53.9% for the surgery-only group vs 71.4% for the chemotherapy group. This rate was much higher than in the whole meta-analysis, suggesting that these patients had a good baseline prognosis. Disease-free survival was not collected in 1 of the 2 trials and hence not analyzed.

Polychemotherapies: Fluorouracil + Mitomycin C + Others Without Anthracyclines. Three Japanese trials with 1053 patients total used combined chemotherapy including fluorouracil derivatives, mitomycin C, and others without anthracyclines.[21-23] Overall, a statistically significant benefit for OS was observed (HR, 0.74; 95% CI,
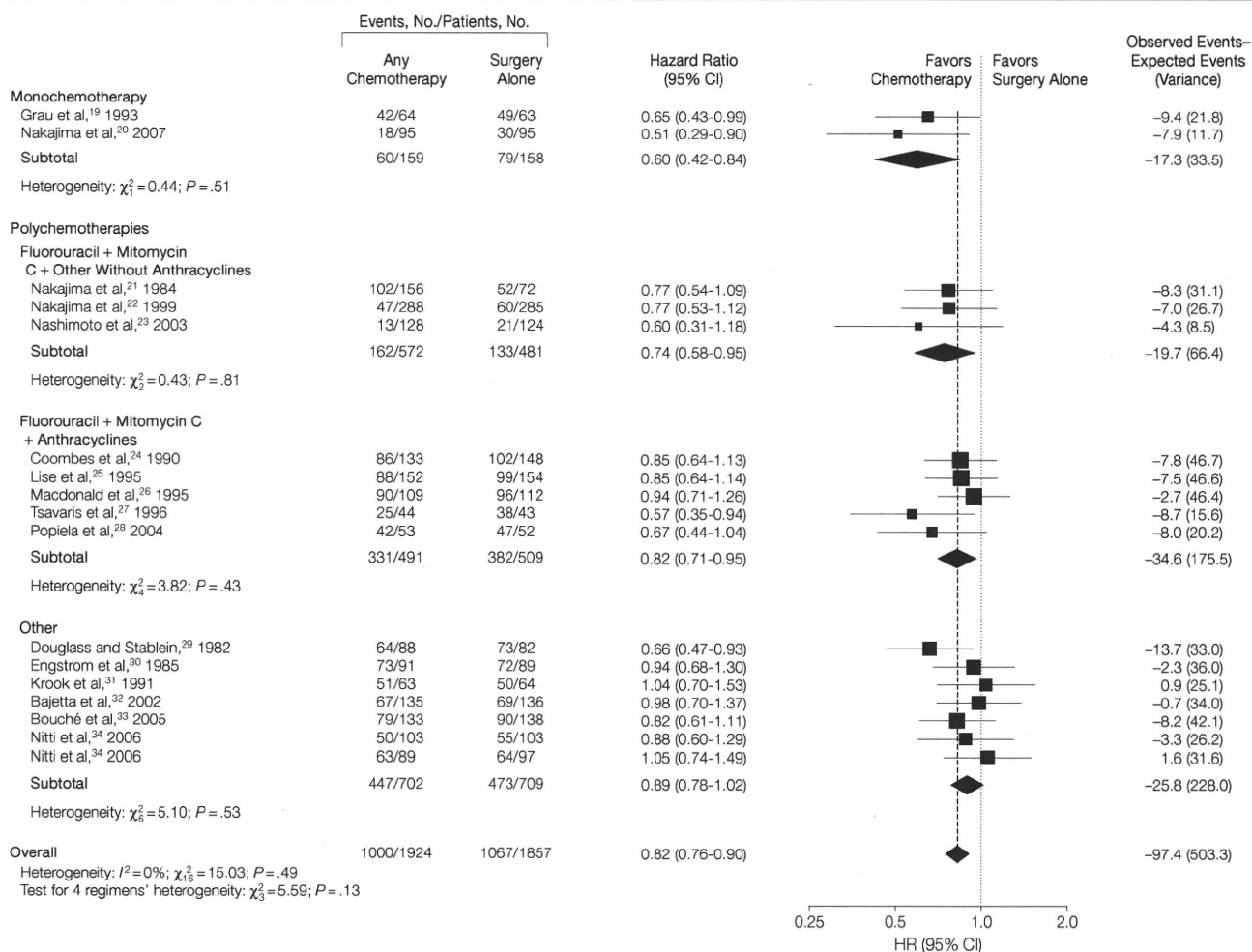
0.58-0.95; P = .03), with 5-year survival rates of 76.6% for the surgery-only group vs 82.8% for the chemotherapy group. A similar effect on DFS was observed in the 2 more recent studies (HR, 0.69; 95% CI, 0.48-0.98) with 5-year DFS rates of 84.2% for the surgery-only group vs 88.2% for the chemotherapy group.

Polychemotherapies: Fluorouracil + Mitomycin C + Anthracyclines. Five trials (4 European, 1 US) using combined chemotherapy including anthracyclines had 1013 patients total and 1000 patients with OS data.[24-28] Overall, a statistically significant hazard re-

duction was observed for OS (HR, 0.82; 95% CI, 0.71-0.96; P = .01). The 5-year survival rate increased from 31.9% to 39.3%, and heterogeneity was not detected (P = .52). The HR for DFS was estimated from 4 trials. The risk of relapse or second primary cancer or death was also statistically significantly reduced (HR, 0.80; 95% CI, 0.69-0.94; P = .006) with 5-year DFS rates of 31.9% for the surgery-only group vs 39% for the chemotherapy group.

Polychemotherapies: Group "Other" vs Surgery Alone. For 1411 of 1448 patients in 7 trials for whom survival data were available,[29-34] we did not detect a

Figure 2. Individual Trial and Overall Hazard Ratio for Overall Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone

	Events, No./Patients, No.		Hazard Ratio (95% CI)	Favors Chemotherapy / Favors Surgery Alone	Observed Events–Expected Events (Variance)
	Any Chemotherapy	Surgery Alone			
Monochemotherapy					
Grau et al,[19] 1993	42/64	49/63	0.65 (0.43-0.99)		−9.4 (21.8)
Nakajima et al,[20] 2007	18/95	30/95	0.51 (0.29-0.90)		−7.9 (11.7)
Subtotal	60/159	79/158	0.60 (0.42-0.84)		−17.3 (33.5)
Heterogeneity: χ_1^2 = 0.44; P = .51					
Polychemotherapies					
Fluorouracil + Mitomycin C + Other Without Anthracyclines					
Nakajima et al,[21] 1984	102/156	52/72	0.77 (0.54-1.09)		−8.3 (31.1)
Nakajima et al,[22] 1999	47/288	60/285	0.77 (0.53-1.12)		−7.0 (26.7)
Nashimoto et al,[23] 2003	13/128	21/124	0.60 (0.31-1.18)		−4.3 (8.5)
Subtotal	162/572	133/481	0.74 (0.58-0.95)		−19.7 (66.4)
Heterogeneity: χ_2^2 = 0.43; P = .81					
Fluorouracil + Mitomycin C + Anthracyclines					
Coombes et al,[24] 1990	86/133	102/148	0.85 (0.64-1.13)		−7.8 (46.7)
Lise et al,[25] 1995	88/152	99/154	0.85 (0.64-1.14)		−7.5 (46.6)
Macdonald et al,[26] 1995	90/109	96/112	0.94 (0.71-1.26)		−2.7 (46.4)
Tsavaris et al,[27] 1996	25/44	38/43	0.57 (0.35-0.94)		−8.7 (15.6)
Popiela et al,[28] 2004	42/53	47/52	0.67 (0.44-1.04)		−8.0 (20.2)
Subtotal	331/491	382/509	0.82 (0.71-0.95)		−34.6 (175.5)
Heterogeneity: χ_4^2 = 3.82; P = .43					
Other					
Douglass and Stablein,[29] 1982	64/88	73/82	0.66 (0.47-0.93)		−13.7 (33.0)
Engstrom et al,[30] 1985	73/91	72/89	0.94 (0.68-1.30)		−2.3 (36.0)
Krook et al,[31] 1991	51/63	50/64	1.04 (0.70-1.53)		0.9 (25.1)
Bajetta et al,[32] 2002	67/135	69/136	0.98 (0.70-1.37)		−0.7 (34.0)
Bouché et al,[33] 2005	79/133	90/138	0.82 (0.61-1.11)		−8.2 (42.1)
Nitti et al,[34] 2006	50/103	55/103	0.88 (0.60-1.29)		−3.3 (26.2)
Nitti et al,[34] 2006	63/89	64/97	1.05 (0.74-1.49)		1.6 (31.6)
Subtotal	447/702	473/709	0.89 (0.78-1.02)		−25.8 (228.0)
Heterogeneity: χ_6^2 = 5.10; P = .53					
Overall	1000/1924	1067/1857	0.82 (0.76-0.90)		−97.4 (503.3)
Heterogeneity: I^2 = 0%; χ_{16}^2 = 15.03; P = .49					
Test for 4 regimens' heterogeneity: χ_3^2 = 5.59; P = .13					

0.25   0.5   1.0   2.0
HR (95% CI)

The inverse of the variance of observed events minus expected events measures the weight of each trial in the analysis. P values are from P-for-effect modification testing for heterogeneity within or across the groups of regimens. The sizes of data markers are proportional to the number of deaths in the trials. CI indicates confidence interval; HR, hazard ratio.

