the results of some of these trials were promising but inconsistent when all trials were considered. Therefore, it was deemed important to assess the benefit of adjuvant chemotherapy quantitatively through an exhaustive meta-analysis based on individual patient data from all relevant trials.

METHODS

Data from all published randomized trials comparing adjuvant chemotherapy with surgery alone for resectable gastric cancers were sought electronically. The strategy filter for computerized bibliographic searches of MEDLINE (1970 to 2009) is described in the eMethods (available at http://www.jama.com). No restriction on language of publication was considered. The Cochrane Central Register of Controlled Trials, the National Institutes of Health trial registry (ClinicalTrials.gov), and proceedings books from major oncologic and gastrointestinal cancer meetings were also examined for published results. To ensure that all relevant trials were included, researchers with expertise in the area were queried for the existence of unpublished trials. Four groups of regimens were specified in the protocol: trials investigating (1) monochemotherapy agents; (2) fluorouracil, mitomycin C, and other therapies without anthracyclines; (3) fluorouracil, mitomycin C, and anthracyclines; and (4) other polychemotherapy regimens.

Study Selection and Data Extraction

Trials were eligible if they were randomized, they ended patient recruitment before 2004, and they compared any adjuvant therapy after curative resection vs surgery alone. Trials investigating immunotherapy or neoadjuvant or perioperative chemotherapy were excluded. Likewise, trials with radiotherapy or intraperitoneal chemotherapy were not in the scope of our research.

The following data were requested for all individual patients: center, randomization date, date of last follow-up (or date of death), survival status, cause of death, relapse status, type and date of relapse if any, TNM stage, overall stage grouping system, performance status (World Health Organization or Karnofsky index), and age at entry. Because the International Union Against Cancer modified the staging system in 1997, stages measured with the old system were expressed according to the new classification. Updated survival status and date of last follow-up were requested from the trialists. Data for patients excluded from the analysis after randomization were obtained whenever possible.

Overall survival (OS) was defined as the time from randomization to death from any cause or to the last follow-up that was used as a date of censoring. Disease-free survival (DFS) was the time to relapse, second cancer, or death from any cause, whichever came first. Detailed information on the type of relapse was not always available. All data were centrally reanalyzed and checked for inconsistencies. In particular, diagnostic tools for randomization quality were systematically applied.[11]

Statistical Methods

Time-related end points (OS and DFS) were analyzed through log-rank tests, with trial as stratification factor. We used a fixed-effects model and the inverse variance method where the weight of each trial was proportional to the variance of the observed minus expected number of events.[12] Heterogeneity between trials and groups of trials (eg, defined by different chemotherapy regimens) was tested using χ^2 statistics[13] and measured with the I^2 statistic.[14] Forest plots were used to display hazard ratios (HRs) within individual trials and overall. Within each trial, HRs were estimated without adjusting for any covariates. When a statistically significant effect was detected, the increase in survival probabilities or absolute benefit at 5 or 10 years after randomization was computed based on the estimates of the survival curves. Estimates of the survival curves used the actuarial approach adjusted for trial proposed by the Early Breast Cancer Trialists' Collaborative Group,[15] yielding a representation consistent with the main log-rank analyses stratified by trial. Their interpretations are similar to the Kaplan-Meier curves.

The hypothesis of proportional hazards was explored graphically and tested by using the Grambsch and Therneau test[16] with linear residual relation and by including a time-dependent covariate in a stratified Cox model. We further investigated the hazard functions through time in each group under study. Median follow-up was estimated using the reversed Kaplan-Meier function.[17] All patients were included in the analyses as randomly assigned based on an intention-to-treat principle, whether or not they were analyzed in the trial publication. In cases where survival data were missing, those patients were excluded from the analysis.

As a sensitivity analysis we investigated the overall treatment effect in all the identified trials, pooling individual patient data with summary statistics extracted from the publication.[18] We also analyzed these summary statistics separately. In addition, we investigated heterogeneity among the regions where the trials were conducted (Europe, Asia, and the United States). All P values were 2-sided at the 5% level, and confidence intervals (CIs) had 2-sided probability coverage of 95%. SAS version 9.1 (SAS Institute, Cary, North Carolina) was used with macros developed at the European Organization for Research and Treatment of Cancer Data Center (Brussels, Belgium) for meta-analysis and at Institut Gustave-Roussy (Villejuif, France) for survival curves. Hazard functions were plotted with Stata version 9.2 (StataCorp, College Station, Texas). All the results were discussed during 4 large international investigators' meetings organized in different countries.

RESULTS

Thirty-one trials that had randomized 6390 patients were identified (FIGURE 1). We obtained individual data for 3838 patients included in 17 trials (TABLE). This represents 60% of the targeted

data. Corresponding authors of the eligible trials were contacted at least 5 times each between January 2007 and February 2010. Data were not obtained for 2552 patients in 14 trials because of no reply or a refusal to share data from the principal investigator[35-39] or because data were lost or inaccessible.[40-48] One trial[21] compared surgery alone against 2 investigational groups with fluorouracil or ftorafur. Both groups were pooled. Central randomization was reported in 14 trials (with block stratification for 8 and minimization for 6). All trials were open without blinding procedures. No trials were found to have major inconsistencies in the randomization procedure, and no difference in follow-up could be detected between the 2 groups.

Patient Characteristics

The characteristics of the 3838 randomly assigned patients are listed by group (eTable 2) and chemotherapy regimen (eTable 3). There were no major differences in patient characteristics between treatment groups. The eTables also show summary statistics on the clinical outcomes of interest: median OS and median DFS. Fifty-seven patients (1.5%) with missing survival data were excluded from analyses (date of randomization, last status, and last date were missing for 25, 8, and 49 patients, respectively). They were balanced between the 2 groups (28 patients with chemotherapy vs 29 patients with surgery only). We identified 361 patients and 103 deaths with a last date after the publication date of the related trial.

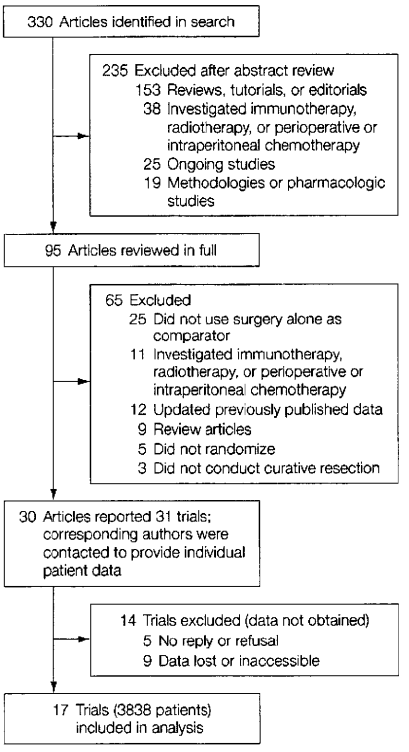
Any Adjuvant Chemotherapy vs Surgery Alone

