

Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer

A Meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumor Research International Collaboration) Group*

ALTHOUGH EPIDEMIOLOGICAL studies describe a reduction in recent years in gastric cancer incidence, gastric cancer is a common and highly fatal disease, with current 5-year survival rates less than 20%.¹ Surgery for disease at an early stage can usually be performed with curative intent, but the 5-year survival rate is disappointing.^{2,3} Over the last 3 decades, numerous phase 3 studies including a surgery-only group have been reported, but definitive evidence of the efficacy of adjuvant chemotherapy is lacking. Recently, the large-scale Japanese phase 3 trial by the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) group⁴ reported the superiority of S-1 as an adjuvant chemotherapy over surgery alone after D2 lymph node dissection. Its applicability outside of East Asia is uncertain, and the First-Line Advanced Gastric Cancer Study (FLAGS) in advanced disease⁵ that compared cisplatin and S-1 vs cisplatin and fluoropyridines in non-Asian countries was negative. Therefore, standard management following curative surgery is heterogeneous throughout the world.

See also pp 1723, 1753 and Patient Page.

Context Despite potentially curative resection of stomach cancer, 50% to 90% of patients die of disease relapse. Numerous randomized clinical trials (RCTs) have compared surgery alone with adjuvant chemotherapy, but definitive evidence is lacking.

Objectives To perform an individual patient-level meta-analysis of all RCTs to quantify the potential benefit of chemotherapy after complete resection over surgery alone in terms of overall survival and disease-free survival, and to further study the role of regimens, including monochemotherapy; combined chemotherapy with fluorouracil derivatives, mitomycin C, and other therapies but no anthracyclines; combined chemotherapy with fluorouracil derivatives, mitomycin C, and anthracyclines; and other treatments.

Data Sources Data from all RCTs comparing adjuvant chemotherapy with surgery alone in patients with resectable gastric cancer. We searched MEDLINE (up to 2009), the Cochrane Central Register of Controlled Trials, the National Institutes of Health trial registry, and published proceedings from major oncologic and gastrointestinal cancer meetings.

Study Selection All RCTs closed to patient recruitment before 2004 were eligible. Trials testing radiotherapy; neoadjuvant, perioperative, or intraperitoneal chemotherapy; or immunotherapy were excluded. Thirty-one eligible trials (6390 patients) were identified.

Data Extraction As of 2010, individual patient data were available from 17 trials (3838 patients representing 60% of the targeted data) with a median follow-up exceeding 7 years.

Results There were 1000 deaths among 1924 patients assigned to chemotherapy groups and 1067 deaths among 1857 patients assigned to surgery-only groups. Adjuvant chemotherapy was associated with a statistically significant benefit in terms of overall survival (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.76-0.90; $P < .001$) and disease-free survival (HR, 0.82; 95% CI, 0.75-0.90; $P < .001$). There was no significant heterogeneity for overall survival across RCTs ($P = .52$) or the 4 regimen groups ($P = .13$). Five-year overall survival increased from 49.6% to 55.3% with chemotherapy.

Conclusion Among the RCTs included, postoperative adjuvant chemotherapy based on fluorouracil regimens was associated with reduced risk of death in gastric cancer compared with surgery alone.

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No patient-level meta-analyses have been carried out to date. Based on published results, recent meta-analyses⁶⁻¹⁰ indicated that adjuvant chemotherapy produces a small survival benefit, if any, in patients with resected gastric carcinoma (eTable 1, available at <http://www.jama.com>) but did not recommend ad-

juvant chemotherapy as routine therapy. Since then, several additional trials have been conducted in this setting. Overall,

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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) monotherapy 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 sta-

tus, 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 statistics¹³ 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 test¹⁶ 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 investigator³⁵⁻³⁹ or because data were lost or inaccessible.⁴⁰⁻⁴⁸ One trial²¹ 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

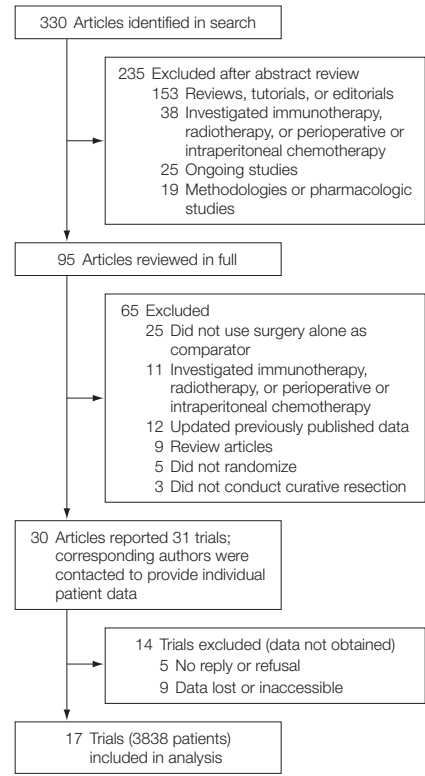
Median follow-up for OS was slightly different between the 2 groups (7 years; range, 0.1-28.2 years in the surgery-only group vs 7.2 years; range, 0.1-30.3 years; $P < .001$), during which 1067 patients in the surgery-only group and 1000 patients in the chemotherapy group died. FIGURE 2 shows the HRs for OS in the individual trials and overall. There was a significant ben-

