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Original article

Prognostic factors in patients with advanced gastric cancer with macroscopic invasion to adjacent organs treated with radical surgery

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Abstract

Background. **The prognosis of patients with gastric cancer with invasion to adjacent organs is poor. The prognostic factors of patients with advanced gastric cancer with macroscopic invasion to adjacent organs (T4) who were treated with radical surgery was determined in the present study.**

Methods. **A total of 86 consecutive patients with advanced gastric cancer who underwent radical (potentially curable) gastrectomy with combined resection of other organs for macroscopic invasion to adjacent organs during surgery, were investigated. The organs invaded macroscopically were the pancreas in 43 patients, mesocolon in 29, liver in 7, transverse colon in 5, adrenal gland in 3, spleen in 1, diaphragm in 1, and other organs in 5. The prognostic factors were evaluated by univariate and multivariate analysis.**

Results. **The cumulative 5-year survival rate of the patients treated by radical surgery with the combined resection of invaded organs was 35.0%. Multivariate analysis demonstrated that location of the tumor, lymph node metastasis, histological depth of invasion, and extent of lymph node dissection were significant prognostic factors in advanced gastric cancer patients treated by radical surgery with combined resection of adjacent organs for macroscopic invasion.**

Conclusion. **For patients with macroscopic T4 gastric cancer located in the middle- or lower-third of the stomach, aggressive resection of invaded adjacent organs with extended lymph node dissection should be performed to improve long-term outcome.**

Key words Gastric cancer · Macroscopic T4 · Radical surgery · Prognostic factors · Lymph node metastasis · Location of tumor · Extended lymph node dissection

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Introduction

The prognosis of patients with gastric cancer with invasion to adjacent organs (T4) was reported to be poor [1]. However, some patients treated by radical surgery can survive for a long time after surgery [2]. There were several studies [3–6] in which the resection of invaded organs with gastrectomy was recommended for T4 gastric cancer to achieve a better prognosis for these patients. However, the clinical efficacy of these radical operations has remained unclear.

In the present study, we investigated the prognostic factors of patients with gastric cancer with macroscopic invasion to adjacent organs (T4) who received potentially curable surgery.

Patients and methods

Of 2345 gastric cancer patients treated at Osaka Medical College Hospital between 1978 and 1995, 86 consecutive patients with advanced gastric cancer who underwent radical (potentially curable) gastrectomy with combined resection of other organs for macroscopic invasion to adjacent organs during surgery were enrolled in this study. They consisted of 59 men (average age, 59.0 years) and 27 women (average age, 58.5 years).

The organs invaded macroscopically were the pancreas in 43 patients, mesocolon in 29 patients, liver in 7 patients, transverse colon in 5 patients, adrenal gland in 3 patients, spleen in 1 patient, diaphragm in 1 patient, and other organs in 5 patients. In the present study, the omentum, esophagus, and the duodenum were excluded. Other intraoperative macroscopic findings were peritoneal metastasis to the adjacent peritoneum in 8 patients, hepatic metastasis limited to one lobe in 2 patients, and paraaortic lymph node metastasis in 9 patients. Total gastrectomy was carried out in 48 patients, distal gastrectomy in 31 patients, and proximal

gastrectomy in 7 patients. Combined resection of adjacent organs was performed in all patients, including the pancreas body, tail, and spleen in 31 patients, left upper abdominal evisceration [7] in 13 patients, and pancreatoduodenectomy in 6 patients.

Clinicopathological factors were evaluated in accordance with the *Japanese classification of gastric carcinoma* [8] and TNM classification [9]. Lymph node metastasis was graded according to the TNM classification, and all metastatic lymph nodes dissected in the abdominal cavity, including paraaortic lymph nodes, were graded (modified TNM classification); pN0, no lymph node metastasis, pN1 (1–6 metastatic lymph nodes), pN2 (7–15 metastatic lymph nodes), pN3 (16 or more metastatic lymph nodes). The cumulative survival rate was calculated by the Kaplan-Meier method, and prognostic significances were evaluated by the log-rank test for univariate analysis. Prognostic factors were also evaluated by multivariate analysis (Cox's proportional hazard model, stepwise selection) using SPSS software (SPSS, Chicago, IL, USA). A P value of <0.05 was considered significant.

Results

The cumulative 5-year survival rate of the patients treated by radical surgery with the combined resection of invaded organs was 35.0%.

Prognostic factors in patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion

Prognostic factors were evaluated in 86 patients treated by radical surgery with combined resection of the adjacent organs. Histological cancerous invasion in adjacent organs (pT4) was found in 46 patients (53.4%). However, in the remaining 40 patients, there was no histological invasion into adjacent organs (pT3 in 17 patients, pT2 in 9 patients).

