Table 1. Post-gastrectomy follow-up schedule at the National Cancer Hospital, Tokyo

Risk of recurrence	3 Months	6 Months	1 Year	1.5 Years	2 Years	2.5 Years	3 Years	3.5 Years	4 Years	4.5 Years	5 Years
Very low (pT1N0)			○●◇□		○●◇		○●◇□				○●◇□
Low to mild (pT1N1/2, pT2N0/1)		○◇	○●▼□	○◇	○●▼	○◇	○●▼□	○◇	○●▼	○◇	○●▼□
Considerable (pT2N2, pT3N0/1/2)		○▼	○●▼□◆	○▼	○●▼◆	○▼	○●▼□◆	○▼	○●▼	○▼	○●▼□
High (pN3)/non-curative[a]	○◇	○▼◆	○●▼□◆	○▼	○●▼◆	○▼	○●▼□◆	○▼	○●▼	○▼	○●▼□

○, Blood test, tumor marker (CEA, CA19-9, CA125); ●, chest X-ray: ◇, abdominal ultrasonography; ▼, abdominal CT: □, endoscopy (except for total gastrectomy); ◆, barium enema (for high risk of peritoneal recurrence)

[a] Besides these tests, patients are seen at the clinic every 2 to 3 months

over the remains of the patients' life. If the test is a false-positive, it can be very difficult to refute and the uncertainty of diagnosis invokes very significant anxiety.

Patient follow-up protocols vary widely [9]. Table 1 shows the follow-up protocol for the NCC, Tokyo. The large numbers of patients undergoing follow-up at the NCC and the recognition of very low recurrence rates for node-negative EGC has led to the routine use of follow-up CT for these patients being abandoned. This is not commonly the case elsewhere in Japan, and many patients have multiple CT scans annually.

In 1996 in Japan there were 103000 cases of gastric cancer, and in 1999, 50500 deaths [66]. The number of patients that would be under follow-up if patients were discharged after 5 years would be in the order of 250000. If patients were followed for 10 years it would be nearly 400000. As well as cost and resource implications, follow-up CT scanning of these patients annually or more frequently results in a considerable cumulative exposure to radiation. A recent publication in the *Lancet* has estimated that 3% of all cancers in Japan are the result of radiation from diagnostic imaging [67]. Potentially, follow-up could cause more deaths than lives saved.

Follow-up is important. Collection of data to assess outcomes of treatment is vital if the quality of treatments is to be improved, and there is little doubt that many patients enjoy seeing their doctors. We should, however, be aware of the limitations of follow-up and that there is a huge amount of time and money being spent on investigations with little evidence of benefit. In these days of evidence-based medicine and stringent financial controls, what is required is a large, prospective RCT to determine what the benefits of intensive follow-up and early treatment of recurrence actually are, and whether they are worthwhile pursuing.

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Original article

Extranodal metastasis is an indicator of poor prognosis in patients with gastric carcinoma

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Background: The aim of this study was to determine the clinical significance and prognostic impact of extranodal metastasis (EM) in gastric carcinoma.
Methods: The study included 1023 patients who underwent gastrectomy with lymphadenectomy for primary gastric carcinoma between January 1993 and December 1996. EM was defined as the presence of tumour cells in extramural soft tissue that was discontinuous with either the primary lesion or locoregional lymph nodes.
Results: EM was detected in 146 (14·3 per cent) of the 1023 patients and in 1060 (3·0 per cent) of the 35 811 nodules that were retrieved as 'lymph nodes' from adipose connective tissues. The incidence of EM was significantly higher in patients with tumours that were large (diameter 10 cm or more), infiltrative, deeply invading or undifferentiated and in those with lymph node, peritoneal or liver metastases, or lymphatic or vascular involvement. After curative operation overall survival was significantly worse for patients with EM than those without ($P < 0·001$). Multivariate analysis identified EM as an independent prognostic factor (hazard ratio 1·82 (95 per cent confidence interval 1·23 to 2·71); $P = 0·003$).
Conclusion: EM is an independent prognostic factor and should therefore be included in the tumour node metastasis (TNM) staging system.

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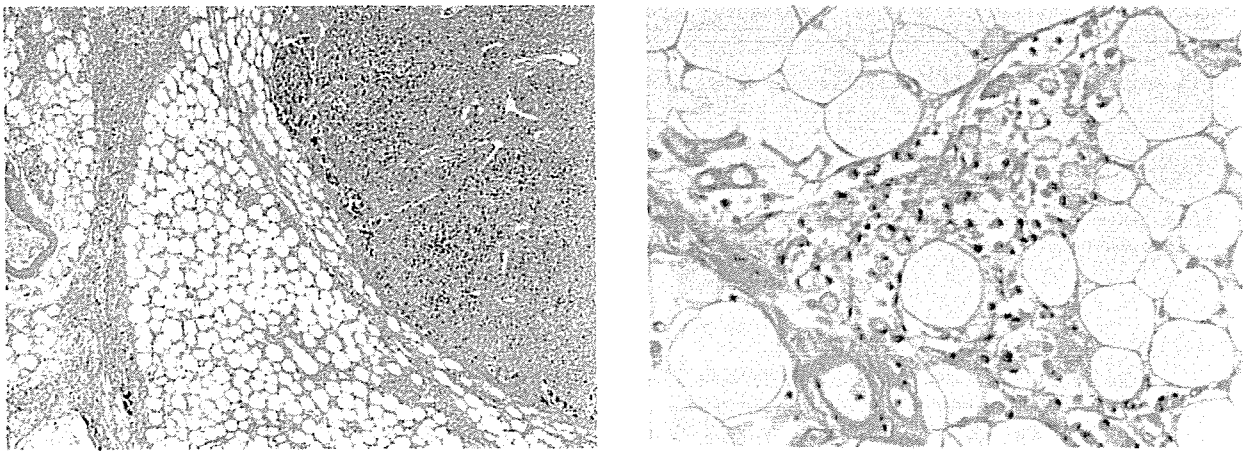
Introduction

Extranodal metastasis (EM), comprising cancer cells in soft tissue discontinuous with the primary lesion, is found during routine examination of about 10–28 per cent of resected gastric carcinoma specimens[1,2]. According to the International Union Against Cancer (UICC), this type of tumour spread should be regarded as lymph node metastasis if the nodule has the form and smooth contour of a lymph node, but should otherwise be regarded as part of the primary tumour[3]. Some studies have, however, suggested that such tumour extension represents peritoneal seeding from either the primary tumour or metastatic lymph nodes. This type of tumour spread has also been reported in carcinomas of the rectum[4], thyroid[5], breast[6], vulva[7] and lung[8], linking such spread to aggressiveness of the disease. The aim of the present study was to evaluate the clinical significance of extranodal and extramural tumour extension in gastric carcinoma.

Patients and methods

One thousand and twenty-three patients who underwent gastrectomy with lymphadenectomy for primary gastric carcinoma, excluding gastric lymphoma or gastrointestinal stromal tumour, at the National Cancer Centre Hospital between January 1993 and December 1996 were included in the study.

All resected specimens were fixed in 10 per cent formalin, embedded in paraffin, and stained with haematoxylin and eosin. All solid structures in adipose connective tissue resected with the stomach were retrieved, including the lymph nodes and any areas of EM. Tumours were classified histologically into differentiated and undifferentiated types according to the World Health Organization tumour classification system[9]. The differentiated type included well and moderately differentiated tubular adenocarcinomas as well as papillary adenocarcinomas, based on the Japanese classification[10],



a ×100 **b** ×400

Fig. 1 Haematoxylin and eosin staining shows extranodal metastasis in gastric carcinoma. Tumour cells are scattered into the perinodal soft tissue distinct from the metastatic lymph node. **a** Original magnification ×100, **b** ×400

whereas the undifferentiated type included poorly differentiated adenocarcinomas, signet-ring cell carcinomas and mucinous adenocarcinomas.

