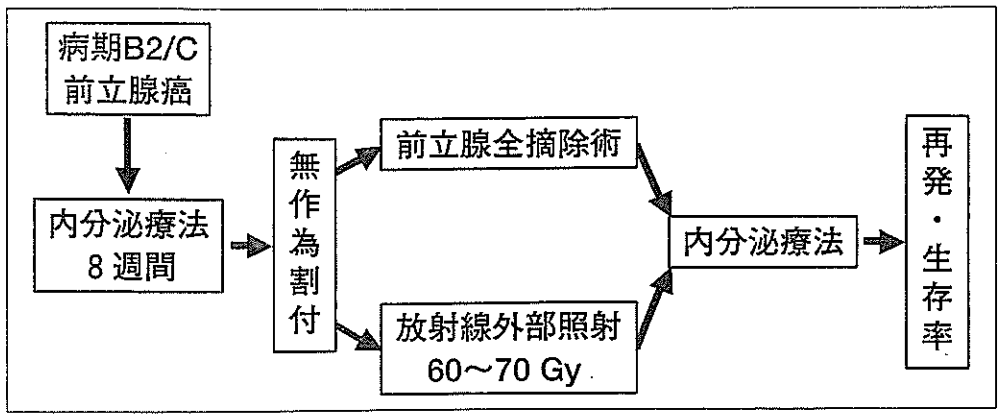

図1　研究デザイン

表1　割付患者数

	手術群	放射線群	計
千葉大学	12	14	26
国立がんセンター	10	10	20
大阪成人病センター	9	10	19
日本大学	7	7	14
京都大学	6	7	13
四国がんセンター	2	1	3
計	46	49	95

ール2燐酸による8週間の内分泌療法の後に，無作為割付により根治的手術または放射線照射を施行した。手術群では骨盤リンパ節郭清および根治的前立腺摘除術を行った。放射線群では全骨盤への40～50Gyの照射の後に前立腺部へ20Gyのブースト照射を施行した。その後も精巣摘除術あるいはLHRHアゴニストを主とした内分泌療法を継続した（図1）。2003年に予後の再調査および解析を行った。PSA（prostate specific antigen）再発は信頼できる濃度での血清PSAの3連続上昇と定義した。臨床的再発は局所の再増大または遠隔転移の出現と定義した。

Ⅱ．結　果

1989～93年に6施設から100例が登録され，5例は割付け前に除外された。評価可能患者95例のうち，46例が手術群に49例が放射線群に割付されて治療をうけた（表1）。年齢，病期，分化度，治療前PSA値に関して，両群間に有意な差はなかった。観察期間の中央値は102ヵ月（範囲6～178ヵ月）であった。10年におけるPSA非再発率，臨床的非再発率，疾患特異生存率および全生存率は，いずれも手術群において良好であったが，その差は有意ではなかった（表2）。ほぼ全例において勃起障害を認めた。尿失禁の頻度は手術群で有意に高かった。それ以外の晩期有害事象に稀であり，両群間に有意差はなかった（図2）。

表2　10年治療成績の比較

	手術群(%)	放射線群(%)	p値
PSA非再発率	76.2	71.1	0.25
臨床的非再発率	83.5	66.1	0.14
疾患特異生存率	85.7	77.1	0.06
全生存率	67.9	60.9	0.30

Ⅲ．考　案

1997年に行った調査解析では，観察期間の中央値は58.5ヵ月で，手術群の方が放射線群と比較して有意に予後良好であった（5年疾患特異生存率：96.6％対84.6％，p=0.024）[4]。今回の検討では，手術群の成績が良好であったものの統計学的に有意な差は認められなかった。この理由としては，局所進行癌における長期予後は内分泌療法の感受性に主に依存するため，観察期間を延長すると両治療群間の差が少なくなるためかもしれない。

高リスク前立腺癌に対して放射線外部照射を施行する場合には，内分泌療法を併用することで有意な予後改善効果が報告されている[5,6]。一方，根治手術に関しては，術前内分泌療法の臨床的有用性は証明されていないが[7]，リンパ節転移陽性例に対する術後内分泌療法は有意に生存率を向上させることが報告された[8]。