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years
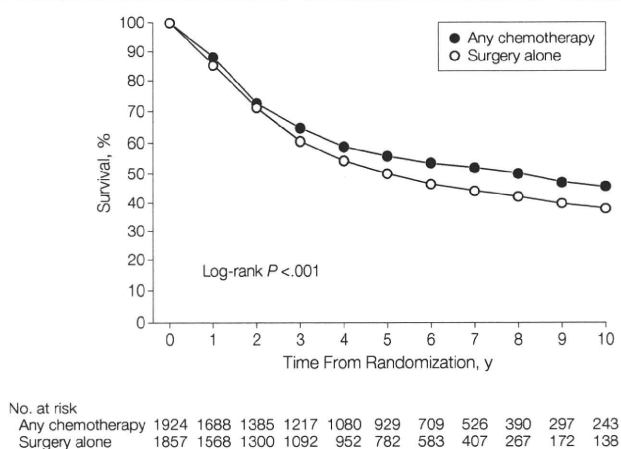
The estimates of the survival curves use an actuarial approach as described in the Methods.

significant effect of adjuvant regimens vs surgery alone (HR, 0.89; 95% CI, 0.78-1.02; P=.09). The 5-year survival rate was 41.5%. Heterogeneity was not detected (P=.51) even though 1 trial[29] that used fluorouracil and semustine showed a significant treatment effect. Five-year DFS was 41.9% for the surgery-only group vs 44.5% for the chemotherapy group, and a marginally significant effect of treatment on DFS was observed (HR, 0.88; 95% CI, 0.78-1.0; P=.05), which was mainly driven by the positive study[29]; in a sensitivity analysis excluding this trial, the DFS effect was not significant (HR, 0.91; 95% CI, 0.79-1.04; P=.18).

Proportionality of the Hazard Functions

Plots of survival curves for all chemotherapy regimens combined or in each regimen group suggested nonproportional hazard functions, as illustrated by late separation of the survival function estimates. Nonproportional hazards were not detected using the Grambsch and Therneau test (P=.35). When a time-dependent model was fitted on the full data set with a cut-point at 2 years, treatment effect before and after 2 years was significantly different (P<.001). Point estimates of the HR by 2-year intervals

showed a regular decrease from 0.91 in the first 2 years from randomization to 0.75 between 2 and 4 years and 0.62 beyond 4 years. After 8 years, the number of events became too small to provide meaningful estimates. Because these cut-points were derived from the data, they should be considered with caution. Hazard functions showed that the rate of death reached a peak at 18 months and steadily decreased thereafter to reach a plateau at about 5 years (eFigure 8).

COMMENT

Adjuvant chemotherapy without radiation for gastric cancer has recently become the standard of care in Japan after the publication of the results of the ACTS-GS trial reporting on S-1[4] but not in Europe or the United States. Numerous randomized phase 2 and phase 3 trials have produced conflicting results. However, many of these trials had limited sample sizes, making it difficult to draw definitive conclusions. Based on the individual data of 3838 patients from 17 different trials with a median follow-up longer than 7 years, the largest patient-level meta-analysis performed so far, we showed a modest but statistically significant benefit associated with adjuvant chemo-

therapy after curative resection of gastric cancers. The mortality hazard was reduced by about 18% and an absolute improvement of about 6% in OS was observed after 5 years. This improvement was maintained at 10 years. An 18% reduction in the risk of relapse, second primary, or death was also observed. This treatment benefit was maintained in 3 of the 4 investigated groups of fluorouracil-based regimens, with reductions in the risk of death ranging from 20% to 40% (nonstatistically significant heterogeneity). Only 1 trial[19] that enrolled 134 patients investigated a non–fluoropyrimidines-based regimen. Sensitivity analysis excluding this trial led to the same results. The absence of interaction with the class of regimen and with the region as well as the long follow-up is reassuring. Patient-level meta-analyses are the most reliable means to provide an exhaustive and unbiased summary of the available evidence on a clinical question of interest and complete large well-conducted trials (such as those that are currently done).

Postoperative chemotherapy is not the only adjuvant treatment for gastric cancer. In 2001, results of a trial that randomized between surgery and surgery with chemoradiotherapy showed an absolute increase in median survival of 9 months.[49] Thereafter, chemoradiation therapy has gained popularity and has been increasingly used as a standard of care, especially in the United States, even though the optimal chemotherapy regimen has not been identified yet. Several trials are currently being conducted to explore this issue, but their results will not be available until 2011. Similarly, neoadjuvant trials have shown the benefit of starting the chemotherapy treatment as early as possible.[50-52] Although the short-term results of delayed surgery are being debated,[53] neoadjuvant treatment, which can be administered to more patients than postoperative chemotherapy, has gained acceptance in western countries.

We could only collect about two-thirds of all data available from randomized trials in early gastric cancer, which is disappointing in view of the intensive efforts made at repeatedly contacting the principal investigators of the trials. However, for all but 3 trials with unavailable individual patient data, we could extract summary statistics from the published articles. Our results remained unchanged when these summary statistics were included in the calculations. Combining unverified published summary statistics with carefully checked individual patient data is not a satisfactory way of estimating an unbiased overall treatment effect, but it provides a way of assessing the robustness of a meta-analysis with respect to unavailable trials.

The optimal design of future adjuvant gastric cancer clinical trials, particularly the choice of an adequate control group, is a delicate issue. It is beyond the scope of our meta-analysis to identify the optimal regimen; however, based on our data, chemotherapy seems justified as a control group. Fluoropyrimidines-based regimens, in particular the oral forms (uracil plus tegafur and recently S-1 monotherapy) that have been shown to be better tolerated,[8] seem reasonable treatment options, although their applicability outside East Asian countries remains uncertain. This raises the question of why fluoropyrimidines (intravenous fluorouracil or oral tegafur) appear to have activity in the adjuvant setting for gastric cancer as well as in colon cancer even though their efficacy is disappointing for the treatment of advanced disease.

In conclusion, this patient-level meta-analysis shows that adjuvant fluorouracil-based chemotherapy, even in monotherapy, is associated with improvement in overall survival (HR, 0.82) and is recommended for patients who have not received perioperative treatments after complete resection of their gastric cancer. Future reports based on data being collected will explore prognostic factors and the surrogacy of disease-free survival for overall survival in this population.

Figure 4. Individual Trial and Overall Hazard Ratio for Disease-Free Survival When Comparing Any Adjuvant Chemotherapy vs Surgery Alone

| | Events, No./Patients, No. | | | | | Observed Events– |
	Any Chemotherapy	Surgery Alone	Hazard Ratio (95% CI)	Favors Chemotherapy · Favors Surgery Alone		Expected Events (Variance)
Monochemotherapy						
Nakajima et al,[20] 2007	20/95	34/95	0.49 (0.29-0.84)			−9.3 (13.1)
Polychemotherapies						
Fluorouracil + Mitomycin C + Other Without Anthracyclines						
Nakajima et al,[22] 1999	36/276	48/270	0.72 (0.47-1.11)			−6.8 (21.0)
Nashimoto et al,[23] 2003	15/128	23/124	0.62 (0.33-1.16)			−4.6 (9.5)
Subtotal	51/404	71/394	0.69 (0.48-0.98)			−11.4 (30.5)
Heterogeneity: $\chi_1^2 = 0.17$; $P = .68$						
Fluorouracil + Mitomycin C + Anthracyclines						
Coombes et al,[24] 1990	89/133	102/148	0.87 (0.66-1.16)			−6.6 (47.5)
Lise et al,[25] 1995	89/152	103/152	0.77 (0.58-1.02)			−12.6 (47.7)
Macdonald et al,[26] 1995	89/107	97/112	0.88 (0.66-1.17)			−6.1 (46.4)
Tsavaris et al,[27] 1996	28/44	38/43	0.57 (0.35-0.92)			−9.2 (16.1)
Subtotal	295/436	340/455	0.80 (0.69-0.94)			−34.6 (157.7)
Heterogeneity: $\chi_3^2 = 2.74$; $P = .43$						
Other						
Douglass and Stablein,[29] 1982	65/90	75/88	0.73 (0.53-1.03)			−10.7 (34.4)
Engstrom et al,[30] 1985	74/91	74/89	0.89 (0.64-1.24)			−4.3 (36.7)
Krook et al,[31] 1991	52/63	51/64	0.94 (0.64-1.39)			−1.5 (25.6)
Bajetta et al,[32] 2002	72/135	77/136	0.90 (0.66-1.25)			−3.7 (37.2)
Bouché et al,[33] 2005	81/133	91/138	0.82 (0.61-1.10)			−8.6 (42.8)
Nitti et al,[34] 2006	52/103	56/103	0.90 (0.61-1.31)			−3.0 (27.0)
Nitti et al,[34] 2006	65/89	63/96	1.06 (0.75-1.50)			1.9 (31.9)
Subtotal	461/704	487/714	0.88 (0.78-1.00)			−29.9 (235.5)
Heterogeneity: $\chi_6^2 = 2.64$; $P = .85$						
Overall	827/1639	932/1658	0.82 (0.75-0.90)			−85.2 (436.8)
Heterogeneity: $I^2 = 0\%$; $\chi_{13}^2 = 11.20$; $P = .60$						
Test for regimens' heterogeneity: $\chi_3^2 = 5.60$; $P = .13$						

