Original article

Pathological features as predictors of recurrence after radical resection of gastric cancer

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Background: The aim of this study was to investigate the pattern and timing of recurrence and to determine associated risk factors after radical resection of gastric cancer including D2 dissection.
Methods: A total of 274 patients who had undergone radical resection of gastric cancer with nodal involvement or T3–4 tumour were randomized to receive chemotherapy or no further treatment (control group). Locoregional recurrence and distant metastasis were analysed in a competing risks framework, by estimating the crude cumulative incidence in each group. Multiple regression models were used to investigate the influence of treatment and pathological features on the risk of recurrence.
Results: Overall, the 7 year rate of locoregional relapse was 15·8 per cent and that of distant recurrence was 34·5 per cent. There was a significant association between pathological node (pN) stage and distant relapse ($P < 0·001$), and between pathological tumour (pT) stage and locoregional recurrence ($P = 0·024$). Chemotherapy had no significant effect on either locoregional or distant recurrence.
Conclusion: The rate of locoregional recurrence after radical surgery for gastric cancer was lower than that in studies based on more conservative surgery. The pT stage was related to the rate of locoregional recurrence whereas pN stage had an impact on distant recurrence.

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Introduction

Gastric cancer represents the fourth leading cause of cancer mortality in the European Union, although there has been a steady decline in incidence and mortality; the latter was estimated at 12·4 per 100 000 population per year in 2004[1]. Locoregional relapse may occur after complete resection of gastric cancer with curative intent, possibly in the form of peritoneal carcinosis and/or distant metastases. Effective adjuvant therapies are therefore needed to improve the long-term outcome and a multidisciplinary approach is being developed to improve the results of surgery. Various preoperative and postoperative regimens, combining chemotherapy with radiotherapy or intraperitoneal chemotherapy, have been designed specifically to eradicate microscopic disease, but none was based on accurate identification of subgroups at different risk[2].

Although a number of randomized controlled studies have been conducted to compare postoperative adjuvant therapies *versus* surgery alone, the clinical relevance of postoperative adjuvant chemotherapy in gastric cancer remains controversial. The four published meta-analyses suggest that postoperative adjuvant chemotherapy may give a small 5-year survival benefit (absolute improvement of 3–5 per cent)[3–6].

In 1992 the Italian Trials in Medical Oncology group initiated a two-arm prospective multicentre randomized trial of adjuvant chemotherapy after radical resection of gastric cancer for patients with unfavourable prognostic factors, with the aim of evaluating treatment efficacy on overall survival. In this study a standardized surgical approach, comprising at least D2 dissection, was performed in all patients. Five-year results have been published previously[7]. In the present analysis, with follow-up

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extended to 7 years, the pattern and timing of locoregional and distant recurrence, and their associated risk factors, were investigated.

Patients and methods

A total of 274 patients who had undergone radical resection of gastric adenocarcinoma with nodal involvement or pathological tumour (pT) stage 3–4 were recruited, and randomized to receive adjuvant chemotherapy comprising two cycles of EAP regimen (etoposide 120 mg/m^2 on days 4, 5 and 6, doxorubicin (Adriamycin®; Pharmacia Corporation, Peapack, New Jersey, USA) 20 mg/m^2 on days 1 and 7, cisplatin 40 mg/m^2 on days 2 and 8) followed by two cycles of the Machover schedule (5-fluorouracil 370 mg/m^2 and folinic acid 100 mg/m^2), or no further treatment (control group). The operation notes and pathology reports confirmed that D2 lymphadenectomy had been performed. Before randomization, the subjects were stratified by centre, on the basis of nodal involvement (N+ or N−), and the time elapsed from surgery to randomization (21 days or less, or more than 21 days)[7].

Postoperative baseline and follow-up investigations were standardized. During follow-up, patients underwent upper gastrointestinal radiography or endoscopy, ultrasonography or computed tomography and chest radiography every 4 months for the first 3 years, every 8 months for the next 2 years, and yearly thereafter or as indicated clinically. During follow-up, any suspected recurrence was confirmed pathologically, if possible, and the first site of recurrence was used to define whether locoregional or distant relapse had occurred. Locoregional relapse included cancer recurrence within the regional resection area or local anastomotic sites or peritoneal recurrence. A peritoneal recurrence was any recurrence within the abdominal cavity resulting in intraperitoneal implantation. Distant recurrence included liver metastasis, metastasis at other extra-abdominal sites, and nodal metastasis beyond the regional nodes.