今回の検討では，尿失禁の頻度が手術群で多か

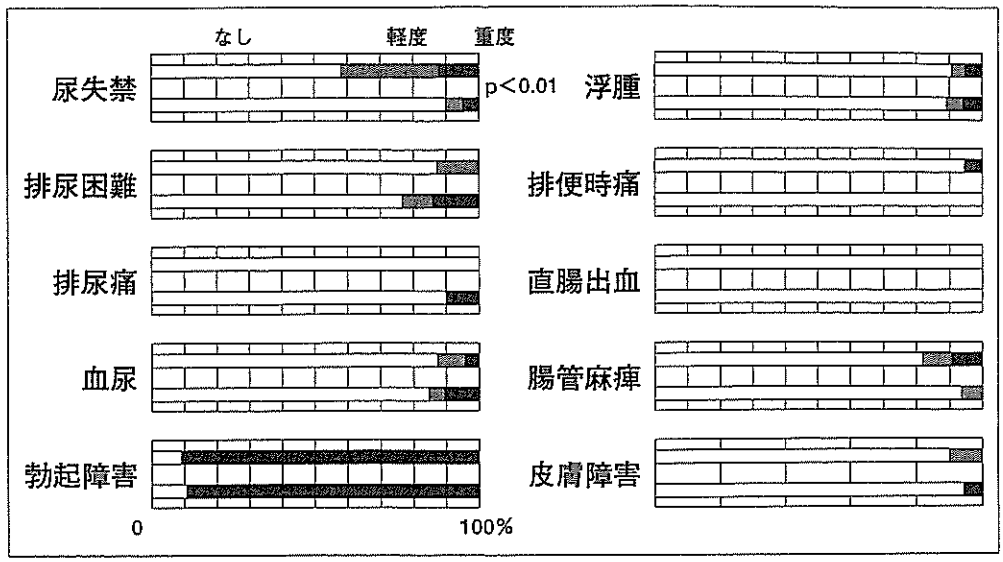

図2　晩期有害事象（約10年後）
上段：手術群
下段：放射線群

った。これは，局所進行癌を対象としたためとも考えられるが，手術手技の工夫により解決可能であろう。また，今回用いた照射線量は現在推奨されているレベルより低く，より高線量を照射すれば放射線群の治療成績の向上が期待される。今後，手術手技および照射方法の改善により，有害事象の少ない効果的な治療法を確立することが望まれる。

まとめ

局所進行前立腺癌に対する治療法として，根治的前立腺摘除術＋内分泌療法および放射線外部照射＋内分泌療法の両者とも，比較的優れた長期成績を示した。照射線量として60～70Gyは不十分である可能性が示唆された。

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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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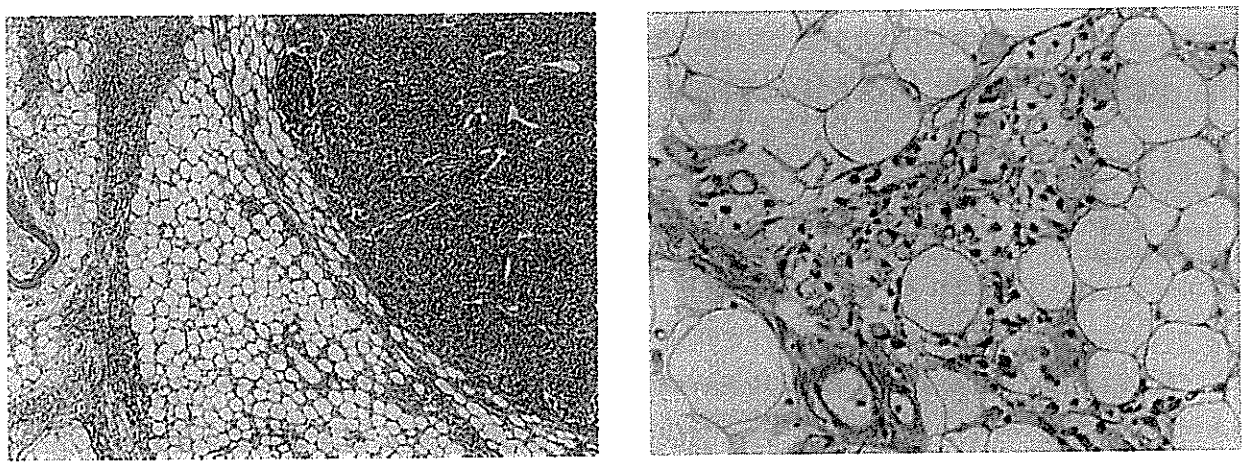
Introduction