Median follow-up for OS was slightly different between the 2 groups (7 years; range, 0.1-28.2 years in the surgery-only group vs 7.2 years; range, 0.1-30.3 years; $P<.001$), during which 1067 patients in the surgery-only group and 1000 patients in the chemotherapy group died. FIGURE 2 shows the HRs for OS in the individual trials and overall. There was a significant benefit from any chemotherapy compared with surgery alone, with an overall HR of death equal to 0.82 (95% CI, 0.76-0.90; $P<.001$), corresponding to an overall 18% reduction of the hazard with chemotherapy. The estimated median OS was 4.9 years (95% CI, 4.4-5.5) in the surgery-only group vs 7.8 years (95% CI, 6.5-8.7) in the group receiving adjuvant chemotherapy. Absolute benefits were 5.8% at 5 years (from 49.6% to 55.3%) and 7.4% at 10 years (from 37.5% to 44.9%) (FIGURE 3). No significant heterogeneity (variability of trial-specific HRs) was apparent across the set of trials ($P=.52$). Globally, there were no time trends in the treatment effect according to the year of last inclusion ($P=.82$). Similarly, no significant heterogeneity was detected across the 3 continents ($P=.27$) (eFigure 1, available at http://www.jama.com).

As a sensitivity analysis, we combined summary statistics extracted from unavailable trials with the collected individual patient data for a total of 5866 patients and 28 trials. For 3 trials,[43,44,47] no summary statistics could be extracted from the report. Neither the general conclusions nor the magnitude of the observed treatment effect (HR, 0.82; 95% CI, 0.77-0.88; $P<.001$) were modified (eFigure 2). Analysis of the 11 trials with available summary resulted in an HR of 0.81 (95% CI, 0.73-0.91; $P<.001$). No significant heterogeneity was detected ($P=.11$).

Disease-free survival was available on a subset of 14 trials with a total number of 3297 patients from the 21 trials that collected this information, representing 78% of the targeted number of patients. On this subpopulation, we observed an HR of death of 0.85 (95% CI, 0.77-0.93), consistent with the estimate on the full database. Hazard ratios for DFS in individual trials and overall are shown in FIGURE 4. Adjuvant chemotherapy improved DFS compared with surgery alone with an overall HR of 0.82 (95% CI, 0.75-0.90; $P<.001$). The absolute benefit at 5 years was 5.3%, from 48.7% to 54.0% (eFigure 3). There was no indication of heterogeneity between trials in treatment effect ($P=.57$).

Figure 1. Study Flowchart



Analysis of Groups of Regimens

An interaction test between the type of regimen (monochemotherapy; fluorouracil and mitomycin C with anthracyclines; fluorouracil, mitomycin C, and others without anthracyclines; other polychemotherapy) and the treatment effect on OS and on DFS were not significant ($P=.13$ for both). In the sensitivity analysis, interaction was of borderline significance for OS ($P=.05$). We further explored these 4 groups. Survival curves are provided as supplementary material (eFigures 4 through 7).

Monochemotherapies. The 2 medium-sized trials[19,20] (1 European, 1 Japanese) included a total of 324 patients of whom 317 patients were eligible for the meta-analysis with OS data. They showed a statistically significant benefit of adjuvant monochemotherapy over surgery alone (HR, 0.60; 95% CI, 0.42-0.84; $P=.03$), with 5-year survival rates of

Table. List of the Included Randomized Trials

Source	Adjuvant Chemotherapy	Dosage	Schedule	Patients, No. CT (n = 1953)	Patients, No. S (n = 1885)	Recruitment Period	UICC Stage, %	Follow-up, Median (Range), y
Monochemotherapy				(n = 163)	(n = 161)			
Grau et al,[19] 1993	Mitomycin C	20 mg/m² IV (day 1)	Every 6 wk (4 cycles)	68	66	1977-1983	I, 14; II, 32; III, 54	11.2 (0.8-20.1)
Nakajima et al,[20] 2007	Uracil plus tegafur	360 mg/m²/d orally	Every wk (16 mo)	95	95	1987-2001	II, 75; III, 25	6.0 (1.2-8.4)
Polychemotherapies: fluorouracil + mitomycin C + others without anthracyclines				(n = 572)	(n = 481)			
Nakajima et al,[21] 1984[a]	Mitomycin C Fluorouracil or ftorafur Cytosine arabinoside Fluorouracil or ftorafur	1.3 mg/m² IV 167 mg/m² or 267 mg/m² IV 13 mg/m² IV, then orally 133 mg/m² or 670 mg/m²	Twice a week for 5 wk Twice a week for 5 wk Twice a week for 5 wk For 2 y	156	72	1974-1977	I, 46; II, 29; III, 21; X, 4	24.2 (11.4-30.3)
Nakajima et al,[22] 1999	Mitomycin C Fluorouracil Uracil plus tegafur	1.4 mg/m² IV 166.7 mg/m² IV 300 mg/m²/d orally	Mitomycin C and fluorouracil: for the first 3 wk Oral uracil plus tegafur: for the next 18 mo	288	285	1988-1992	I, 90; II, 9; III, 1	6.7 (2.9-8.6)
Nashimoto et al,[23] 2003	Mitomycin C Fluorouracil Cytosine arabinoside Fluorouracil	1.3 mg/m² IV 167 mg/m² IV 13 mg/m² IV 134 mg/m² orally	Fluorouracil IV: for the first 3 wk Fluorouracil orally: for the next 18 mo	128	124	1993-1994	I, 94; II, 6	5.9 (2.7-8.2)
Polychemotherapies: fluorouracil + mitomycin C + anthracyclines				(n = 497)	(n = 516)			
Coombes et al,[24] 1990	Fluorouracil Doxorubicin Mitomycin C	600 mg/m² IV 30 mg/m² IV 10 mg/m² IV	8-wk cycle (6 cycles)	133	148	1981-1984	I, 20; II, 24; III, 40; IV: 16	13.0 (0.1-21.6)
Lise et al,[25] 1995	Fluorouracil Doxorubicin Mitomycin C	400 mg/m² IV 40 mg/m² IV 10 mg/m² IV	Every 6 wk (7 cycles)	155	159	1979-1989	I, 17; II, 25; III, 40; IV, 18	6.5 (0.9-12.3)
Macdonald et al,[26] 1995	Fluorouracil Doxorubicin Mitomycin C	600 mg/m² IV 30 mg/m² IV 10 mg/m² IV	8-wk cycle (6 cycles)	109	112	1978-1991	I, 19; II, 41; III, 40	16.6 (2.9-23.9)
Tsavaris et al,[27] 1996	Fluorouracil Epirubicin Mitomycin C	600 mg/m² IV 30 mg/m² IV 10 mg/m² IV	8-wk cycle (3 cycles)	47	45	1988-1994	I, 16; II, 39; III, 45	4.9 (0.6-6.2)
Popiela et al,[28] 2004[b]	Fluorouracil Doxorubicin Mitomycin C	600 mg/m² IV 30 mg/m² IV 10 mg/m² IV	8-wk cycle (6 cycles)	53	52	1988-1992	III, 76; IV, 24	13.0 (2.5-15.5)
Other polychemotherapies				(n = 721)	(n = 727)			
Douglass and Stablein,[29] 1982	Semustine Fluorouracil	150 mg/m² orally 325 mg/m² IV 325 mg/m² IV	Every 10 wk (for 2 y)	91	88	1975-1980	NA	12.1 (2.2-13.9)
Engstrom et al,[30] 1985	Semustine Fluorouracil Fluorouracil	150 mg/m² orally 350 mg/m² IV 375 mg/m² IV	Day 1 Every 10 wk (for 2 y)	100	96	1975-1980	NA	16.5 (0.4-24.9)
Krook et al,[31] 1991	Fluorouracil Doxorubicin	350 mg/m² IV 40 mg/m² IV	5 d every mo (3 cycles)	63	64	1979-1989	NA	15.6 (5.7-19.8)
Bajetta et al,[32] 2002	Etoposide Doxorubicin Cisplatin Leucovorin Fluorouracil	120 mg/m² IV 20 mg/m² IV 40 mg/m² IV 100 mg/m² IV 375 mg/m² IV	For 2 cycles	135	136	1994-1997	I, 8; II, 31; III, 51; IV, 10	6.2 (0.1-9.5)
Bouché et al,[33] 2005	Fluorouracil Cisplatin	800 mg/m² IV then 1 g/m² 100 mg/m² IV	5 d Every 4 wk (4 cycles)	138	140	1989-1997	I, 34; II, 29; III, 25; IV, 12	8.1 (0.4-12.7)
Nitti et al,[34] 2006[c]	Fluorouracil Doxorubicin Methotrexate with leucovorin	1.5 g/m² IV 30 mg/m² IV 1.5 g/m² IV with 15 mg/m² (oral or IV)	For 6 cycles	103	103	1991-1998	I, 13; II, 25; III, 61; IV, 1	7.0 (2.6-11.3)
Nitti et al,[34] 2006[c]	Fluorouracil Epirubicin Methotrexate with leucovorin	1.5 g/m² IV 70 mg/m² IV 1.5 g/m² IV with 30 mg/m² (oral or IV)	For 6 cycles	91	100	1990-1998	I, 9; II, 87; IV, 4	6.9 (0.5-11.1)

