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Special Paper

Adjuvant Chemotherapy after Curative Resection for Gastric Cancer in Non-Asian Patients: Revisiting a Meta-analysis of Randomised Trials

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The aim of this study was to assess whether adjuvant chemotherapy after curative resection of gastric cancer increases survival rates. Data sources: *MEDLINE* (1966–1999), *CancerLit* (1983–1999), bibliographies, personal reprint files, and review articles were searched for relevant articles. Studies had to be randomised controlled trials of adjuvant chemotherapy versus observation following curative resection of stomach cancer that took place in non-Asian countries. Two reviewers independently evaluated the trials for eligibility, quality assessment and data abstraction. 13 trials met the eligibility criteria. The odds ratio for death in the treated group was 0.80 (95% confidence interval (CI) 0.66–0.97), corresponding to a relative risk of 0.94 (95% CI 0.89–1.00). Subgroup analyses showed a trend towards a larger magnitude of the effect when analysis was restricted to trials in which at least 2/3 of patients had node-positive disease. Our results suggest that adjuvant chemotherapy may produce a small survival benefit of borderline statistical significance in patients with curatively resected gastric carcinoma. Continued trials to find and confirm an effective adjuvant strategy are warranted. © 1999 Elsevier Science Ltd. All rights reserved.

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INTRODUCTION

THE INCIDENCE of gastric cancer has been steadily decreasing since the 1930s [1]. Despite this, it remains the eighth leading cause of cancer death because the majority of patients present with advanced disease [2]. In patients with localised disease, survival is approximately 75% if there is no regional lymph node involvement [3]. The prognosis worsens drastically, with N1–2 spread [4]. As a result, there is great interest in finding ways to improve the prognosis for this potentially curable group of patients.

Adjuvant chemotherapy improves survival in several other cancers [5]. Moreover, gastric cancer is relatively chemo-responsive. Many clinical trials have looked at the value of adjuvant chemotherapy, radiotherapy and immunotherapy in gastric cancer, but these have shown conflicting results, leaving the role of adjuvant therapy as yet unproven.

In 1993 Hermans and colleagues published a meta-analysis of 11 randomised trials reported between 1980 and 1991 in which postoperative adjuvant chemotherapy for gastric cancer was compared with surgery alone [6]. They found a non-significant trend towards improved survival (odds ratio 0.88, 95% confidence interval (CI): 0.78,1.08). This meta-analysis was later criticised, for lacking sufficient power to detect a difference [7], and for its choice of trials [7, 8]. In response, the authors published an update of their meta-analysis in 1994 in which they recalculated a significant odds ratio (0.82, 95% CI: 0.68, 0.97) [9]. This result was published only in letter form, and has not been widely recognised.

There have been several randomised trials reported since the Hermans meta-analysis [10–19]. Therefore, we decided to revisit the question of adjuvant chemotherapy. Our objective was to assess whether adjuvant chemotherapy after potentially curative resection of gastric cancer increases survival, as measured by decreased risk of mortality.

MATERIALS AND METHODS

Search strategy

Several methods were used to identify trials. *MEDLINE* (from 1966) and *CancerLit* (from 1983) were searched up to January 1999 inclusive, using the search strategy described by Haynes and colleagues [20]. The content terms stomach neoplasms and adjuvant chemotherapy, and the methodological terms clinical trial, phase III, randomised control trial, double-blind method, and random allocation were used. Also searched were the bibliographies of all papers, as well as personal reprint files and review articles, to identify other relevant studies. Where results were reported or updated in more than one publication, only the most recent publication was used. There was no language restriction and published abstracts were included.

Abstracts were screened and potentially relevant papers were retrieved which were examined in detail to determine whether they met the eligibility criteria. Disagreements were resolved by consensus.

Inclusion criteria

To be included in the review, studies had to meet the following criteria:

Population. Patients must all have had a potentially curative surgery. Studies that included patients with metastatic disease or residual disease after surgery were not evaluated. Some trials included retrospective pathology reviews after treatment, sometimes detecting previously unrecognised residual disease such as microscopically positive resection margins. However, for this study complete resection was defined as one that would be considered curative at the time of the initial medical oncology consultation, as this is the situation the practising physician is faced with. Consequently, *post-hoc* reviews showing that some patients might be ineligible did not exclude a trial from the meta-analysis. Trials including patients whose residual disease was known immediately after surgery were excluded.