EM was defined as the presence of cancer cells in soft tissue that was discontinuous with the primary lesion or in perinodal soft tissue distinct from the lymph node. Clinicopathological data were analysed according to the Japanese classification system for gastric carcinoma as outlined by the Japanese Gastric Cancer Association[10].

Follow-up continued until death or for more than 5 years in surviving patients. Information was obtained from medical charts and death certificates in the hospital population survey office. Recurrence was confirmed by physical examination, carcinoembryonic antigen testing and imaging, including computed tomography. In some patients, initial recurrence was diagnosed at two or more sites. In this instance, all the sites were counted as the site of initial recurrence.

Statistical analysis

The correlation between EM and clinicopathological features was determined using Fisher's exact test, χ^2 test or Mann–Whitney U test. Cumulative overall and disease-free survival rates were calculated using the Kaplan–Meier method and compared using the log rank test. Multivariate analysis was performed using the Cox proportional hazard model together with factors described previously[11]. $P < 0{\cdot}050$ was considered statistically significant.

Results

EM was detected in 146 (14·3 per cent) of the 1023 patients and in 1060 (3·0 per cent) of the 35 811 nodules retrieved as 'lymph nodes'. In the 146 patients with EM, the mean number of metastases of this type was 7 (median 3, range 1–79). *Figure 1* shows an example of EM.

The incidence of EM was significantly higher in patients with large tumours (diameter 10 cm or more) and in those with macroscopic infiltrative tumours. Histologically, EM was significantly associated with relatively deep invasion, undifferentiated tumours, lymph node metastasis, and lymphatic and vascular involvement. Overall, patients with EM had a significantly larger number of lymph node metastases, but nine patients with EM had no lymph node metastases. Liver metastasis and peritoneal dissemination were found more frequently at surgery in patients with EM (*Table 1*). Tumour stage was III or higher in 117 (80·1 per cent) of the 146 patients with EM.

Eight hundred and eighty-five (86·5 per cent) of all patients and 66 (45·2 per cent) of 146 patients with EM underwent curative surgery. After a potentially curative procedure, 45 (68 per cent) of 66 patients with EM developed recurrence, compared with 131 (16·0 per cent) of 819 patients without EM. Of those with EM, 20 patients (30 per cent) developed recurrence locally or in the lymph nodes, 16 patients (24 per cent) had distant metastases of whom 11 had hepatic involvement, and other sites of recurrence included the peritoneum in 25 (38 per cent). The primary site of recurrence was unknown in five patients.

Table 1 Correlation between extranodal metastasis and clinicopathological features in gastric carcinoma

	Extranodal metastasis		
	Positive ($n = 146$)	Negative ($n = 877$)	P
Age (years)*	61(9)	60(9)	0·582†
Sex			0·551‡
M	100 (68·5)	620 (70·7)	
F	46 (31·5)	257 (29·3)	
Tumour size (cm)			< 0·001§
< 10	61 (41·8)	798 (91·0)	
≥ 10	85 (58·2)	79 (9·0)	
Tumour type			< 0·001§
Superficial	2 (1·4)	585 (66·7)	
Circumscribed	16 (11·0)	126 (14·4)	
Infiltrative	128 (87·7)	166 (18·9)	
Histology			< 0·001‡
Differentiated	38 (26·0)	444 (50·6)	
Undifferentiated	108 (74·0)	433 (49·4)	
Tumour depth			< 0·001§
pT1	2 (1·4)	520 (59·3)	
pT2	17 (11·6)	195 (22·2)	
pT3	102 (69·9)	126 (14·4)	
pT4	25 (17·1)	36 (4·1)	
Lymph node metastasis			< 0·001‡
Yes	137 (93·8)	330 (37·6)	
No	9 (6·2)	547 (62·4)	
Lymphatic involvement			< 0·001‡
Yes	131 (89·7)	382 (43·6)	
No	15 (10·3)	495 (56·4)	
Vascular involvement			< 0·001‡
Yes	94 (64·4)	203 (23·1)	
No	52 (35·6)	674 (76·9)	
Peritoneal metastasis			< 0·001‡
Yes	59 (40·4)	20 (2·3)	
No	87 (59·6)	857 (97·7)	
Liver metastasis			< 0·001‡
Yes	12 (8·2)	14 (1·6)	
No	134 (91·8)	863 (98·4)	
Curability			< 0·001‡
Curative	66 (45·2)	819 (93·3)	
Non-curative	80 (54·8)	58 (6·7)	

Values in parentheses are percentages, except *values are mean(s.d.). pT, Pathological tumour; †Mann–Whitney U test; ‡Fisher's exact test; §χ^2 test.

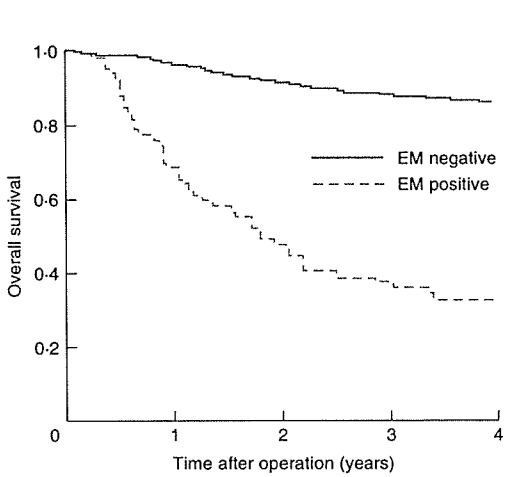
Patients who underwent potentially curative resection were included in a survival analysis. Survival curves were truncated at 4 years because of the small number of patients in some groups. Overall survival was significantly worse for patients with EM than for those without ($P < 0·001$) (*Fig. 2a*). Five-year survival rates were 26 and 84·5 per cent respectively. Disease-free survival was also significantly worse for patients with EM ($P < 0·001$). Among node-negative patients (pathological (p) N0), overall survival was poorer in patients with EM ($P < 0·001$); 5-year survival rates for patients with or without EM were 57 and 91·4 per cent respectively. Similarly, in both the pN1 and pN2 subgroups, overall survival was significantly worse in those with EM (both $P < 0·001$). The presence of EM had no significant impact on survival among patients with N3 disease ($P = 0·098$). Analysis of patients grouped according to the number of EMs revealed that number of metastases was significantly associated with a worse prognosis ($P < 0·001$) (*Fig. 2b*).

Multivariate analysis of factors associated with survival after curative surgery showed that EM was an independent prognostic factor, along with depth of tumour invasion and lymph node metastasis (*Table 2*).

Discussion

The incidence of peritoneal metastasis found during surgery and the rate of peritoneal recurrence was high in patients with EM. There are two possible explanations for the association between EM and peritoneal metastasis. First, it is feasible that tumour cells released from a primary lesion spread directly into the extranodal and extramural spaces. This is consistent with the finding that EM showed a close correlation with cancer aggressiveness measured in terms of serosal invasion. Furthermore, tumour cells from poorly differentiated adenocarcinomas were found to be scattered into both soft and connective tissues by means of peritoneal seeding in both the present and previous studies[1,2,12]. Another possibility is that EM occurs subsequent to lymph node involvement. Burn[13] hypothesized that lymphaticovenous communication occurs when cancer cells metastasize to a lymph node or lymphatic vessels and obstruct lymph flow. Yamagata *et al.*[14] demonstrated this experimentally in animal models. Few previous reports have shown a correlation between peritoneal metastasis and lymph node metastasis[15]. The present study showed a significant correlation between EM and the incidence of lymph node metastasis.