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

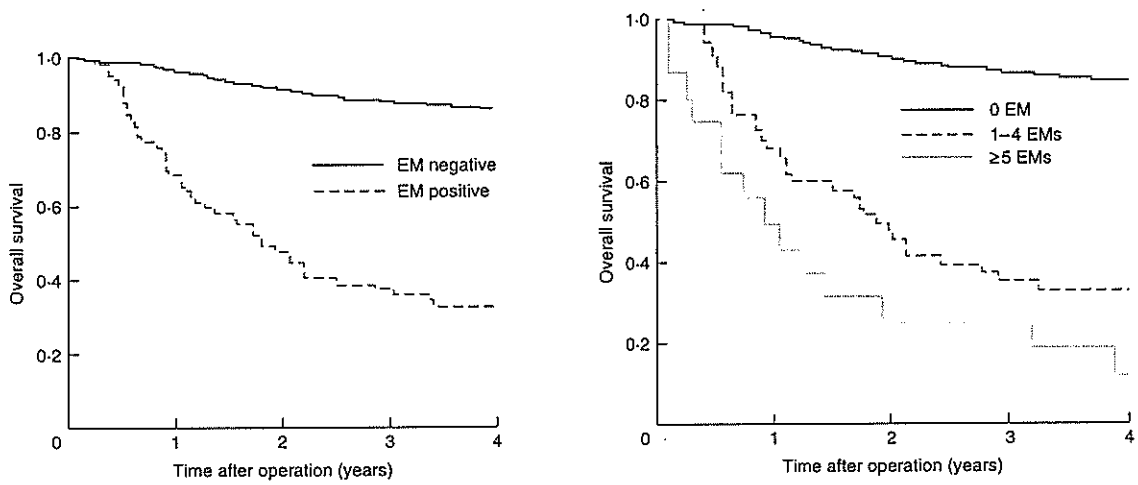


Fig. 2 Overall survival curves after curative resection **a** in patients with or without extranodal metastasis (EM) ($P < 0{\cdot}001$, log rank test) and **b** in patients grouped according to the number of EMs ($P < 0{\cdot}001$)

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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Favorable Indications for Hepatectomy in Patients With Liver Metastasis From Gastric Cancer

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Background: The prognosis of patients with liver metastasis from gastric cancer (LMGC) is dismal. The purpose of this study was to review our recent outcomes of hepatectomy for LMGC and to determine the suitable candidates for surgery.
Study Design: The outcomes of 37 patients with LMGC who underwent hepatectomy between 1990 and 2005 were assessed. No extrahepatic distant metastasis and feasibility of macroscopic curative resection were requisite indications for surgery. The prognostic values of clinicopathological factors were assessed by univariate and multivariate analyses.
Results: There was no in-hospital mortality. The median survival time and overall 5-year survival rate after hepatectomy of the patients with LMGC were 31 months and 11%, respectively. Intrahepatic recurrence following hepatectomy was found in 23 patients (62%). Variables independently associated with poor survival were bilobar metastasis ($P = 0.002$, CI = 1.9–16.3) and a maximum tumor diameter of ≥ 4 cm ($P = 0.006$, CI = 1.4–7.7). The depth of the primary tumor and the timing of metastasis were not associated with survival.
Conclusions: Surgical resection for LMGC may be indicated in patients with unilobar metastasis and/or tumors less than 4 cm in diameter. Synchronous metastasis is not a contraindication for hepatectomy.
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KEY WORDS: **liver metastasis; gastric cancer; hepatectomy; surgical indication**

INTRODUCTION

Liver metastasis can be found in 5–9% of patients with gastric cancer [1–3]. Surgical resection of liver metastasis from gastric cancer (LMGC) is rarely indicated, because LMGC is often associated with extrahepatic disease, such as peritoneal dissemination, lymph node metastasis, and direct cancer invasion of other organs [1]. Most of the patients with LMGC are thus treated by systemic administration or hepatic arterial infusion of 5-FU, adriamycin, mitomycin C (MMC), cisplatin, and/or S-1 [3–9] (Table I). The response rates and median overall survival time of patients treated with chemotherapeutic regimens have been reported to be 25–73% and 7–15 months, respectively, and the long-term survival is dismal. Therefore, curative surgical resection may bring some hope of long-term survival. Several authors have reported on their limited experiences of surgical resection of the metastatic tumors in selected patients of LMGC, with the 5-year survival rates ranging from 0–38% [1–3,10–17]. It has been reported that the stage of the primary gastric cancer [10,14], number of liver metastases [2,11,16], timing of hepatectomy [13,14,16], and surgical margin [11,13] would be the significant prognostic factors. To the best of

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TABLE I. Review of Surgical and Non-Surgical Treatments of Liver Metastasis From Gastric Cancer

Author	Year	Number of patients	Method of treatment (regimen, method of administration)	Response rate (%)	Median survival time (M)	1-year survival (%)	5-year survival (%)
Chemotherapy for LMGC							
Okuyama [3]	1985	21	5FU, MMC	NA	5	10	
Arai [4]	1990	30	FAM, HAI	73	15	NA	
Kim [5]	1993	33	FP, IV	51	9	NA	
Vanhoefer [6]	2000	165	ELF, FP, FAM	9–20	7	NA	
Koizumi [7]	2000	28	S1, oral	43	(7)	(36)	
Takahashi [8]	2003	10	S1, oral	30	(14)	(50)	
Tsujitani [9]	2003	6	S1+CDDP	50	NA	NA	
Hepatectomy for LMGC							
Koga [1]	1980	9	Hepatectomy + MMC[a]		6		NA
Okuyama [3]	1985	9	Hepatectomy+5FU, MMC		24		NA
Ochiai [10]	1994	21	Hepatectomy		19		NA
Miyazaki [11]	1997	21	Hepatectomy		NA		NA
Elias [12]	1998	11	Hepatectomy		NA		20
Ambiru [13]	2001	40	Hepatectomy + 5FU, aclarubicin[a]		12		18
Imamura [14]	2001	17	Hepatectomy		12		0
Saiura [15]	2002	10	Hepatectomy + 5FU[a]		25		20
Okano [16]	2002	19	Hepatectomy		21		34
Sakamoto [2]	2002	22	Hepatectomy		21		38
Shirabe [17]	2003	36	Hepatectomy		NA		26

