Benefit of Adjuvant Chemotherapy for Resectable Gastric Cancer: A Meta-Analysis of Individual Patient Data from 17 Randomized Trials

The GASTRIC (Global **A**dvanced/Adjuvant **S**tomach **T**umor **R**esearch through **I**nternational **C**ollaboration) Group*

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Abstract (300 words)

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

Objective: To perform an individual patient data based meta-analysis of all RCTs to quantify the potential benefit of chemotherapy after complete resection over surgery alone in terms of overall survival (OS) and disease free survival (DFS), and to further study the role of regimens including mono-chemotherapy, combined chemotherapy with 5-fluorouracil derivatives, mitomycin-C with or without 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 (upto 2009), the Cochrane Central Register of Controlled Trials, the NIH trial registry, as well as proceedings books from major oncologic and gastrointestinal cancer meetings.

Study Selection: All RCTs closed to patient accrual before 2004 were eligible. Trials testing radiotherapy, neo-adjuvant, perioperative or intraperitoneal chemotherapy or immunotherapy were excluded. Thirty-one eligible trials (6,390 patients) were identified.

Data Extraction: As of 2010, individual patient data were available from 17 trials (3,838 patients representing 60% of the targeted data) with a median follow-up exceeding 7 years.

Results: There were 1,000 deaths in 1,924 patients assigned to chemotherapy arms and 1,067 death in 1,857 patients assigned to surgery alone arms, which translated into overall statistically significant benefits in favour of adjuvant therapy in terms of OS (HR=0.82, 95%CI 0.76-0.90, p <0.0001) and DFS (HR=0.82, 95%CI 0.75-0.90, p<0.0001). There was no significant heterogeneity for OS neither across RCTs (p=0.52) nor across the four regimens groups (p=0.13). Five-year OS increased from 49.6% to 55.3%.

Conclusions: Among the RCTs included, post-operative adjuvant chemotherapy based on 5-fluorouracil regimens reduces the risk of death in gastric cancer by approximately 18% as compared to surgery alone.

Key words: gastric cancer; adjuvant chemotherapy, individual patient data; meta-analysis; randomized trial

Introduction

Although epidemiological studies describe a reduction in recent years in gastric cancer incidence, gastric cancer is a common and highly fatal disease, with current five-year survival rates less than 20% [1]. Surgery for disease at an early stage can usually be performed with a curative intent, but the five-year survival rate is disappointing [2,3]. Over the last three decades numerous phase III studies including a surgery alone arm have been reported, but definitive evidence of the efficacy of adjuvant chemotherapy is lacking. Recently, the large-scale Japanese phase III (ACTS-GC) [4], concluded to the superiority of the S-1 as an adjuvant chemotherapy over surgery alone after D2 dissection. Its applicability out of East Asia is uncertain and the FLAGS study in advanced disease [5] that compared cisplatin and S1 versus cisplatin and fluoropyridines in non-Asian countries was negative. Therefore, standard management following curative surgery is heterogeneous throughout the world.

No individual patient based meta-analyses have been carried out to date. Based on published results, recent meta-analyses [6-10] indicated that adjuvant chemotherapy produces, if any, a small survival benefit in patients with resected gastric carcinoma (eTable 1) but did not recommend adjuvant chemotherapy as routine therapy. Since then, several additional trials have been conducted in this setting. Overall, 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 (IPD) from all relevant trials.

Methods

Literature Search

Data from all published randomized trials comparing adjuvant chemotherapy to 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. No restriction on language of publication was considered. The Cochrane Central Register of Controlled Trials and the NIH 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 (i) mono-chemotherapy agents, (ii) 5-fluorouracil, mitomycin C and other without anthracyclines and (iii) with anthracyclines and (iv) trials investigating "other" polychemotherapy regimens.

Study Selection

Trials were eligible if they were randomized, closed to patient accrual before 2004, and if they compared any adjuvant therapy after curative resection versus surgery alone. Trials investigating immunotherapy, neo-adjuvant or perioperative chemotherapy were excluded. Likewise, trials with radiotherapy or intraperitoneal chemotherapy were not in the scope of our research.

Data Extraction

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, the TNM Classification of Malignant Tumours, the overall stage

grouping system, the performance status (WHO or Karnofsky index) and the age at entry. As UICC 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 re-analyzed and checked for inconsistencies. In particular, diagnostic tools for randomization quality were systematically applied [11].

Statistical Methods

Time-related endpoints (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 (O–E) [12]. Heterogeneity between trials and groups of trials (e.g., defined by different chemotherapy regimens), was tested using chi-squared statistics [13] and measured with the I² statistic [14]. Forest plots were used to display hazard ratios (HR) 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 as proposed by Peto [15], yielding a representation consistent with the main logrank 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 arm 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 ITT principle, whether or not they were analyzed in the trial publication. In cases where the survival data was missing, the patient was excluded from the analysis. As a sensitivity analysis we investigated the overall treatment effect in all the identified trials, pooling IPD with summary statistics extracted from the publication [18]. We also analyzed these summary statistics separately. Finally, we investigated the heterogeneity among the regions of the world where the trials were conducted (Europe, Asia and the USA). All P-values were two–sided at the 5% level and confidence interval (CI) had two-sided probability coverage of 95%. The SAS v9.1 software was used with macros developed at the European Organization for Research and Treatment of Cancer (EORTC) Data Center (Brussels, Belgium) for meta-analysis and at Institut Gustave-Roussy (Villejuif, France) for survival curves. Hazard functions were plotted with Stata v9.2.