Setting. Eligible studies had to have taken place in a Western (non-Asian) country. Because gastric cancer appears to behave differently in Asian countries such as Japan, many have speculated that it may have a different aetiology or biology in those countries. Also, differences in treatment include the use of extended lymph node dissection and commencement of chemotherapy immediately post-surgery. Treatment results often cannot be replicated in Western trials [21]. Therefore, it was felt that patients from studies in Asian countries may not be comparable to those in non-Asian countries. The location of the study rather than the ethnic background of the patients was chosen because migration studies have shown that geographic location is more important than ethnicity [5].

Study design. To be included, studies had to be randomised and controlled, comparing adjuvant treatments after curative surgery to observation alone. Studies need not have been either singly or doubly blinded. Patients in the intervention group must have received systemic chemotherapy. Systemic administration was defined as oral or intravenous routes, but not intraperitoneal (i.p.) treatment. The kinetics of i.p. treatments are less well characterised than for other routes, and the goal of therapy is targeted more to local recurrence [22].

There is an extensive literature on other types of adjuvant therapies in gastric cancer [2]. Chemotherapy was defined as a cytotoxic drug or drug combination, distinct from immu-

notherapy and radiotherapy. Combinations of chemotherapy with immunotherapy and/or radiotherapy were not included. It was felt that including such studies would add unacceptably to the heterogeneity of the interventions, making it less rational to combine them quantitatively. Finally, the report of the study must have provided, either in numerical or graphical form, the number of deaths and the total number of patients in each group.

Data extraction

Both reviewers independently extracted the outcome data using a pre-designed data extraction form. They were not blinded to the authors or source of the trials. Data extracted included assessments of eligibility and trial quality, the type of chemotherapy used, the number of patients in the intervention and control groups, and the number of deaths in each group. Both reviewers also independently assessed study quality using the Jadad 5-point scale [23]. Quality was assessed only for descriptive purposes and subgroup analysis; studies were not excluded or weighted based on these results.

Analysis

The results of eligible trials were pooled using the Meta-Analyst$^{0.988}$ software package assuming a DerSimonian and Laird random effects model [24]. A random effects model was chosen in order to obtain a conservative estimate of the treatment effect, as this type of model takes 'between study' variation into account that is ignored in fixed effects models. Crude odds ratio of mortality in treated and untreated patients was chosen as the primary endpoint [25] to allow the results to be comparable to previously reported meta-analysis. This method preserves stratification by study and, therefore, the advantages of randomisation, but does not adjust for prognostic variables. Relative risk was also calculated. Publication bias was assessed using the inverted funnel plot approach recommended for meta-analyses with few studies [26]. Rosenthal's 'failsafe' number [27] was also calculated, an estimate of the number of unpublished studies with a relative risk of 0 that would be required to change the results of the analysis. Statistical heterogeneity was assessed with the Q statistic [28].

Subgroup analyses were conducted by producing separate summaries for subsets of studies with different characteristics. Trials with quality scores > 2 were compared with those with quality scores ≤ 2. Trials evaluating 'modern' regimens were defined as those containing 5-FU (5-fluorouracil) and an anthracycline, the results of which were compared with others. Trials with follow-up time > 5 years versus those with ≤ 5 years were also examined. Based on the median proportion of lymph node-positive patients in the studies, a cut-off of 2/3 of patients with positive lymph nodes was used to define trials containing 'high' and 'low' proportions of lymph node-positive patients for comparison. Lastly, a summary was produced that included the two trials excluded for containing patients with postoperative residual disease despite an initial attempt at curative resection.

RESULTS

Study selection

Table 1 shows the flow of the trial selection process. There was good agreement between the two reviewers on eligibility, and any minor differences were easily resolved. There was perfect agreement on the quality scores and data extraction.

Table 1. *Progress through the various stages of the meta-analysis*

Number of trials	Remarks
756	Abstracts (634 *MEDLINE* +122 *CancerLit*) identified as potentially relevant and screened for retrieval
−731	Excluded based on the abstract
= 25	Studies retrieved for more detailed evaluation
−7	Excluded for either not being randomised, or for including palliative patients
= 18	Potentially appropriate randomised controlled trials independently reviewed by both authors
−5	Excluded for other reasons shown in Table 3
= 13	Trials included in the quantitative analysis

13 trials involving a total of 1990 patients were included in the meta-analysis.

