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# Introduction

Previous studies have shown that surgical resection produces good treatment results in patients with early gastric cancer (EGC), in both Japan and Western countries [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12]. However, recent results from long-term follow-up of a large number of patients who underwent gastric resection for EGC have not yet been fully evaluated. Rate of recurrence is reportedly low, and death from causes other than cancer recurrence is frequently observed in these patients [13, 14, 15, 16]. Reported long-term survival rates vary, due, in part, to differences in statistical methods between studies, as survival figures are influenced by the way deaths from causes other than recurrence are handled.

**Abstract** Background and aims: Recent results from long-term follow-up of a large number of patients who have undergone gastric resection for early gastric cancer (EGC) have not yet been fully evaluated. Patients and methods: A total of 848 patients who had undergone gastric resection for EGC (262 female, 586 male; mean age 58.0 years; range 20-86 years) were studied with respect to surgical technique, long-term survival and prognostic factors on the basis of current TNM classification. Results: Death related to recurrence occurred in only eight patients (0.9%). Hematogenous metastasis to the liver or bone represented the most common pattern of recurrence, developing in six of the eight recurrences (75%). The 5-year and 10-year cancer-related survival rates were

98.6% and 94.8%, respectively. The 5-year and 10-year overall survival rates were 95.2% and 85.0%, respectively. Lymph node metastasis represented an independent prognostic factor when analyzed on the basis of cancer-related survival. Conclusion: The present findings indicate that long-term survival of patients who undergo gastric resection for EGC is extremely good and that lymph node metastasis represents an independent prognostic factor when analyzed according to cancer-related survival. Future developments for the treatment of EGC are expected to improve quality of life for patients after gastric resection.

**Keywords** Early gastric cancer · Surgical treatment · Prognostic factor · Long-term survival

We present, herein, clinicopathological features, surgical techniques, survival figures and prognostic factors from long-term follow-up of a large number of patients who underwent gastric resection for EGC, including information regarding number of observed survivors and cause of death during the follow-up period. Based on the findings of the present study and other recent reports, we also discuss post-operative quality of life (QOL) for patients who undergo gastric resection for EGC.

# Survival after surgical treatment of early gastric cancer: surgical techniques and long-term survival

## **Patients and methods**

#### Patients

From June 1986 to May 1998, a total of 851 patients with EGC and no evidence of other malignancy underwent gastrectomy combined with lymphadenectomy at Kitasato University East Hospital, Japan. Of these, three deaths that were considered operation-related were excluded from the present analysis. The remaining 848 patients (262 female, 586 male; mean age 58.0 years; range 20–86 years) were enrolled in this study.

Clinicopathological factors were recorded, including type of gastrectomy, splenectomy, extent of lymphadenectomy, tumor size, location, macroscopic type, histopathological grading, depth of invasion and extent of lymph node metastasis. Among these factors, depth of invasion (Tis: carcinoma in situ, intra-epithelial tumor without invasion of lamina propria; or T1: tumor invasion of lamina propria or submucosa), extent of lymph node metastasis (N0: no regional lymph node metastasis; N1: metastasis in 1-6 regional nodes; N2: metastasis in 7-15 regional lymph nodes; N3: metastasis >15 regional nodes), distant metastasis (M0: no distant metastasis; M1: distant metastasis) and histopathological grading (G1: well differentiated; G2: moderately differentiated; G3: poorly differentiated) were determined according to TNM classifications [17]. For determination of TNM histopathological grading, papillary adenocarcinoma or well-differentiated tubular adenocarcinoma, as classified by the Japanese classification of gastric carcinoma (JCGC) [18], was considered G1; moderately differentiated tubular adenocarcinoma, classified by JCGC, was considered G2; signet ring cell carcinoma, poorly differentiated adenocarcinoma or mucinous carcinoma, classified by JCGC, was considered G3. In addition, extent of lymphadenectomy and macroscopic tumor type were reclassified according to the following guidelines, based on the JCGC. Limited lymphadenectomy was considered as incomplete dissection of second-tier nodes (D1 dissection), and extended lymphadenectomy as complete dissection of both first-tier and second-tier nodes (D2 dissection). Protruded and superficial elevated carcinomas were grouped together as elevated type, while superficial depressed carcinomas, excavated carcinomas and flat carcinomas were grouped together as depressed type. In the present patients, 91 (10.7%) displayed multiple simultaneous EGCs (85 double carcinomas, four triple carcinomas, two quadruple carcinomas). For such cases, the lesion that displayed the deepest level of invasion, or the largest diameter when multiple lesions had invaded to the same layer, was considered representative of all tumors.