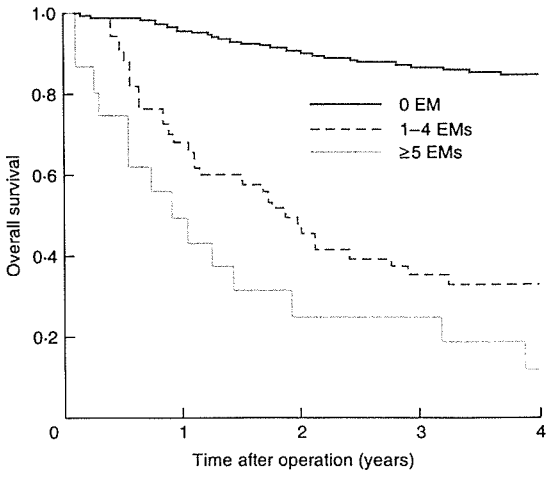
To determine whether EM should be included in the pN category, patterns of survival were examined in relation to lymph node involvement or EMs. The 5-year survival rate decreased linearly with increasing nodal involvement, classified according to the UICC tumour node metastasis (TNM) system: 88·5 per cent (pN0), 67·6 per cent (pN1), 34·7 per cent (pN2) and 14·0 per cent (pN3) based on a review of 4362 patients with gastric carcinoma at the National Cancer Centre Hospital[16]. Although the 5-year overall survival rate also worsened as the number of EMs increased, the deterioration was not linear and a sharp decline was noted if just one EM was present. EM in gastric carcinoma may therefore more closely resemble



No. at risk

EM negative	819	782	729	681	648
EM positive	66	46	26	19	15

a Presence of EM



No. at risk

0 EM	819	782	728	681	648
1–4 EMs	50	33	21	15	12
≥5 EMs	16	11	5	4	3

b No. of EMs

Fig. 2 Overall survival curves after curative resection **a** in patients with or without extranodal metastasis (EM) ($P < 0{\cdot}001$, log rank test) and **b** in patients grouped according to the number of EMs ($P < 0{\cdot}001$)

Table 2 Multivariate analysis of factors affecting prognosis after curative resection

	Standard error	Hazard ratio	P*
Depth of invasion	0·13	1·83 (1·42, 2·35)	<0·001
Extranodal metastasis	0·20	1·82 (1·23, 2·71)	0·003
Lymph node metastasis	0·20	1·70 (1·14, 2·51)	0·009
Macroscopic type	0·26	1·44 (0·87, 2·40)	0·158
Lymphatic invasion	0·21	1·44 (0·95, 2·17)	0·088
Venous invasion	0·18	1·23 (0·86, 1·75)	0·253

Values in parentheses are 95 per cent confidence intervals. *Cox proportional hazard model.

peritoneal metastasis than lymph node metastasis but, as there were long-time survivors with EM, it should be considered separately from peritoneal disease.

Although EM was identified as an independent predictor of a poor prognosis, about a half of patients with four or fewer EMs survived for more than 2 years without adjuvant treatment. This suggests that *en bloc* clearance of adipose connective tissue by D2 dissection is effective in some but not in all situations. If *en bloc* dissection of the gastric bed is not carried out, radiotherapy combined with chemotherapy may be effective[17].

EM in gastric carcinoma was closely related to cancer aggressiveness and a poor prognosis. Its presence should be included in the clinical classification of gastric carcinoma.

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Original article

Stage migration caused by D2 dissection with para-aortic lymphadenectomy for gastric cancer from the results of a prospective randomized controlled trial

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Background: Extended lymphadenectomy (D2) provides accurate nodal staging of gastric cancer. The aim of this study was to clarify the degree of stage migration seen with D2 combined with para-aortic lymph node dissection for gastric cancer invading the subserosa, the serosa and adjacent structures (T2ss–4) in patients considered not to have distant metastases (M0).

Methods: Between July 1995 and April 2001, 523 patients were recruited and randomized in a prospective phase III trial comparing D2 with D2 and para-aortic nodal dissection for T2ss–4 gastric cancer without macroscopic para-aortic nodal metastases. Stage migration was evaluated by Japanese Gastric Cancer Association staging in 260 patients who underwent D2 with para-aortic dissection by analysing pathological information from the dissected lymph nodes.

Results: Node (N)-stage migration was observed in 1 per cent (1 of 82) of patients with N1 disease, 20 per cent (12 of 59) with N2, 43 per cent (10 of 23) with N3 and 8·8 per cent (23 of 260) of all patients. Final stage migration occurred in 9 per cent (5 of 58) of patients with stage IIIa, 19 per cent (8 of 42) with stage IIIb, 56 per cent (9 of 16) with stage IVa and 8·5 per cent (22 of 260) of all patients. Metastasis to N4 nodes was found in 4 per cent (four of 95) of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. The overall incidence of N4 involvement was 8·8 per cent (23 of 260).

Conclusion: Extended para-aortic lymphadenectomy for gastric cancer provides accurate nodal staging and results in stage migration, which may improve stage-specific survival regardless of overall survival benefit.

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Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most common malignancy in Japan, South America and Eastern Europe[1]. Radical gastrectomy with regional lymphadenectomy is the mainstay of curative treatment for gastric cancer that has penetrated beyond the submucosa[2]. The procedure can be undertaken in the context of total or subtotal gastrectomy where (D2) lymphadenectomy indicates nodal dissection to the N2 level[3]. This has been the standard treatment for gastric cancer in Japan since the 1960s[4].

In the 1980s extended lymphadenectomy procedures were practised in many Japanese centres with the intention of improving the prognosis of patients with locally

The Editors have satisfied themselves that all authors have contributed significantly to this publication

advanced gastric cancer. In addition to D2 lymphadenectomy, lymph nodes around the upper abdominal aorta were dissected on the basis that 20–30 per cent of patients with non-early gastric cancer (more than T1) had microscopic metastasis present in para-aortic nodes[5–8]. The reported 5-year survival rate for patients with these nodal metastases was in the range of 14–30 per cent after extended para-aortic lymphadenectomy[5–9].

Based on these results, the Japanese Gastric Cancer Association defined para-aortic nodes as regional lymph nodes[10]. Conversely, the International Union Against Cancer (UICC)–tumour node metastasis (TNM) system classified metastases to para-aortic lymph nodes not as regional lymph node metastases (N) but as distant metastases (M)[11]. Keighley *et al.*[12] reported that median survival was less than 5 months in British patients with tumours involving para-aortic nodes, even after extended para-aortic nodal dissection.

From retrospective studies, it has been suggested that extended para-aortic lymphadenectomy improved prognosis compared with standard D2 dissection[9,13]. It may be, however, that extended surgery only provides more accurate staging information and that this stage migration may improve apparent stage- and N stage-specific survival[14]. The impact of stage migration has not yet been clarified.

A multi-institutional randomized clinical trial was therefore conducted by the Japan Clinical Oncology Group (JCOG) to evaluate the survival benefit of D2 gastrectomy with extended para-aortic dissection for T2ss–4 M0 gastric cancer (ss, subserosal) without macroscopic para-aortic nodal metastases. Morbidity and mortality results from this trial showed that D2 as well as extended surgery could be performed safely in specialized hospitals in Japan[15]. The present report evaluated the stage migration caused by D2 with para-aortic lymphadenectomy by analysing pathological information from dissected lymph nodes in this prospective trial. This is the first study to evaluate stage migration caused by para-aortic dissection.

Patients and methods

The randomized trial[15] was approved by the JCOG and the local ethics committees of each institution. Initially, the 12 institutions of the Gastric Cancer Surgery Study Group of the JCOG participated in the trial, followed by 12 additional institutions to increase recruitment. All data management and quality assurance were done by the JCOG data centre.