Abbreviations: CT, chemotherapy; IV, intravenous; NA, not available; S, surgery alone; UICC, International Union Against Cancer.
[a] Investigated 2 regimens; in the second one, ftorafur replaced fluorouracil. The data are pooled.
[b] Investigated chemotherapy + bacille Calmette-Guerin in a third group that was not included.
[c] Relied on a combined analysis of 2 databases that are analyzed separately.

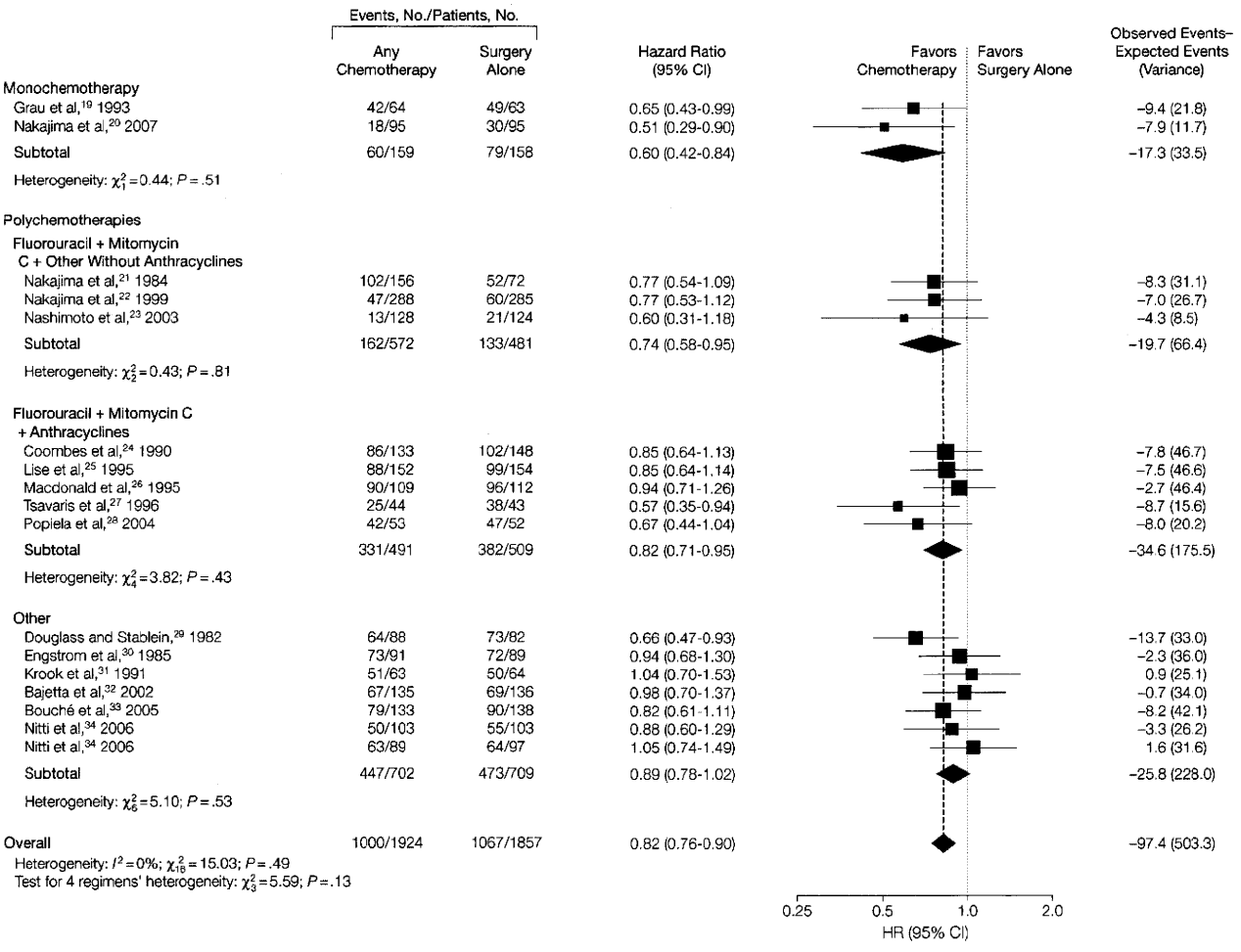
53.9% for the surgery-only group vs 71.4% for the chemotherapy group. This rate was much higher than in the whole meta-analysis, suggesting that these patients had a good baseline prognosis. Disease-free survival was not collected in 1 of the 2 trials and hence not analyzed.

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 reduction 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.

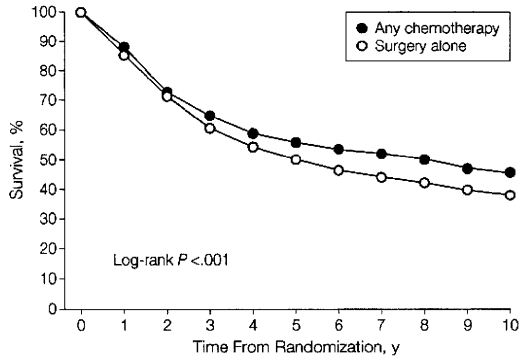
Polychemotherapies: Group "Other" vs Surgery Alone. For 1411 of 1448 patients in 7 trials for whom survival data were available,[29-34] we did not detect a

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



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



No. at risk

Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

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 chemotherapy 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).