Table 2 shows the characteristics of the 13 trials included in the analysis. The studies were published between 1980 and 1996 and were all reported in English. Most contained a small number of patients. Because chemotherapy trials are rarely blinded for treatment, the quality scores were usually 2 or 3. The mean death rate in the control group was 0.64 with a standard deviation (S.D.) of 0.15. There was no significant correlation between event rate and either the proportion of patients with lymph node involvement, or with follow-up time. Statistical testing found no significant heterogeneity in the effect of adjuvant chemotherapy between the trials, so it was considered reasonable to combine them. Table 3 lists the trials reviewed by both authors but not included in the analysis, and the reason for their exclusion. Neither the funnel plot (not shown) nor the 'failsafe' number of 9 suggested any important publication bias.

Meta-analysis

Figure 1 shows the result of the meta-analysis. Using a random effects model, the odds ratio was 0.80 (95% CI: 0.66–0.97), a just statistically significant effect in favour of adjuvant chemotherapy. Cumulative analysis showed that the result only became significant with the addition of the recent trial by Neri and colleagues in 1996 [18].

The relative risk was 0.94, (95% CI: 0.89–1.00), in favour of adjuvant chemotherapy. Using this point estimate for the relative risk, we can infer that for a group of patients similar to those included in these trials, 65% of untreated patients would suffer recurrence and die compared with approximately 61% of those treated. The absolute risk reduction

Table 2. Randomised trials of adjuvant chemotherapy compared to surgical control in resected gastric cancer included in the meta-analysis

	Author (Country) [ref.]	Treatment	*n*	Deaths	Control rate	OR (95% CI)	RR (95% CI)	% LN+	Quality score	Follow-up (months)
1	Huguier	FU, VLB, cyclo	27	23		1.37	1.05	56	3	60+
	(France) [42]	Observation	26	21	0.81	(0.32, 5.79)	(0.83, 1.35)	38		
2	Douglass/GTSG	FU+mCCNU	71	29		0.54	0.73	62	3	48
	(U.S.A.) [40]	Observation	71	40	0.56	(0.27, 1.04)	(0.51, 1.03)	62		
3	Schlag	FU+BCNU	49	10		0.56	0.65	†	2	36
	(Germany) [43]	Observation	54	17	0.31	(0.23, 1.37)	(0.33, 1.28)			
4	Higgins/VASOG	FU+mCCNU	66	36		1.07	1.03	44	3	42*
	(U.S.A.) [39]	Observation	68	36	0.53	(0.54, 2.10)	(0.75, 1.41)	51		
5	Engstrom	FU+mCCNU	91	57		1.25	1.09	62	2	64
	(U.S.A.) [38]	Observation	89	51	0.57	(0.69, 2.27)	(0.86, 1.39)	56		
6	Bonfanti	FU+mCCNU	75	63		1.22	1.03	60	3	48*
	(Italy) [37]	Observation	69	56	0.81	(0.51, 2.89)	(0.89, 1.20)	52		
7	Coombes/ICCG	FAM	133	73		0.76	0.89	68	3	68
	U.K. [36]	Observation	148	91	0.61	(0.47, 1.23)	(0.73, 1.09)	68		
8	Krook	FU+doxorubicin	61	41		1.00	1.00	70	3	84
	U.S.A. [10]	Observation	64	43	0.67	(0.47, 2.11)	(0.78, 1.28)	72		
9	Grau	MMC	68	40		0.50	0.79	62	1	105
	Spain [44]	Observation	66	49	0.74	(0.24, 1.03)	(0.62, 1.01)	62		
10	Lise/EORTC	FAM	155	88		0.80	0.91	75	2	78
	(Italy) [15]	Observation	159	99	0.62	(0.51, 1.25)	(0.76, 1.10)	70		
11	Macdonald/SWOG	FAM	93	63		0.86	0.95	82	2	114
	(U.S.A.) [12]	Observation	100	71	0.71	(0.46, 1.58)	(0.79, 1.15)	78		
12	Tsavaris	Epirubicin+FU+MMC	42	36		0.63	0.95	71	3	60
	(Greece) [11]	Observation	42	38	0.90	(0.16, 2.42)	(0.81, 1.11)	76		
13	Neri	Epirubicin+FU+FA	48	36		0.44	0.86	100	2	36
	(Italy) [18]	Observation	55	48	0.87	(0.16, 1.22)	(0.71, 1.04)	100		

*Median follow-up estimated from graphs †not reported. CI, confidence interval; BCNU, carmustine; mCCNU, semustine; cyclo, cyclophosphamide; FA, folinic acid; FAM, fluorouracil, doxorubicin, and mitomycin-C; FU, 5-fluorouracil; LN, lymph node; MMC, mitomycin-C; *n*, sample size; OR, odds ratio; RR, relative risk; VLB, vinblastine.