LMGC, liver metastasis of gastric cancer; M, months; FAM, 5-fluorouracil + adriamycin + mitomycin C; HAI, hepatic artery infusion; FP, 5-fluorouracil + cisplatin; IV, intravenous administration; ELF, etoposide + folinic acid + 5-fluorouracil (), results including extrahepatic metastasis or recurrence; CDDP, cisplatin; MMC, mitomycin C; 5FU, 5-fluorouracil; NA, not available.
[a]Adjuvant chemotherapy.

our knowledge, however, only two reports have included more than 35 patients, therefore, the most favorable indications for hepatectomy in patients with LMGC still remain unclear.

We previously reported our initial experience of hepatectomy in 21 patients with LMGC between 1985–1992 [10]. Here, we review the outcomes of surgical resection in patients with LMGC conducted by us between 1990 and 2005, with the objective of reassessing the appropriate indications for this surgery.

PATIENTS AND METHODS

Between 1990 and 2005, 5,209 patients underwent gastrectomy for gastric adenocarcinoma at the Division of Gastric Surgery, National Cancer Center Hospital. Of these, 2.2% had synchronous liver metastases and 1.3% developed metachronous liver metastases after resection of the primary gastric cancer. Of these patients with liver metastasis, 37 (29 males and 8 females; median age, 64 years; age range, 39–76 years), accounting for one-fifth of all the patients with LMGC, underwent hepatectomy as curative treatment for the metastatic gastric adenocarcinomas. Although some of the patients were overlapped with our previous report [10], we collected our data from 1990, because the safety of hepatectomy procedure was established in 1990s and we need to analyze data of relatively large number of patients. We have used the following criteria as indications for hepatic resection in our cases of LMGC: (1) absence of extrahepatic distant metastases such as peritoneal dissemination or distant lymph node metastasis, and (2) feasibility of macroscopically curative resection. Based on the results of our previous study [10], we considered (1) the presence of serosal invasion by the primary gastric cancer and (2) presence of lymphatic or venous invasion by the primary tumor in cases with metachronous tumors, as unfavorable indications for surgery, however, they were not contraindications.

Medical records of the hepatectomized 37 patients were collected, and the prognostic factors for better survival were assessed using univariate and multivariate analyses.

Statistical Analysis

The primary end-point was survival, and the overall survival rates were estimated using the Kaplan–Meier method. The log-rank test was used to compare significant differences between subgroups using a univariate analysis. A multivariate stepwise Cox's regression analysis (backward elimination method) was performed to identify factors that were independently associated with mortality. Statistical significance was defined as a P-value of less than 0.05. The statistical analyses were performed using a statistical analysis software package

(SPSS 9.0, SPSS, Inc., Chicago, IL). The following clinicopathologic factors were analyzed by comparing subgroups of patients divided according to each variable: age ($<65, \geq 65$), sex, status of serosal, venous and lymphatic invasion and histologic differentiation of the primary tumor, status of lymph node metastasis, clinical stage of the primary tumor, temporal relationship of metastases with the primary disease (synchronous or metachronous), serum carcinoembryonic antigen (CEA) ($<5, \geq 5$ ng/ml) and carbohydrate antigen 19–9 (CA19-9) levels (<37, ≥ 37 IU/L) before hepatectomy, number of metastatic tumors, intrahepatic distribution, size of the liver metastases ($<4, \geq 4$ cm), hepatectomy procedure (anatomical, non-anatomical resection), extent of differentiation of the metastatic tumor, surgical margin, blood transfusion, and administration of adjuvant chemotherapy. Multivariate analysis was performed using the variables found to be significant based on the results of the univariate analysis.

RESULTS

The location of the primary gastric cancer was the cardia in 6 patients, fundus in 17 patients, and antrum in 14 patients. The depth of the tumor was T1 in 6 patients, T2 in 19 patients, T3 in 11 patients, and T4 in 1 patient [18]. The surgical procedures used for the primary tumors included distal gastrectomy in 26 patients, total gastrectomy with or without splenectomy in 9 patients, pylorus-preserving gastrectomy in 1 patient, and partial gastrectomy in 1 patient. The primary gastric tumor proved to be well to poorly differentiated adenocarcinoma of the stomach in all of the patients.

The median duration of hospitalization following gastrectomy was 19 (11–61) days. Of the 37 patients, 21 had a solitary tumor and 16 had multiple (2–12) tumors. The distribution of the tumors was unilobar in 30 patients and bilobar in 7 patients. The median maximum tumor diameter was 3.8 (0.6–8.7) cm. The hepatectomy procedure consisted of non-anatomic limited resections in 25 patients, segmentectomy in 7 patients, left hemihepatectomy in 3 patients, and right hemihepatectomy in 2 patients. Blood transfusion was required in 11 patients.