All the results were discussed during four large international investigators' meetings organized in different countries.

Results

<u>Collected trials</u>

Thirty one trials that had randomized 6,390 patients were identified (Figure 1). We obtained individual data for 3,838 patients included in 17 trials (Table 1). This represents 60% of the targeted data. Each corresponding author of the eligible trials was contacted at least five times between January 2007 and February 2010. Data were not obtained for 2,552 patients included in 14 trials, for the following reasons: no reply or refusal to share data by the principal investigator [25,28,33,52, 53], data lost or inaccessible [27,29,34,37,40,41,44,45,48]. Figure 1 describes the percentages of collected IPD in the different pre-specified groups. One trial [26] compared surgery alone against two investigational arms with 5-fluorouracil or ftorafur. Both arms were pooled. Central randomization was reported in fourteen trials (with block stratification for eight and minimization for six). 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 between the two arms could be detected.

<u>Patients' Characteristics</u>

ETable 2 lists the characteristics of the 3,838 randomly assigned patients by arm and eTable 3 according to the chemotherapy regimens. There were no major differences in patient characteristics between treatment arms. These tables also show summary statistics on the clinical outcomes of interest: median OS, and median DFS. Fifty-seven patients (1.5%) with missing survival data (date of randomization, last status and last date were missing for 25, 8 and 49 patients respectively) were excluded from analyses. They were balanced between the two arms (28 vs 29). We identified 361 patients and 103 deaths with a last date after the publication date of the related trial.

Any adjuvant chemotherapy versus surgery alone

Survival

Median follow-up for OS was slightly different between the two arms (7 years; range 0.1 to 28.2 in the surgery alone arm versus 7.2 years; range 0.1 to 30.3, P=.0002) during which respectively 1,067 and 1,000 patients assigned to the surgery alone and the chemotherapy arms died. Figure 2 shows the HRs for overall survival in the individual trials and overall. There was a significant benefit from any chemotherapy compared to surgery alone, with an overall HR of death equal to 0.82 (95% CI, 0.76 to 0.90; P<0.0001), corresponding to an overall 18% reduction of the hazard with chemotherapy. The estimated median OS was 4.9 years (95% CI, 4.4 to 5.5) in the surgery alone group vs. 7.8 years (95% CI, 6.5 to 8.7) in the group receiving adjuvant chemotherapy. Absolute benefits at 5 and 10 years were 5.8% (from 49.6% to 55.3%) and 7.4% (from 37.5% to 44.9%) respectively (Figure 3). No significant heterogeneity (variability of trial-specific HRs) was apparent across the set of trials (homogeneity test P=0.52). Globally, there were no time trends in the treatment effect according to the year of last inclusion (P=0.82). Similarly, no significant heterogeneity was detected across the three continents (homogeneity test P=0.27 (eFigure 1). As a sensitivity analysis, we combined summary statistics extracted from unavailable trials with the collected IPD for a total of 5,866 patients and 28 trials. For three trials [37, 40, 45], 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 to 0.88; P<0.0001) were modified (eFigure 2). Analysis of the eleven trials with available summary resulted in HR=0.81 (95%CI 0.73 to 0.91, P<0.001). No significant heterogeneity was detected (p=0.11).

Disease-Free Survival

DFS was available on a subset of 14 trials with a total number of 3,297 patients from the 21

trials which collected this information, representing 78% of the targeted number of patients. On this sub-population, we observed a HR of death of 0.85 (95%CI, 0.77 to 0.93), consistent with the estimate on the full database. HRs for DFS in individual trials and overall are shown in Figure 4. Adjuvant chemotherapy improved DFS compared to surgery alone with an overall HR of 0.82 (95%CI, 0.75 to 0.90; P<0.0001). 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=0.57).

Analysis of groups of regimens

An interaction test between the type of regimen (mono-chemotherapy, 5-fluorouracil, mitomycin C with or without anthracylines, other polychemotherapy) and the treatment effect on OS and on DFS were not significant (P=0.13 for both). In the sensitivity analysis, interaction was of borderline significance for OS (P=0.05). We further explored these four groups. Survival curves are provided as supplementary material (eFigures 4 to 7).

Monotherapies (n=324, 2 trials)

The two medium-sized trials [24,51] (one European and one Japanese) that included a total of 317 patients eligible for the meta-analysis with OS data showed a statistically significant benefit of adjuvant mono-chemotherapy over surgery alone (HR=0.60, 95% CI, 0.42 to 0.84; P=0.03), with 5-year survival rates of 53.9% versus 71.4%. This rate was much higher than in the whole meta-analysis suggesting that these patients had a good baseline prognosis. DFS was not collected in one of the two trials and hence not analyzed.