Statistical analysis

The outcomes of interest were overall survival and first recurrence of disease. Survival time was calculated from the date of surgery to the date of death from any cause, or the last available follow-up for survivors. The overall survival curves stratified by study group were estimated by the Kaplan–Meier method and compared with the log rank test. The effect of locoregional and distant relapse on overall survival was investigated by including these two events in a different Cox model as time-dependent co-variates, together with treatment.

A competing risks analysis[8] of locoregional recurrence (competing events: distant metastasis, second malignancy, death from an unrelated condition) and distant metastasis (competing events: locoregional recurrence, second malignancy, death from an unrelated condition) was performed. Concomitant locoregional recurrence and distant metastasis (ten events overall) were considered as distant metastases in the analysis. Crude cumulative incidence (CCI) curves for the above endpoints were estimated in each study group and compared by means of the Gray test[9]. Fine and Gray multiple regression models[10] were used to investigate the joint effect of locoregional or distant relapse of treatment and the co-variates pathological node (pN) stage (pN2–3 *versus* pN0–1), pT stage (pT3–4 *versus* pT1–2) and tumour site (upper third *versus* other sites). The binary classification of the above co-variates was adopted in order to fulfil the 'ten events per variable rule', being the cut-offs based on the authors' past experience. To test the heterogeneity of treatment effect in the categories of each co-variate, the terms of interaction between treatment and each co-variate were included in the Fine and Gray models.

All the recorded events were included in the analysis, regardless of treatment duration and compliance levels, on the basis of intention to treat. The proportional hazards assumption implied by both the Cox and the Fine and Gray models was checked by analysis of Schoenfeld residuals[11]. All the statistical tests were two sided and $P \leq 0{\cdot}050$ was considered significant. To perform the modelling and statistical calculations, SAS™ software (SAS Institute, Cary, North Carolina, USA) and the S-Plus Design[12] and Cmprsk[13] libraries were used.

Results

Three patients were lost to follow-up soon after randomization, so 271 patients were included in the analysis. *Table 1* summarizes the main patient and tumour characteristics. The median (interquartile range) follow-up time was 80 (72–84) months in the control group and 76 (72–81) months in the chemotherapy group. The first events and causes of death during follow-up are shown in *Table 2*. Overall, 133 patients died, 121 (91·0 per cent) from tumour-related causes.

The 7-year overall survival estimates were 49·1 (range 40·9–58·9) per cent in the chemotherapy group and 47·2 (range 39·1–56·9) per cent in the control group ($P = 0{\cdot}825$) (*Fig. 1*). In the Cox model aimed at investigating the time-dependent effects of locoregional and distant relapse on overall survival, highly significant results were obtained for both events ($P < 0{\cdot}001$).

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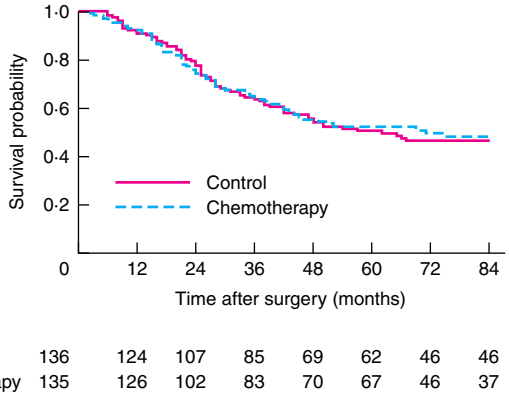
Table 1 Patient and tumour characteristics