HR (95% CI): 0.25 0.5 1.0 2.0

The inverse of variance of observed events minus expected events measures the weight of each trial in the analysis. P values are from P-for-effect modification testing for heterogeneity within or across the groups of regimens. The sizes of the data markers are proportional to the number of events. CI indicates confidence interval; HR, hazard ratio.

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Significance of Lavage Cytology in Advanced Gastric Cancer Patients

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Abstract

Background Lavage cytology positive (Cy1) is well known as a poor prognostic factor in advanced gastric cancer patients. However, the optimal therapeutic strategy for patients with Cy1 has not yet been established. The aim of this study was to evaluate the clinical significance of Cy1 for the purpose of establishing a suitable therapeutic strategy.

Methods The data of 996 consecutive advanced gastric cancer patients who underwent gastrectomy between 1992 and 1998 at the National Cancer Center Hospital were retrospectively studied.

Results The 2- and 5-year survival rates of the patients who underwent gastrectomy without any other noncurative factors besides Cy1 were 25.3 and 7.8%, respectively. When the analysis was limited to type 4 advanced gastric cancer patients, none of the patients with Cy1 survived for more than 40 months.

Conclusions The prognosis of gastric cancer patients with Cy1 is very poor. Some patients show long survival after standard gastrectomy with D2 lymph node dissection; however, the prognosis of type 4 gastric cancer patients with Cy1 is so poor that multimodality therapy, including perioperative chemotherapy, is essential.

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Introduction

Recently, standard therapeutic strategies have been established for gastric cancer patients based on the results of some clinical trials [1–3]. The treatment outcomes of early gastric cancer patients are now favorable [4] due to the remarkable progress in endoscopic treatments [5, 6] and minimally invasive surgery, including function-preserving gastrectomy [7] and laparoscopic gastrectomy [8]. However, many surgeons believe that the treatment outcomes of advanced gastric cancer patients remain poor.

Peritoneal dissemination is one of the most frequent modes of metastasis in advanced gastric cancer. The possibility of cure in patients with this metastasis is considered to be low because no effective curative therapy has been established so far. Even after curative surgery in patients without evidence of peritoneal dissemination at the time of the operation, many patients develop peritoneal recurrence, which is extremely difficult to overcome [9].

The majority of patients showing lavage cytology-positive (Cy1) intraoperatively develop peritoneal recurrence [9]. Cy1 can be interpreted as a state in which free cancer cells are floating in the abdominal cavity, with small peritoneal foci already established in the peritoneum [10]. However, despite Cy1 being recognized as a definite predictive factor for peritoneal recurrence of gastric cancer[11–13], no effective treatment strategies have been established for Cy1 gastric cancer patients. In some cases prolonged survival has been achieved, even in Cy1 patients. When the analysis is limited to patients with type

4 advanced gastric cancer, however, the prognosis of Cy1 seems to be particularly severe [14].

In this study, the exact relevance of Cy1 and the clinical outcomes of these patients were evaluated based on data from a large-volume center of gastric cancer patients. This is expected to be helpful for developing a suitable new therapeutic strategy for this condition.

Patients and methods

The data of 996 consecutive patients who underwent gastrectomy between 1992 and 1998 for advanced gastric cancer that invaded the gastric wall deeper than the muscularis propria, as assessed by histopathological examination performed after the surgery at the National Cancer Center Hospital, were studied retrospectively. All patients underwent partial or total gastrectomy with lymph node dissection. Basically, patients with peritoneal dissemination underwent simple gastrectomy with minimum dissection; other patients underwent standard dissection. Patients with preoperative, clinically definitive peritoneal dissemination, i.e., ascites, hydronephrosis, and colonic stenosis by barium enema study, were not included in this study. Both the patients with diffuse peritoneal dissemination detected at surgery and those with locally resectable peritoneal dissemination were included in this study.

The former Japanese Classification of Gastric Carcinoma defined peritoneal dissemination as P0, P1, P2, and P3 according to its extent, while the current classification (13th) is P0 and P1: with or without. All patients were classified according to the Japanese Classification of Gastric Carcinoma. Macroscopic features of advanced gastric cancer are classified as type 0: superficial, flat tumors; type 1: polypoid tumors; type 2: ulcerated tumors; type 3: ulcerated tumors without definite limits; type 4: diffusely infiltrating carcinomas; and type 5: nonclassifiable carcinomas. For the purpose of the present analysis, the patients were divided into two groups based on the macroscopic features of type 4 gastric cancer and others.

Cytopathology

Cytological samples were obtained just after laparotomy. Approximately 100 ml of sterile saline was instilled into the pouch of Douglas and then aspirated. The samples were subjected to cytocentrifugation onto slide glasses at 1700 rpm for 60 s at room temperature. The slides were then fixed in 95% ethanol, followed by Papanicolaou and alcian blue stains. Additional slides were stained immunocytochemically for CEA (Mochida, CEA010,Tokyo, Japan), and also for epithelial antigen using the BerEP4 antibody (DAKOPATTS, Glostrup, Denmark). Two to

three cytotechnologists and cytopathologists independently examined all the slides to arrive at a diagnosis by consensus. A patient was considered to have positive peritoneal cytology (Cy1) if adenocarcinoma cells were detected, regardless of the number of cells. In cases where atypical cells were present but could not be definitely identified as cancer cells, the peritoneal cytology was estimated as class 3, or indeterminate. Basically, lavage cytology was carried out intraoperatively for advanced gastric cancer cases. The data of cytology in this article, recorded in our database, is the final result confirmed by immunohistochemistry several days after surgery.

Statistical analysis

Statistical analysis was carried out using SPSS software version 11.5 (SPSS Inc., Chicago, IL). The Kaplan–Meier method was used for constructing the survival curves, and the log-rank test was used for evaluating the statistical significance of differences between the survival curves.

Results

Among the 996 cases included in our study, cytological examination was performed in 779 (Table 1). Cytological examination was positive for cancer cells mainly in advanced gastric cancer patients in whom the tumor had invaded outside the serosal surface (T3) or directly invaded adjacent organs (T4) (Table 1).

As expected, many of the patients with peritoneal dissemination (P1) were cytology-positive (Cy1) but 27 patients with peritoneal dissemination (P1) were cytology-negative (Cy0) (Table 2).

Among the 996 consecutive patients, 217 patients who did not undergo cytological examination and 13 whose cytological examination revealed an indeterminate result were excluded from the analysis; in addition, 65 patients who had distant metastasis to the liver, lung, and supraclavicular lymph nodes were also excluded. The remaining

Table 1 Correlation between cytological examination and the depth of the tumors

	T2 (MP)	T2 (SS)	T3	T4	Total
Cy0	78	156	251	56	541
Cy1	1	5	137	82	225
Indeterminate	0	0	9	4	12
Undone	105	58	44	10	217
	184	219	441	152	996

MP muscularis propria, *SS* subserosa, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 2 Correlation between the results of cytological examination and presence/absence of peritoneal dissemination

	P0	P1	Total
Cy0	514	27	541
Cy1	101	124	225
Indeterminate	8	5	13
Undone	196	21	217
	819	177	996

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

Table 3 Number of patients per peritoneal dissemination and cytology type of tumors

	Type4	Other Types	Total
P0Cy0	53	432	485
P0Cy1	33	55	88
P1Cy0	9	13	22
P1Cy1	61	45	106
	156	545	701

P0 without peritoneal dissemination, *P1* with peritoneal dissemination, *Cy0* cytology-negative, *Cy1* cytology-positive

701 patients were divided into four groups: (1) peritoneal dissemination-negative and cytology-negative (P0Cy0), (2) peritoneal dissemination-negative and cytology-positive (P0Cy1), (3) peritoneal dissemination-positive and cytology-negative (P1Cy0), and (4) peritoneal dissemination-positive and cytology-positive (P1Cy1). The number of patients in each category is given in Table 3.