efit 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

Figure 1. Study Flowchart



heterogeneity between trials in treatment effect ($P = .57$).

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.		Recruitment Period	UICC Stage, %	Follow-up, Median (Range), y
				CT (n = 1953) (n = 163)	S (n = 1885) (n = 161)			
Monochemotherapy				(n = 163)	(n = 161)			
Grau et al, ¹⁹ 1993	Mitomycin C	20 mg/m ² 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/m ² /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	1.3 mg/m ² IV	Twice a week for 5 wk	156	72	1974-1977	I, 46; II, 29;	24.2 (11.4-30.3)
	Fluorouracil or ftorafur	167 mg/m ² or 267 mg/m ² IV	Twice a week for 5 wk				III, 21; X, 4	
	Cytosine arabinoside	13 mg/m ² IV, then orally	Twice a week for 5 wk					
	Fluorouracil or ftorafur	133 mg/m ² or 670 mg/m ²	For 2 y					
Nakajima et al, ²² 1999	Mitomycin C Fluorouracil Uracil plus tegafur	1.4 mg/m ² IV 166.7 mg/m ² IV 300 mg/m ² /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	1.3 mg/m ² IV	Fluorouracil IV: for the first 3 wk	128	124	1993-1994	I, 94; II, 6	5.9 (2.7-8.2)
	Fluorouracil	167 mg/m ² IV						
	Cytosine arabinoside	13 mg/m ² IV	Fluorouracil orally: for the next 18 mo					
	Fluorouracil	134 mg/m ² orally						
Polychemotherapies: fluorouracil + mitomycin C + anthracyclines				(n = 497)	(n = 516)			
Coombes et al, ²⁴ 1990	Fluorouracil Doxorubicin Mitomycin C	600 mg/m ² IV 30 mg/m ² IV 10 mg/m ² 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/m ² IV 40 mg/m ² IV 10 mg/m ² 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/m ² IV 30 mg/m ² IV 10 mg/m ² 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/m ² IV 30 mg/m ² IV 10 mg/m ² 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/m ² IV 30 mg/m ² IV 10 mg/m ² 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	150 mg/m ² orally	Every 10 wk (for 2 y)	91	88	1975-1980	NA	12.1 (2.2-13.9)
	Fluorouracil	325 mg/m ² IV 325 mg/m ² IV						
Engstrom et al, ³⁰ 1985	Semustine	150 mg/m ² orally	Day 1	100	96	1975-1980	NA	16.5 (0.4-24.9)
	Fluorouracil Fluorouracil	350 mg/m ² IV 375 mg/m ² IV	Every 10 wk (for 2 y)					
Krook et al, ³¹ 1991	Fluorouracil Doxorubicin	350 mg/m ² IV 40 mg/m ² 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/m ² IV 20 mg/m ² IV 40 mg/m ² IV 100 mg/m ² IV 375 mg/m ² 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	800 mg/m ² IV then 1 g/m ²	5 d	138	140	1989-1997	I, 34; II, 29; III, 25; IV, 12	8.1 (0.4-12.7)
	Cisplatin	100 mg/m ² IV	Every 4 wk (4 cycles)					
Nitti et al, ³⁴ 2006 ^c	Fluorouracil Doxorubicin Methotrexate with leucovorin	1.5 g/m ² IV 30 mg/m ² IV 1.5 g/m ² IV with 15 mg/m ² (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/m ² IV 70 mg/m ² IV 1.5 g/m ² IV with 30 mg/m ² (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,