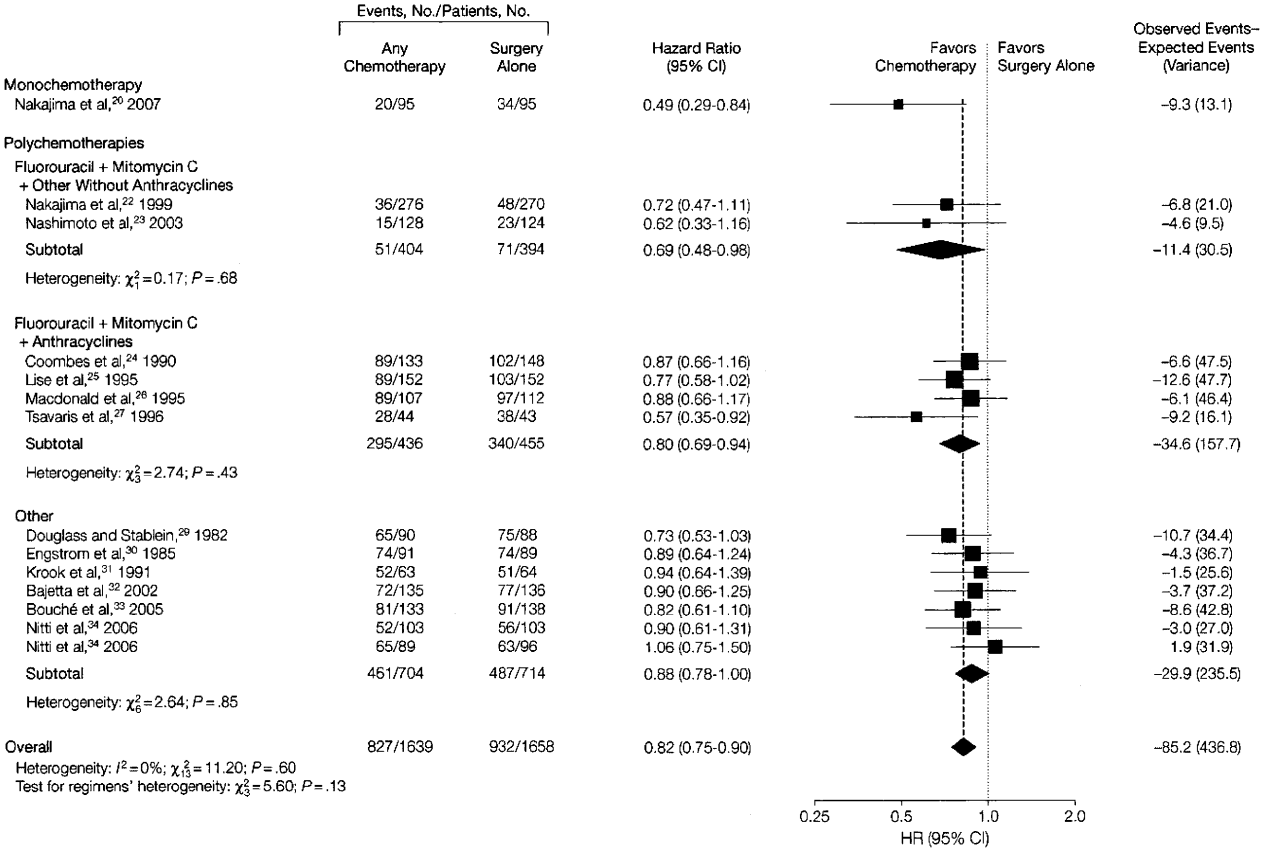
Postoperative chemotherapy is not the only adjuvant treatment for gastric cancer. In 2001, results of a trial that randomized between surgery and surgery with chemoradiotherapy showed an absolute increase in median survival of 9 months.[49] Thereafter, chemoradiation therapy has gained popularity and 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



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% 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).

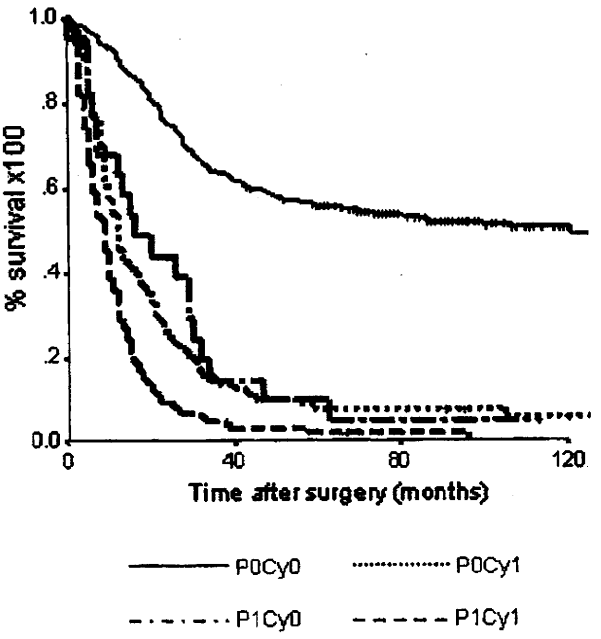

Fig. 1 Overall survival curves of gastric cancer patients (P0Cy0, P0Cy1, P1Cy0, and P1Cy1) are shown. The survival of P0Cy1 patients was poor but better than that of P1Cy1 patients ($p = 0.0002$)

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)

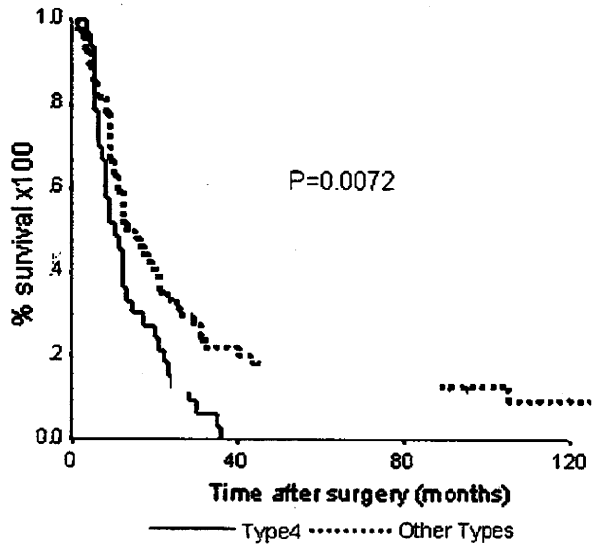

Fig. 2 The survival of P0Cy1 patients with type 4 advanced gastric cancer was significantly worse than that of patients with other types of advanced gastric cancer ($p = 0.0072$)