#### Statistics

Postoperative course was reviewed for all patients and included patient records at outpatient clinics and cause of death in patients who had died during the follow-up period. Survival curves of all 848 patients were analyzed by Kaplan–Meier methods and log-rank tests. Median follow-up time for the 774 survivors was 77.7 months, and 566 survivors (73.1%) were followed  $\geq$ 60 months after surgery. Cox's proportional hazard model was used for multivariate analysis, and model selection was based on a forward stepwise procedure (adopted *P* value <0.05). Data were analyzed independently by either overall survival (cause of death not considered) or cancer-related survival (patients who died from causes other than recurrence were considered to be alive for the duration of the follow-up). Stat View software (version 5.0, SAS Institute, N.C., USA) was used for all statistical analyses, and values of *P*<0.05 were considered to be statistically significant.

#### Results

Clinicopathological features of all patients with EGC are shown in Table 1. Total gastrectomy was performed in 97 patients (11%), and splenectomy in 77 patients (9%).

Table 1 Clinicopathological features of 848 patients with early gastric cancer, and univariate analysis of prognostic factors

Factors	No. (%)	Overall survival rate (%) <sup>a</sup>			Cancer-related survival rate (%) <sup>b</sup>			
			5-Year	10-Year	Р	5-Year	10-Year	Р
Age (years)	<60	457 (54)	99.0	92.6	< 0.0001	99.5	97.7	0.7606
	$\geq 60$	358 (46)	90.6	76.9		98.9	98.9	
Gender	Female	262 (31)	96.9	90.2	0.0190	99.6	97.3	0.6593
	Male	586 (69)	94.4	82.6		99.1	98.8	
Operation	Total gastrectomy	97 (11)	88.9	85.7	0.2751	98.8	98.8	0.9813
-	Partial gastrectomy	751 (89)	96.0	84.5		99.3	98.1	
Splenectomy	Splenectomy	77 (9)	90.2	82.7	0.2745	98.6	98.6	0.7764
	None	771 (91)	95.7	85.2		99.3	98.1	
Lymphadenectomy	Extended	454 (54)	95.7	85.4	0.5178	99.1	97.7	0.3222
	Limited	394 (46)	94.6	84.3		99.4	99.4	
Tumor diameter (mm)	<30	490 (58)	95.7	88.9	0.0163	99.6	99.6	0.0750
	>30	358 (42)	94.5	80.6		98.8	96.8	
Main site of tumor	$\overline{\mathrm{Pr}}$ oximal third	117 (14)	90.8	81.2	0.0594	100	100	0.2437
	Middle or distal third	731 (86)	95.9	85.6		99.1	97.9	
Macroscopic type	Elevated	170 (20)	90.1	77.1	0.0010	98.0	98.0	0.1806
I DI	Depressed	678 (80)	96.4	87.0		99.5	98.3	
Histopathological grading	G1 or G2	464 (55)	93.9	80.2	0.0100	99.1	99.1	0.8163
1 6 6 6	G3	384 (45)	96.7	91.6		99.5	97.1	
Depth of invasion	Tis	509 (60)	96.6	90.4	0.0008	99.8	99.5	0.0411
L	T1	339 (40)	93.0	77.4		98.4	96.3	
Lymph node metastasis	Positive	69 (8)	89.0	66.5	0.0027	96.9	87.2	0.0021
J I	Negative	779 (92)	95.7	86.8		99.4	99.2	

