (1) no preoperative chemotherapy; (2) no other primary malignancy; (3) no previous abdominal operations resulting in dense adhesions that would preclude accurate sampling; and (4) a peritoneal lavage sample which was sufficient for definitive diagnosis.

Upon entering the abdominal cavity prior to tumor handling, 200ml of warm normal saline was introduced and manually dispersed. At least 20ml of fluid was subsequently recovered from several regions of the abdominal cavity, including the pelvis and paracolic gutters. The fluid was then centrifuged for 5 min at 1500 rpm. The nucleated cell layer was smeared onto a glass slide and stained by the Papanicolaou method. Cytological examination was performed by experienced cytopathologists. Cytological findings were graded from class I to V according to Papanicolaou's classification, with classes IV and V defined as positive [9]. Standard D2 lymphadenectomy, according to the criteria described by the Japanese Research Society for Gastric Cancer [3], was routinely performed for all resections intended for cure. Resections were deemed curative when no gross residual disease was evident at the time of the operation, with tumor-free resection margins on histological examination. Resected specimens were examined histopathologically, with depth of invasion (pT) and the number of nodal metastases (pN) evaluated and staged according to the 1997 International Union Against Cancer (UICC)/American Joint Committee on Cancer (AJCC) TNM classification (fifth edition).

All patients were followed up for at least 1 year or until death. Postoperative evaluation included interim history, physical examination, and hematological and blood biochemistry panels. Check upper endoscopy was performed 6- to 12-monthly. Computerized tomography of the abdomen, bone scintigraphy, and chest X-ray were performed whenever clinical symptoms, physical findings, or investigations implied recurrence. Diagnoses of disease recurrence were made on the basis of radiological or endoscopic findings. Peritoneal recurrence was determined clinically, based on symptoms or physical examination of bowel obstruction and ascites. Cytological confirmation was obtained only for patients who underwent paracentesis or re-laparotomy. Disease-free survival was defined as the

time from the date of the primary treatment to the date of first recurrence. Overall survival was defined as the time from the date of the primary treatment to the date of death.

Prognostic analyses were performed with cancer-related death and disease recurrence as primary endpoints. Statistical comparisons were made using the χ^2 test and Fisher's exact test as appropriate. The sensitivity, specificity, and predictive value of peritoneal lavage cytological examination were calculated using Confidence Interval Analysis (CIA) software for clinical studies version 2.1.0 (Trevor N Bryant, Bristol, UK). Clinicopathological factors associated with positive cytological examination were analyzed by univariate and multivariate logistic regression. To determine which variables were independent prognostic factors for overall survival and disease-free survival, Cox regression analysis, in a backward stepwise procedure, was applied. We used $P < 0.1$ as the cutoff value for statistical significance for variable selection for the multivariate modeling in order not to miss any potentially important predictors. Statistical significance remained conventionally defined as $P < 0.05$ in the univariate and multivariate models. Survival rates were obtained by the Kaplan-Meier method and compared by log rank test. Statistical calculations were performed using the SPSS (Chicago, IL, USA) version 11.5 advanced statistical software module.

Results

A total of 142 patients were studied. There were 91 men and 51 women (male-to-female ratio, 1.78:1). The median age was 67.2 years (range, 24.0–86.1 years). There was no operative-related mortality, and the overall morbidity was 17.6% (25/142). Common complications included chest infection ($n = 11$) and wound infection ($n = 5$). The median follow-up time was 11.8 months for all patients (range, 2 to 59 months) and 36 months (range, 13 to 59 months) for surviving patients. Two patients were lost to follow-up. Two patients died of other causes (one, stroke and the other, acute cardiovascular event). These four patients were negative for free peritoneal malignant cells and were excluded from the survival analysis. At the last follow-up, 52 patients (36.6%) were dead of disease.