Table 3. Excluded randomised trials

	Author [ref.]	Publication year	Reason excluded
14	Serlin [45]	1969	Includes palliative resections
15	Dent [46]	1979	Includes palliative resections
16	Blake [47]	1980	Includes palliative resections
17	Alcobendas [48]	1983	Same as Grau [44]
18	Fielding [49]	1983	Same as Allum [29]
19	Jakesz [31]	1988	Pooled chemo- and immunotherapy arms
20	Allum	1989	Same as Hallissey [30]
21	Allum	1989	Includes resections with residual disease
22	Estape [51]	1991	Same as Grau [44]
23	Hallissey [30]	1994	Includes resections with residual disease
24	Carrato [19]	1995	Unable to extract outcome
25	Cirera [13]	1997	Unable to extract outcome

would be approximately 4%, and the 'number needed to treat' (NNT) to prevent a death would be 25. However, because the relative risk was not statistically significant, this figure should be treated with caution.

Subgroup analysis

Table 4 shows the subgroup analyses performed. Statistically significant heterogeneity between subgroups was not detected. Studies in which over 2/3 of the patients had disease involving the lymph nodes showed a trend towards a larger magnitude of the effect with chemotherapy. Restricting studies to those using modern chemotherapy regimens containing 5-FU and an anthracycline also produced a trend towards a lower relative risk. However, there was not enough power in this subgroup for a statistically significant result. The group of trials with more than 5 years of follow-up showed a smaller benefit for chemotherapy than those with shorter follow-up.

As is commonly observed, the subset of higher quality studies showed a smaller magnitude of the effect than those of lower quality. Trials that included patients with postoperative residual disease produced, as expected, less favourable results than those that only included patients with curative resections. Sequentially excluding each study had no important effect on the results.

DISCUSSION

Our analysis suggests that adjuvant chemotherapy may confer a small survival benefit of borderline statistical significance to patients after curative resection of gastric cancer. Our odds ratio of 0.80 is similar to that of the Hermans meta-analysis [6], which initially found a non-significant trend in favour of adjuvant treatment with an odds ratio of 0.88 (95% CI 0.78–1.08).

The main difference between our analysis and the one by Hermans and colleagues is the inclusion of recent studies that
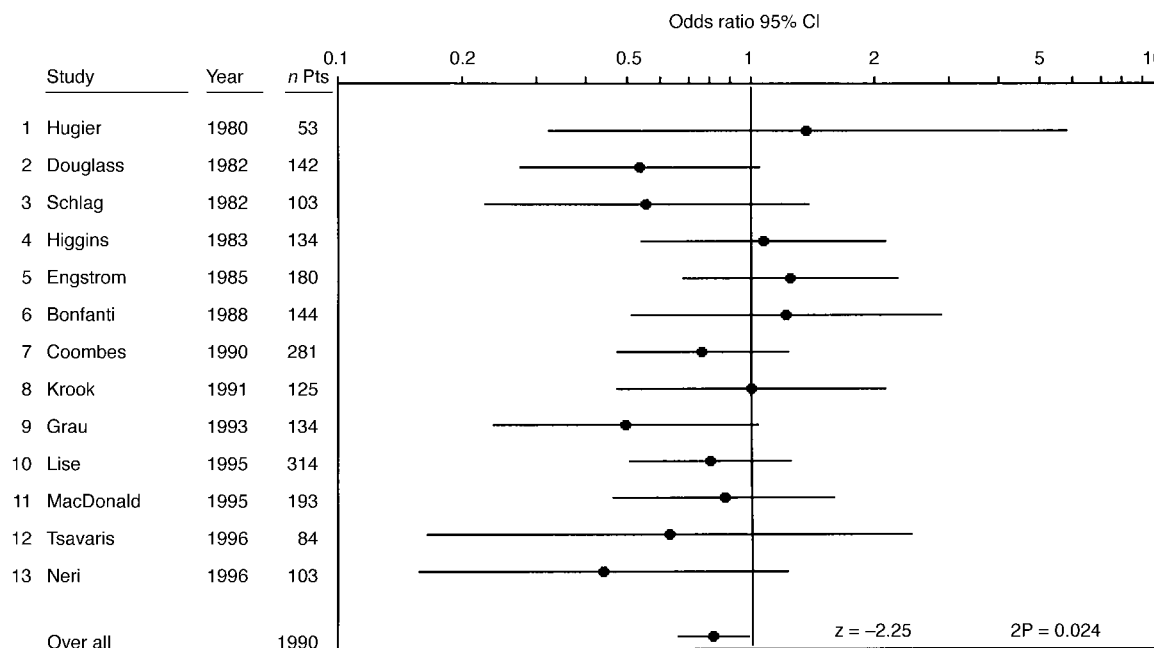

Figure 1. Forrest plot of meta-analysis of randomised trials comparing adjuvant chemotherapy with observation after curative resection of gastric cancer. The overall crude odds ratio of death was 0.80 (0.66–0.97) in favour of the chemotherapy-treated group. CI, confidence interval.