Between July 1995 and April 2001, 523 patients with T2ss–4 M0 tumours, without gross metastases in para-aortic nodes, were randomly assigned to D2 (263 patients) or D2 with para-aortic dissection with curative intent (260). Para-aortic lymph nodes of 1 cm in diameter or larger were diagnosed as metastases by computed tomography. After mobilization of the duodenum, nodal status was finally judged by palpation. The effects of stage migration were evaluated in the 260 patients who underwent D2 with para-aortic lymphadenectomy.

The 12th edition of the Japanese Gastric Cancer Association staging system was used[10]. Lymph nodes were divided to four groups: group 1 or N1 consisted of the perigastric nodes along the lesser curvature (stations 1, 3 and 5) and the greater curvature (stations 2, 4 and 6); group 2 or N2 consisted of the nodes along the left gastric artery (station 7), along the common hepatic artery (station 8), around the coeliac artery (station 9) and along the splenic artery (stations 10 and 11); group 3 or N3 consisted of nodes along the hepatoduodenal ligament (station 12), around the pancreas (stations 13, 15, 17 and 18) and along the superior mesenteric vein (station 14); and group 4 or N4 consisted of para-aortic lymph nodes (station 16). D2 dissection involved removal of all N1 and N2 nodes for tumours in the proximal and middle stomach, and additionally stations 12, 13 and 14 for tumours in the distal stomach. For D2 with para-aortic dissection, the para-aortic lymph nodes were removed in addition to the D2 dissection. Quality control concerning nodal dissection has been described; the median number of retrieved nodes was 54 (range 14–161) in D2 and 74 (range 30–235) in D2 with para-aortic dissection[15].

The lymph nodes of each station were retrieved individually from the specimen and numbered according to the Japanese Gastric Cancer Association staging system. The stomach and lymph nodes were stained with haematoxylin and eosin for histopathological examination.

Stage migration was calculated by assuming that patients had undergone hypothetical D2 dissection without para-aortic lymphadenectomy. Lymph nodes were staged according to the N1, N2 and N3 status, without N4 information (standard staging). Restaging was then undertaken after considering N4 status obtained by true extended para-aortic lymphadenectomy (extended staging). In this way, N-status migration could be determined when metastatic nodes were detected in the N4 levels. A final stage was determined in both the standard and extended staging by combining microscopic depth of invasion into the gastric wall (T status).

Results

Lymph node metastases according to standard and extended staging are shown in *Table 1*. By applying extended staging, N-stage migration was observed in 1 per cent (1 of 82) of patients with N1 disease, 20 per cent (12 of 59) with N2, 43 per cent (10 of 23) with N3 and 8·8 per cent (23 of 260) of all patients. The final staging is shown in *Table 2*. Overall stage migration occurred in 9 per cent (five of 58) of patients with stage IIIa disease, 19 per cent (8 of 42) with stage IIIb, 56 per cent (9 of 16) with stage IVa and 8·5 per cent (22 of 260) of all patients.

Table 3 shows lymph node metastases classified according to depth of invasion. Metastases to N4 nodes were found in 4 per cent (four of 95) of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. The overall incidence of N4 involvement was 8·8 per cent (23 of 260).

Discussion

This study has clarified the incidence of microscopic metastases in patients with T2ss–4 M0 tumours and macroscopically negative para-aortic nodes.

Limited nodal dissection often provides inaccurate staging. Bunt *et al.*[14] analysed the migration effects in Japanese Gastric Cancer Association staging from the results of D1 and D2 surgery in a Dutch phase III trial and found that the rate of stage migration was 30 per cent when D2 surgery was applied instead of D1[14]. They also calculated the stage-specific survival rate based on reported survival rates and stage migration, and clarified that stage migration could improve stage-specific survival without a real survival benefit from D2 lymphadenectomy[14].

In this study, N-stage migration occurred in 8·8 per cent and overall stage migration was noted in 8·5 per cent of patients by applying extended staging instead of standard D2 staging. N- and stage-specific survival may therefore be improved owing to N stage and overall stage migration. Some Japanese surgeons have reported that extended nodal dissection can improve overall survival in patients with N2 tumours compared with standard D2 dissection[9,13]. These survival differences could be explained, in part, by the N-stage migration observed in this study. There seems no sense, therefore, in comparing D2 and more extended dissection by retrospective survival analyses based on the Japanese Gastric Cancer Association staging system.

Extended para-aortic lymphadenectomy influences Japanese Gastric Cancer Association staging and UICC–TNM staging. Metastases to para-aortic nodes are treated as distant metastases (M1) by TNM staging[11]. According to eligibility criteria in the present study, patients with metastases to distant organs such as liver and peritoneum were excluded. Para-aortic nodes were also negative macroscopically. The present results demonstrate that 8·8 per cent (23 of 260) of patients with T2ss–4 M0 gastric cancer and macroscopically negative para-aortic nodes have microscopic para-aortic nodal metastases. These patients then become classified as M1, so that extended lymphadenectomy causes M-stage migration, impacting on M-specific survival in the TNM classification.

In the present study, nodal metastases to N4 were observed in 8·8 per cent (23 of 260) of all patients and these positive nodes were found in 4 per cent (four of 95)

Table 1 Staging and migration of lymph node metastases

	Standard staging				Extended
	N0	N1	N2	N3	total
Extended staging					
N0	96				96
N1		81			81
N2			47		47
N3				13	13
N4		1	12	10	23
Standard total	96	82	59	23	260

Table 2 Disease stage and stage migration

	Standard staging							Extended
	Ia	Ib	II	IIIa	IIIb	IVa	IVb	total
Extended staging								
Ia	10							10
Ib		67						67
II			64					64
IIIa				53				53
IIIb					34			34
IVa						7		7
IVb				5	8	9	3	25
Standard total	10	67	64	58	42	16	3	260

Table 3 Depth of invasion and lymph node metastases

	Lymph node metastasis					
	N0	N1	N2	N3	N4	Total
Depth of invasion						
M	3					3
SM	7	4				11
MP	19	14	3	1		37
SS	44	28	14	5	4	95
SE	22	35	28	5	19	109
SEI	1		2	2		5
Total	96	81	47	13	23	260

M, mucosa; SM, submucosa; MP, muscular is propria; SS, subserosa; SE, serosa exposed; SEI, serosa exposed and invading adjacent organs.

of tumours invading the subserosa and 17·4 per cent (19 of 109) of tumours penetrating the serosa. Previous Japanese studies have reported that 20–30 per cent of patients with non-early gastric cancer had histological metastasis in the para-aortic nodes[5–8]. The present study confirmed N4 disease in localized advanced gastric cancer invading the subserosa or deeper. The slightly lower incidence of this finding in the present compared with previous studies may have been due to the inclusion of patients with macroscopically involved para-aortic nodes in the earlier studies.

Extended para-aortic lymphadenectomy for T2ss–4 M0 gastric cancer provides a revised nodal staging. This results in stage migration that may improve stage-specific survival regardless of a real survival benefit.

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Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial

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Summary

Background Because of the inaccessibility of mediastinal nodal metastases, the left thoracoabdominal approach (LTA) has often been used to treat gastric cancer of the cardia or subcardia. In a randomised phase III study, we aimed to compare LTA with the abdominal-transhiatal approach (TH) in the treatment of these tumours.

Methods Between July, 1995, and December, 2003, 167 patients were enrolled from 27 Japanese hospitals and randomly assigned to TH (n=82) or LTA (n=85). The primary endpoint was overall survival, and secondary endpoints were disease-free survival, postoperative morbidity and hospital mortality, and postoperative symptoms and change of respiratory function. The projected sample size was 302. After the first interim analysis, the predicted probability of LTA having a significantly better overall survival than TH at the final analysis was only 3·65%, and the trial was closed immediately. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00149266.