In total, 36 patients (25.4%) had positive peritoneal malignant cytology. The patients' demographic, clinical, and tumor characteristics are listed in Table 1. The patients in both groups were comparable in distribution of age, sex, ethnic group, and presence of comorbidities. There was a significant association between the tumor stage, depth of tumor invasion, nodal involvement, intent of operation, disease recurrence, and overall mor-

Table 1. Patients' demographic and clinical features and tumor characteristics

Clinicopathologic factors	Negative cytology (<i>n</i> = 106)	Positive cytology (<i>n</i> = 36)	<i>P</i> value
	Number (%)	Number (%)	
Age (years)			
≤67	56 (52.8)	16 (44.4)	0.39
>67	50 (47.2)	20 (55.6)	
Sex			
Female	37 (34.9)	14 (38.9)	0.67
Male	69 (65.1)	22 (61.1)	
Ethnicity			
Chinese	96 (90.6)	35 (97.2)	0.21
Non-Chinese	10 (9.4)	1 (2.8)	
Presence of comorbidities			
No	48 (45.3)	19 (52.8)	0.34
Yes	58 (54.7)	17 (47.2)	
Tumor stage (TNM)			
1	36 (34)	0 (0)	<0.001*
2	10 (9.4)	2 (5.6)	
3	37 (34.9)	9 (25)	
4	23 (21.7)	25 (69.4)	
Depth of tumor invasion (pT)			
T1	23 (21.7)	0 (0)	<0.001*
T2	23 (21.7)	0 (0)	
T3	53 (50)	19 (52.8)	
T4	7 (6.6)	17 (47.2)	
Nodal involvement			
No	62 (58.5)	8 (22.2)	<0.001*
Yes	44 (41.5)	28 (77.8)	
Intent of operation			
Curative (R0 resection)	83 (78.3)	10 (27.8)	<0.001*
Palliative (R2 resection)	23 (21.7)	26 (72.2)	
Type of operation			
Total gastrectomy	34 (32.1)	10 (27.8)	0.76
Distal gastrectomy	70 (66)	14 (38.9)	
Proximal gastrectomy	2 (1.9)	1 (2.8)	
Bypass	0 (0)	3 (8.3)	
Open-close	0 (0)	8 (22.2)	
Postoperative complications			
No	89 (84)	28 (77.8)	0.14
Yes	17 (16)	8 (22.2)	
Recurrence			
No	67 (63.2)	5 (13.9)	0.005*
Yes	16 (15.1)	6 (16.7)	
Not applicable ^a	23 (21.7)	25 (69.4)	
Overall mortality			
Alive	82 (77.4)	8 (22.2)	<0.001*
Dead	24 (22.6)	28 (77.8)	

* Significant

^a Due to presence of residual tumor or distant metastasis at the time of surgery

tality with peritoneal cytology positivity. For patients with positive peritoneal cytology, all had tumor invasion of the serosal surface. Peritoneal dissemination was grossly evident in 17 patients and was confirmed histopathologically. Excluding tumors with serosal involve-

ment alone (T3), the sensitivity of peritoneal lavage cytology in detecting peritoneal disease was 70.8% (95% confidence interval, 50.8–85.1) and specificity was 70.8% (95% confidence interval, 58.8–80.4). The positive predictive value of peritoneal lavage cytology was

Table 2. Factors influencing the positivity of peritoneal cytological examination, using univariate and multivariate logistic regression, among patients with serosa-positive (pT3, pT4) tumors ($n = 96$)

Clinicopathologic factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	<i>P</i> value	OR	95% CI	<i>P</i> value
Age (years)						
≤67	1	—	—			
>67	1.40	0.65–3.00	0.39			
Sex						
Female	1	—	—			
Male	1.19	0.54–2.59	0.67			
Ethnicity						
Non-Chinese	1	—	—			
Chinese	3.14	0.45–29.5	0.23			
Presence of comorbidities						
No	1	—	—			
Yes	1.21	0.42–2.89	0.28			
Macroscopic type						
Other types	1	—	—	1	—	—
Diffuse ulcerative and infiltrative	5.49	1.50–20.11	0.01*	2.69	0.65–11.17	0.17
Histologic type						
Differentiated	1	—	—	1	—	—
Poorly differentiated	2.87	0.97–8.55	0.06	1.82	0.53–6.28	0.34
Vascular involvement						
Negative	1	—	—	1	—	—
Positive	7.58	2.59–22.15	<0.001*	7.37	2.33–23.26	0.001*
Lauren's classification						
Intestinal or mixed	1	—	—			
Diffuse	0.76	0.32–1.82	0.54			
Depth of invasion (pT)						
T3	1	—	—	1	—	—
T4	6.77	2.43–18.87	<0.001*	6.56	2.11–20.34	0.001*
Nodal involvement						
Negative	1	—	—	1	—	—
Positive	2.68	1.05–6.83	0.04*	0.61	0.18–2.15	0.45
Distant metastasis						
Negative	1	—	—	1	—	—
Positive	5.20	2.10–12.86	<0.001*	4.32	0.41–7.29	0.01*