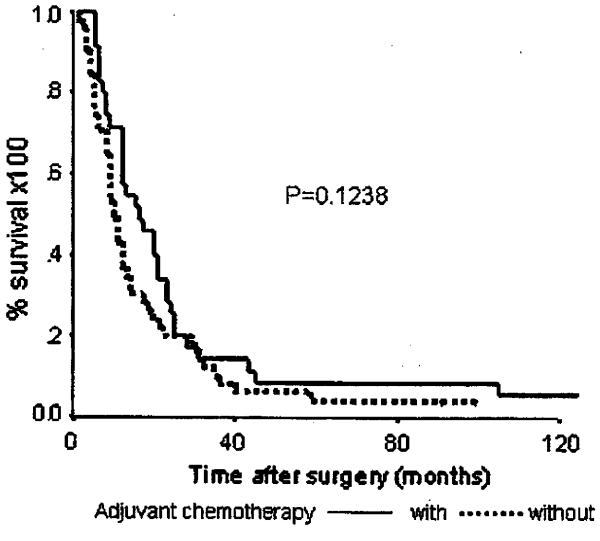

Fig. 3 There was no significant difference in the survival curves between P0Cy1 patients treated/not treated by adjuvant chemotherapy ($p = 0.1238$)

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) ($P = 0.0028$, log-rank). 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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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, fluoropyrimidines 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 fluoropyrimidines/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

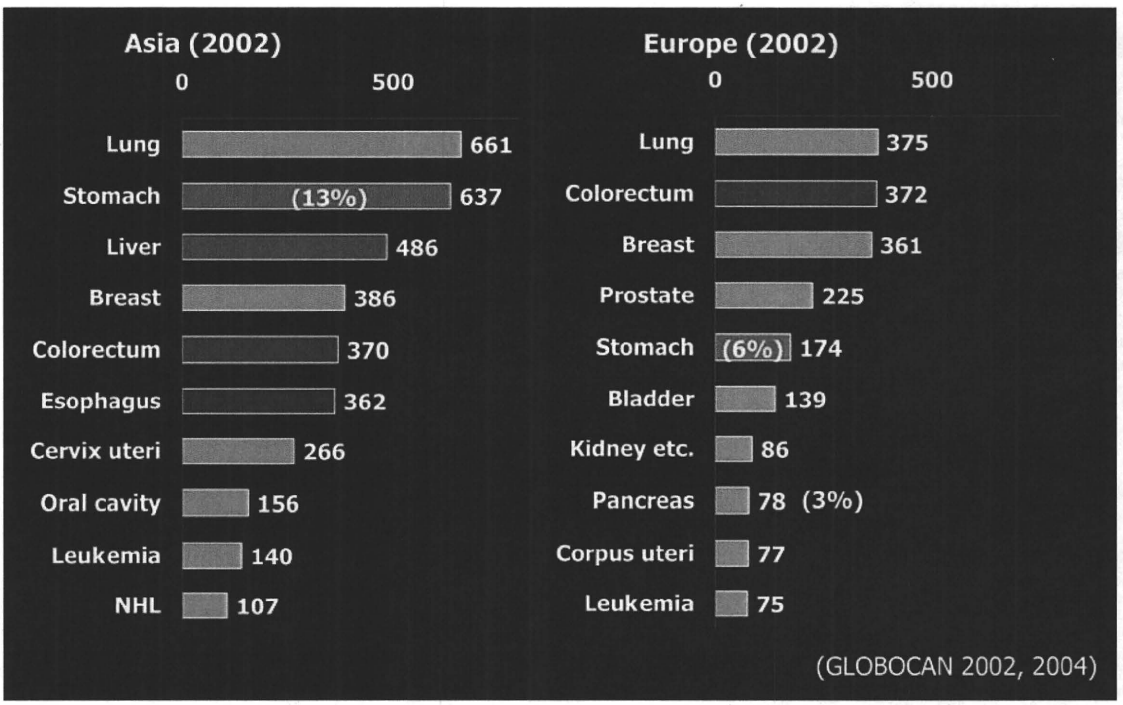

Figure 1. Number of new cases for 10 common cancers (both sexes).

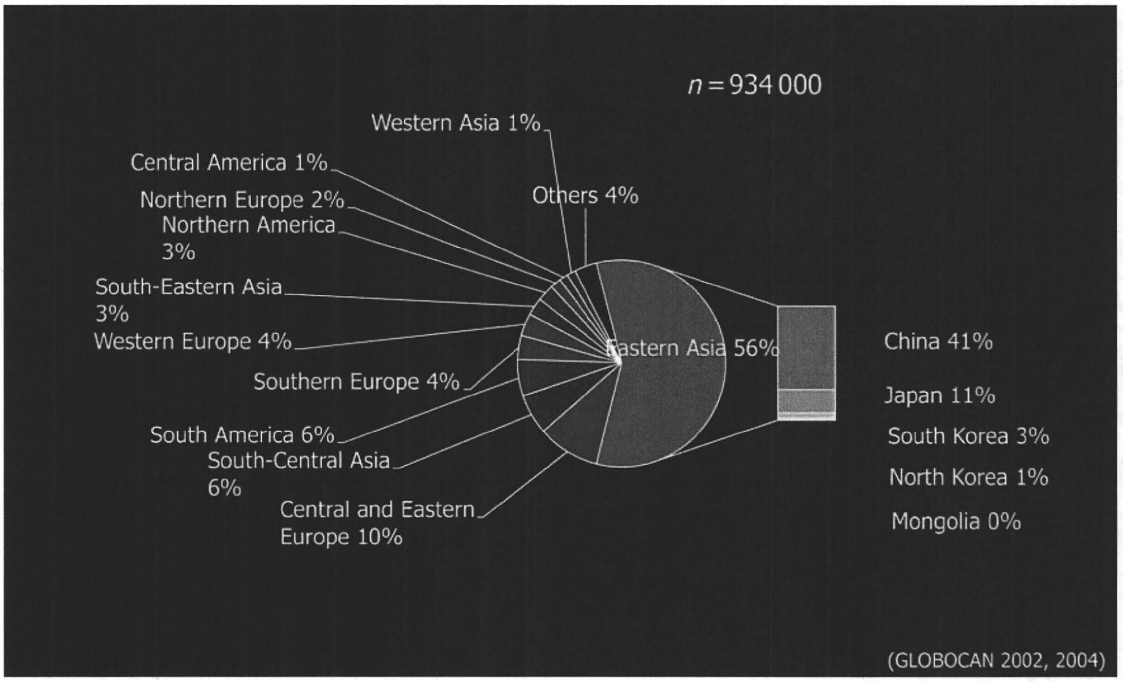

Figure 2. Estimated distribution of gastric cancer in the world in 2002.