Chemotherapy after hepatectomy was administered in 6 patients using S-1 [7–9], cisplatin, 5-FU, and UFT at the discretion of each attending surgeons. After the hepatectomy, all the patients were followed up in the outpatient clinic every 3–4 months, annual measurements of the serum CEA and CA19-9 and annual CT scan were performed.

In-hospital and 30 day postoperative mortality was zero. There were two major complications; sick sinus syndrome in one patient and perforation of the colon in another patient. Minor complications included bile leakage, pancreatic fistula, and wound infection. The overall morbidity rate was 24%. The median duration of hospitalization following hepatectomy was 19 (9–189) days.

Microscopical curative resection was accomplished in 32 patients (86%). The median overall survival time of the patients was 31 months and the overall 5-year survival rate was 11%. Two patients survived for more than 5 years after the hepatectomy. Twenty-three patients out of the thirty-seven (62%) developed recurrence in the remaining liver, seven (19%) in the lung, and five (14%) in the lymph nodes, with an overall recurrence rate of 81% ($n=30$) during the follow-up period. None of the patients underwent a second hepatic resection for recurrent intrahepatic metastases, and systemic chemotherapy was administered in 20 out of the 30 patients with recurrent tumors. The first-line chemotherapeutic regimens for recurrence included CPT-11 + cisplatin in 4 patients, CPT-11 + MMC in 2 patients, methotrexate + 5-FU in 5 patients, 5-FU + cisplatin in 3 patients, paclitaxel in 2 patients, UFT + mitomycin C in 1 patient, UFT in 1 patient, 5-FU in 1 patient, and NK911 in 1 patient.

Univariate analysis revealed the following factors to be associated with poor survival: presence of venous invasion of the primary tumor ($P=0.02$); bilobar metastasis ($P=0.004$); tumor diameter ≥ 4 cm (Table I; Figs. 1 and 2). No survival difference was found between patients with and without serosal invasion, and between patients who underwent synchronous and metachronous hepatectomies. The results of the multivariate analysis (Table II) indicated that bilobar metastasis and the maximum tumor diameter (≥ 4 cm) were independently associated with poor survival ($P<0.003$ and $P<0.07$, respectively) (Table III).

DISCUSSION

The overall 5-year survival of the patients with LMGC was 11%, a relatively low survival rates as compares with previous reports, but still, may be acceptable [1–3,10–16]. We excluded patients with extrahepatic recurrences and performed hepatectomy in only 37 patients accounting for one-fifth of all the patients with LMGC (2.3 hepatectomies/year). Nonetheless, even with the relatively good patient selection, the survival rate after hepatectomy was rather unsatisfactory. Despite curative hepatectomy, we found that 62% of the patients developed intrahepatic recurrence. This high recurrence rate within 2 years of the surgery might suggest the presence of occult intrahepatic metastases even at the time of hepatectomy. Repeat hepatectomy was not conducted in our series, and patients with recurrence

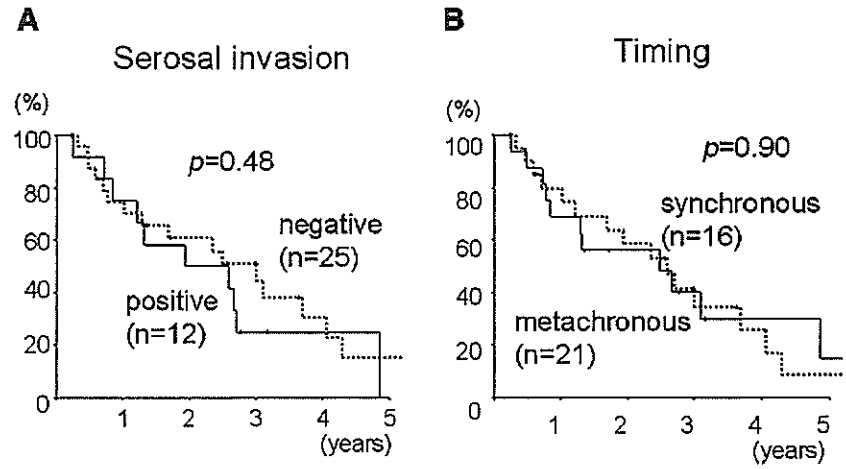

Fig. 1. Overall survivals of patients who underwent hepatectomy for liver metastasis of gastric cancer. A: No survival difference was found between patients with (solid line) and without (dotted line) serosal invasion by the primary gastric cancer. B: No survival difference was found between patients with synchronous metastasis who underwent hepatectomy with gastrectomy (solid line) and those with metachronous metastasis who underwent hepatectomy on a subsequent date (dotted line).

were administered systemic chemotherapy. These results suggest the extreme difficulty of obtaining surgical cure in patients with LMGC, and also the necessity of better patient selection and effective adjuvant chemotherapy in order to prolong the patients' survival. As the median overall survival time following hepatectomy in patients with multiple, bilobar metastasis or positive surgical margin was shorter than the median overall survival time of patients administered some effective chemotherapeutic regimens [4,8] (Table I), strict patient selection and informed consent from the patients would be mandatory.