Survival

The overall survival curves of the four groups are shown in Fig. 1. The prognosis of the patients with P1 and/or Cy1 was worse than that of the patients with P0Cy0. The prognosis of the P0Cy1 patients was better than that of the P1Cy1 patients ($p = 0.0002$, log-rank). The median survival time of the P0Cy1 patients was 12 months. The 2-year and 5-year survival rates in the P0Cy1 patients were 25.3% (95% confidence interval [CI] = 16.2–34.4%), and 7.8% (95% CI = 2.0–13.5%) (Table 4). Five (5.7%) of the 88 P0Cy1 patients survived for more than 5 years without evidence of recurrent disease.

The 88 P0Cy1 patients consisted of 33 patients with type4 gastric cancer and 55 with other types of gastric cancer. The survival of P0Cy1 patients with type 4 gastric cancer was significantly worse than that of the patients with other types of gastric cancer, as shown in Fig. 2 ($p = 0.0072$, log-rank). The median survival time was 10 months. The 2-year survival rate was 12.1% (95%
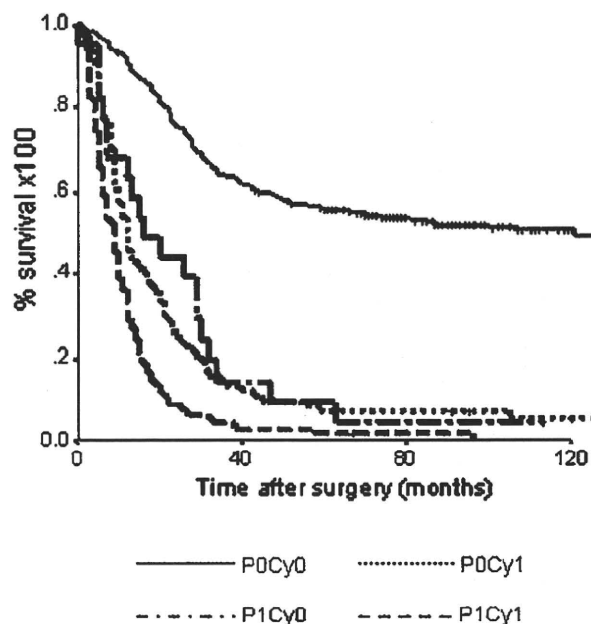
Fig. 1 Overall survival curves of gastric cancer patients (P0Cy0, P0Cy1, P1Cy0, and P1Cy1) are shown. The survival of P0Cy1 patients was poor but better than that of P1Cy1 patients ($p = 0.0002$)

CI = 0.12–22.1%) (Table 4). None of the patients survived for more than 40 months. Among the 88 P0Cy1 patients, 51 patients received postoperative adjuvant chemotherapy, mainly based on fluorouracil, while 35 did not, although this was not randomized. There was no information about adjuvant therapy for two patients who had moved to other hospitals soon after surgery. There was no significant difference in the survival curves between the P0Cy1 patients who received and did not receive adjuvant chemotherapy ($p = 0.1238$, log-rank) (Fig. 3).

Discussion

Lavage cytology-positive (Cy1) is most commonly encountered among gastric cancer patients with deeply invading tumors that extend outside the gastric wall [9, 15]; therefore, it is thought that the cancer cells escape from the surface of the tumors into the intraperitoneal cavity [16]. This is not clearly supported by some experiments, but Cy1 may reflect systemic spread of the tumor cells via the lymphatic pathway, which can cause retroperitoneal invasion, hydronephrosis, and rectal stenosis [17].

The prognosis of the patients who are found at the time of surgery to show peritoneal dissemination is expectedly very poor. The indication of mass reductive or palliative surgery should be evaluated by clinical trial [18], but it is regarded, by consensus, that gastric cancer patients with

Table 4 Survival rate and median survival time of P0Cy1 gastric cancer patients per type of tumor

	1 year	2 years	3 years	5 years	MST
P0Cy1					
All ($n = 88$)	46.0 (35.5–56.5)	25.3 (16.2–34.4)	13.8 (6.5–21.0)	7.8 (2.0–13.5)	12 (9.7–14.3)
Type 4 ($n = 33$)	45.5 (28.5–62.4)	12.1 (0.1–22.1)	0	0	10 (6.8–13.2)
Others ($n = 55$)	51.9 (38.5–65.2)	33.3 (20.8–45.9)	22.2 (11.1–33.3)	12.5 (3.5–21.5)	13 (7.6–18.4)

MST median survival time in months (95% confidence interval)

Values are % (95% confidence interval)
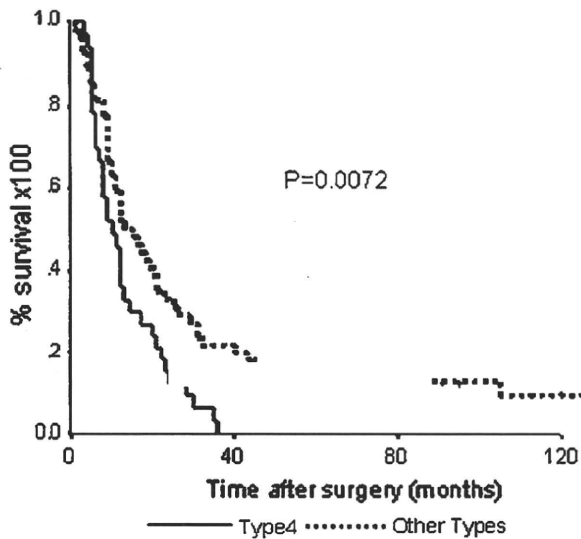
Fig. 2 The survival of P0Cy1 patients with type 4 advanced gastric cancer was significantly worse than that of patients with other types of advanced gastric cancer ($p = 0.0072$)
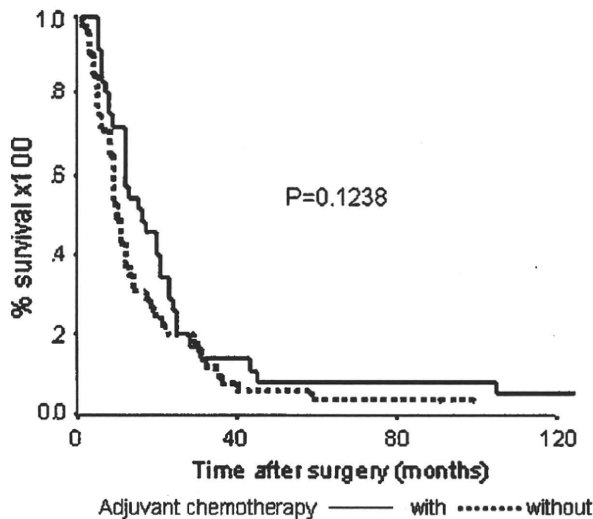
Fig. 3 There was no significant difference in the survival curves between P0Cy1 patients treated/not treated by adjuvant chemotherapy ($p = 0.1238$)

definite peritoneal dissemination are not suitable candidates for gastrectomy.

Cytological examination of intraperitoneal lavage fluid is performed in many institutions in Japan. In some institutions the result is confirmed intraoperatively, while in others it is confirmed on the following day. Cy1 is now included as one of the factors defining Stage IV in the Japanese classification of gastric carcinoma [19] because the prognosis of these patients with Cy1 is poor. However, the knowledge of a patient being Cy1 alone does not seem to be sufficient to decide on the therapeutic procedure [20]. The current consensus is that gastric cancer patients with intraoperatively confirmed Cy1 undergo standard gastrectomy and postoperative adjuvant chemotherapy [21]. Extended lymph node dissection and resection of other organs have gradually become less frequent in these patients. The efficacy of adjuvant chemotherapy with S-1 (1 M tegafur-0.4 M gimestat-1 M otastat potassium) after curative surgery has been reported [3]; however, no satisfactory postoperative adjuvant chemotherapy regimen for gastric cancer patients with Cy1 has been established. In our study, adjuvant chemotherapy using agents other than S-1 yielded no survival benefit. At our institution, S-1 was given as adjuvant chemotherapy to the patients, mainly after the end of the study period. In a future article we shall report on the efficacy of adjuvant chemotherapy with S-1 in gastric cancer patients with Cy1 compared with that in the subjects of this study as the historical control.