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

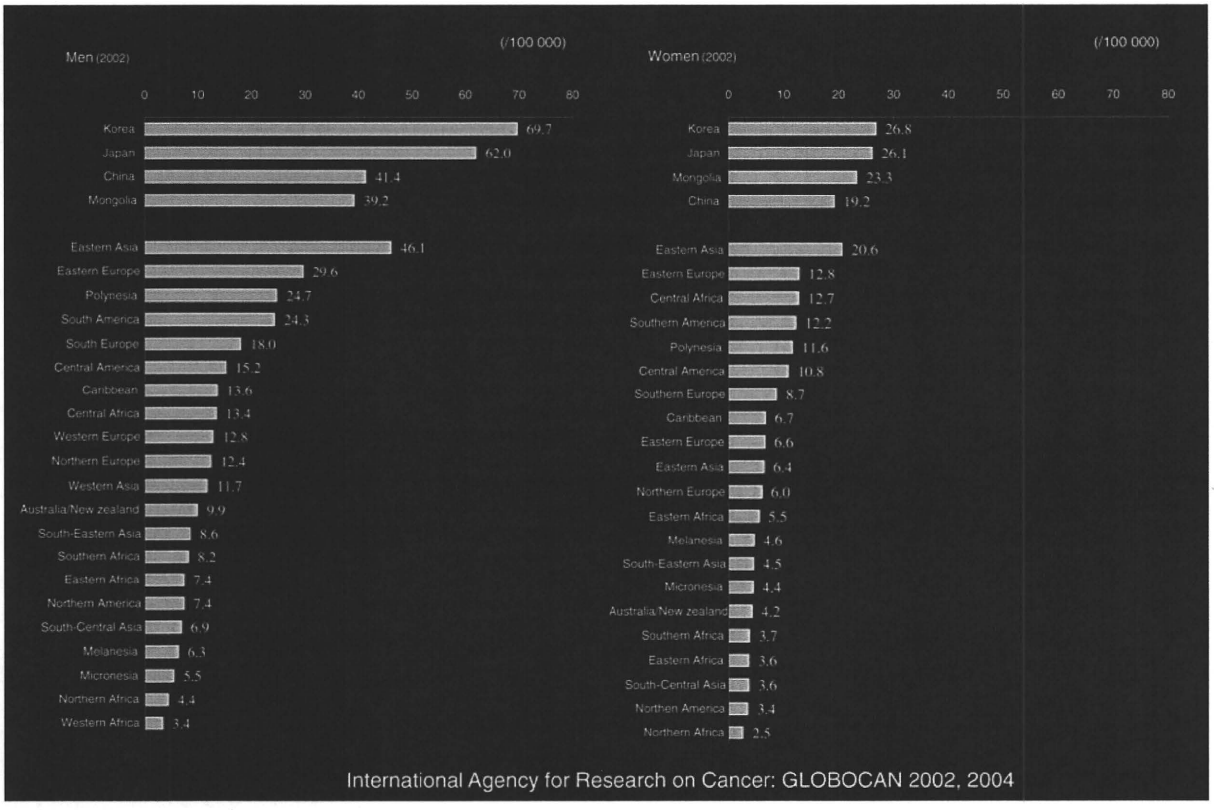

Figure 3. Age-standardized incidence rate of gastric cancer in various area of the world (2002 estimate).

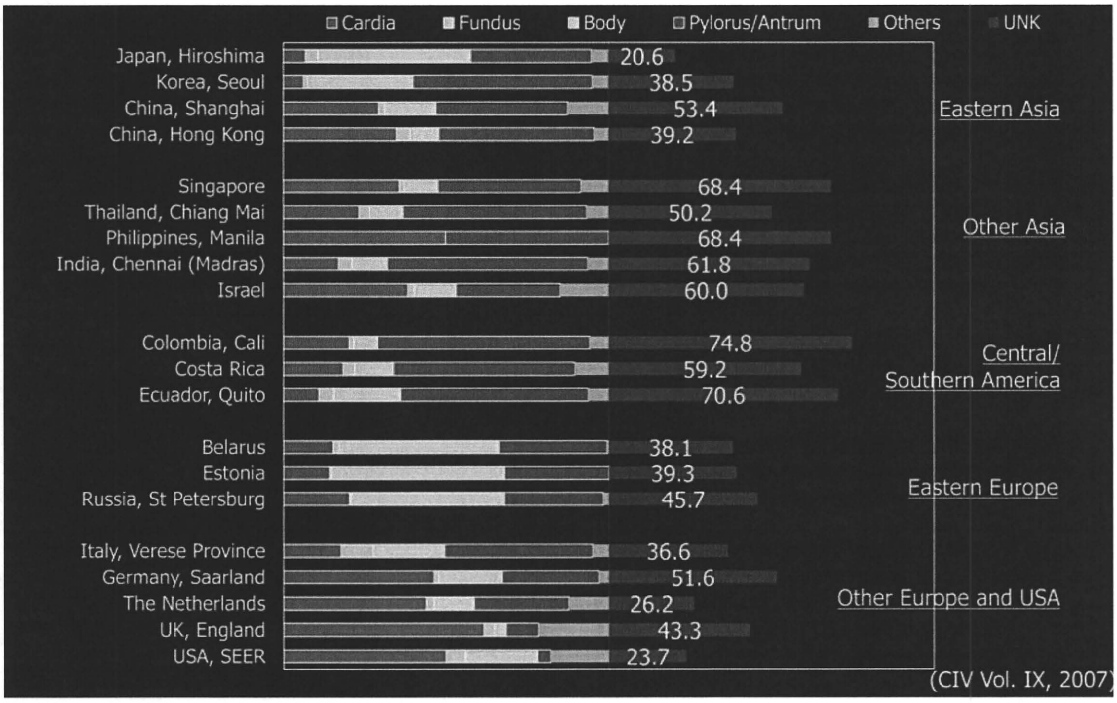

Figure 4. Subsite distribution of gastric cancer, 2000.

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

2.9% of 1246 cases with *H. pylori* infection developed gastric cancer over a period of 7.8 years. A randomized controlled study in China also showed that *H. pylori* eradication was more effective in patients without atrophic gastritis than those with it (5). Dr Fukase in Japan reported that in a randomized controlled study comparing eradication of *H. pylori* with no eradication after endoscopic mucosal resection (EMR) of early gastric cancer at the 3-year follow-up point significantly reduced the number (9 versus 24) of metachronous gastric cancer developed in the eradication group compared with the control group. It was concluded that prophylactic eradication of *H. pylori* after EMR for early gastric cancer should be performed to prevent the development of metachronous gastric cancers (Fig. 5) (6). These results suggested that it was never too late to eradicate *H. pylori* for prevention of gastric cancer. An Italian group performed a meta-analysis of the published data regarding whether *H. pylori* eradication treatment can reduce the risk of gastric cancer. It was concluded that 1.1% of treated patients would develop gastric cancer, in contrast to 1.7% of untreated patients. In six studies with about 6700 participants followed for 4–10 years, the relative risk was 0.65, and it was concluded that *H. pylori* eradication treatment seemed to reduce gastric cancer (7). In Taiwan, a nationwide cohort study followed 80 000 patients with *H. pylori*-infected peptic ulcers for 10 years. These patients were divided into early- and late-eradication cohorts. It was concluded that early *H. pylori* eradication showed no significant difference in the gastric cancer risk compared with the general population, but late eradication was associated with an increased risk of gastric cancer. Older age, male gender, gastric ulcer, no regular NSAIDs use and late *H. pylori* eradication represented independent risk factors for gastric cancer development (Fig. 6) (8).