* Significant

OR, odds ratio; 95% CI, 95% confidence interval

47.2% and its negative predictive value, 86.8%. Patients who had advanced macroscopic features, presence of vascular invasion, nodal involvement, increased depth of tumor invasion (pT), and metastatic disease tended to have positive lavage results by univariate analysis. Using multiple logistic regression analysis by a backward stepwise selection procedure, the most significant factors were depth of tumor invasion (pT) and vascular invasion (Table 2).

Among patients who had undergone curative resections ($n = 93$), those with positive peritoneal lavage (5/10) had a 15 times higher risk of peritoneal recurrence than those with negative lavage (5/83) results (odds ratio [OR], 15.6; 95% confidence intervals [CI],

2.71–97.67, $P = 0.001$). Further, there was a trend towards earlier recurrences in patients with positive lavage (median, 8 months versus 11 months; $P = 0.37$ by log rank test). Peritoneal dissemination occurred in 42% (10/24) of those with recurrent disease and was the most common clinical presentation in this study population. Recurrence secondary to hematogenous spread was diagnosed in 4 patients, including 2 patients with hepatic, 1 with pulmonary, and 1 with bone metastases. Recurrence at regional lymph nodes was found in 3 patients, while 5 patients had recurrence in the gastric bed or remnant. Disease-free survival was worse for those with positive lavage (median, of 27 months versus 53 months; $P = 0.004$ by log rank test; Fig. 1). By

Fig. 1. Disease-free survival for curative resections according to lavage status

Fig. 3. Overall survival of patients with serosa-positive gastric cancer (pT3, pT4) according to cytology status

Fig. 2. Overall survival by depth of invasion (pT stage)

multivariate Cox regression analysis by stepwise backward procedure, advanced depth of tumor invasion and positive lavage cytology were independent poor prognostic factors for disease-free survival (Table 3).

Because advanced depth of tumor invasion exerted a significant effect on overall survival (Fig. 2), the group of patients with serosa-positive tumors was analyzed separately. Those with positive cytology had a more, dismal overall survival (Fig. 3), with a median survival of 7 months versus 23 months ($P < 0.0001$ by log rank test). Positive lavage cytology remained as a significant factor for poor disease-free survival among those who underwent curative resections (Table 4). Even among patients who had undergone a non-curative procedure, their survival was significantly worse if their lavage cytology had been positive (median survival, 7 months

Fig. 4. Overall survival for palliative procedures according to lavage status

versus 14 months for negative lavage cytology ($P = 0.003$ by log rank test; Fig. 4).

Discussion

The prognosis of gastric cancer has altered little despite extensive nodal resection and advances in the adjuvant chemotherapeutic armamentarium. Increased detection of earlier-stage disease, and advances in preoperative staging and perioperative care have improved patient selection and operative survival, translating into improved long-term survival for patients with resectable

Table 3. Univariate and multivariate Cox regression analysis to predict disease-free survival for patients who underwent curative resections ($n = 93$)

Clinicopathologic factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age (years)						
≤67	1	—	—			
>67	1.24	0.46–3.34	0.67			
Sex						
Female	1	—	—			
Male	1.80	0.67–4.79	0.24			
Ethnicity						
Non-Chinese	1	—	—			
Chinese	1.88	1.24–19.86	0.36			
Presence of comorbidities						
No	1	—	—			
Yes	1.18	0.24–3.19	0.54			
Macroscopic type						
Other types	1	—	—	1	—	—
Diffuse ulcerative and infiltrative	4.01	1.49–15.20	0.01*	1.15	0.25–4.26	0.46
Histologic type						
Differentiated	1	—	—			
Poorly differentiated	1.16	0.38–3.53	0.80			
Vascular involvement						
Negative	1	—	—	1	—	—
Positive	4.20	7.38–13.00	0.01*	1.20	0.33–4.36	0.78
Lauren's classification						
Intestinal or mixed	1	—	—			
Diffuse	1.53	0.50–4.68	0.46			
Depth of invasion (pT)						
T1,T2	1	—	—	1	—	—
T3	7.11	1.57–20.52	0.01*	8.98	2.52–15.46	0.02*
Nodal involvement						
Negative	1	—	—	1	—	—
Positive	4.77	1.31–17.39	0.02*	4.31	1.45–24.32	0.07
Peritoneal cytology						
Negative	1	—	—	1	—	—
Positive	7.12	2.18–18.24	0.01*	11.51	3.05–28.12	<0.001*