Polychemotherapies: 5-fluorouracil + mitomycin C + other without anthracyclines (n=1053, 3 trials)

Three Japanese trials used combined chemotherapy including fluorouracil derivatives, mitomycin C without anthracyclines [26,30,31]. Overall, a statistically significant benefit for OS was observed (HR=0.74, 95% CI, 0.58 to 0.95; P=0.026), with 5-year survival rates of 76.6% versus 82.8%. A similar effect on DFS was observed in the two more recent studies (HR= 0.69; 95% CI, 0.48 to 0.98) with 5-year DFS rates of 84.2% versus 88.2%.

Polychemotherapies: 5-fluorouracil + mitomycin C + anthracyclines (N=1,013 from 5 trials)

Five trials (four European and one American) with 1,000 patients and OS data used combined chemotherapy including anthracyclines [32,35,36,38,39]. Overall, a statistically significant hazard reduction was observed for OS (HR=0.82, 95% CI, 0.71 to 0.96; P=0.01). The 5-year survival rate increased from 31.9% to 39.3%, and the homogeneity test was not rejected (P=0.52).

The HR for DFS was estimated from four trials. The instantaneous risk of relapse or second primary or death was also statistically significantly reduced (HR=0.80, 95% CI, 0.69 to 0.94; P=0.006) with 5-year DFS rates of 31.9% versus 39%.

Polychemotherapies: group "other" versus surgery alone (N=1,448 from 7 trials)

On the 1,411 subjects for whom survival data were available [42,43,46,47,49,50], we did not detect a significant effect of adjuvant regimens versus surgery alone (HR=0.89, 95%CI, 0.78 to 1.02; P=0.09). The 5-year survival rate was 41.5%. The test for homogeneity was not rejected (P = 0.51) even though one trial [42] which used 5-fluorouracil+ semustine showed a significant treatment effect. Five-year DFS was of 41.9% versus 44.5% and a marginally significant effect of treatment on DFS was observed (HR=0.88, 95%CI, 0.78 to 1.0; P=0.05)

which was mainly driven by the positive study[42]; in a sensitivity analysis excluding this trial, the DFS effect was not significant (HR=0.91, 95%CI, 0.79 to 1.04; P =0.18).

Proportionality of the hazard functions

Plots of survival curves for all chemotherapy regimens combined or in each regimen group suggest non-proportional hazard functions, as illustrated by late separation of the survival function estimates. Test for proportional hazards did not reject a linear time trend in HR. When fitting a time-dependent model on the full dataset with a cut-point at 2 years, the hypothesis of a constant treatment effect before and after 2 years was rejected (P<0.01). Point estimates of the HR by 2 years 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. As these cut-points were derived from the data, they should be considered with caution.

Hazard functions showed that the rate of death reaches a peak at eighteen months and steadily decreases 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 ACT-GS trial reporting on the S1 [4] but not in Europe or in the USA. Numerous randomized phase II and phase III 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 3,838 patients from 17 different trials with a median follow-up longer than 7 years, the largest IPD-based meta-analysis performed so far, we showed a modest but statistically significant benefit of 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 three of the four investigated groups of 5-fluorouracil-based regimens, with reductions in the instantaneous risk of death ranging from 20% to 40% (non-statistically significant heterogeneity). Only one trial [24] 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. IPD based 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).

Post-operative 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 [19]. Thereafter, chemoradiation therapy has gained popularity and has been increasingly used as a standard of care, especially in the USA, even though the optimal chemotherapy regimen has not been identified yet.

Several trials are currently being conducted to inform this issue but their results will not be available until 2011. Similarly, neo-adjuvant trials have shown the benefit of starting the chemotherapy treatment as early as possible [20,21,22]. Despite the short-term results of delayed surgery is debated [23], neoadjuvant treatment, that can be administered to more patients than post-operative 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 all trials. However, for all but three trials with unavailable IPD, we could extract summary statistics from the published papers. Our results remained unchanged when these summary statistics were included in the calculations. Combining unverified published summary statistics with carefully checked IPD 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 arm, 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 arm. Fluoropyrimidines-based regimen, in particular their oral forms (UFT and recently S-1 monotherapy) that have been shown to be better tolerated [8], seem reasonable treatment options, although its applicability outside East Asian countries remains uncertain. This raises the question of why fluoropyrimidines (5-fluorouracil iv or oral tegafur) appear to have activity in the adjuvant setting in gastric cancer as well as in colon cancer even though their efficacy is disappointing in the advanced setting.

In conclusion, this IPD-based meta-analysis shows that adjuvant 5-fluorouracil-based chemotherapy, even in monotherapy, produces a definite improvement in overall survival (HR=0.82) and is recommended for patients who have not received peri-operative treatments,

after R0 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.