Fock et al. concluded that fruits and vegetables are associated with a reduced risk of gastric cancer in his paper in the *Journal of Gastroenterology and Hepatology*. Supplementation of vitamins and minerals may be unnecessary, at least in healthy subjects with no nutritional deficiencies (9). In a meta-analysis study, all studies proved that both aspirin and NSAIDs are useful for preventing cardia and non-cardia gastric cancer (10). There is insufficient evidence for any benefit from green tea, vitamins and antioxidants. The biological behaviors of distal and proximal gastric cancers are quite different, but the prevention regimens have been the same, centered on eradication of *H. pylori* infection.

The Working Group concluded that the etiology of gastric cancer consists of genetic susceptibility, *H. pylori* infection and environmental risk factors. *Helicobacter pylori* eradication treatment, consumption of fresh vegetables and fruits and use of aspirin and NSAIDs (11) seem to reduce the risk of gastric cancer.

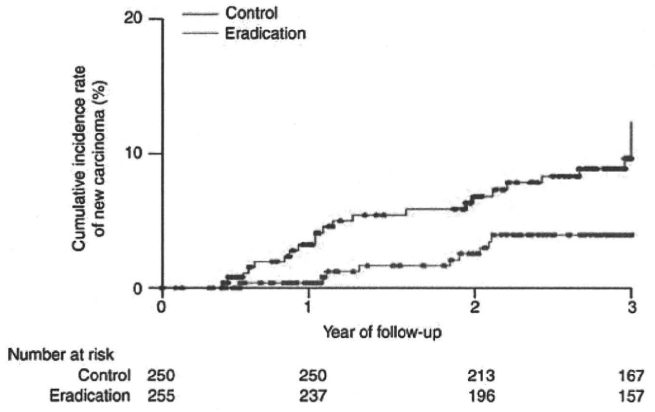

Figure 5. Kaplan–Meier analysis of the cumulative incidence rate of new carcinoma. Source: Fukase et al. (6).

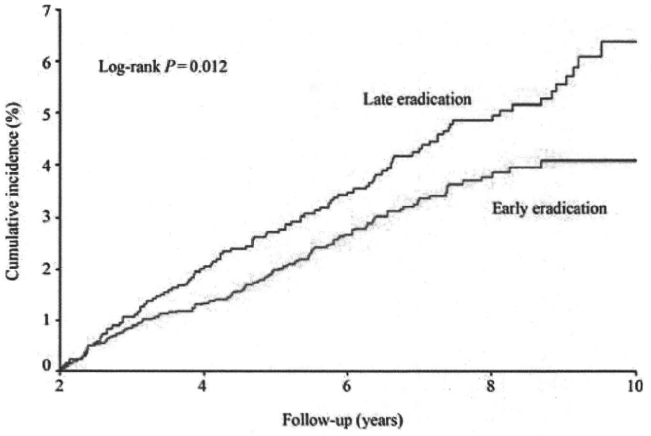

Figure 6. Cumulative incidence of gastric cancer in two groups, early eradication and late eradication groups. Source: Wu et al. (8).

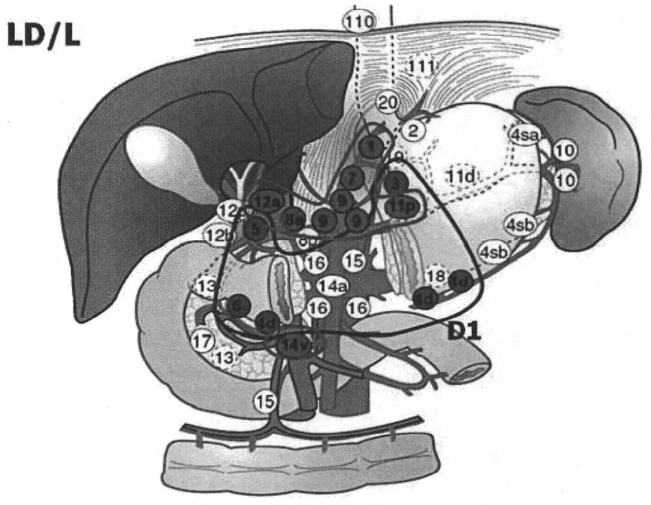

Figure 7. Regional lymph node group according to the location of tumor. Source: Sasako et al. (21) and Yoon and Yang (22).

ENDOSCOPY AND DIAGNOSIS

Experience in Japan has shown that access to screening and early endoscopy increased the proportion of early-stage

gastric cancers, leading to improved survival (12). Cost is a major barrier to screening. Screening is considered to be cost-effective in high-incidence countries, but perhaps not where the incidence of gastric cancer is moderate or low. Risk stratification may help to focus limited resources on patients at greatest risk, and thereby increase the cost-effectiveness of screening (13). Serum pepsinogen-based tests may help to identify a subset of patients with atrophic gastritis, who are especially at a high risk. In a country with high incidence of gastric cancer, such as Japan, it is still very cost-effective to screen even if the cost of endoscopy is high. Singapore and some other countries in East Asia have a moderate incidence of gastric cancer, and screening these populations could be cost-effective if the cost were moderate (13). In Japan, the government-supported screening program has been based on barium, and although very successful, it accounts for less than 10% of all cancers that are diagnosed by screening. Most are detected due to early or easy access to endoscopy, either through outpatient clinics or through health screening outside of the government's screening program (14).

High-quality endoscopy is important and may be facilitated by endoscope preparation, such as lens cleaning, and by patient preparation ahead of endoscopy by the use of defoaming agents, mucolytics and antispasmodics, which make the field of interest much clearer. Techniques such as adequate air insufflation, systematic examination of the entire stomach, use of contrast agents, image enhancement and cognitive training may also help improve yield rates.

Accurate specimen collection and recording of endoscopic findings are important. There is some discordance between Western- and Japanese-trained pathologists in the biopsy definition of early gastric cancer. In the West, the gold standard for diagnosing cancer is to detect invasion of tumor cells into the lamina propria, muscularis mucosae or submucosal layer, whereas in Japan, it is more important to detect cellular atypia or structural atypia, regardless of invasion, when making a diagnosis of cancer. The revised Vienna classification has helped resolve some of these differences and may be a good starting point for consensus between Western and Japanese pathologists (15).

Gotoda et al. (16) reported that there is a clearly defined subgroup of patients with early gastric cancer that has a virtually negligible risk of nodal metastasis. Such patients could be treated definitively by local resection, with the expected long-term outcome equivalent to radical surgery. Further development led to the expanded criteria for endoscopic therapy of early gastric cancer, with *en bloc* resection being the primary goal (17). Endoscopic resection can be considered curative if the lesion shows differentiated histopathology, is limited to the mucosal layer or <500 μm submucosal invasion, with clear vertical and lateral margins, and no lymphovascular involvement. EMR has the advantages of short procedure time and low risk of perforation, which make it an attractive option for small lesions. EMR for differentiated, non-ulcerated early cancer <20 mm in diameter is associated with an excellent 10-year survival rate of 99% (18). Endoscopic submucosal dissection (ESD) is associated with a lower local recurrence rate than EMR because the technique permits *en bloc* resection without size limitation. Procedure times for ESD are longer, however, with higher delayed bleeding and perforation risk (19). A recent long-term follow-up study showed that ESD for early gastric cancer, which met the expanded criteria, resulted in 5-year overall and disease-specific survival rates of 97% and 100%, respectively (20). Training opportunities in ESD for endoscopists from outside Japan and Korea, however, remain limited.