* Significant

HR, hazard ratio; 95% CI, 95% confidence interval

cancers [10]. However, the prognosis for advanced cancer remains dismal, with an overall 5-year survival rate of about 20% [11,12].

Peritoneal metastasis is the most frequent cause of death in such patients, with an average survival of only 6 months after peritoneal recurrence [13]. In patients with serosal involvement, 50% developed peritoneal recurrence even if curative resections were performed [14,15]. In our series, our findings reflect this trend, with 41% (20/49) of T3 tumors ending up with disease recurrence despite curative resections; out of which half (10/20) recurred as peritoneal disease. Analysis of prognostic factors is therefore important in this group of patients.

Cytological examination of peritoneal lavage fluid has been proposed as a useful predictor of peritoneal recurrence in gastric cancer patients, based on several studies reporting a close correlation between peritoneal carcinomatosis and serosal invasion or the seeding of free cancer cells [16,17]. Iitsuka et al. [18] had observed that the presence of free intraperitoneal cancer cells relied on cancer invasion of the serosa, because cytological positivity did not occur in patients without serosal invasion. Similarly, our study found serosal invasion to be associated with a higher likelihood of cytological positivity. None of the patients with pT1 and pT2 tumors had positive cytology results. Further, several large series have demonstrated a prognostic role for

Table 4. Univariate and multivariate Cox regression analysis to predict disease-free survival for patients with serosa-positive tumors who underwent curative resections ($n = 45$)

Clinicopathologic factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age (years)						
≤67	1	—	—			
>67	1.15	0.38–3.42	0.81			
Sex						
Female	1	—	—			
Male	0.19	0.14–1.14	0.39			
Ethnicity						
Non-Chinese	1	—	—			
Chinese	1.92	0.74–4.23	0.41			
Presence of comorbidities						
No	1	—	—			
Yes	1.02	0.12–2.21	0.76			
Macroscopic type						
Other types	1	—	—	1	—	—
Diffuse ulcerative and infiltrative	6.41	1.51–17.20	0.01*	2.33	1.01–5.40	0.08
Histologic type						
Differentiated	1	—	—			
Poorly differentiated	0.86	0.37–1.97	0.72			
Vascular involvement						
Negative	1	—	—	1	—	—
Positive	1.87	0.84–4.14	0.12	1.04	0.40–2.69	0.93
Lauren's classification						
Intestinal or mixed	1	—	—			
Diffuse	1.01	0.46–2.20	0.98			
Nodal involvement						
Negative	1	—	—	1	—	—
Positive	1.95	0.86–4.41	0.11	1.21	0.56–3.54	0.21
Peritoneal cytology						
Negative	1	—	—	1	—	—
Positive	8.06	1.33–15.56	0.02*	4.23	1.24–12.63	0.01*

* Significant

HR, hazard ratio; 95% CI, 95% confidence interval

cytological findings [1,10,15,16]. Nakajima et al. [10] found that survival rates were significantly lower when cytological examination was positive — even when patients were in the same clinical stage. Bando et al. [1] proposed peritoneal lavage cytological examination as a useful predictor of peritoneal recurrence after curative resections, with a sensitivity of 56% and specificity of 97%. Their series found a 30% incidence of positive malignant cytology among serosal-invasive tumors and a 49% incidence among those with gross peritoneal disease. Positive cytology was an independent poor prognostic factor for overall survival, with 5-year survival rates of 2% and 58% for those with positive and negative cytology, respectively. Though the study population in our series was small, close parallels can be observed — we found a 26.4% incidence of positive malignant cytology among serosa-positive tumors and an inci-

dence of 70.8% among those with gross peritoneal disease. Positive cytological examination, advanced serosal invasion, and metastatic disease, including peritoneal dissemination, were independent prognostic indicators for poor overall survival (Table 5). Multivariate analysis, using the Cox stepwise hazard model, revealed that the cytological findings were statistically significant for disease-free survival among the other prognostic factors selected by univariate analysis (Table 3). This remained true even after controlling for T stage (Table 4). These results suggest that peritoneal cytological findings have a strong independent prognostic influence following curative resection. Even for those who underwent palliative procedures, survival was significantly worse for those with positive cytology results (mean, 7 months versus 14 months; $P = 0.003$ by log rank test). We also observed a trend of earlier recurrences in the group