Table 4. Subgroup analyses

Manoeuvre	No. of trials	OR	95% CI	RR	95% CI
Quality score >2	7	0.84	(0.63, 1.11)	0.97	(0.90, 1.05)
Quality score ≤2	6	0.76	(0.57, 1.02)	0.91	(0.83, 1.00)
5-FU+anthracycline	6	0.78	(0.61, 1.01)	0.92	(0.86, 1.00)
Other regimens	7	0.83	(0.59, 1.16)	0.95	(0.84, 1.08)
>5 year follow-up	8	0.84	(0.67, 1.05)	0.95	(0.88, 1.02)
≤5 year follow-up	5	0.73	(0.49, 1.07)	0.91	(0.79, 1.06)
>2/3 with+lymph nodes	7	0.74	(0.59, 0.95)	0.91	(0.85, 0.99)
≤2/3 with+lymph nodes*	5	0.98	(0.68, 1.42)	1.00	(0.90, 1.11)
Quality score >2 and >2/3 with+lymph nodes	4	0.73	(0.52, 1.02)	0.92	(0.83, 1.02)
Post-operative residual disease†	14	0.85	(0.71, 1.02)	0.98	(0.93, 1.03)

*Not reported in one study †Including two trials excluded from the main analysis because of patients having postoperative residual cancer [30, 50]. OR, odds ratio; CI, confidence interval; RR, relative risk.

provided us with more statistical power. Also, we had stricter criteria for trial eligibility, excluding trials in which patients could have postoperative residual disease [29, 30], immunotherapy [31–34], or i.p. treatment [35]. Consequently, only six trials overlap in the two analyses [10–40].

In this group of patients with a relatively high baseline mortality rate, the odds ratio overestimates the relative risk substantially. Based on the relative risk estimated, for a group of patients similar to those included in these trials, 25 would have to be treated in order to prevent one extra death. This would probably be considered clinically significant. However, the significant odds ratio but non-significant relative risk reflects the questionable statistical significance of this result. Furthermore, because of the retrospective nature of this review and the small sample size of most of the component studies, the magnitude of the effect is probably overestimated.

In an effort to restrict our study to the most homogeneous group possible, Asian studies were excluded, mostly from Japan. There is an extensive literature on adjuvant treatments from that part of the world. However, gastric cancer appears to behave differently in the Asian setting, possibly due to different biology, aetiology, or treatment. Attempts to replicate the findings of intervention studies in the West have generally not been successful [21]. As the results of Asian adjuvant studies tend to favour the use of chemotherapy [8], their inclusion would have probably further supported the benefit of adjuvant chemotherapy.

Our subgroup analysis produced some intriguing findings. As expected, there was a trend towards better results with more modern chemotherapy regimens. Although the magnitude of the effect was smaller for trials with more than 5 years of follow-up than for those of shorter duration, they did maintain a trend towards benefit from adjuvant treatment. This indicates that long-term survival may be afforded by adjuvant treatment, as opposed to simply delaying relapse.

The finding that trials which included more node-positive patients had better results with chemotherapy is interesting because it is consistent with effects seen in other studies [11], as well as with adjuvant treatments in breast and colon cancer. However, because this was a subgroup analysis based on trials, not individuals, it can only serve to generate hypotheses. Nevertheless, it suggests that higher risk patients may be the ones who benefit most from adjuvant strategies. Future trials might increase their efficiency by concentrating on this group of patients.

The general perception in the oncology community is that adjuvant chemotherapy does not work in gastric cancer. However, our results suggest that this may be too pessimistic a view. Meta-analyses of published literature tend to overestimate treatment effects [41]. As a result, this analysis should not be interpreted as definitive. Rather, it suggests that efforts to find effective adjuvant treatment should not be abandoned. Randomised trials in this area should continue to be undertaken, with a supportive care only control arm, until a satisfactory strategy can be identified.

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