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Table 1. List of the included randomized trials

Trials	Adjuvant Chemotherapy	Chemotherapy schedule		No. of patients CT	No. of patients S	Accrual period	UICC Stage	Median (range) follow-up, in years
Mono chemotherapy								
Grau (1993) [24]	MMC	20 mg/m^2 i.v. (day 1)	every 6 wks (4 cycles)	68	66	77-83	I: 14% - II: 32% - III: 54%	11.2 (0.8-20.1)
Nakajima NSAS (2007) [51]	UFT	360 mg/m^2/day orally	every wk (16 months)	95	95	87-01	II: 75% - III: 25%	6.0 (1.2-8.4)
subtotal				163	161			
Polychemotherapies with 5-fluorouracil + MMC without anthracyclines								
Nakajima JCOG (1984)[a] [26]	MMC / 5FU/F / Ara-C / 5-FU/F	1.3 mg/m^2 i.v. / 167 mg/m^2 / F 267mg/m^2 i.v. / 13 mg/m^2 i.v. then orally / 133 mg/m^2 / F 670 mg/m^2		156	72	74-77	I: 46% - II: 29% - III: 21% - X: 4%	24.2 (11.4-30.3)
Nakajima JCOG (1999) [31]	MMC / 5FU / UFT	1.4 mg/m^2 i.v. / 166.7 mg/m^2 i.v. / 300 mg/m^2/day orally	for the first 3 wks / for the next 18 months	288	285	88-92	I: 90% - II: 9% - III: 1%	6.7 (2.9-8.6)

Nashimoto JCOG (2003) [30]	MMC	1.3 mg/m^2 i.v.		128	124	93-94	I: 94% - II: 6%	5.9 (2.7-8.2)
	FU	167 mg/m^2 i.v.						
	Ara-C	13 mg/m^2 i.v.	for the first 3 wks					
	FU	134 mg/m^2 orally	for the next 18 months					
subtotal				572	481			
Polychemotherapies: 5FU + MMC + anthracyclines								
Coombes ICCG (1990) [32]	5FU	600 mg/m^2 i.v.		133	148	81-84	I: 20% - II: 24% - III: 40% - IV: 16%	13.0 (0.1-21.6)
	Doxorubicin	30 mg/m^2 i.v.						
	MMC (FAM)	10 mg/m^2 i.v.	8-wk cycle (6 cycles)					
McDonald SWOG (1995) [35]	5FU	600 mg/m^2 i.v.		109	112	78-91	I: 19% - II: 41% - III: 40%	16.6 (2.9-23.9)
	Doxorubicin	30 mg/m^2 i.v.						
	MMC (FAM)	10 mg/m^2 i.v.	8-wk cycle (6 cycles)					
Lise EORTC (1995) [36]	5FU	400 mg/m^2 i.v.		155	159	79-89	I: 17% - II: 25% - III: 40% - IV: 18%	6.5 (0.9-12.3)
	Doxorubicin	40 mg/m^2 i.v.						
	MMC (FAM)	10 mg/m^2 i.v.	every 6 wks (7 cycles)					
Tsavaris (1996) [38]	5FU	600 mg/m^2 i.v.		47	45	88-94	I: 16% - II: 39% - III: 45%	4.9 (0.6-6.2)
	Epirubicin	30 mg/m^2 i.v.						
	MMC (FEM)	10 mg/m^2 i.v.	8-wk cycle (3 cycles)					

Popiela (2004) [b] [39]	5FU	600 mg/m^2 i.v.		53	52	88-92	III: 76% - IV: 24%	13.0 (2.5-15.5)
	Doxorubicin	30 mg/m^2 i.v.						
	MMC (FAM)	10 mg/m^2 i.v.	8-wk cycle (6 cycles)					
subtotal				497	516			
Other polychemotherapies								
Douglass GITSG (1982) [42]	MeCCNU	150 mg/m^2 orally		91	88	75-80	-	12.1 (2.2-13.9)
	5FU	325 mg/m^2 i.v.						
		5FU 325 mg/m^2 i.v.	every 10 wks (2 years)					
Engstrom ECOG (1985) [49]	MeCCNU	150 mg/m^2 orally	day 1	100	96	75-80	-	16.5 (0.4-24.9)
	5FU	350 mg/m^2 i.v						
	5FU	375 mg/m^2 i.v.	every 10 wks (2 years)					
Krook NCCTG (1991) [47]	5FU	350 mg/m^2 i.v.		63	64	79-89	-	15.6 (5.7-19.8)
	Doxorubicin	40 mg/m^2 i.v.						
Bajetta (2002) [46]	Etoposide	120 mg/m^2 i.v.		135	136	94-97	I: 8% - II: 31% - III: 51% - IV: 10%	6.2 (0.1-9.5)
	Doxorubicin	20 mg/m^2 i.v.						
	Cisplatin	40 mg/m^2 i.v.	for 2 cycles					
	LV	100 mg/m^2 i.v.						
	5FU	375 mg/m^2 i.v.						

				S	CT			
Rougier FFCD (2005) [43]	5FU Cisplatin	800 mg/m^2 i.v. then 1 g/m^2 100 mg/m^2 i.v.	5 days every 4 wks (4 cycles)	138	140	89-97	I: 34% - II: 29% - III: 25% - IV: 12%	8.1 (0.4-12.7)
Nitti EORTC (2006)[c] [50]	5FU Doxorubicin MTX with LV (FAMTX)	1.5 g/m^2 i.v. 30 mg/m^2 i.v. MTX 1.5 g/m^2 i.v. LV 15 mg/m^2 (oral or i.v.)	for 6 cycles	103	103	91-98	I: 13% - II: 25% - III: 61% - IV: 1%	7.0 (2.6-11.3)
Nitti ICCG (2006)[c] [50]	5FU Epirubicin MTX with LV (FEMTX)	1.5 g/m^2 i.v. 70 mg/m^2 i.v. MTX 1.5 g/m^2 i.v. LV 30 mg/m^2 (oral or i.v.)	for 6 cycles	91	100	90-98	I: 9% - II: 87% - IV: 4%	6.9 (0.5-11.1)
subtotal				721	727			
TOTAL				**1953**	**1885**			
				3,838				

a: Nakajima's study (1984) investigated 2 regimens. In the second one Ftorafur replaced 5-fluorouracil used in the first one. They are pooled.

b: Popiela's study (2004) investigated CT+BCG in a third arm that was not included

c: Nitti's publication (2006) relied on a combined analysis of 2 databases that are analysed separately.