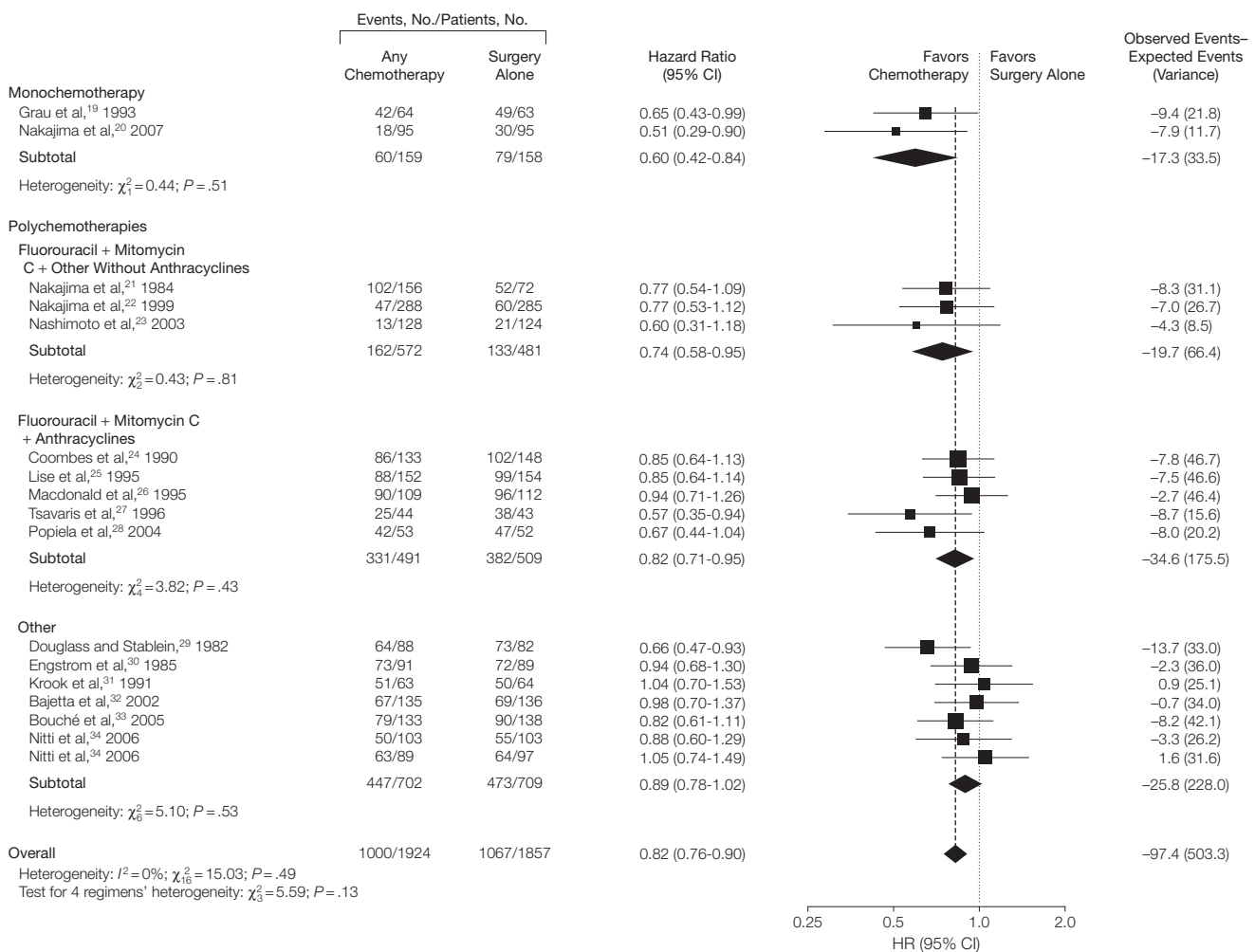
0.58-0.95; $P = .03$), with 5-year survival rates of 76.6% for the surgery-only group vs 82.8% for the chemotherapy group. A similar effect on DFS was observed in the 2 more recent studies (HR, 0.69; 95% CI, 0.48-0.98) with 5-year DFS rates of 84.2% for the surgery-only group vs 88.2% for the chemotherapy 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 re-

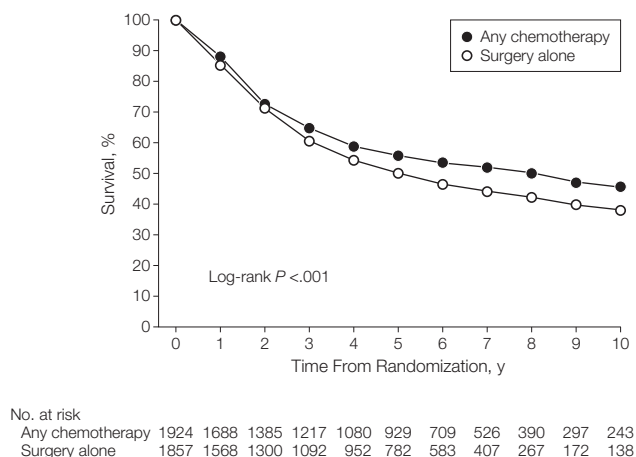
duction was observed for OS (HR, 0.82; 95% CI, 0.71-0.96; $P = .01$). The 5-year survival rate increased from 31.9% to 39.3%, and heterogeneity was not detected ($P = .52$). The HR for DFS was estimated from 4 trials. The risk of relapse or second primary cancer or death was also statistically significantly 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