<sup>a</sup> Cause of death was not considered

<sup>b</sup> Patients who died from causes other than recurrence were considered to be alive for the duration of follow-up

**Table 2** Cause of death in 70patients who died within 10years of gastric resection

Cause of death	No. (%)	Survival time (months), range (average)
Malignancy in other organ	19 (27)	2–117 (67.1)
Respiratory disease	11 (16)	4–97 (50.6)
Recurrence	8 (11)	11–117 (38.1)
Intestinal obstruction	4 (6)	45–108 (75.0)
Heart disease	3 (4)	23-48 (32.7)
Carcinoma of gastric remnant	3 (4)	80-106 (94.7)
Cerebrovascular disease	3 (4)	55-62 (57.3)
Renal failure	1 (1)	26
Suicide	1 (1)	2
Unknown	17 (24)	4-96 (58.5)

 Table 3 Clinicopathological findings in eight patients who died from recurrence

No.	Age (years)	Gender	Tumor diameter (mm)	Main area of tumor	Macro- scopic type	Histopatho- logical grading	Depth of invasion	Nodal status (TNM)	Cause of death	Survival time (months)
1	66	М	35	Middle third	Depressed	G3	Tis	N0	Hematogenous (liver)	15
2	33	М	26	Distal third	Elevated	G1	T1	N0	Hematogenous (liver)	15
3 <sup>a</sup>	73	Μ	50	Distal third	Elevated	G2	T1	M1	Lymphatics	11
4	81	М	40	Distal third	Elevated	G1	T1	N0	Peritoneal dissemination	21
5	54	М	30	Distal third	Depressed	G3	Tis	N0	Hematogenous (bone)	67
6 <sup>b</sup>	78	М	70	Middle third	Depressed	G1	T1	N0	Hematogenous (liver)	35
7	44	F	8	Middle third	Depressed	G3	T1	N1	Hematogenous (bone) Lymphatics	24
8	46	F	55	Middle third	Depressed	G3	T1	N2	Hematogenous (bone), Peritoneal dissemination	117

<sup>a</sup> Patient had para-aortic lymph node metastasis at time of surgery

<sup>b</sup> Patient had liver metastasis at time of surgery

Extended lymphadenectomy was performed in 454 patients (54%). A total of 25,960 lymph nodes (mean 30.6 nodes/patient; range 1-136 nodes/patient) were dissected, and metastasis was histologically identified in 166 lymph nodes (0.6% of dissected nodes; mean 2.4 metastatic nodes/patient with lymph node metastasis; range 1-22metastatic nodes/patient with lymph node metastasis). A total of 490 tumors (58%) was <30 mm in diameter; 731 (86%) were located in the distal two-thirds of the stomach, and 170 (20%) were elevated type. A histological diagnosis of G1 or G2 was made in 464 cases (55%) (340 G1 tumors, 124 G2 tumors), while 384 tumors (45%) were classified as G3, 509 tumors (60%) as Tis and 339 tumors (40%) as T1. One patient had lymph node metastasis beyond regional nodes (M1), and another patient had liver metastasis (M1) at the time of gastrectomy. Except for these patients, curative resection was performed for all patients. Lymph node metastasis was seen in 69 patients (8%; 62 patients with N1 tumor; two patients with N2; one patient with N3; one patient with metastasis to distant nodes (M1); three unclassified patients). Stage grouping could not be classified by TNM in seven patients, as four patients had Tis tumors and lymph node metastasis, and  $\geq$ 15 regional nodes were not dissected in another three patients with lymph node metastasis. Consequently, 505 patients were classified as stage 0, 273 as stage IA, 58 as stage IB, two as stage II, and three as stage IV, according to TNM classifications.