S and CT stand for surgery alone and chemotherapy respectively

i.v.: intra-venous; wk: week; UFT= Uracil plus Tegafur; LV=Leucovorin; 5FU=5-Fluorouracyl; F= Ftorafur; MeCCNU= Semustine; MTX= Methothrexate

Figure 1. Identified and collected data

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┌─────────────────────────────────────┐
│ 330 potentially relevant articles    │
└─────────────────────────────────────┘
          │
          │    ┌──────────────────────────────────────────────────────────┐
          ├───▶│ 235 excluded after abstract review                        │
          │    │     153 were reviews, tutolials or editorials             │
          │    │     38 investigated immunotherapy, radiotherapy, peri-    │
          │    │     operative or intraperitoneal chemotherapy             │
          │    │     25 were on going                                      │
          │    │     19 were methodologies or pharmacologic studies        │
          │    └──────────────────────────────────────────────────────────┘
          ▼
┌─────────────────────────────────────┐
│ 95 full text articles reviewed       │
└─────────────────────────────────────┘
          │
          │    ┌──────────────────────────────────────────────────────────┐
          ├───▶│ 65 excluded after full review                             │
          │    │     25 did not use surgery alone as comparator            │
          │    │     11 investigated immunotherapy, radiotherapy, peri-    │
          │    │     operative or intraperitoneal chemotherapy             │
          │    │     12 updated previously published data                  │
          │    │     9 were review article                                 │
          │    │     5 did not randomize                                   │
          │    │     3 did not conduct curative resection                  │
          │    └──────────────────────────────────────────────────────────┘
          ▼
┌─────────────────────────────────────┐
│ 30 articles reporting 31 trials and  │
│ 6,390 individual patient data were   │
│ searched                             │
└─────────────────────────────────────┘
```

| 21 from Europe | 6 from Asia | 4 from USA |