Findings 5-year overall survival was 52·3% (95% CI 40·4–64·1) in the TH group and 37·9% (26·1–49·6) in the LTA group. The hazard ratio of death for LTA compared with TH was 1·36 (0·89–2·08, p=0·92). Three patients died in hospital after LTA but none after TH. Morbidity was worse after LTA than after TH.

Interpretation Because LTA does not improve survival after TH and leads to increased morbidity in patients with cancer of the cardia or subcardia, LTA cannot be justified to treat these tumours.

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Introduction

By contrast with the notable decrease in the incidence of distal gastric cancer, frequency of adenocarcinoma in the oesophagogastric junction has increased, especially in developed countries.[1–3] The Siewert classification for these tumours is now widely accepted.[4] Studies of adjuvant treatment for gastric cancer with chemotherapy or chemoradiotherapy have included tumours in the oesophagogastric junction.[5,6] However, no evidence suggests that oesophagogastric-junction tumours can be treated in the same way as gastric cancers; if thoracotomy is mandatory for oesophagogastric-junction tumours, they should not be included in studies on the treatment of gastric cancers. So far, only one prospective randomised controlled trial[7] has been undertaken to compare the effects of surgical treatments in Siewert type 1 and 2 tumours in the oesophagogastric junction. Although the trial was slightly underpowered, it suggested that extended transthoracic resection resulted in better survival than a restricted transhiatal resection. However, a systematic review[8] comparing surgical treatments for lower oesophageal carcinoma showed a higher morbidity for transthoracic resection than for transhiatal resection, but with similar survival.

In eastern Asian countries, including Japan, most tumours in the oesophagogastric junction are of Siewert type 2 and 3.[9] The occurrence of lower mediastinal lymph-node metastasis from type 2 and 3 tumours is reported to be 10–40%.[10–16] Some researchers[10,11] claim that a thoracotomy is needed to thoroughly dissect the mediastinal nodes and to obtain a safe surgical margin, although mediastinal lymph-node metastasis is an indicator of poor prognosis. Other studies[12,13] recommend the use of a transhiatal resection, because patients with mediastinal-lymph-node metastasis have poor prognosis even if a more extensive procedure was done. Advances in circular stapling devices have enabled surgeons to make safe intrathoracic or mediastinal anastomosis without thoracotomy.

In 1995, the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (GCSSG/JCOG) initiated a multicentre, randomised controlled trial with the aim to compare the effects of the left thoracoabdominal approach (LTA) with the abdominal-transhiatal approach (TH) on patients with cancer of the cardia or subcardia (JCOG 9502).

Methods

Patients

Our study was designed as a multicentre, prospective, randomised phase III trial. The study protocol was approved by the clinical trial review committee of JCOG and the institutional review boards of all 27 participating Japanese hospitals before the initiation of the study, and all patients provided written informed consent. Eligibility criteria included: histologically proven adenocarcinoma of the gastric body or cardia with oesophageal invasion

of 3 cm or less, tumour status T2–4, age 75 years or younger, no distant metastasis, no lymph nodes larger than 1 cm in the hepatoduodenal ligament or in the para-aortic area, at least 50% forced expiratory volume in 1 s, and at least 9·3 kPa arterial oxygen pressure in room air. Exclusion criteria included: carcinoma in the remnant stomach, linitis plastica; synchronous or metachronous double cancer in previous 10 years, apart from carcinoma in situ; history of left thoracotomy or findings suggesting severe left-pleural adhesion; history of myocardial infarction or positive results of exercise electrocardiogram; and liver cirrhosis or chronic liver disease with indocyanine green excretion test at 15 min of 15% or more.

Procedures

Since the two surgical approaches included different skin incisions, patients underwent randomisation before surgery and after precise clinical assessment of tumour stages, with abdominal and thoracic CT scans, endoscopy, barium meal study, and laboratory tests. Endoscopic ultrasonography was optional, but staging laparoscopy was not included because its use was uncommon in Japan when this study started. Therefore, some patients were expected to be incurable after laparotomy, mainly because of peritoneal seeding. Clinical assessments; informed consent; and postoperative morbidity, hospital mortality, postoperative symptoms, and respiratory function were all obtained by doctors from participating centres, who were also responsible for the quality control of surgery (but not for the quality control of data management or statistical analysis).

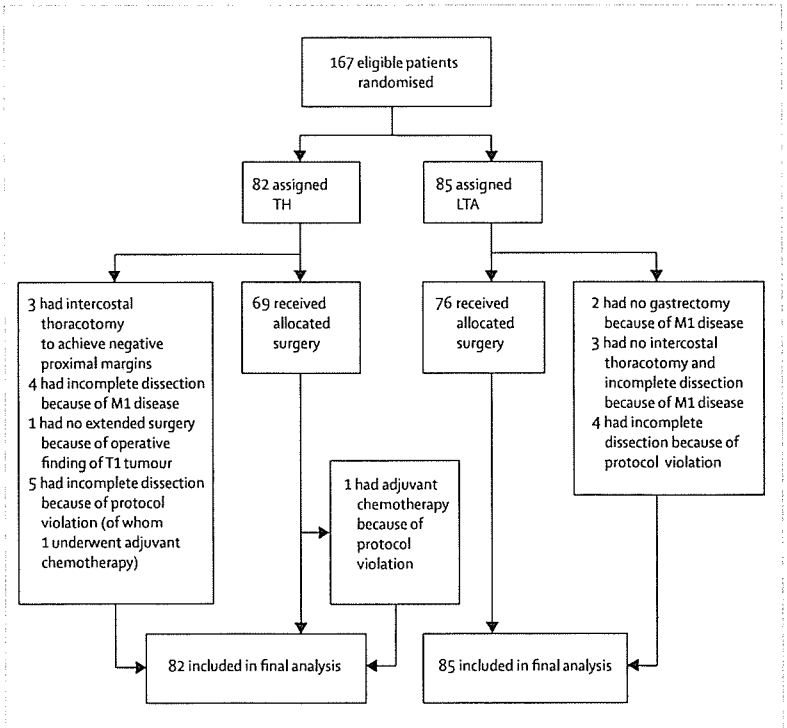

Figure 1: **Trial profile**
M1 disease denotes metastatic stage 1 of tumour.

	TH (n=82)	LTA (n=85)
Age (years)		
Median (range)	60 (36–75)	63 (38–75)
Sex		
Male	71	63
Female	11	22
Tumour stage (macroscopic)		
T2	20	20
T3 and T4	62	65
Macroscopic type		
Borrman 0–2	36	37
Borrman 3 and 5	46	48
Siewert classification*		
Type 2	52	43
Type 3	27	36
Non-oesophagogastric-junctional tumour	3	4
Histological type*		
Differentiated	42	43
Undifferentiated	40	40
Tumour depth (histological)*		
T1b	2	1
T2a	10	6
T2b	24	35
T3	39	37
T4	7	4
Tumour size (cm)		
Median (range)	6·2 (2·5–19)	7·0 (2·0–18)
Tumour stage (histological)		
Ia	1	0
Ib	9	15
II	14	15
IIIa	23	17
IIIb	15	14
IVa	3	7
IVb	17	17
Nodal stage (histological)*		
N0	14	15
N1	24	27
N2	30	25
N3	1	6
N4	13	10
Number of positive nodes		
Median (range)	5 (0–53)	5 (0–52)
Proximal margin*		
Negative	80	79
Positive	2	4

(Continues on next page)

(Continued from previous page)		
Oesophageal invasion (cm)		
Median (range)	1·6 (0–4·5)	1·2 (0–7·0)
Washing cytology		
Negative	69	73
Positive	11	9
Not done	2	3
Residual tumour		
R0	76	75
R1/2	6	10
Para-aortic nodal metastasis		
Positive	13	9
Negative	59	64
Not dissected	10	12
Mediastinal nodal metastasis		
Positive	3	9†
Negative	79	74
Not dissected	0	2

Data are number of patients unless stated otherwise. *Data not available for two patients in LTA group who did not undergo resection because of peritoneal seeding. †Includes five patients with Siewert type 2 tumours and four with other types.