Death within 10 years after gastrectomy was observed in 70 patients. Table 2 shows cause of death in these patients. Death related to recurrence was found in only eight patients (11%), and survival time in patients who died from recurrence ranged between 11 and 117 months (mean 38.1 months). Most common cause of death after surgical resection was secondary malignancy in another organ (19 patients, 27%), followed by unknown cause (17 patients, 24%) and respiratory disease (11 patients, 16%). Table 3 shows clinicopathological findings for the eight patients who died from recurrence. Death related to recurrence was found not only in patients with T1 tumor, but also in patients with Tis tumor. Hematogenous metastasis to the liver or bone represented the most

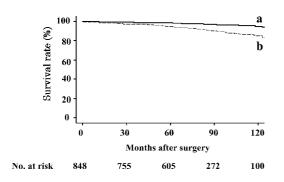


Fig. 1 Survival curves for 848 patients with early gastric cancer who underwent surgical resection. Curve a the 5-year and 10-year overall survival rates were 95.2% and 85.0%, respectively. Curve b the 5-year and 10-year cancer related survival rates were 98.6% and 94.8%, respectively. The number of patients eligible for analysis at each point is given

common pattern of recurrence and was found in six of the patients (75%) who died from recurrence.

Figure 1 shows survival curves for the 848 patients who underwent gastrectomy for EGC. The 5-year and-10 year overall survival rates were 95.2% and 85.0%, respectively. The 5-year and-10 year cancer-related survival rates were 98.6% and 94.8%, respectively. Table 1 also shows results of univariate analysis of prognostic factors in patients who underwent gastrectomy for EGC. When analyzed using overall survival, significant differences in survival rate were found with respect to age (P<0.0001), gender (P=0.0190), tumor size (P=0.0163), macroscopic type (P=0.0010), histopathological grading (P=0.0100), depth of invasion (P=0.0008) and lymph node metastasis (P=0.0027). When analyzed using cancer-related survival, significant differences in survival rate were found with respect to depth of invasion (P=0.0411) and lymph node metastasis (P=0.0021).

All 11 factors listed in Table 1 were examined by multivariate analysis using Cox's hazard model. The results are shown in Tables 4 and 5. Multivariate analysis indicated that age (P<0.0001; relative risk 0.308), gender (P=0.0449; relative risk 0.059), tumor diameter (P=0.0361; relative risk 0.608), macroscopic type (P=0.0384; relative risk 1.664) and depth of invasion (P=0.0188; relative risk 1.747) represented independent prognostic factors when analyzed on the basis of overall survival. Only lymph node metastasis represented an independent prognostic factor (P=0.0081; relative risk 6.908) when analyzed on the basis of cancer-related survival.

## Discussion

Post-operative recurrence has been reported as being relatively rare, occurring in 1.4-6.5% of patients with EGC [9, 14, 15, 16]. In the present study, death from recurrence was observed in only eight patients (0.9%) during the follow-up period. The most common pattern of recurrence was blood-borne metastasis, and prognosis of patients with recurrence was very poor, confirming previous reports on recurrence from EGC [9, 13, 14, 15, 16]. Most deaths were from unrelated causes, and death due to secondary malignancy in another organ was common, as reported elsewhere [13, 14, 15, 16]. These findings indicate that post-operative follow-up of other organs in patients who undergo gastric resection for EGC seems to be important for improving prognosis.

Previous studies have reported that the 5-year and 10year overall survival rates are 70.0-82.8% and 70.4-77.3%, respectively [2, 6, 8], and that 5-year and 10-year cancer-related survival rates are 91.7-98.3% and 87.8-95.2%, respectively [1, 2, 4, 6, 14, 19]. The present results also showed excellent survival rates (5-year and 10-year

 
 Table 4
 Multivariate analysis
 Factor Р SE Regression coefficient Relative risk Cox's hazard model based on -1.1790.308 <60 < 0.0001 0.268 Age >60Female 0.0449 0.559 Gender 0.290 -0.581Male Tumor diameter (mm) <30 0.0361 0.237 -0.4890.608 >30 0.0384 Macroscopic type Elevated 0.246 0.509 1.664 Depressed Depth of invasion 0.0188 0.238 0.558 1.747 Tis **T**1