Univariate analysis. Table 1 shows the findings using univariate analysis. Significant differences in prognosis were demonstrated for the following factors: macroscopic type (Fig. 1), location of tumor (Fig. 2), maximum dimension of tumor (Fig. 3), number of invaded organs (Fig. 4), extent of lymph node metastasis according to the Japanese classification (Fig. 5), and grade of lymph node metastasis according to the modified TNM classification (Fig. 6). In relation to the macroscopic type, the cumulative 5-year survival rate was 0% for type 1 ($n = 1$), 51.5% for type 2 ($n = 23$), 37.0% for type 3 ($n = 40$), 11.1% for type 4 ($n = 19$), and 33.3% for unclassified ($n = 3$). In relation to location of the tumor, there was no significant difference between the survival rate of patients with tumors located in the lower-third of the stomach (5-year survival, 52.9%; $n = 31$) and those with tumors located in the middle-third of the stomach (5-year survival, 58.7%; $n = 14$). Concerning lymph node metastasis, (according to the Japanese classification), the prognosis of patients with negative lymph node metastasis was significantly better than the prognosis of those with positive lymph node metastasis, but no significant difference was demonstrated between groups with different extents of lymph node metastasis (n1, n2, and n3 groups). The grade of lymph node metastasis according to the TNM classification was closely related to the prognosis of the patients.

In the 76 patients with one invaded organ, the cumulative 5-year survival rate in patients with invaded liver (66.7%; $n = 6$) was better than that in patients with invaded pancreas (32.4%; $n = 36$), invaded transverse colon or mesocolon (40.3%; $n = 29$), and invasion of

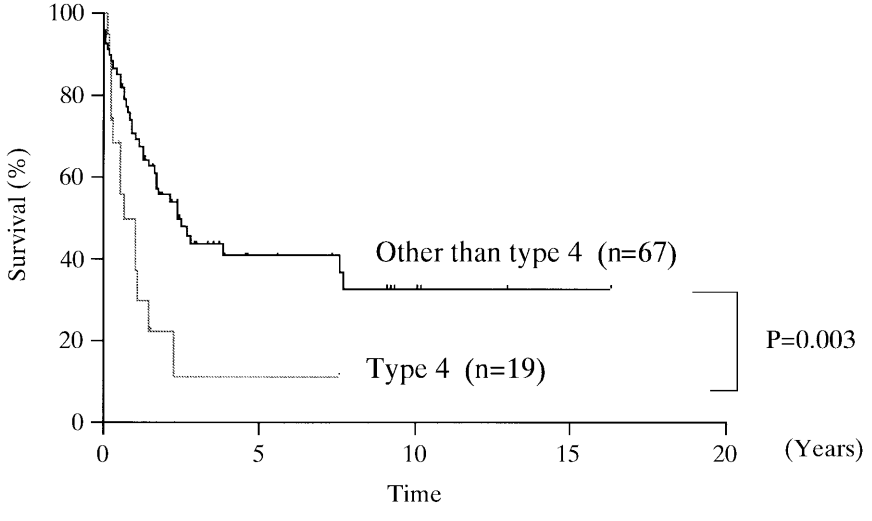

Fig. 1. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to macroscopic type). *Type 4*, Borrmann type 4

Table 1. Univariate analysis of prognostic factors in patients with advanced gastric cancer with combined resection of adjacent organs for macroscopic invasion

Variable	No. of patients	Cumulative 5-year survival rate	*P* value (log-rank test)
Sex			
Male	59	31.1	0.176
Female	27	43.5	
Macroscopic type			
Borrmann type 4	19	11.1	
Other than Borrmann type 4	67	40.8	0.003
Location of tumor			
Lower or middle-third of stomach	45	54.3	
Upper-third of stomach	26	20.9	0.041
Whole stomach	15	11.1	0.0004
Maximum dimension of tumor			
<90 mm	43	39.6	
>90 mm	43	31.2	0.035
No. of invaded organs			
One	76	38.6	
Two or more	10	10.0	0.0043
Histological depth of invasion			
pT2	9	46.7	
pT3	31	35.8	0.287
pT4	46	32.6	0.055
Histological type			
Differentiated	32	45.7	
Poorly differentiated	54	28.2	0.392
Extent of lymph node metastasis (JCGC)			
n0	13	74.0	
n1	27	34.2	0.026
n2	24	23.5	0.013
n3	22	27.8	0.015
Grade of lymph node metastasis TNM[a]			
pN0	13	74.0	
pN1	36	41.9	0.059
pN2	25	8.4	0.0008
pN3	12	18.5	0.014
Lymph node dissection			
D2	34	28.8	
D3[b]	52	48.1	0.346

pT2, Muscularis propria or subserosa; pT3, serosa; pT4, adjacent structures; JCGC, Japanese classification of gastric carcinoma
[a] TNM, Modified TNM classification
[b] D3 includes paraaortic lymph node dissection