In this study, the 5-year survival rate of gastric cancer patients with P0Cy1 was 7.8%. This poor result must be interpreted as suggesting that previously used treatment, including surgery alone, was not suitable for these patients [22]. If those patients undergo surgery first, more intensive adjuvant chemotherapy would be needed. Currently, S-1 is given to these patients as adjuvant therapy [21, 23], but is S-1 monotherapy sufficient? A feasibility study of S-1 plus platinum as adjuvant therapy is ongoing (data not published); however, compliance with this therapy may not be favorable due to the unstable postoperative status of the gastric cancer patients. It is quite natural to expect that preoperative chemotherapy might be useful for those patients [24].

In order to carry out preoperative chemotherapy, information on Cy1 must be confirmed by staging laparoscopy [25]. In Japan, staging laparoscopy has been popular, but it may be difficult for it to be routinely performed in every advanced gastric cancer patient at every institution. Definitive evidence on the efficacy of preoperative chemotherapy, such as that from the MAGIC trial [26], is mandatory for encouraging the use of this therapy in Japan.

When only type 4 advanced gastric cancer patients are included in the analysis, the prognosis of those with Cy1 is extremely poor. No patient survived for more than 40 months after surgery in this study. The survival curve of the patients with P0Cy1 was almost the same as that of the patients who were found to have peritoneal dissemination (P1Cy1) at the time of the surgery (data not shown). The indication for gastrectomy for these patients must be discussed [27]. No surgeon performs gastrectomy for linitis plastica with peritoneal dissemination, except for palliating stenosis or bleeding. The former therapeutic strategy of immediate surgery and adjuvant chemotherapy has a less curative power for these patients with such a poor prognosis, and preoperative chemotherapy should be tried. Controlled arm may be the chemotherapy without surgery [28]. Information on Cy1 is necessary for determining the therapeutic strategy in patients with type 4 advanced gastric cancer, therefore, staging laparoscopy must be carried out first.

The patients with peritoneal dissemination are not always cytology-positive. The survival of P1Cy0 patients is better than that of P1Cy1 patients (Fig. 1) (P = 0.0028, logrank). When the analysis is limited to type 4 gastric cancer, the survival of P1Cy0 patients is also better than that of P0Cy1 and P1Cy1patients (not shown), but the sample size (P1Cy0: $n = 9$) is too small for statistical evaluation. The P1Cy0 patients with local disseminated nodules may be the subset that can benefit from intraoperative chemotherapy.

In conclusion, curative treatment has been scarce for gastric cancer patients with Cy1 until now. The prognostic benefit of adjuvant chemotherapy with S-1 has been expected for years, but more intensive adjuvant chemotherapy, preoperative chemotherapy, and intraperitoneal chemotherapy [29] also warrant trials. The prognosis of type 4 gastric cancer patients with Cy1 is especially poor; therefore, it is recommended that such patients be treated at large-volume institutions with new therapeutic strategies developed based on clinical trials.

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Original article

The prognostic significance of isolated tumor cells in the lymph nodes of gastric cancer patients

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Abstract
Background. The clinical significance of isolated tumor cells (ITC) detected immunohistochemically in the lymph nodes of gastric cancer patients is controversial. The aim of this study was to examine the prognostic impact of ITC in patients with gastric cancer.
Methods. The data of a total of 402 patients with pathological T2N0 and T2N1 gastric cancer who underwent gastrectomy with D2 lymph node dissection between 1984 and 1990 at four participant hospitals were analyzed. All resected lymph nodes were reexamined by serial sectioning with hematoxylin & eosin (H&E) staining, and evaluated by immunohistochemistry using antibody against cytokeratin (AE1/3). The prevalence and prognostic significance of ITC were investigated.
Results. ITC were detected in 187 of the 402 (47%) patients. A multivariate analysis identified the nodal status, histological type, and tumor size as significant factors predictive of the presence/absence of ITC. The 5-year and 10-year overall survival rates of patients with vs those without ITC were 84.4% (95% confidence interval [CI], 79.1–89.0) and 70.4% (95% CI, 64.1–76.7) vs 83.9% (95% CI, 78.6–89.2) and 72.0% (95% CI, 65.4–78.5), respectively. The hazard ratio for death in patients with ITC as compared with those without ITC was 0.90 (95% CI, 0.64–1.26; $P = 0.53$).
Conclusions. The presence of ITC in the lymph nodes does not affect the prognosis of patients with gastric cancer who have undergone gastrectomy with D2 lymph node dissection.

Key words ITC · Lymph node metastases · Gastric cancer · Immunohistochemistry · Lymph node dissection

Introduction

The major prognostic factors in patients with gastric carcinoma are the depth of the primary tumor and the presence/absence of lymph node, peritoneal, and distant metastases. Complete tumor removal is deemed to be the only potentially curative treatment in patients with gastric cancer. Locally advanced gastric cancer frequently recurs after a curative operation, and even early gastric cancer relapses occasionally [1]. In patients with recurrent disease, it is considered that such disease arises, presumably from residual tumor cells, in the form of occult micrometastases, left behind at the time of apparently curative surgery.

Recent advances in immunohistochemistry (IHC) and molecular biological techniques [2] allow the identification of discrete and occult tumor cells in the lymph nodes [3], peripheral [4] blood, and bone marrow [5–7] of patients with malignant diseases that remain undetected during routine pathological examination. After some debate regarding the terminology for occult tumor cells, micrometastases (MM) are now defined as deposits of tumor cells measuring 2 mm or less but larger than 0.2 mm, while the term "isolated tumor cells (ITC)" refers to single tumor cells or clusters of tumor cells measuring 0.2 mm or less [8, 9]. The prevalence and prognostic significance of ITC are still controversial.

The aim of this study was to analyze whether the presence of ITC in the lymph nodes of gastric cancer patients treated by curative resection portends a worse prognosis.

Methods

Patients

A total of 402 patients with pathological T2N0M0 or T2N1M0 gastric cancer (T2, tumor invades the muscularis propria or subserosa; N0, no lymph node metastases; N1, with perigastric lymph node metastases; M0, no distant metastases) who underwent gastrectomy with

D2 lymph node dissection between January 1984 and December 1990 at any of the four participant hospitals in this study in Japan were included in this study. One hundred seventy-seven patients were treated at the National Cancer Center Hospital, Tokyo; 130 at Aichi Cancer Center Hospital, Nagoya; 67 at Teikyo University Hospital, Tokyo; and 28 at Kagoshima University Hospital, Kagoshima.

The patients in this study were basically consecutive, except for a few whose follow-up or material blocks were not available. All patients underwent partial or total gastrectomy with systematic lymphadenectomy, including complete dissection of perigastric lymph nodes and the second-tier lymph nodes along the common hepatic, proper hepatic, celiac, and splenic arteries.

Pathology and immunohistochemistry

All specimens containing the primary tumors were histologically classified according to the Japanese classification of gastric carcinoma [10] and the World Health Organization tumor classification system [11], and the following data were recorded at each hospital: tumor size, histological type, depth of invasion, and presence/absence of vascular or lymphatic invasion. Lymph nodes were examined in one cross-section obtained through the center of each lymph node.

Two consecutive sections measuring 4 μm in thickness were newly cut from 15 899 lymph nodes of the 402 patients for H&E staining and IHC. The median number of lymph nodes examined per patient was 32.5 (range, 6–124). The diagnosis in 32 patients who had been diagnosed as node-negative was revised to node-positive at this review, based on the examination of sections stained with H&E (T2N0 to T2N1).

IHC was performed using AE1/AE3 (Boehringer Mannheim, Indianapolis, IN, USA), a monoclonal antibody reactive with a broad spectrum of human cytokeratins. The procedure has been reported in detail previously [12]. Lymph nodes stained by IHC were evaluated by the pathologists at each hospital and revised by T.S., without any knowledge of any clinical information about the patients. ITC were defined as single tumor cells or clusters of tumor cells measuring 0.2 mm or less; they could not be detected by routine H&E staining and were detected by cytokeratin-specific IHC. When ITC were detected in a lymph node without overt metastases, this case was regarded as ITC-positive. When both single cells and clusters were observed in a lymph node, the ITC were classified as the cluster type.

Statistical analysis

Statistical analysis was carried out using the SPSS software, version 11.5 (SPSS, Chicago, IL, USA). The clini-copathological features of the studied cases were compared by a χ^2 test or Student's t-test. Multivariate analysis was conducted using a logistic regression model and Cox's proportional hazard model. The Kaplan-Meier method was used for drawing the survival curves, and the log-rank test was used for evaluating the statistical significance of the differences between the survival curves.

Results

Frequency and location of ITC

ITC were identified in 187 of the total of 402 patients (46.5%), in 81 of the 221 T2N0 patients (36.7%), and in 106 of the 181 T2N1 patients (58.6%). The median number of lymph nodes containing ITC was 2 (range, 1–25) per patient.