Table 1: **Baseline characteristics**

Patients deemed eligible were randomly assigned to receive TH or LTA by the JCOG data centre according to the order in which information on enrolment was received by telephone. As a randomisation algorithm, minimisation methods were used by a computer-based randomisation programme to balance the groups according to institution, tumour stage (T2 *vs* T3 and 4), and Borrman type (type 0–2 *vs* 3 and 5). Assignment of the interventions was not masked. The JCOG data centre undertook assignment of the intervention, data management, central monitoring, and statistical analysis. It also produced monitoring reports twice a year, in which morbidity data were masked by treatment group. None of the surgeons administering the interventions participated in the data analysis.

All patients underwent the allocated procedure. If the operation was curative, no adjuvant treatment was allowed until recurrence was diagnosed. If the cancer was incurable, the choice of treatment was decided by the local surgeon, and included resection and any other treatment such as chemotherapy. Patients who had positive lavage cytology but no macroscopic peritoneal metastasis were regarded as curable. The type of reconstruction was selected by every surgeon.

TH consisted of a total gastrectomy with D2 lymphadenectomy (including splenectomy)[17] via a laparotomy. Additional dissection of the lymph nodes along the left inferior phrenic vessels and the para-aortic nodes lateral to the aorta and above the left renal vein was done in curable patients. All the procedures were undertaken via laparotomy, and the lower mediastinum was accessed transhiatally. Mediastinal resection included the lower oesophagus and only the peri-oesophageal lymph nodes. Thoracotomy on either side was allowed to achieve a complete (R0) resection only when the proximal surgical margin was positive (determined either macroscopically or microscopically by frozen section) and no further transhiatal oesophageal resection was possible.

For LTA, an oblique incision over the left thorax and the abdomen was made. The same procedure as that for TH was done in the abdominal cavity, including lymphadenectomy. In the thoracic cavity, a thorough mediastinal nodal dissection below the left inferior pulmonary vein was undertaken with oesophagectomy of sufficient length.

Local surgeons and pathologists of participating hospitals made surgical and histological assessments according to the Japanese Classification of Gastric Carcinoma.[17] Peritoneal lavage cytology in the pouch of Douglas or left subphrenic space (or both) had to be done immediately after laparotomy.

Postoperative complications such as anastomotic leakage, pancreatic fistula, intra-abdominal abscess, pyothorax, pneumonia, and mediastinitis were recorded as expected events. All in-hospital deaths and deaths within 1 month after surgery were defined as hospital mortality. Postoperative use of respirator, bronchoscope, and tracheotomy, including tube tracheotomy, to prevent or manage respiratory complications were recorded. The operation time, blood loss, blood transfusion needs, and reoperation details were also noted. All these assessments were undertaken and recorded by the local surgeons.

27 institutions of the GCSSG/JCOG took part in the study. All participating surgeons agreed to the technical details for both types of surgery during the planning stages of the trial. We selected surgeons with experience of more than 100 gastrectomies with D2 dissection,[17] or institutions with a specialised unit that did at least 50 gastrectomies a year.

In addition to the review of the half yearly monitoring report, some videos of either procedure were presented for critique by several institutions, and the technical details discussed. To assess the compliance of lymphadenectomy, we recorded dissection and node retrieval in all regional nodal sites and the number of dissected nodes in the lower mediastinum and the para-aortic area as case-report forms, and monitored the results over time.

The primary endpoint was overall survival, and secondary endpoints were disease-free survival, postoperative morbidity and hospital mortality, and postoperative symptoms and respiratory function.

Statistical analysis

We planned initially to recruit 302 patients, with one-sided alpha error of 0·05 and statistical power of 80% to predict an improvement of 10·5% with LTA over TH. The difference was estimated on the basis of results showing 5-year survival to be 20–40% in cardia and subcardia cancer,[18–20] and an expected 30% of incurable patients to have a 5-year survival of 5%.[9,10] The projected accrual

	TH (n=82)	LTA (n=85)*
Type of gastrectomy		
Total	79	80
Proximal	3	3
Not resected	0	2
Reconstruction method		
Roux-en-Y	75	76
Interposition	5	3
Other	2	4
Length of resected oesophagus (cm)		
Median (range)	4·2 (2·0–9·5)	4·5 (2·0–8·5)
Splenectomy		
Yes	78	81
No	4	4
Pancreatic-tail resection		
Yes	22	13
No	60	72
Thoracotomy		
Intercostal	3	79
Transabdominal	10	3
None	69	3
Dissected lymph nodes (median [range])		
Total	68 (14–147)	60 (16–160)
Mediastinal	2 (0–13)	8 (0–24)
Para-aortic	7 (0–63)	6 (0–60)
Operation time (min)		
Median (range)	305 (100–620)	338 (73–635)
Blood loss (mL)		
Median (range)	673 (55–3500)	655 (55–2174)
Allogeneic blood transfusion		
Yes	25	39
No	57	46

Data are number of patients unless stated otherwise. *Two patients undergoing simple laparotomy without gastrectomy not included in data for reconstruction method, length of resected oesophagus, and dissected lymph nodes; one of these patients was not included in data for operation time and blood loss.

Table 2: **Details of surgical procedures**

	TH (n=82)	LTA (n=85)	p
Any complication*	28 (34%)	42 (49%)	0·06
Anastomotic leak	5 (6%)	7 (8%)	0·77
Pancreatic leak	10 (12%)	14 (16%)	0·51
Abdominal abscess	7 (9%)	12 (14%)	0·33
Pyothorax	1 (1%)	4 (5%)	0·37
Pneumonia	3 (4%)	11 (13%)	0·05
Mediastinitis	0	4 (5%)	0·12
Other	13 (16%)	17 (20%)	0·55
Postoperative respiratory care			
Respirator use after surgery	6 (7%)	12 (14%)	0·21
Tracheotomy	2 (2%)	3 (4%)	1·00
Tube tracheotomy	2 (2%)	4 (5%)	0·68
Bronchoscopic toilet	2 (2%)	12 (14%)	0·01
Reoperation	2 (2%)	5 (6%)	0·44
Hospital death	0	3 (4%)	0·25

Data are number of patients (%). *Some patients had multiple complications.

Table 3: **Postoperative morbidity, respiratory care, and hospital mortality**

period was 4 years. After 8 years of slow accrual, the JCOG data and safety monitoring committee approved an amendment to the sample size and analysis plan. The amended sample size was 250, with one-sided alpha error of 0·1 and beta error of 0·2, with a 12-year accrual period (in total) and 8-year follow-up. The trial was planned to be one-sided because LTA was expected to be a more invasive approach and therefore more effective than TH as a standard procedure.

Three interim analyses were planned, with adjustment for multiple comparisons by the method of DeMets and Lan.[21] The O'Brien–Fleming type alpha spending function was used. The first interim analysis was planned for the date on which two-thirds of the revised sample size of patients had been enrolled, the second interim analysis when half the expected number of events would be observed, and the third interim analysis when three-quarters of expected events would be observed. The trial was also to be stopped if LTA showed no benefit.[22,23] We did not need to show that LTA did worse than TH to stop the study, since LTA was postulated to be better than a standard treatment because of its increased invasiveness compared with TH. We also planned to stop the trial if the predictive probability that LTA was significantly better than TH was lower than 5%.

We retrospectively calculated two-sided p values for overall survival only in the updated analysis. Analysis was by intention to treat.