```
          │
          │    ┌──────────────────────────────────────────────────────────┐
          ├───▶│ 14 trials (2,552 patients) were not obtained              │
          │    │     5 no reply or refusal                                 │
          │    │     9 data lost or inaccessible                           │
          │    └──────────────────────────────────────────────────────────┘
          ▼
```

| 9 received from Europe | 4 received from Asia | 4 received from USA |

| Data from 3,838 on 6,390 patients collected |

| Mono-chemotherapy

N=324/450 | 5-fluorouracil + Mitomycin C + other (w/o anthracyclines) N=1,053/2,071 | 5-fluorouracil + Mitomycin C + anthracyclines N=1,013/1,296 | Other Polychemotherapy

N=1,448/2,573 |

Figure 2. Individual trial and overall hazard ratio for overall survival when comparing any adjuvant chemotherapy versus surgery alone

	Events / Patients		Statistics		HR & 95% CI
	Any CT	Surgery alone	(O-E)	Var.	(Any CT: Surgery alone)
group :Mono chemo					
Grau-93[24]	42/64	49/63	-9.4	21.8	
Nakajima-07 NSAS[51]	18/95	30/95	-7.9	11.7	
Subtotal	**60/159**	**79/158**	**-17.3**	**33.5**	0.6 (0.42,0.84)
Heterogeneity Chi-square=0.44, df=1: p>0.1					
group :5FU + MMC+ other (except Anthra)					
Nakajima-84 JCOG[26]	102/156	52/72	-8.3	31.1	
Nakajima-99 JCOG[31]	47/288	60/285	-7	26.7	
Nashimoto-03 JCOG[30]	13/128	21/124	-4.3	8.5	
Subtotal	**162/572**	**133/481**	**-19.7**	**66.4**	0.74 (0.58,0.95)
Heterogeneity Chi-square=0.43, df=2: p>0.1					
group :5FU + MMC+ Anthra					
Coombes-90 ICCG[32]	86/133	102/148	-7.8	46.7	
Lise-95 EORTC[36]	88/152	99/154	-7.5	46.6	
McDonald-95 SWOG[35]	90/109	96/112	-2.7	46.4	
Tsavaris-96[38]	25/44	38/43	-8.7	15.6	
Popiela-04[39]	42/53	47/52	-8	20.2	
Subtotal	**331/491**	**382/509**	**-34.6**	**175.5**	0.82 (0.71,0.95)
Heterogeneity Chi-square=3.82, df=4: p>0.1					
group :any other polychemo					
Douglass-82 GITSG[42]	64/88	73/82	-13.7	33	
Engstrom-85 ECOG[49]	73/91	72/89	-2.3	36	