Table 5. Univariate and multivariate Cox regression analysis to predict overall survival for patients with serosa-positive (pT3, pT4) tumors ($n = 96$)

Clinicopathologic factors	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i> value	HR	95% CI	<i>P</i> value
Age (years)						
≤67	1	—	—			
>67	0.71	0.42–1.17	0.18			
Sex						
Female	1	—	—			
Male	1.19	0.70–2.01	0.52			
Ethnicity						
Non-Chinese	1	—	—			
Chinese	2.04	0.67–11.22	0.20			
Presence of comorbidities						
No	1	—	—			
Yes	1.42	0.82–3.02	0.62			
Macroscopic type						
Other types	1	—	—	1	—	—
Diffuse ulcerative and infiltrative	3.50	1.38–8.86	0.008*	1.51	0.55–4.14	0.43
Histologic type						
Differentiated	1	—	—			
Poorly differentiated	0.99	0.52–1.92	0.99			
Vascular involvement						
Negative	1	—	—	1	—	—
Positive	1.77	0.96–3.27	0.07	0.91	0.42–1.94	0.80
Lauren's classification						
Intestinal or mixed	1	—	—	1	—	—
Diffuse	0.60	0.32–1.12	0.11	1.24	0.56–2.75	0.59
Depth of invasion (pT)						
T3	1	—	—	1	—	—
T4	5.51	3.04–9.98	<0.001*	2.21	1.11–4.41	0.02*
Nodal involvement						
Negative	1	—	—	1	—	—
Positive	2.30	1.19–4.44	0.01*	1.06	0.48–2.33	0.89
Distant metastasis						
Negative	1	—	—	1	—	—
Positive	5.32	3.23–11.52	<0.001*	3.89	2.62–10.35	0.01*
Peritoneal cytology						
Negative	1	—	—	1	—	—
Positive	4.35	2.42–7.81	<0.001*	2.31	1.19–4.47	0.01*

*Significant

HR, hazard ratio; 95% CI, 95% confidence interval

with positive cytology results (median, 8 months versus 11 months; $P = 0.37$). This trend failed to reach statistical significance, although this could be explained by the small sample size and perhaps an inadequate follow-up period. Moreover, analysis of recurrence patterns varies widely — with inconsistencies related to different surgical treatments, as well as the mode and timing of detection of recurrence.

Our study also revealed that tumors with vascular invasion had a significantly higher rate of positive cytological findings than those without (Table 2). These re-

sults suggest that such tumors may have a propensity for peritoneal dissemination. This adds to the existing theories of peritoneal carcinomatosis that suggest the shedding of cancer cells from the serosal surface of the primary tumor [17] and metastatic routes via the lymphatic system [19].

In the West, peritoneal lavage for cytological examination is not routine. The Dutch Gastric Cancer Trial demonstrated positive cytology in only 7.1% of all patients with gastric cancer and in 12% of those with serosal invasion [20]. Though the incidence of positive

cytology was lower in their series than that in Japanese studies, a 10.65% (57/535) incidence of missing or inconclusive cytology results probably implied inconsistent handling and interpretation of results, hence reducing the detection rate. Nonetheless, they demonstrated a significant association of positive cytology results with serosal invasion and lymph node infiltration, and they showed that the survival of patients with positive cytology results was significantly worse than that of patients with negative findings. Hayes et al. [21] from the Northern Oesophagogastric Cancer Unit in the United Kingdom, found a 27% incidence of positive peritoneal malignant cytology. In their study, they had gone further to demonstrate that the yield of free cells could be significantly increased by the addition of both brush cytology and imprint cytology. Again, survival was significantly worse in the group with positive cytology, with a survival of 22% at 2-year follow-up compared to 66% for the cytology-negative group ($P < 0.0001$).