	Chemotherapy ($n = 135$)	Control ($n = 136$)
Median (range) age (years)	57 (23–70)	57 (31–70)
Sex ratio (M : F)	81 : 54	93 : 43
Primary localization		
Upper third	19 (14·1)	25 (18·4)
Middle third	30 (22·2)	30 (22·1)
Lower third	83 (61·5)	78 (57·4)
Whole stomach	3 (2·2)	3 (2·2)
Primary tumour stage		
T1–2 N1	37 (27·4)	42 (30·9)
T1–2 N2/N3	23/5 (17/4)	13/8 (10/6)
T3–4 N0/N1	12/32 (9/23)	15/33 (11/24)
T3–4 N2/N3	22/4 (16/3)	19/6 (14/4)
No. of resected lymph nodes		
≤ 14	31 (23·0)	22 (16·2)
15–24	48 (35·6)	47 (34·6)
≥ 25	50 (37·0)	66 (48·5)
Not specified	6 (4·4)	1 (0·7)
Median (range)	25 (2–87)	26 (2–65)

Values in parentheses are percentages unless specified otherwise.

Table 2 Number of events in chemotherapy and control groups

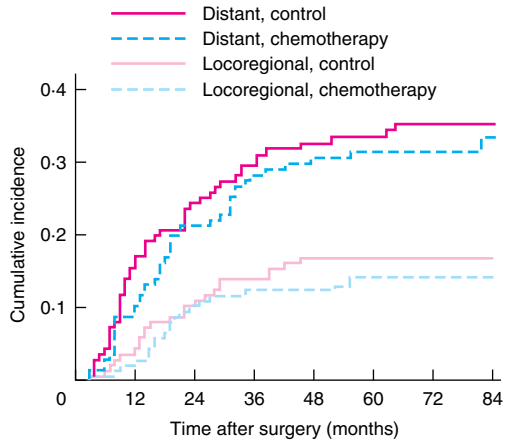
	Chemotherapy ($n = 135$)	Control ($n = 136$)	Total ($n = 271$)
First events	71	76	147
Locoregional relapse	19	23	42
Distant metastases	38	42	80
Second malignancy	2	2	4
Locoregional and distant	5	5	10
Death from unrelated condition	7	4	11
Deaths	65	68	133
Tumour related	58	63	121
Treatment related	2	0	2
Second malignancy	1	1	2
Related to other causes	4	4	8



No. at risk

Control	136	124	107	85	69	62	46	46
Chemotherapy	135	126	102	83	70	67	46	37

Fig. 1 Kaplan–Meier survival curves for patients in control and chemotherapy groups



No. at risk

Control	136	106	87	71	60	56	43	29
Chemotherapy	135	116	86	71	65	57	49	25

Fig. 2 Crude cumulative incidence of locoregional and distant relapse in control and chemotherapy groups

The CCI curves for locoregional and distant relapse for the two groups are shown in *Fig. 2* and 7-year CCI estimates in *Table 3*. The 7-year recurrence rate was 15·8 per cent for locoregional relapse and 34·5 per cent for distant recurrence. There were no significant differences in the rate of locoregional or distant recurrence at 7 years between groups. When stratifying by pN, pT or tumour site, relatively small P values for comparison of treatments were obtained for distant relapse in the subgroup of patients with tumour at a site other than the upper third of the stomach, and for locoregional relapse in the pN2–3 and pT1–2 subgroups. However, in some subgroups the number of events was too small to draw any conclusions.

In accordance with univariate analysis (*Table 3*), the Fine and Gray models failed to show a significant effect of chemotherapy on locoregional ($P = 0·550$) and distant ($P = 0·420$) relapse. Furthermore, no significant interaction between chemotherapy and the co-variates pN, pT and tumour site was detected. A significant association was observed between distant relapse and pN ($P < 0·001$), and between locoregional relapse and pT ($P = 0·024$). The association between distant recurrence and tumour site approached significance ($P = 0·082$). In particular, the cumulative incidence of locoregional relapse was higher in the pT3–4 group than in the pT1–2 group (*Table 3*). The cumulative incidence of distant relapse was higher in the pN2–3 group than in the pN0-1 group, and in patients

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Table 3 Cumulative incidence estimates at 7 years