In conclusion, 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. Barium meal-based screening is government-funded in Japan, but is less accurate than gastroscopy. Gastroscopic screening is desirable in high-risk populations. High-quality endoscopy may increase diagnostic yield in early cancer. Endoscopic resection is curative in a subset of patients with early cancer as defined by the expanded criteria. EMR has shown long-term outcomes comparable with surgery in patients with small lesions, and similar outcomes with ESD for larger lesions in experienced hands. Standardization between Western- and Japanese-trained pathologists in diagnosing gastric cancer is urgently needed. Structured training programs for ESD should be set up in high-volume centers and made accessible to suitable regional candidates.

SURGERY AND ADJUVANT TREATMENT

For gastric cancer, so-called D1, or perigastric lymph node, dissection is common in Western countries, whereas in high-incidence countries like Japan and Korea, so-called D2 dissection is considered to be the standard (Fig. 7) (21,22).

An RCT from UK comparing D1 versus D2 found very high mortality but failed to show a difference (23,24). The trial was flawed due to the very high mortality, inclusion of a large proportion of stage I and absence of any description regarding the quality of lymph node dissection. A Dutch trial started 20 years ago also showed much higher mortality for D2 compared with D1 dissection and demonstrated no survival benefit (25,26). These two trials were closed before reaching the plateau of the learning curve, and the high post-operative mortality offset the effect of the D2. D2 dissections should be carried out in specialized centers.

An RCT in Taiwan compared D1 and D2 showed survival benefit of D2 dissection with reasonable morbidity and mortality (Fig. 8) (27).

To investigate even more extensive dissection of gastric cancer, a Japanese group compared D2 with D2 plus para-aortic nodal dissection (28,29). The results showed slightly higher morbidity, but without increase in mortality. These morbidity and mortality results were acceptable. However,

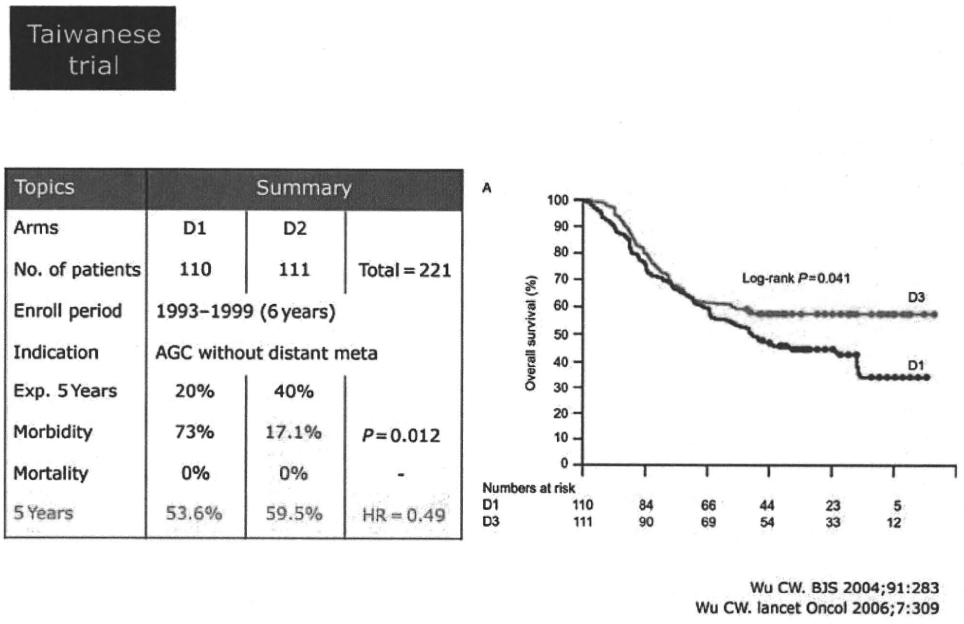

Figure 8. Nodal dissection for patients with gastric cancer: a randomized controlled trial. Source: Wu et al. (27).

no survival difference was observed, and D2 was thus the optimal surgery in that RCT. Comparison of reports from various countries reveals that the mortality is higher when the volume is lower, again demonstrating that D2 dissection should be performed in high-volume and/or specialized centers.

Regarding the role of adjuvant treatment, a major trial in Europe showed survival benefit from perioperative chemotherapy, but less than half of the patients underwent D2 dissection and the study also included esophageal cancer cases (30).

An RCT performed in the USA investigated the role of post-operative chemoradiotherapy and also showed significant survival benefit (31,32). However, only 10% of the patients underwent D2 dissection, there was a very high rate of local recurrence, and the surgery was not standardized among the participating hospitals. Subgroup analysis found survival benefit only in D0 or D1, but not in the D2-dissected group. The study thus showed that D0/D1 dissection was insufficient treatment.

In a Japanese randomized trial, curative D2 dissection alone was compared with D2 followed by post-operative chemotherapy by oral S-1 (33). In contrast to the Western studies, almost all of the cases in this study underwent D2 dissection, and the 3-year survival rate showed a 10% improvement (Fig. 9). A clinical trial of adjuvant treatment is being conducted in Korea, China and Taiwan, and 1024 cases have been enrolled. The results will be available within a few years. A Japanese group and a Korean group are working together to assess, for the first time, the role of reductive gastrectomy in Stage IV gastric cancer treatment (34). The chemotherapy applied in both arms is S-1 plus cisplatin. Although a very difficult project, it is very important, and it is hoped that other Asian countries will join this collaboration in the future.

In conclusion, with regard to the extent of surgery, 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. In areas with a high incidence of gastric cancer, the quality of treatment can be kept very high, with both endoscopic treatment and surgery. At the moment, at least in Asia, D2 dissection should be considered as the standard.

CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

There are now four active cytotoxic agents for advanced gastric cancer, consisting of fluorouracils, platinum, taxanes and irinotecan. The fluorouracils include 5-FU, S-1 and capecitabine, and the platinum include cisplatin and oxaliplatin. During the last decade, various randomized trials investigated the optimal combination of these four chemotherapy drug groups in Japan, Korea and China (Table 1). Capecitabine plus platinum was at least non-inferior to 5-FU plus cisplatin in terms of survival (35,36). S-1 plus cisplatin showed a comparable median time to progression to those in capecitabine or 5-FU plus cisplatin in Western studies (37,38), whereas the Japanese studies yielded relatively longer survival than the Western studies. These favorable survival in Japanese studies compared with the Westerns might be caused by longer survival after failure of the first-line therapy associated with higher rates of subsequent therapy than in the Western studies (Fig. 10).