Despite these encouraging reports, the overall accuracy of cytological examination has been criticized as being variable; ranging from 22% to 30% in gastric carcinoma involving the serosa [6–8]. This can be explained by the non-standardized methods of performing peritoneal lavage and the presence of interobserver bias between cytopathologists in grading the cytological findings. Abe et al. [7] pointed out that false-negative cases might arise from technical flaws, such as incomplete sampling, that were not representative of the lavage process. In patients with early peritoneal dissemination, cancer cells may reside deep in the mesothelial cell layer and, hence, would not be exposed to the peritoneal surface.

More sensitive methods for the early detection of peritoneal dissemination were deemed necessary. This brought about various methods aimed either at refining the cell-yield technique through molecular approaches or targeting a different factor altogether.

Nakanishi et al. [22] demonstrated that carcinoembryonic antigen (CEA) concentrations in peritoneal washings were independent of those in paired serum samples and could predict peritoneal metastasis more reliably than conventional cytological study. Kodera et al. [23] followed this with the use of reverse transcriptase-polymerase chain reaction (RT-PCR) analysis with primers specific for CEA to improve the sensitivity of peritoneal lavage analysis. Based on investigations by Ohta et al. [24] showing that human gastric cancers immunoreacted with a monoclonal antibody against pancreatic trypsinogen, Fujimura et al. [25] found that trypsinogen protein and trypsinogen-1 mRNA expression demonstrated by RT-PCR could serve as a novel marker to detect early peritoneal dissemination of gastric cancer.

These novel methods suffer from being tedious to perform, time-consuming, and costly; as well, they require specialized laboratory facilities and trained expertise to carry out. More importantly, definitive results for diagnosis could not be reached at the time of the operation. Further technical refinements have been suggested to achieve rapid analysis [26,27]. Having a diagnostic result while the operation is still in progress could help guide surgical and adjuvant therapy.

Though it has long been appreciated that patients with advanced gastric cancer offered surgery alone have little hope of being cured, the past decade has witnessed renewed interest in adjuvant therapeutic approaches aimed at improving the survival of these patients. A recently published meta-analysis of 21 randomized studies on the value of adjuvant treatment for gastric cancer revealed a survival benefit for treated patients [28]. The recently concluded findings of the United Kingdom MAGIC trial [29] marked the first large randomized trial to support the efficacy of perioperative chemotherapy for advanced gastric cancer. Progression-free survival was significantly prolonged (hazard ratio [HR], 0.70; 95 CI, 0.56–0.88; $P = 0.002$) in the group randomized to chemotherapy. However, comparison of overall survival at 2 years between the group who received perioperative chemotherapy (48%) and the group who underwent surgery alone (40%) showed no statistically significant difference. The trial has been criticized both for lacking routine standardized preoperative staging assessments and for lacking surgical quality control concerning the extent of lymphadenectomy.

If we recognize peritoneal recurrence as the chief cause of surgical treatment failure and mortality after curative resections, then intraperitoneal chemotherapy is a viable modality to eradicate microscopic residual disease, or as a prophylactic measure. However, like systemic chemotherapy, this too remains controversial. Although randomized trials of adjuvant perioperative intraperitoneal chemotherapy have demonstrated significant improvement in survival compared with surgery alone [5,30], this finding was not supported by multicenter phase III studies [31; Miyashiro et al., unpublished data]. Other modalities that have been explored include intraperitoneal administration of carbon-adsorbed mitomycin C [32] or OK432 [33] and cytoreductive surgery, together with systemic intraoperative hyperthermochemotherapy [34].

Adjuvant chemotherapy, whether systemic or intraperitoneal, is costly, with no added benefit to patients without residual disease; and it is not without menacing toxicity and morbidity. Detection of free cancer cells can therefore be of great value in the selection of patients who may benefit from further aggressive therapy. Such detection helps to select candidates

for neoadjuvant and adjuvant chemotherapy trials and avoids unnecessary laparotomies in patients in whom only palliation is appropriate. A prospective multicenter study in Europe — Evolution of Peritoneal Carcinomatosis (EVOCAPE) 2 — is currently investigating the prognostic value of peritoneal cytological examination for predicting peritoneal carcinomatosis. The results would better define a patient group for whom adjuvant chemotherapy would be indicated. Setting our findings in perspective, this simple procedure should be included in our current management of our patients with gastric cancer.

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