Among the 81 T2N0 patients detected as having ITC, 59 had the ITC in the perigastric lymph nodes, 19 in the second-tier lymph nodes, and 3 in distant lymph nodes including paraaortic lymph nodes. Among the 106 T2N1 patients detected as having ITC, 76 had the ITC in the perigastric nodes, 28 in the second-tier nodes, and 2 in distant nodes. Seventy-five patients had the single-cell type of ITC, while 112 had the cluster type.

Relationship between the presence of ITC and clinicopathological factors

The correlations between the presence of ITC and clinicopathological factors are shown in Table 1. Tumor size, histological type (differentiated or undifferentiated), lymphatic invasion, tumor depth (mp, muscularis propria; ss, subserosa) and nodal status (N0 or N1) were identified by univariate analysis as significant factors predictive of the presence/absence of ITC in the lymph nodes. Among these factors, the histological type, size of the tumor (<50 or ≥50 mm), and nodal status were identified as significant factors by multivariate analysis based on a logistic regression model (Table 2). Tumors of the undifferentiated type, large-sized tumors, and originally node-positive tumors were more likely to be associated with ITC in the lymph nodes; the odds ratios were 1.78 (95% CI, 1.18–2.69; $P = 0.006$), 1.67 (95% CI, 1.05–2.66; $P = 0.029$), and 2.11 (95% CI, 1.36–3.26; $P = 0.001$), respectively.

Relationship between the presence of ITC and the prognosis of patients

The median follow-up period of the surviving patients was 127 months (range, 3–215 months). Disease recurrence was observed in 32 patients. Of these, 18 patients

Table 1. Relationships between ITC and clinicopathological factors

	Positive	Negative	P value
Age (years)	59.0 ± 11.9	61.4 ± 11.9	0.04
Tumor diameter (mm)	50.6 ± 25.2	40.5 ± 19.0	<0.001
Sex			
Male	124	162	0.03
Female	63	53	
Histology			
Diff.	84	130	0.001
Undiff.	103	85	
V			
−	152	180	0.30
+	35	35	
Ly			
−	68	101	0.02
+	119	114	
Depth			
mp	105	147	0.008
ss	82	68	
Nodal status			
N0	81	140	<0.001
N1	106	75	

ITC, isolated tumor cells; Diff, differentiated; Undiff, undifferentiated; V, vascular invasion; Ly, lymphatic invasion; mp, muscularis propria; ss, subserosa; −, negative; +, positive

Table 2. Multivariate analysis to determine the relationship between the presence of ITC and clinicopathological factors

	OR	95% CI	P value
Histology (diff./undiff.)	1.780	1.179–2.687	0.006
Depth (mp/ss)	1.271	0.814–1.986	0.292
Tumor diameter (>50 / ≤50 mm)	1.673	1.053–2.658	0.029
Nodal status (N0/N1)	2.111	1.366–3.262	0.001
Lymphatic invasion (−/+)	1.146	0.734–1.791	0.549

OR, odds ratio; CI, confidence interval

had ITC, while 14 did not. The incidence of recurrence was not related to the presence of ITC ($P = 0.26$).

The 5-year and 10-year overall survival rates of the patients with and without ITC were 84.4% (95% CI, 79.1–89.0) and 70.4% (95% CI, 64.1–76.7); and 83.9% (95% CI, 78.6–89.2) and 72.0% (95% CI, 65.4–78.5), respectively. The hazard ratio for death in the patients with ITC as compared to those without ITC was 0.90 (95% CI, 0.64–1.26; $P = 0.53$).

There were no significant differences in the survival curves between patients with and without ITC ($P = 0.53$ by log-rank test; Fig. 1). The type of ITC (single cell, cluster), and the number of lymph nodes with ITC did not affect the prognosis. The effects of the clinicopathological factors on the prognosis of the patients are shown in Table 3. Age (<60 / ≥60 years), histological type (differentiated type/undifferentiated), depth of invasion (mp/ss), and nodal status (N0/N1) were identified as significant prognostic factors by univariate analysis. Multivariate analysis using representative factors from
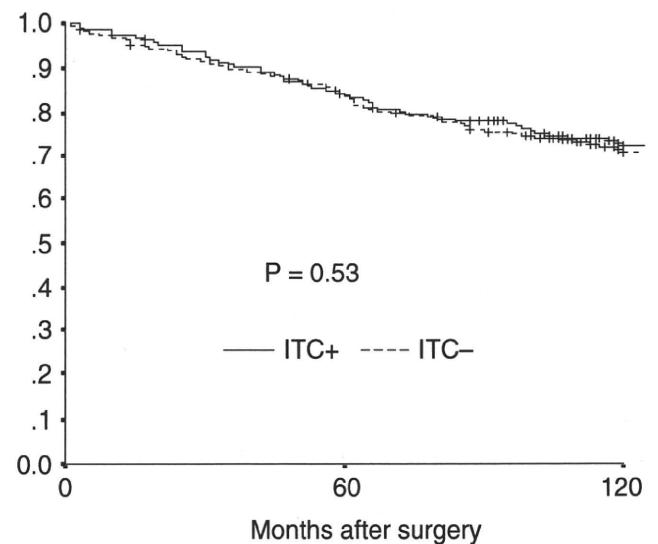
Fig. 1. Overall survival of pT2N0 and pT2N1 gastric cancer patients. There was no significant difference in survival between patients with and without isolated tumor cells (*ITC*)

Table 3. Univariate analysis to determine the clinicopathological factors related to overall survival

	HR	95% CI	P value
Age (<60/≥60 years)	3.539	2.375–5.273	<0.001
Histology (diff./undiff.)	0.531	0.371–0.760	0.001
Depth (mp/ss)	1.414	1.005–1.989	0.047
Tumor diameter (<50/≥50 mm)	1.035	0.716–1.495	0.855
ITC (−/+)	0.897	0.638–1.262	0.534
Nodal status (N0/ N1)	1.763	1.251–2.485	0.001
Sex (male/female)	0.762	0.515–1.130	0.176
Lymphatic invasion (−/+)	1.503	1.052–2.148	0.025
Vascular invasion (−/+)	1.413	0.936–2.113	0.100

HR, hazard ratio

Table 4. Multivariate analysis to identify the clinicopathological factors determining the overall survival

	HR	95% CI	P value
Age (>60 / ≤60 years)	3.189	2.113–4.814	<0.001
Histology (diff./undiff.)	0.693	0.476–1.008	0.055
Depth (mp/ss)	1.178	0.821–1.689	0.374
Nodal status (N0/N1)	1.800	1.229–2.638	0.003
Ly (−/+)	1.127	0.765–1.661	0.546
ITC (−/+)	0.888	0.621–1.268	0.513

Table 3 showed that age and nodal status were the most significant prognostic factors (Table 4). The presence of ITC did not have any impact on the prognosis of the patients.

Discussion

The results of this study suggest that the presence of ITC in lymph nodes does not imply systemic involvement by the disease, and has no influence on the prognosis of gastric cancer patients who have undergone gastrectomy and systematic lymph node dissection.

There is increasing interest in the presence and prognostic relevance of occult tumor cells in various malignant diseases [13]. In breast cancer and melanoma, lymph nodes involved with tumor metastases are no longer the objects of drastic dissection, but are an indicator of patients with a poor prognosis needing intensive adjuvant therapy. Lymph nodes containing occult tumor cells have been considered similarly in some other reports as well [14, 15], and this concept has been adopted even in the sentinel nodes theory [16, 17]. In contrast, metastatic lymph nodes are targets for local control in gastric cancer patients [18], although extended lymph node dissection is still controversial [10]. The clinical significance of the detection of occult tumor cells in the lymph nodes of gastric cancer patients is an important subject for more intensive study, because it

may provide some directions regarding the extent of lymph node dissection [19] and the necessity for adjuvant therapy after curative surgery.

The biology of ITC in the lymph nodes has not been fully elucidated, but several conclusions can be drawn from a recent analysis [20]. ITC may be present in many lymph nodes that are originally diagnosed as tumor-negative by H&E staining, as previously reported. In the present study, such an occurrence was significantly more frequent in T2N1 than in T2N0 gastric cancer patients. In addition, ITC were detected in second-tier lymph nodes more frequently in N1 patients than in N0 patients (29 of 181 patients vs 19 of 221 patients, P = 0.02). This behavior of ITC is consistent with the concept that lymph node metastases proceed from the perigastric area to the next area in order. ITC were found even in distant lymph nodes, including paraaortic lymph nodes, as reported before [21]. This shows that ITC can also reach lymph node stations far away from the primary tumor, but further discussion may have to be limited because only a proportion of patients in the present study underwent super-extended lymph node dissection including the paraaortic area. In this study, the frequency of ITC in lymph nodes was higher in patients with larger and more undifferentiated tumors. It is conceivable that tumor cells can escape more easily from such tumors.