Overall survival curves and disease-free survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test, stratified by factors used in the randomisation. Disease-free survival was measured as the date of randomisation to the date of the first observation of disease recurrence or death from any cause. Overall survival was also assessed by the Cox regression analysis stratified by tumour stage (T2 *vs* T3 and 4) and Borrman type (type 0–2 *vs* 3 and 5), the adjustment variables in randomisation; and adjusted with para-aortic nodal metastasis (negative *vs* positive), mediastinal nodal metastasis (negative *vs* positive), residual tumour (R0 *vs* R1 and 2), washing cytology (negative *vs* positive), and number of positive nodes (0 *vs* 1–6 *vs* 7–15 *vs* ≥16), as potential confounding factors. Operative morbidity and mortality were based on the proportion of the number of events divided by all eligible patients. Statistical analysis was done with SAS version 8.02. This study is registered with ClinicalTrials.gov, number NCT00149266.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of

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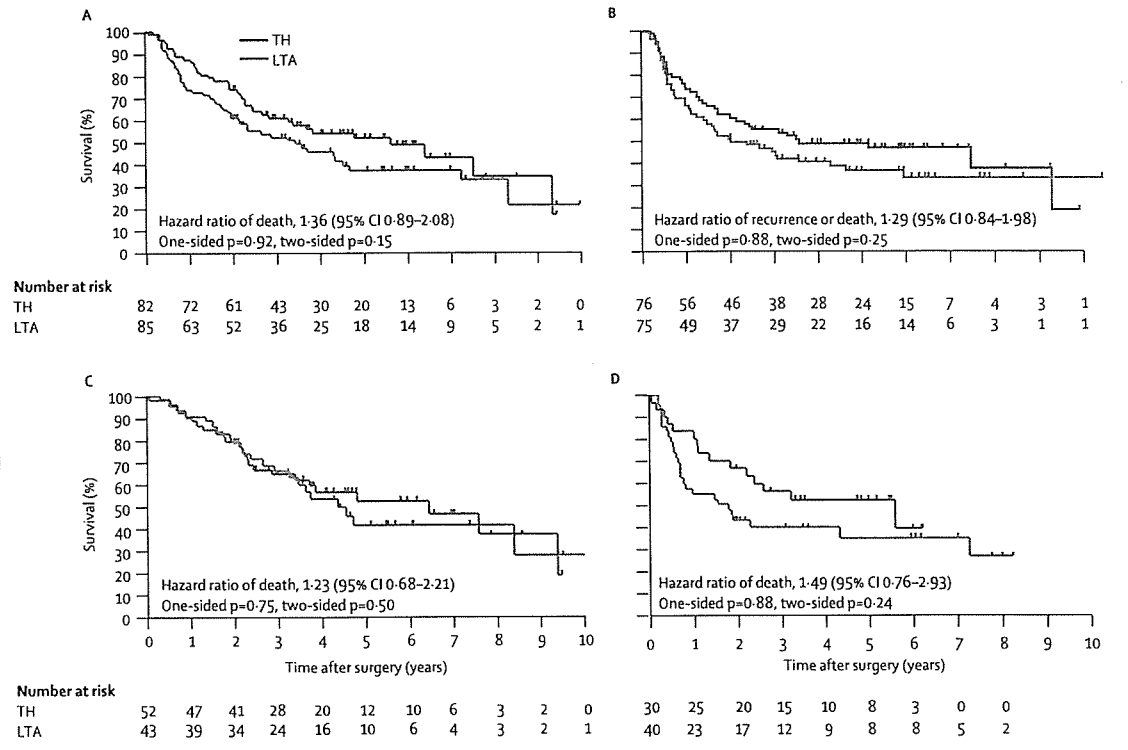

Figure 2: Overall survival (A) or disease-free survival (B) in all patients, and overall survival in patients with Siewert type 2 tumours (C) and type 3 tumours (D), by treatment group

the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between July, 1995, and December, 2003, 82 patients were randomly assigned to TH and 85 to LTA (figure 1). One patient was ineligible because of a second lesion in the distal stomach. Ten cases of protocol violation were reported. Two patients underwent adjuvant chemotherapy after surgery because of positive peritoneal lavage cytology. Nine patients did not complete the lymph-node dissection required in the protocol, one of whom underwent adjuvant chemotherapy.

The first interim analysis was done as scheduled in the amended protocol for the 165 patients enrolled before October, 2003, and survival analysis was undertaken for 146 patients for whom data were available. At the time, the observed number of events was 28% of the expected number at the final analysis, and the alpha used for this analysis was 0·00173. The median overall survival time was 6·5 years (95% CI 3·4–∞) for the TH approach and 4·4 years (2·2–7·3) for the LTA approach. Corresponding overall survival at 5 years was 53·4% (38·1–68·6) and 38·9% (22·4–55·4; p=0·93). At the final analysis, the predicted probability of LTA being significantly better than TH was 3·65%. The JCOG data and safety monitoring committee reviewed the results independently from the GCSSG and recommended to close the accrual and publish the results. This recommendation was accepted by the GCSSG and the accrual was closed in December, 2003.

Table 1 shows patient demographics and tumour characteristics. We could not classify seven patients by the Siewert classification because they had large gastric tumours invading the oesophagus. 95 tumours were classified as Siewert type 2, and 63 as type 3. We recorded para-aortic nodal metastasis in 13 patients assigned TH and nine assigned LTA. Mediastinal nodal metastasis was seen in three patients assigned TH, compared with nine assigned LTA. 151 (90%) of 167 patients received R0 resection, a much higher proportion than expected. Two patients in the LTA group did not undergo surgical resection because they had substantial peritoneal seeding.

Table 2 lists the surgery details. Although most patients received total gastrectomy, proximal gastrectomy was done for six patients with incurable tumours. The surgery took longer for the LTA group than for the TH group (table 2). Although the amount of blood loss was similar between groups, allogeneic blood transfusion was needed more often for LTA than for TH. Overall morbidity was 42% (70 of 167 patients, table 3). The three patients who

died in hospital had all been assigned LTA. Patients allocated LTA had more complications and needed more intensive respiratory care, such as respirator support or bronchoscopic tracheal toileting, than did those allocated TH.

Survival data were updated up to March, 2006. Median overall survival was 5·7 years (95% CI 3·3–9·4) for patients assigned TH and 3·5 years (2·2–4·7) for those assigned LTA, at which point 40 patients in the TH group and 49 in the LTA group died (figure 2A). 5-year overall surival was 52·3% (40·4–64·1) for patients assigned TH and 37·9% (26·1–49·6) for patients assigned LTA. When further adjusted by prognostic factors, the hazard ratio of death for LTA compared with TH was 1·30 (0·83–2·02). Median disease-free survival was longer for TH than for LTA (3·6 years [2·0–9·4] *vs* 2·0 years [1·3–4·4]; figure 2B). Known disease-free survival at 5 years was higher in patients assigned TH than in those assigned LTA (48·6% [37·1–60·1] *vs* 35·8% [24·2–47·4]).

We assessed 165 patients with the Siewert classification, after excluding two who had missing data. The median overall survival was 4·7 years (95% CI 3·6–8·4) in the 95 patients with type 2 tumours, compared with 2·4 years (1·6–7·3) in the 70 patients with type 3 or non-oesophagogastric-junction tumours (hazard ratio in multivariate analysis 1·36 [0·69–1·83], two-sided p=0·64). Figures 2C and 2D and table 4 show median survival and 5-year overall survival by Siewert classification and treatment group.

At the time of surgery, one patient in the TH group and two in the LTA group had liver metastasis, and seven in the TH group and nine in the LTA group had peritoneal metastasis. In patients who developed recurrence after surgery (38 in TH, 41 in LTA), initial sites were found in: the lymph nodes (29), peritoneum (18), liver (16), lung (nine), pleura (four), distant organs (four), and other sites (one). Some patients had metastasis to two different sites. Sites of recurrence did not differ between TH and LTA for Siewert type 2 tumours, but for patients with Siewert type 3 tumours and non-oesophagogastric-junction tumours, recurrence in the peritoneum was more frequent in those assigned LTA than those assigned TH (seven of 40 *vs* one of 30).