None of the clinicopathological factors related to the primary gastric cancer were independent predictors of survival. Previously, Ochiai et al. [10] reported from our institute that (1) the absence of serosal invasion in all cases, and (2) the absence of lymphatic invasion or venous invasion in metachronous cases were favorable factors for better survival. These criteria affected to some extent, our indication for the selection of suitable candidates for hepatectomy, and 70% of the 37 patients had no serosal invasion. This selection bias might directly reduce the deaths associated with dissemination of the primary gastric cancer. In addition, the limited number of patients and/or the difference in this study period might explain the discrepant conclusions in the two series. The diagnostic accuracy of imaging

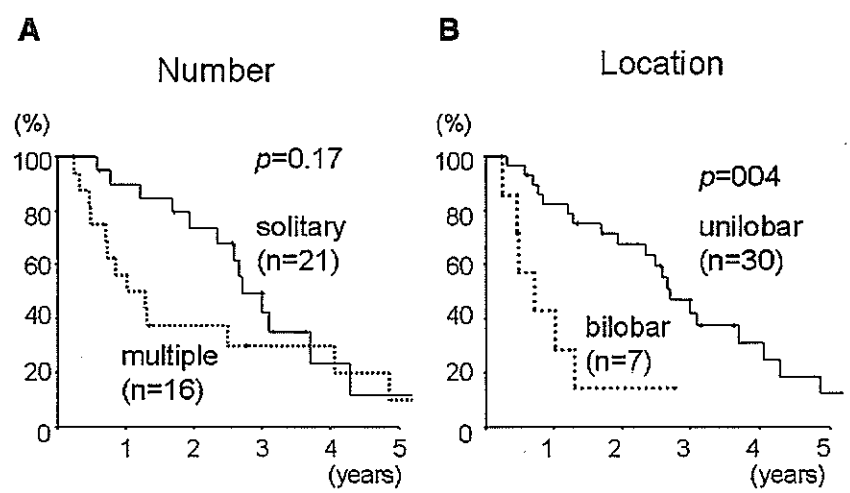

Fig. 2. Overall survivals of patients who underwent hepatectomy for liver metastasis of gastric cancer. A: No survival difference was found between patients with solitary (solid line) and multiple (dotted line) liver metastases. B: Survival of patients with unilobar metastasis (solid line) was significantly longer than that of those with bilobar metastasis (dotted line).

TABLE II. Clinicopathological Factors Associated With the Survival of Patients With Liver Metastasis From Gastric Cancer After Hepatectomy

Characteristic	Number of patients	Median survival time (months)	5-year survival rate (%)	*P*-value
Primary tumor				
Differentiation				
Well, pap	11	30	0	0.30
Mod, por	25	32	14	
Serosal invasion				
Absent	25	36	15	0.48
Present	12	23	0	
Venous invasion				
Absent	11	44	32	0.02
Present	26	28	0	
Lymphatic invasion				
Absent	9	44	0	0.08
Present	28	20	9	
Lymph node metastasis				
Absent	6	44	42	0.09
Present	31	28	6	
Clinical stage[a]				
Stage I, II	16	36	12	0.52
Stage III, IV	21	23	12	
Liver metastasis				
Temporal relationship				
Synchronous	16	30	15	0.90
Metachronous	21	31	9	
Tumor number				
Solitary	21	32	12	0.17
Multiple	16	12	10	
Intrahepatic distribution				
Unilobar	30	32	12	0.004
Bilobar	7	8	NA	
Tumor size				
<4 cm	19	37	29	0.02
≥4 cm	17	20	0	
Differentiation				
Well, pap	4	12	NA	0.31
Mod, por	26	32	14	
Portal vein invasion				
Absent	22	32	18	0.08
Present	13	28	0	
Surgical margin				
Negative	32	31	8	0.95
Positive	5	8	20	
Treatment				
Anatomical resection	11	31	15	0.81
Non-anatomical resection	26	32	8	
Blood transfusion during hepatectomy				
Not performed	26	31	26	0.30
Performed	11	16	0	
Adjuvant chemotherapy				
Not performed	31	32	12	0.37
Performed	6	28	NA	

NA, not available.
[a]Clinical stage was determined according to General Rules for Gastric Cancer Study, 1999.

studies has improved dramatically in the last two decades, which might make it easier to identify occult hepatic metastasis and contribute to modification of the patient selection criteria.

In the present study, patients with unilobar metastasis had a favorable prognosis. The first author (YS) previously reported, based on his experience in 22 patients at the Cancer Institute Hospital, another cancer center in

TABLE III. Risk Factors for Poor Survival After Hepatectomy Evaluated by a Multivariate Analysis Using Cox Proportional Hazard Model

Clinical variables	Odds ratio	95% C.I.	*P*-value
Bilobar metastasis	5.598	1.918–16.339	0.002
Tumor size ≥ 4 cm	3.295	1.413–7.687	0.006

C.I., confidence interval.