Many authors have reported on the clinical significance of occult cancer cells in the lymph nodes of gastric cancer patients. Morgagni et al. [22] and Choi et al. [23] reported a negative impact on the prognosis for early gastric cancer, while others have refuted such a suggestion [24–26] by the analysis of patients including those with early and advanced gastric cancer. The studies including a majority of patients with early gastric cancer have the problem of too low an incidence of disease-specific death to allow reasonable prognostic evaluation. If many cases of locally advanced gastric cancer invading the serosal surface of the stomach were to be included, the prognostic significance of occult tumor cells in the lymph node would be confounded by the

high frequency of peritoneal recurrence. For this reason, we previously carried out a study similar to the present one in patients with T2N0 disease [27]; in the present study, T2N1 gastric cancer patients with perigastric lymph node metastases were examined in addition for the purpose of including a larger number of patients. T2N2 patients with lymph node metastases in the second-tier lymph nodes were not included, because such patients might include those with paraaortic lymph node metastases which cause potential stage migration.

Previous discussions about occult tumor cells in the lymph nodes have always included diagnostic problems. Occult tumor cells detected by IHC have been divided into ITC and MM, as mentioned above. Some of the reported MMs may actually be small metastases, associated with a worse prognosis, which could probably have been detected by routine H&E staining by well-experienced pathologists. Many lymph node metastases diagnosed at our institution measure less than 2 mm in greatest dimension [28]. Furthermore, decisions reached among pathologists for resolving this delicate problem are quite mandatory, as shown by some studies reporting difficult reproducibility of the diagnosis of occult tumor cells [29, 30].

In the present study, the presence of ITC was not found to be an independent factor for worse prognosis, as assessed by both multivariate analysis of prognostic factors and survival analysis. Although one of the purposes of an investigation of ITC might be to find a target for additional therapy after curative surgery, based on the results of the present study, it will not be necessary hereafter to take into account the presence of ITC in the lymph nodes of gastric cancer patients. In Japan, pT2N1 gastric cancer patients are already candidates for adjuvant chemotherapy, based on the results of a clinical trial [31]. In the West, node-positive gastric cancer patients are included as candidates for postoperative chemoradiotherapy, based on the results of the INT0116 trial [32].

The viability and clinical significance of the presence of ITC in lymph nodes is better discussed separately. Some reports [6, 33] suggest that ITC do not progress to become metastatic lesions, and will probably die or be eliminated by the host immune response, even if they have reached distant sites, but the potential tumorigenicity of single cells in the lymph nodes has also been reported [20, 34]. Therefore, what is the malignant potential of ITC? Evaluation of the viability of a small number of tumor cells and the discrimination of actual malignant tumor cells are probably subjects of great interest and importance that need to be studied [34, 35]; however, further basic investigation will be needed before there are clinical applications. We still cannot provide a clear answer to the essential question of whether or not a lymph node containing ITC should be dissected. The similar outcomes in patients with and without ITC in our study may have occurred because all of the participants in this study underwent standard D2 lymph node dissection, but these similar outcomes could also be interpreted to suggest that ITC in the lymph nodes may be basically ignorable without dissection. However, these essential issues are so far from being clearly resolved that any discussion about the indications for limited surgery or the necessity for extended lymph node dissection based on the prevalence of ITC in the lymph nodes is futile.

In conclusion, the results of this study, an analysis of a large group of patients with limited disease, may provide some suggestions regarding the clinical impact of ITC in the lymph nodes of gastric cancer patients.

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Gastric Cancer Working Group Report

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Epidemiology: Gastric cancer is the second most common cancer in Asia, more than half of the world's gastric cancer cases arise in Eastern Asia, and the majority of Asia's cases still occur in the distal part of the stomach.

Etiology and Prevention: The etiology of gastric cancer consists of genetic susceptibility, *Helicobacter pylori* infection and environmental risk factors. *Helicobacter pylori* eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and non-steroidal anti-inflammatory drugs seem to reduce the risk of gastric cancer.

Endoscopy and Diagnosis: Screening for gastric cancer is cost-effective in countries with high incidence. Risk stratification may increase the cost-effectiveness of screening in populations at moderate risk. Endoscopic resection is curative in a subset of patients with early cancer.

Surgery and Adjuvant Treatment: R0 resection with D2 lymph node dissection has produced the best survival data. Some kind of post-operative adjuvant chemotherapy including S-1 is recommended after D2 surgery.

Chemotherapy for Advanced Gastric Cancer: As chemotherapy for gastric cancer, fluorouracils plus platinum are the most widely accepted first-line regimens, whereas taxanes or irinotecan are mostly used in second- and third-line settings. Differences in the approval and medical insurance systems may influence the status of these regimens. Trastuzumab in combination with fluorouracils/platinum will be a standard regimen for HER2-positive gastric cancer. Many new targeting agents are currently under investigation, and Asian countries are playing important roles in investigation and development of new and better treatments for this malignancy.

Key words: gastric cancer – Helicobacter pylori – D2 lymphadenectomy – adjuvant chemotherapy – endoscopic treatment – chemotherapy

The Gastric Cancer Working Group report was divided into five chapters: epidemiology, etiology and prevention, endoscopy and diagnosis, surgery and adjuvant treatment and chemotherapy for advanced gastric cancer.

EPIDEMIOLOGY

In spite of the remarkable spontaneous decline in the incidence of stomach cancer in most Western countries, in Asia it is still one of the two most common cancers, following only lung cancer and accounting for 13% of all cancers in Asia (Fig. 1) (1). Estimation of the distribution of gastric cancer in the world in 2002 showed that 56%, more than half of all new cases in the world, occurred in Eastern Asia, with 41% from China and 11% from Japan (Fig. 2) (1). The highest incidences occurred in Korea and Japan. Gastric cancer is relatively common in Asia, Eastern Asia, other Asia, South America and Central and Eastern Europe, whereas it is rare in other European areas and Northern America (Fig. 3) (1). In the common areas, including Eastern Asia, cancer of the distal part of the organ is still the
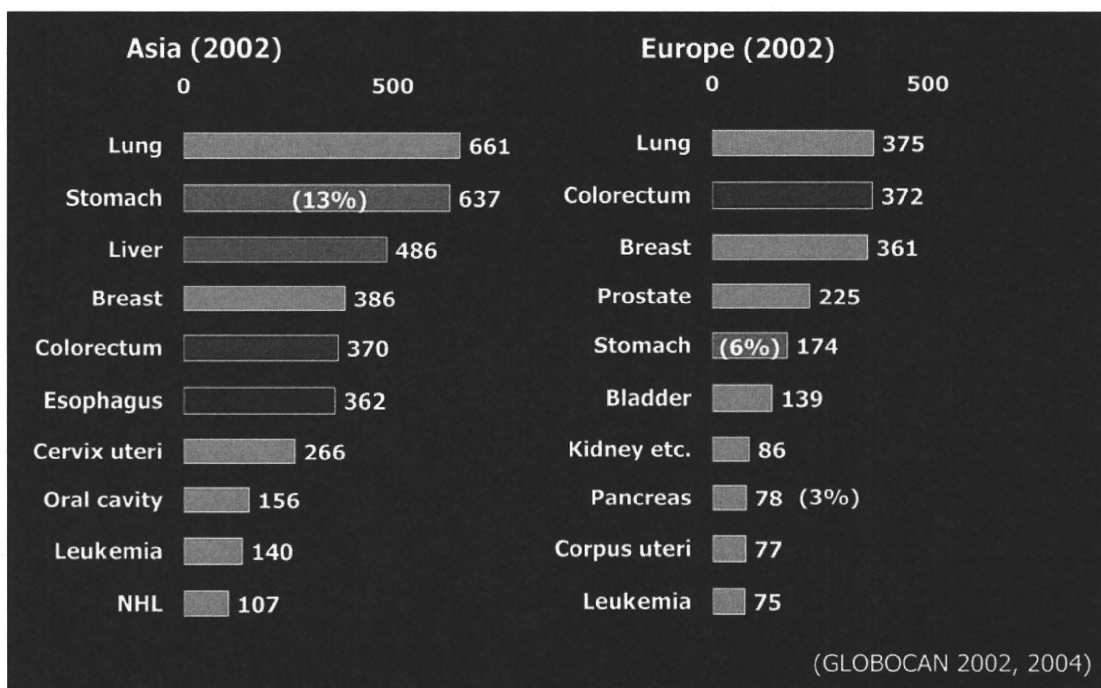
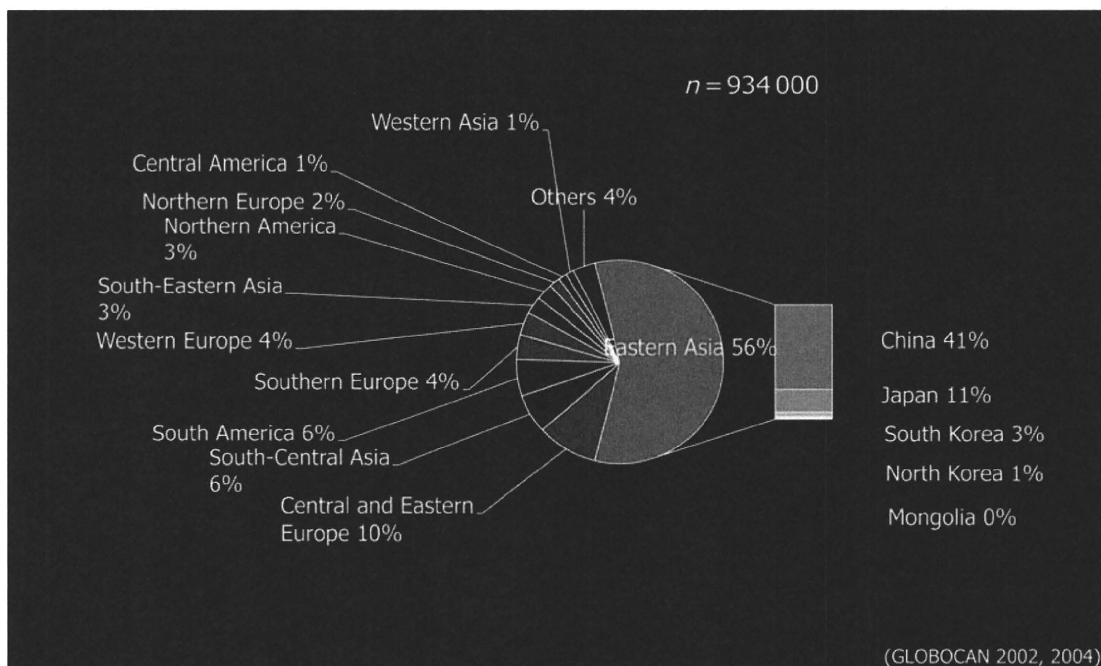**Figure 1.** Number of new cases for 10 common cancers (both sexes).