	TH	LTA
Overall survival (median [95% CI], years)		
All	5·7 (3·3–9·4)	3·5 (2·2–4·7)
Siewert type 2	6·5 (3·4–9·4)	4·4 (3·3–∞)
Siewert type 3*	5·7 (1·9–∞)	1·8 (0·8–7·3)
5-year survival (% [95% CI])		
All	52·3% (40·4–64·1)	37·9% (26·1–49·6)
Siewert type 2	52·2% (36·6–67·8)	41·5% (24·2–58·8)
Siewert type 3*	52·4% (34·2–70·6)	34·9% (19·0–50·8)
Disease-free survival		
Median (range, years)	3·6 (2·0–9·4)	2·0 (1·3–4·4)
At 5 years (% [95% CI])	48·6% (37·1–60·1)	35·8% (24·2–47·4)

*Includes seven patients with tumours not in the oesophagogastric junction.

Table 4: **Survival analysis**

Discussion

This study shows that LTA does not provide a survival advantage compared with TH in the treatment of curable gastric cancers with an oesophageal invasion of 3 cm or less, which corresponds mainly to tumours classified as Siewert type 2 or 3. The study was stopped after the interim analysis, because patients assigned LTA were unlikely to have an improved overall survival compared with those assigned TH for Siewert type 2 or 3 tumours.

Some controversy exists about whether type 2 tumours should be treated like type 1 tumours (by thoracotomy) or like type 3 tumours (by TH). In this trial, we included both type 2 and type 3 tumours, and noted no difference between these two subtypes in terms of survival.

In a randomised controlled trial, Hulscher and colleagues[7,24] compared right thoracotomy with TH to treat oesophagogastric-junction tumours classified as Siewert type 1 (n=90) or 2 (n=115). No significant difference was noted between the TH group and the thoracotomy group for 5-year disease-free survival (difference 12% [95% CI −1 to 24]) or for overall survival (10% [−3 to 23]). A retrospective analysis by Siewert subtype[24] showed a difference between groups in 5-year overall survival of 17% (95% CI −3 to 37) for type 1 tumours and of 1% (95% CI not indicated) for type 2 tumours. On the basis of the much higher morbidity after thoracotomy than after TH, the researchers concluded that TH would be better for type 2 tumours, but thoracotomy would be better for type 1 tumours. This trial clearly answered the question of whether Siewert type 2 should be treated as type 1 or type 3. Furthermore, from the results of a clinicopathological study (n=1002),[25] Siewert noted that type 1 and type 2 tumours had several important differences, whereas type 2 and type 3 tumours were more similar. Siewert concluded that type 2 tumours should be treated in the same way as type 3 tumours, with the use of TH. The more extensive technique of thoracotomy is probably more effective in treatment of Siewert type 1 tumours because they tend to have more metastasis in the lymph nodes of the middle or upper mediastinum than do type 2 tumours.[16] In our trial, mediastinal lymph-node metastasis could be measured accurately only in the LTA group in which thorough mediastinal nodal dissection was done; we recorded similar amounts of metastasis in patients with type 2 and type 3 tumours (five [12%] of 43 patients *vs* four [10%] of 40 patients).

Our results showed clearly that LTA had no survival benefit for Siewert type 2 and 3 tumours, although they did not indicate that TH had a survival benefit over LTA. In this study, we did not need to prove that LTA was worse than TH, since LTA should be better as a standard treatment because of its more invasive nature. Our study

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was stopped before the planned sample size was accrued, which meant that we had restricted power to detect a difference between the groups. Had the trial reached full accrual, the predicted probability of LTA having a significantly better overall survival than TH would have been 3·65%, calculated from futility analysis, which is based on the Bayesian approach by Spiegelhalter.[42]

We recorded more peritoneal seeding in type 3 tumours treated by LTA than in those treated by TH. Although this difference could have been due to chance, we suggest that it might also have been related to an immunosuppressive effect of surgery. Raa and colleagues[26] reported the results of an experimental study showing that not only a laparotomy but also an isolated thoracotomy (unlike our trial using thoraco-laparotomy) promotes seeding of tumour cells in the peritoneum.[26] In 1980, Hattori and co-workers[27] showed that tumour growth was increased and survival time reduced in mice that received thoraco-laparotomy, compared with those that received laparotomy only. The researchers also recorded a linear increase in the number of metastatic nodules and a linear decrease in survival time, from laparotomy to thoracotomy and then to thoraco-laparotomy.

Toge and colleagues[28] suggested that this immunosuppressive effect of thoraco-laparotomy was related to a reduction in activity of natural-killer cells, proliferative response of spleen cells, and cytostatic activity of macrophages in rats. The increased frequency of peritoneal seeding in our study might also be related to a raised number of patients who received perioperative blood transfusion in the LTA group than in the TH group. Dutch surgeons have shown that blood transfusion does not have direct tumour-promoting effects,[29] but it has been strongly linked with poor prognosis. However, in our study, the hazard ratio adjusted for blood transfusion was almost the same as the unadjusted hazard ratio. Thus, no convincing theory so far can explain the difference between TH and LTA.

We postulated that LTA would improve survival over TH with an acceptable increase of morbidity. As expected, overall postoperative morbidity was much worse in patients assigned LTA than in those assigned TH. Pneumonia and bronchoscope use for tracheobroncheal toileting was significantly more frequent in the LTA group than in the TH group. All patients with curable tumours underwent a total gastrectomy with classic D2 dissection and 159 patients underwent splenectomy. The LTA approach had an increase of 30 min in operation time, but had no increase of blood loss. However, more patients assigned LTA than those assigned TH received allogeneic blood transfusion, probably because of the unstable cardiorespiratory condition immediately after surgery in LTA. Reasons for the need of allogeneic blood transfusion could not be ascertained from case report forms, but longer operation time, more frequent use of ventilator, tracheotomy, or tube tracheotomy in postoperative respiratory care, and more frequent re-operation suggest that patients in the LTA group had a less stable general condition than did those in the TH group.

As an intrinsic limitation of a multicentre surgical trial, complete uniformity of surgical techniques in detail in both procedures is impossible. Until 1995, indications for these two procedures have differed between participants. However, all the surgeons in our study used LTA for tumours with oesophageal invasion of greater than 4 cm, and all prefer TH for older (>80 years) or high-risk patients with tumours of the oesophagogastric junction. Therefore, all of the surgeons in our study had had sufficient experience of both procedures. Although the unbalance of Siewert classification subtypes between treatment groups might have affected survival data, the effect seems small because the adjusted hazard ratio by Cox regression analysis including Siewert subtype was similar to the unadjusted hazard ratio. Theoretically, small differences in the median age and sex ratio could affect the results; however, older age worsens survival and a higher proportion of females improves survival usually,[30] so we can disregard these factors. Since patients had to be randomly assigned before surgery, 10% of patients were found to be incurable. Thus the proportion of the patients who underwent R0 resection (90%) was much higher than planned in the protocol (70%). Incurable tumours were well balanced between treatment groups (p=0·39) and did not affect the results.

In conclusion, the LTA approach cannot be justified to treat Siewert type 2 or 3 tumours of the oesophagogastric junction if the length of oesophageal invasion is 3 cm or less.

Contributors

M Sasako had the original idea, wrote the original protocol, and had the role of primary investigator. T Sano was the deputy primary investigator. M Sasako, T Sano, M Sairenji, K Arai, T Kinoshita, A Nashimoto, and M Hiratsuka enrolled most of the patients. S Yamamoto is a statistician at the JCOG data centre, who was responsible for the statistical design and analyses, apart from the interim analysis.

Conflict of interest

We declare no conflicts of interest.

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