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 trial²⁹ 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 study²⁹; 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-1⁴ 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 trial¹⁹ 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 assess-

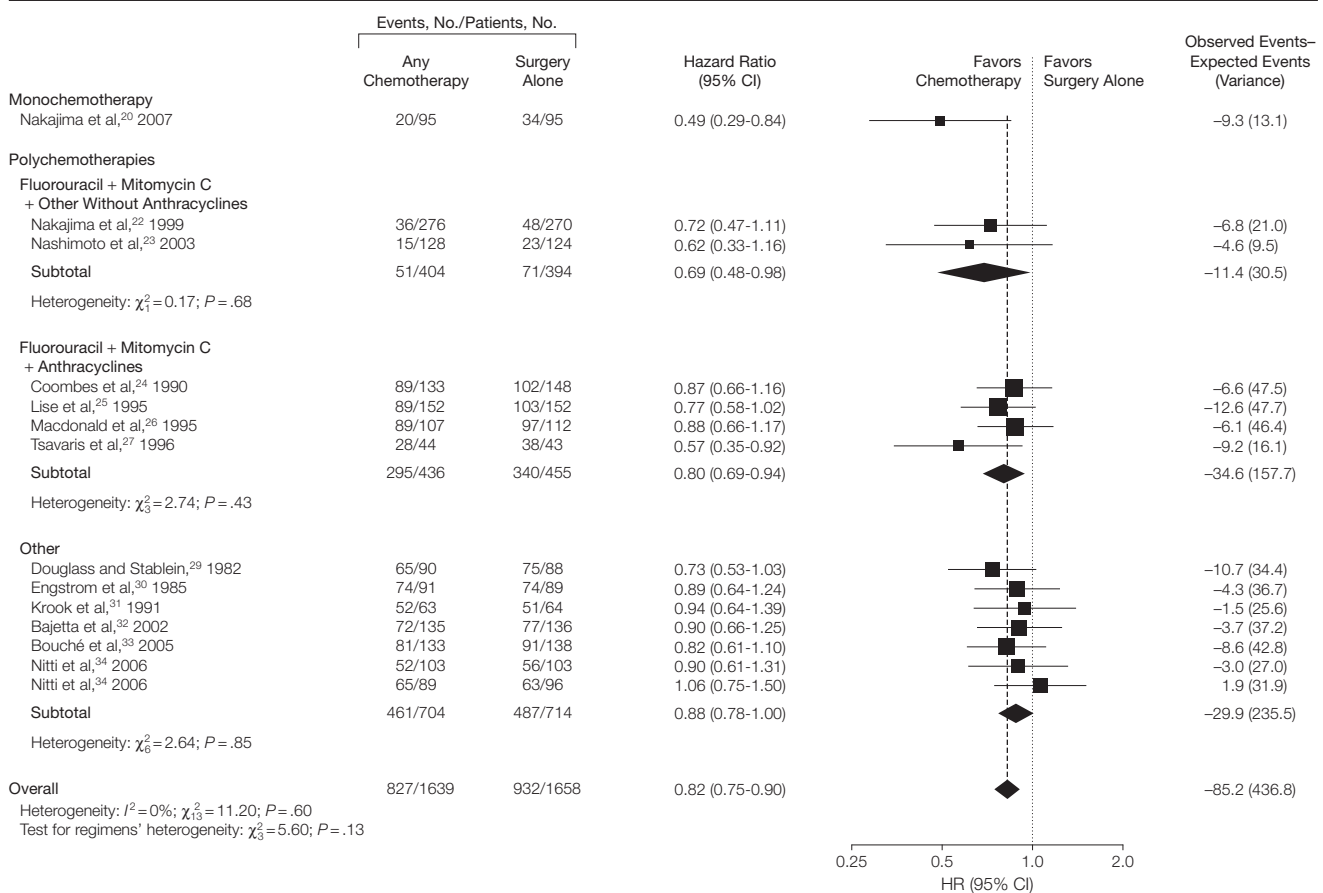
ing the robustness of a meta-analysis with respect to unavailable trials.

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 fluoropyrimi-

dines (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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