Figure 2. Estimated distribution of gastric cancer in the world in 2002.

most frequent, whereas the proximal gastric cancer is more common in Western countries (Fig. 4) (2).

In conclusion, gastric cancer is the second most common cancer in Asia, more than half of the world's gastric cancer cases still arise in Eastern Asia, and the majority of those cases still occur in the distal part of the stomach. An increased trend for EC-junction adenocarcinoma is suggested in Western countries, but there is no evidence of such a trend in Asia.

ETIOLOGY AND PREVENTION

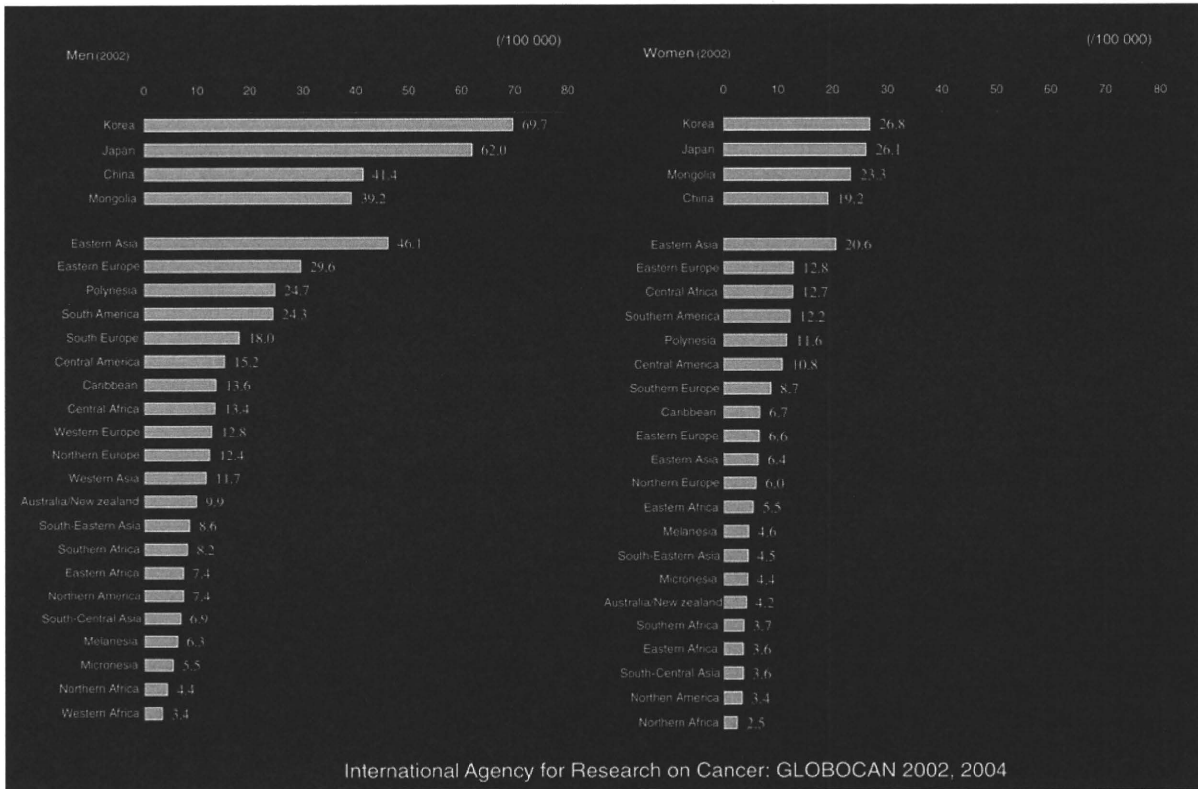Three major factors are involved in the development of gastric cancer: *Helicobacter pylori* infection, genetic

Figure 3. Age-standardized incidence rate of gastric cancer in various area of the world (2002 estimate).
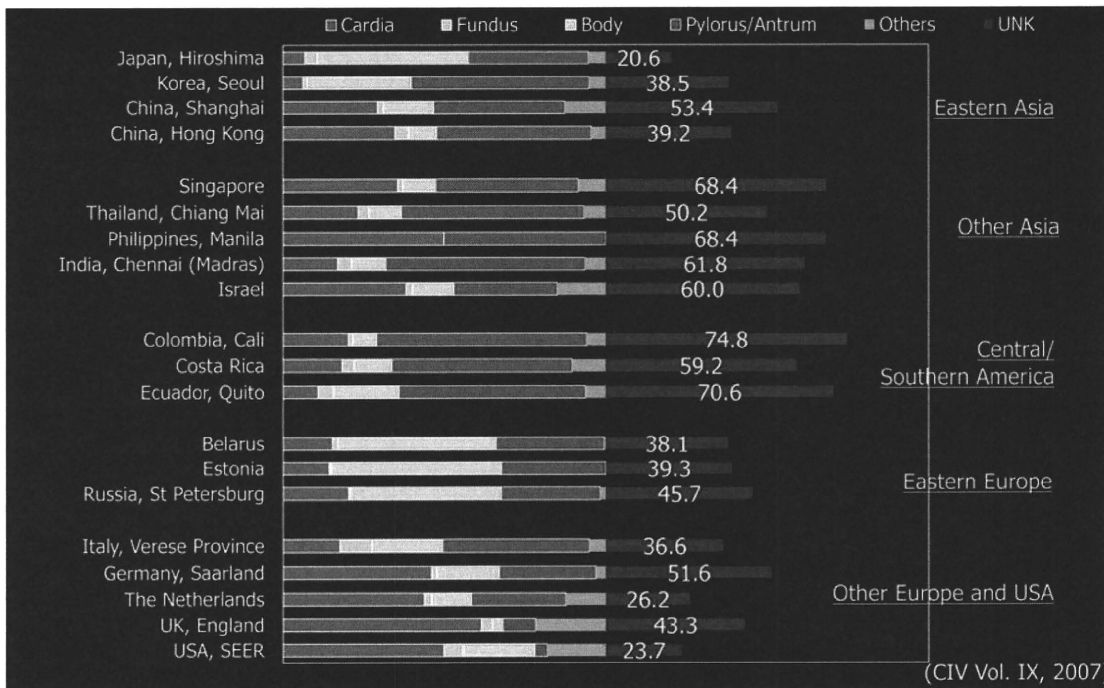

Figure 4. Subsite distribution of gastric cancer, 2000.

susceptibility (CDH1 etc.) and environmental factors (such as smoking, a high-salt diet and low vegetable consumption) (3). *Helicobacter pylori* infection is the most important. A study by Dr Uemura et al. (4), published in the *New England Journal of Medicine*, found no development of gastric cancer in cases without *H. pylori* infection, whereas