 
 Table 5
 Multivariate analysis
 of prognostic factors using Cox's hazard model based on cancer-related survival (SE standard error)

of prognostic factors using

overall survival (SE standard

error)

Factor		Р	SE	Regression coefficient	Relative risk
Lymph node metastasis	Positive Negative	0.0081	0.730	1.933	6.908

overall survival rates: 95.2% and 85.0%; 5-year and 10year cancer-related survival rates: 98.6% and 94.8%). Moreover, Farley et al. [2] demonstrated that the overall survival rate of patients with EGC was equivalent to that of an age-matched and gender-matched control population. These findings indicate that long-term survival of patients who undergo gastric resection is extremely good when analyzed according to cancer-related survival.

Using univariate analysis, several authors have identified lymph node metastasis [1, 4, 6, 7, 8, 14], macroscopic type [9], tumor size [6, 7, 9, 14], depth of invasion [3, 6, 7, 8, 9], age [2, 8, 14], lymph node dissection [4], DNA ploidy status [2], Eastern Cooperative Oncology Group (ECOG) score [2] and histological type [14], as important prognostic factors in patients who undergo gastric resection for EGC. In the present study, significant differences in survival rate were found with respect to age, gender, tumor size, macroscopic type, histological grading, depth of invasion and lymph node metastasis, when analyzed using overall survival. Significant differences were found with respect to lymph node metastasis and depth of invasion when analyzed using cancer-related survival. Previous multivariate analyses have demonstrated that depth of invasion [6], lymph node metastasis [4, 6, 11, 14], histological type [8, 11, 14], tumor size [6], lymph node dissection [4], DNA ploidy status [2], ECOG score [2] and age [8, 11], are independent prognostic factors that influence survival. In the present study, age, gender, tumor diameter and macroscopic type represented independent prognostic factors when analyzed on the basis of overall survival. However, only lymph node metastasis was an independent prognostic factor when analyzed on the basis of cancer-related survival. Treatment factors, including type of gastrectomy, splenectomy and lymph node dissection, were not found to be important factors influencing survival under either univariate or multivariate analysis. Comparison of results from previous studies and the present investigation with regard to prognostic factors is difficult, due to differences in statistical methods and patient populations. However, the present findings indicate that age is the most important factor when analyzed by overall survival, and that lymph node metastasis is an independent prognostic factor when analyzed by cancer-related survival.

Metastasis to the regional nodes is found in 9.1–20.1% of patients who undergo gastrectomy with lymph node dissection for EGC [1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11]. Treatment results for EGC patients with lymph node metastasis are reportedly worse than for patients without lymph node metastasis [3, 6, 7, 8, 9]. Previous reports have demonstrated that most patients with lymph node metastasis are also curable by radical surgery, suggesting that metastasis to regional lymph nodes can be managed locally in this carcinoma [1, 3, 5, 6, 7, 8, 9, 10, 20]. However, the optimal extent of lymph node dissection for EGC remains controversial [4, 7, 12, 19, 21, 22, 23, 24, 25, 26]. Low incidence of lymph node metastasis and recurrence in EGC has led us to consider post-operative QOL by avoiding radical surgery. Recently, greater efforts have been made to improve post-operative QOL for patients with EGC by reducing the extent of gastrectomy (wedge resection, segmental resection) [27, 28, 29, 30], preserving the vagal nerve [28, 30, 31], conducting reconstruction with jejunal pouch interposition [31, 32, 33], and reducing abdominal wall destruction by using laparoscopic surgery [27, 34, 35]. Further developments for the treatment of EGC in these fields are expected to improve QOL after gastric resection in the future.

In conclusion, the findings of the present study indicate that long-term survival of patients who undergo gastric resection for EGC is extremely good, and that lymph node metastasis represents an independent prognostic factor when analyzed according to cancer-related survival. Future developments for the treatment of EGC are expected to improve QOL after gastric resection.

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