Tokyo, that the number of tumors in LMGC was an important factor influence the prognosis [2]. Considering the present results with this previous report, the number and distribution of tumors in LMGC might be significant prognostic factors.

Regarding the difference between synchronous and metachronous metastases, several authors have reported significantly better survival in patients with metachronous metastasis than in those with synchronous disease [13,16]. Neither the results of the present study nor the previous reports from the two cancer centers suggested that the timing of hepatectomy as a factor influencing the survival. We believe that synchronous metastasis is not a contraindication for hepatectomy, provided extrahepatic disease is absent.

Metachronous hepatectomy necessitates the dissection of adhesions between the pancreas, liver, and residual stomach to prepare for Pringle's maneuver. Especially, the upper part of the pancreas adheres to the inferior part of left liver following lymphadenectomy during gastrectomy for the primary tumor. Dissection of such severe adhesion is sometimes technically demanding for surgeons in comparison with hepatectomy for colorectal metastasis, in which minimal dissection of the upper abdominal organs is required. Therefore, hepatectomy should be performed with careful attention paid to the prevention of pancreatic leakage and injury to the bile duct and other adjacent organs.

We also encountered some patients who developed rapidly growing multiple hepatic metastases or peritoneal dissemination while waiting for surgery, who were then excluded. In order to exclude these cases with progressive disease, careful preoperative evaluation of hepatic/extrahepatic metastasis by repeated imaging studies will also be important.

In conclusion, we reviewed the outcomes of highly selected 37 patients who underwent hepatectomy for LMGC. Patients with unilobar LMGC, and/or metastatic tumors measuring < 4 cm in diameter, may be good candidates for a hepatectomy. Synchronous metastasis is not a contraindication for hepatectomy.

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Treatment Strategy for Locally Recurrent Rectal Cancer

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Review Article

Treatment Strategy for Locally Recurrent Rectal Cancer

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Despite radical surgery, up to 33% of patients with rectal cancer will develop locoregional relapse. The management of these patients is particularly challenging. Surgery is the mainstay of treatment for those with a mobile recurrence. However, the majority of patients develop recurrence involving the pelvic wall. In these patients, multimodality therapy including radical surgery and intraoperative radiotherapy have been reported with 5-year survival of up to 31% and local control rates of 50–71%. The most important factor for obtaining long-term local control and survival is R0 resection. Extended surgery such as abdomino-sacral resection has not been popular because of 5-year survival rates of 16–31%, and significant postoperative morbidity. Re-recurrence following surgery occurs locally and in the lung, and remains a significant problem. In surgical treatment for local recurrence, surgeon-related factors are crucial. A staging system using degree of fixation and other prognostic factors should be developed so that appropriate treatment modalities are applied to each case.

Key words: locally recurrent rectal cancer – multimodality therapy – extended surgery

INTRODUCTION

In patients who undergo radical surgery for rectal cancer, 4–33% develop locoregional relapse. Without treatment, these patients with locally recurrent rectal cancer (LRRC) have a median survival of ~8 months. If no treatment is given, they suffer from severe symptoms, especially pain, and their quality of life (QOL) becomes extremely poor (1–4). Nearly half of LRRCs are located in the pelvis without distant metastasis. The best treatment for LRRC in this setting is a complete resection of the recurrent tumor.

There are a number of different options for treating LRRC. There options are influenced by the nature of the LRRCs, which may present as a mobile recurrence or a huge mass occupying the pelvis.

In non-fixed recurrent tumors, complete resection can be achieved with limited surgery such as abdomino-perineal resection and the outcomes are relatively favorable.

When an LRRC grows within the narrow pelvis, it can easily invade the pelvic wall, appearing in the form of fixed recurrent tumor (FRT). If FRT involves only anterior structures, total pelvic exenteration achieves adequate margins. However, the majority of patients with LRRC present with dorsal and/or dorsolateral involvement of the pelvis. These patients present a particular challenge. Extensive surgery such as abdomino-sacral resection may be required. However, inappropriate surgical intervention in these patients may cause an iatrogenic cancer spread, leading to impaired QOL.

CONVENTIONAL TREATMENT

In patients with LRRC who are unsuitable for surgical intervention, chemoradation is the main therapeutic option available. The effect of radiotherapy depends on the tumor size and the total radiation dose given. A dose of 45 Gy provides good palliation of pain in 50–80% of patients (5), with low risk of toxicity to the small intestine. However, an anti-tumor effect that may achieve complete response or survival benefit cannot be expected at this dose. Another approach is to administer a dose of 50 Gy to the same radiation field used for the treatment of the primary rectal cancer. The radiation field is then reduced to include only the site of tumor recurrence and a total dose of 60–70 Gy is delivered to this site. However, external beam radiotherapy (EBRT) alone has not been shown to achieve significant survival benefit.