	7-year cumulative incidence (%)		
	Chemotherapy	Control	*P**
Distant relapse			
Overall	33·6 (44)	35·8 (47)	0·557
pN			
pN0–1	18·6 (16)	28·6 (25)	0·143
pN2–3	54·3 (28)	51·6 (22)	0·919
pT			
pT1–2	34·3 (22)	31·3 (19)	0·780
pT3–4	32·4 (22)	39·7 (28)	0·283
Tumour site			
Upper third	42·2 (7)	48·5 (9)	0·629
Other	20·0 (37)	36·0 (38)	0·104
Locoregional relapse			
Overall	14·3 (19)	17·3 (23)	0·506
pN			
pN0–1	16·4 (13)	13·6 (12)	0·620
pN2–3	11·3 (6)	24·7 (11)	0·090
pT			
pT1–2	6·2 (4)	14·5 (9)	0·115
pT3–4	22·1 (15)	19·6 (14)	0·700
Tumour site			
Upper third	24·5 (4)	10·5 (2)	0·331
Other	15·6 (15)	16·8 (21)	0·953

Values in parentheses are number of events. pN, pathological node; pT, pathological tumour. *Gray test.

with tumour localized in the upper third compared with other sites.

Discussion

Many randomized trials have been carried out to assess the survival benefit of adjuvant chemotherapy in patients with gastric cancer, but their results are inconsistent[14–17]. The role of adjuvant chemotherapy has also been addressed in several meta-analyses[3–6], which showed that the overall survival benefit in terms of 5-year follow-up is much lower (3–5 per cent) than that which individual studies were powered to detect. This is also true for the present study, in which non-significant results were obtained at the latest update.

Much less attention has been focused on the relative impact that locoregional and distant tumour recurrences have on patient survival, and the extent to which adjuvant treatments differentially affect the two types of recurrence. The present study aimed to shed light on these aspects, by investigating the incidence of locoregional and distant recurrence in the two treatment groups, which prognostic factors are associated with each type of recurrence, and the relationship between each type of recurrence and patient survival.

Adjuvant chemotherapy was found to have no significant effect on either locoregional or distant relapse, even within specific patient subgroups. With regard to prognostic factors for tumour recurrence, significant associations were detected between pT and locoregional relapse, and between pN and distant relapse. In particular, the incidence of locoregional relapse was increased in patients with stage pT3–4 compared with pT1–2 disease, and the incidence of distant metastasis increased in those with stage pN2–3 *versus* pN0–1 tumours. The importance of pathological serosal and lymph node-based variables, regardless of the site of recurrence after D2 dissection, has been noted previously[18]. In the Cox model investigating the time-dependent effects of locoregional and distant relapse on survival, the two events had a similar negative impact, implying that locoregional disease control should be considered as important as distant control.

These present results differ from those of the US Intergroup trial (INT-116)[19], which included patients treated mainly by limited lymphadenectomy (D0 54 per cent, D1 36 per cent, D2 10 per cent), and demonstrated a therapeutic benefit in terms of overall survival for postgastrectomy chemoradiation. Long-term recurrence rates at 7 years were 15·8 per cent for locoregional relapse and 34·5 per cent for distant recurrence in the present study. In contrast, in the INT-116 trial control group, the overall 75 per cent was mainly due to locoregional relapse (53 per cent) while it played a minor role (23 per cent) in our control group. Accordingly, the efficacy of chemoradiation, which is now considered the standard treatment after radical resection in the USA, was primarily related to a reduction in locoregional recurrence rate. In contrast to the INT-116 trial, patients in the present study underwent D2 dissection and use of this approach is the most likely explanation for the relatively low locoregional recurrence rate. The ability of adequate surgery to decrease the incidence of locoregional recurrence has been noted by other investigators[20,21].

The present study demonstrated that locoregional and distant tumour recurrence both have a prognostic impact on survival, but showed no significant survival benefit for postoperative chemotherapy after potentially curative resection of gastric cancer. These results contrast with some published data on postoperative chemoradiation and raise questions about which therapeutic strategy should be adopted to achieve optimal locoregional control. Further trials are required to address this issue in more detail. Indeed, a trial including more than 1000 patients is already under way in which the therapeutic efficacy of new drug combinations is being evaluated.

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