Krook-91 NCCTG[47]	51/63	50/64	0.9	25.1	
Bajetta-02 ITMO[46]	67/135	69/136	-0.7	34	
Rougier-05 FFCD[43]	79/133	90/138	-8.2	42.1	
Nitti-06 EORTC[50]	50/103	55/103	-3.3	26.2	
Nitti-06 ICCG[50]	63/89	64/97	1.6	31.6	
Subtotal	**447/702**	**473/709**	**-25.8**	**228**	0.89 (0.78,1.02)
Heterogeneity Chi-square=5.1, df=6: p>0.1					
Total	**1000/1924**	**1067/1857**	**-97.4**	**503.3**	0.82 (0.76,0.9)

Test for heterogeneity
Chi-square=15.03, df=16, p>0.1

I²=0%

Test for the 4 regimens heterogenity
Chi-2=5.59, df=3, p>0.1)

Any CT better | Surgery alone better
Treatment effect: p<0.0001

CT; Chemotherapy. O and E respectively denote the number of observed and expected events under the hypothesis of absence of treatment effect at all time points. Var is the variance of the statistics (0-E). The inverse of variance measures the weight of each trial in the analysis. The center of the square or of the diamond corresponds to hazard ratio (HR) and the horizontal line or the width of the diamond to the associated 95% confidence intervals (CI) . P values are p-for-effect modification testing for heterogeneity within or across the group of regimens. Sizes of square are proportional to the number of deaths of the trials.

Figure 3. Overall survival estimate after any chemotherapies or surgery alone truncated at 10 years

Patients at risk

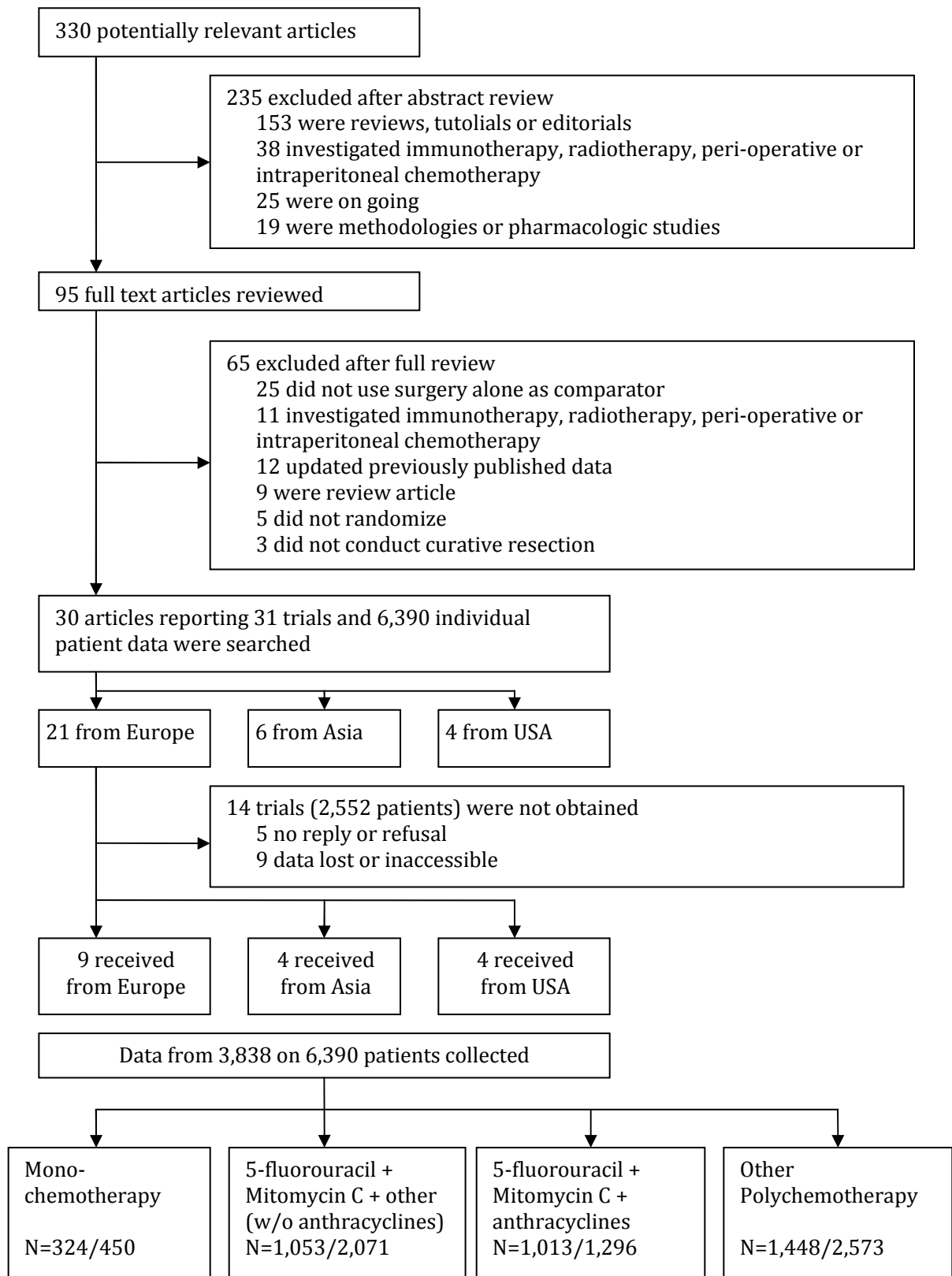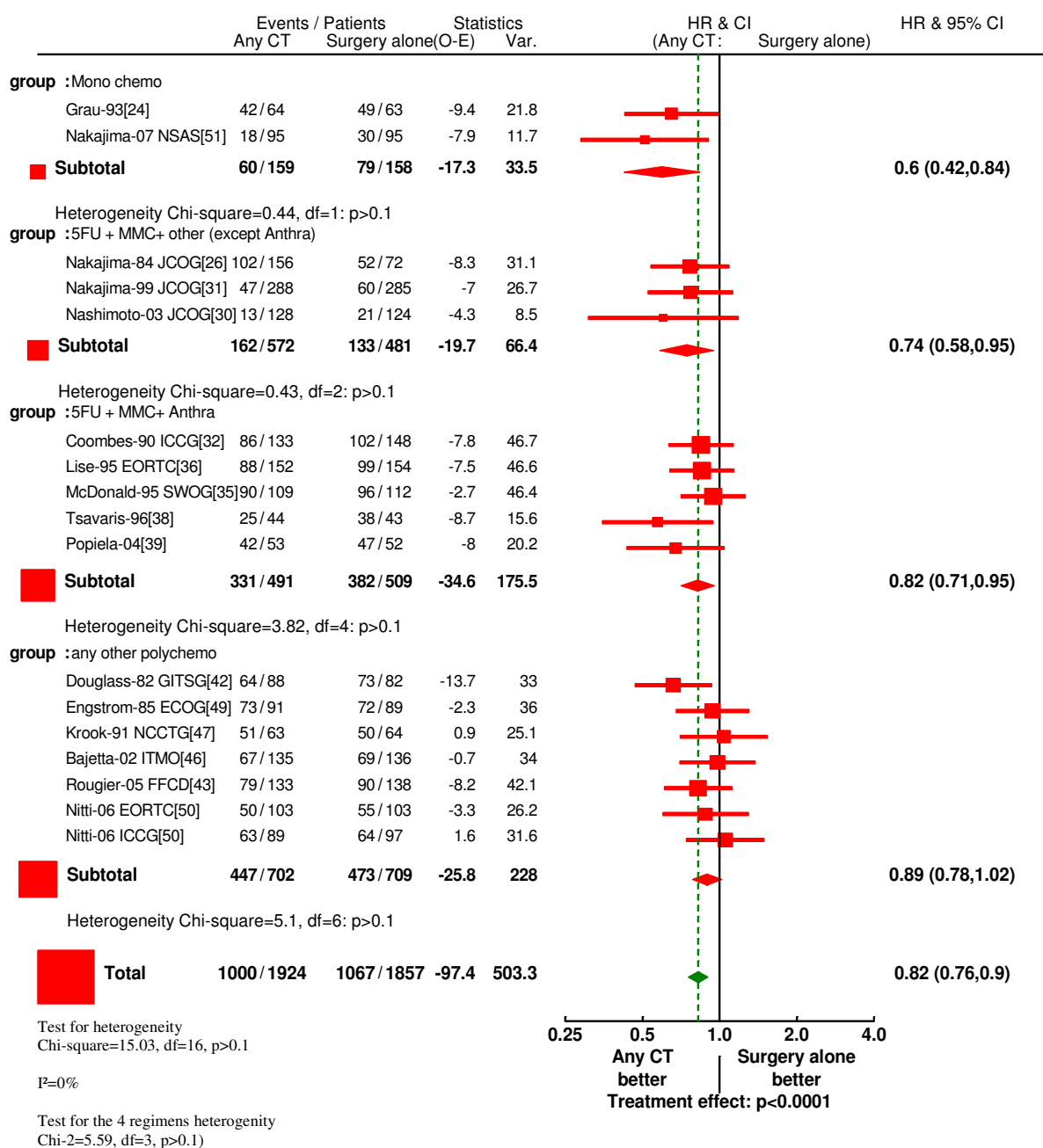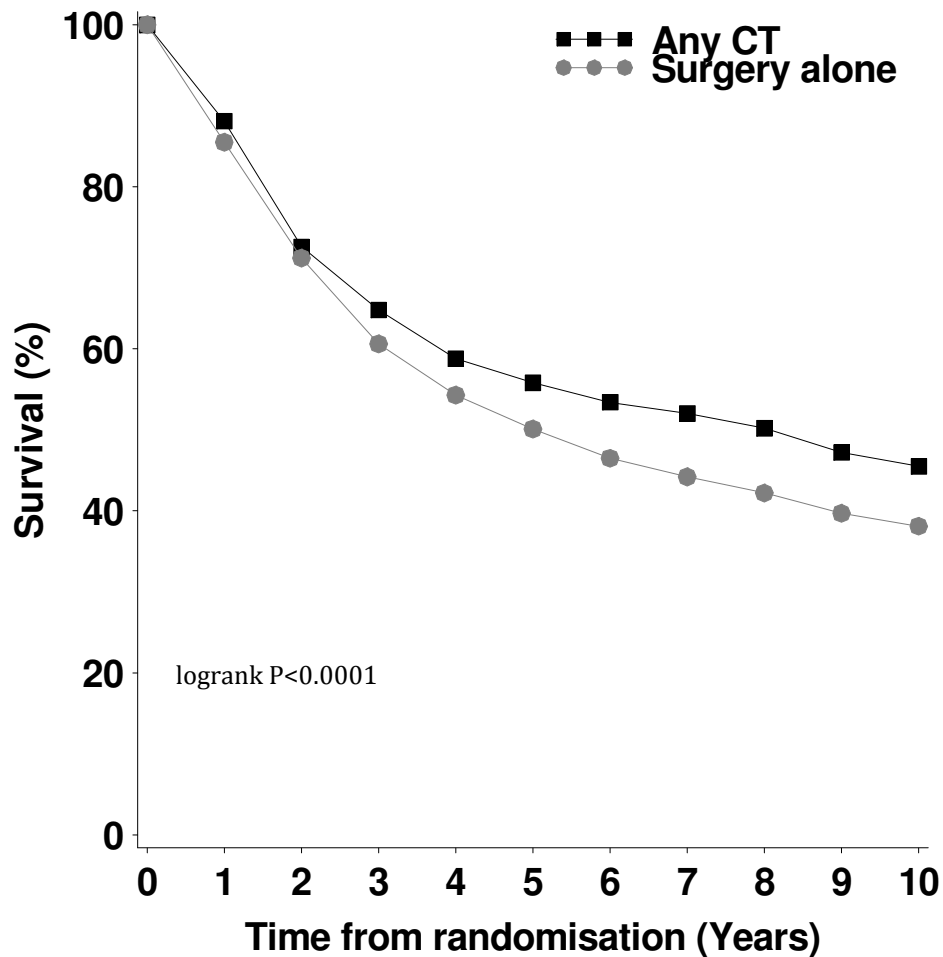|											
Any CT	1,924	1,688	1,385	1,217	1,080	929	709	526	390	297	243
Surgery	1,857	1,568	1,300	1,092	952	782	583	407	267	172	138

Any-CT stands for any chemotherapies

Figure 4. Individual trial and overall hazard ratio for disease free survival when comparing any adjuvant chemotherapy versus surgery alone

	Events / Patients Any CT	Surgery alone	Statistics (O-E)	Var.	HR & CI (Any CT : Surgery alone)	HR & 95% CI
group : Mono chemo						
Nakajima-07 NSAS[51]	20 / 95	34 / 95	-9.3	13.1		