For this reason, the combination of radiotherapy and chemotherapy is usually employed. The rationale for combined therapy includes (i) enhancement of cytotoxicity

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using an antitumor agent and radiation, (ii) use of chemotherapy, which provides treatment of distant metastasis in addition to the local control of the tumor provided by radiotherapy and (iii) the potential to reduce the dosage of agents and therefore their toxicity by combining different treatment modalities without reducing the overall efficacy (6,7).

EBRT used alone or in combination with chemotherapy provides temporary symptomatic improvement in most patients. Median survival time is 14 months and time of local control is 5 months. Five-year survival rate in these patients is usually <5% (8).

Preoperative chemoradiation is used for primary rectal cancer to downstage the tumor and improve resectability. The same approach has also been used for LRRC. Rodel et al. (9) administered chemoradiotherapy preoperatively in 35 patients with LLRC using 5-FU (1000 mg/m^2/day). They reported that they achieved margin-free resections in 17 cases (61%). Other chemotherapy agents such as CPT-11 and Oxaliplatin are expected to play an important role in the management of these patients in the future (10).

MULTIMODALITY TREATMENT

Reports from some western centers suggest that improved local control and survival can be achieved in selected patients by the use of preoperative chemoradiotherapy, radical surgery and intraoperative radiotherapy (IORT) (11–22). This approach recognizes that satisfactory antitumor effect cannot be achieved by chemoradiation alone. The addition of IORT means that the maximum radiation dose possible can be delivered to the recurrent tumor. This has the potential to allow less extensive surgery to be undertaken.

One of the benefits of IORT is that it produces up to three times the biological effect produced by fractionated EBRT. In addition, IORT has the advantage of delivering radiation accurately to the tumor bed while displacing adjacent normal structures from the irradiation field. The use of IORT allows a reduction of the EBRT dose and so reduces toxicity of this modality. Mayo Clinic researchers reported a 3-year survival rate of 39% and a 5-year survival rate of 20% in 123 patients with LRRC who were treated with IORT and surgery (14). Mannaerts et al. (16,18) in the Netherlands used a preoperative radiotherapy dose of 50.4 Gy (30 Gy in patients who had received ratiotherapy) before surgery, during which they carried out IORT. The dose of IORT was determined by the R status of the resection. Patients who had undergone R0 resection (microscopically negative margins) were treated with a dose of 10 Gy, R1 resections (microscopically positive margins) with a dose of 15 Gy and R2 cases (macroscopically positive margins) with a dose of 17.5 Gy. Overall 3-year survival rate reached 58%. However, patients who had undergone R2 resection showed a worse prognosis in this series. Wiig et al. (19) reported a 5-year survival rate of 60% in patients given preoperative irradiation who had R0 resection. This does raise the question as to whether IORT is really necessary in cases with previous R0 resection, particularly as not all R0 cases in this series received IORT. It can be argued that a true R0 resection leaves no cancer cells to be eradicated by IORT. In clinical practice, however, because it is not always easy to differentiate fibrosis from recurrent cancer, some patients who undergo R0 resection may have residual disease and may benefit from IORT (20,21).

Abuchaibe et al. (12) and Bussieres et al. (15) have reported on patients with R2 resection given IORT but no postoperative EBRT. This strategy resulted in a poor outcome and suggests that additional EBRT is important in achieving local control. Irradiation of patients who have received radiotherapy previously has generally been avoided because of the fear of severe late radiation toxicity. Mohiuddin et al. (2,23) reported on 103 cases who received reirradiation and showed acceptable late toxicity (17% with chronic severe diarrhea, 15% with small bowel obstruction and 4% with fistula).

Despite the use of multimodality therapy, 5-year survival rates of patients with LRRC remain 22–31% and local control rates 50–71% (Table 1). IORT cannot be expected to compensate for R2 resection (13) and is itself associated with potential complications. The commonest side effects are ureteric stenosis and peripheral neuropathy. In a series of 123 cases at the Mayo Clinic (14), partial ureteric stenosis as a complication occurred in 6% of patients with 10% requiring insertion of ureteric stents. Peripheral neuropathy was observed in 16–34% of the patients.

Table 1. Outcome after multimodality therapy

Author	Year	No. of cases	Resection (%)	Surgery	5-YSR (%)	Re-local recurrence (%
Willet et al. (11)	1991	30			27	38
Magrini et al. (32)	1996	16	100	Extended	48 (2Y)	36
Bussieres et al. (15)	1996	73	57	Mixed	31	29
Valentini et al. (17)	1999	47	45	Limited	22	31
Wiig et al. (19)	2000	107	41	Limited	30	50
Mannaerts et al. (18)	2001	33	64	Mixed	60 (3Y)	27
Hahnloser et al. (21)	2003	304	100	Limited	25	

5-YSR: 5-year survival.