Subtotal	**20 / 95**	**34 / 95**	**-9.3**	**13.1**		0.49 (0.29,0.84)
group : 5FU + MMC+ other (except Anthra)						
Nakajima-99 JCOG[31]	36 / 276	48 / 270	-6.8	21		
Nashimoto-03 JCOG[30]	15 / 128	23 / 124	-4.6	9.5		
Subtotal	**51 / 404**	**71 / 394**	**-11.4**	**30.5**		0.69 (0.48,0.98)
Heterogeneity Chi-square=0.17, df=1: p>0.1						
group : 5FU + MMC+ Anthra						
Coombes-90 ICCG[32]	89 / 133	102 / 148	-6.6	47.5		
Lise-95 EORTC[36]	89 / 152	103 / 152	-12.6	47.7		
McDonald-95 SWOG[35]	89 / 107	97 / 112	-6.1	46.4		
Tsavaris-96[38]	28 / 44	38 / 43	-9.2	16.1		
Subtotal	**295 / 436**	**340 / 455**	**-34.6**	**157.7**		0.8 (0.69,0.94)
Heterogeneity Chi-square=2.74, df=3: p>0.1						
group : any other polychemo						
Douglass-82 GITSG[42]	65 / 90	75 / 88	-10.7	34.4		
Engstrom-85 ECOG[49]	74 / 91	74 / 89	-4.3	36.7		
Krook-91 NCCTG[47]	52 / 63	51 / 64	-1.5	25.6		
Bajetta-02 ITMO[46]	72 / 135	77 / 136	-3.7	37.2		
Rougier-05 FFCD[43]	81 / 133	91 / 138	-8.6	42.8		
Nitti-06 EORTC[50]	52 / 103	56 / 103	-3	27		
Nitti-06 ICCG[50]	65 / 89	63 / 96	1.9	31.9		
Subtotal	**461 / 704**	**487 / 714**	**-29.9**	**235.5**		0.88 (0.78,1)
Heterogeneity Chi-square=2.64, df=6: p>0.1						
Total	**827 / 1639**	**932 / 1658**	**-85.2**	**436.8**		0.82 (0.75,0.9)

HR & CI scale: 0.25   0.5   1.0   2.0   4.0

Any CT better — Surgery alone better

Treatment effect: p<0.0001

Test for heterogeneity
Chi-square=11.2, df=13: p>0.1

I²=0%

Test for regimen heterogeneity
Chi-square=5.6, df=3: p>0.1

CT; Chemotherapy. O and E respectively denote the number of observed and expected events under the hypothesis of absence of treatment effect at all timespoints. Var is the variance of the statistics; the inverse of variance measures the weight of each trial. Hazard ratio (HR) and their associated 95% confidence intervals (CI) are provided. P values are p-for-effect modification testing for heterogeneity within or across the group of regimens. Size of the data markers is proportional to the sample size of the trial populations.