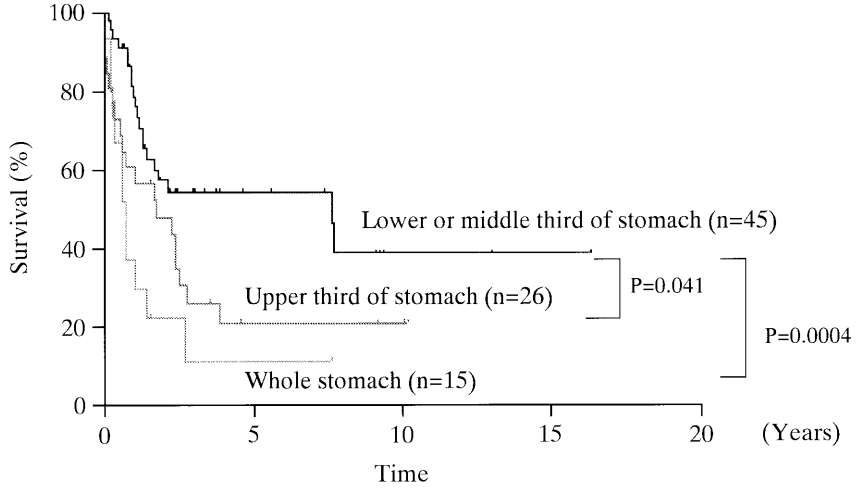

Fig. 2. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to location of tumor)

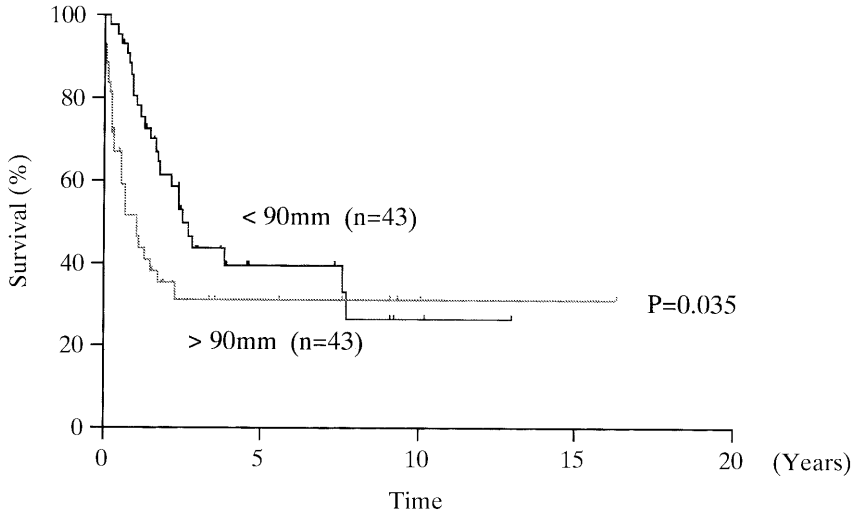

Fig. 3. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to maximum dimension of tumor)

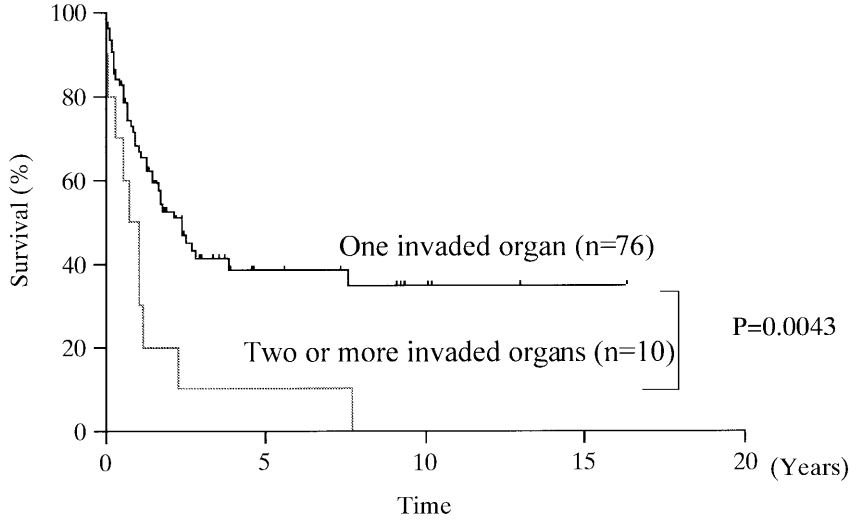

Fig. 4. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to number of invaded organs)

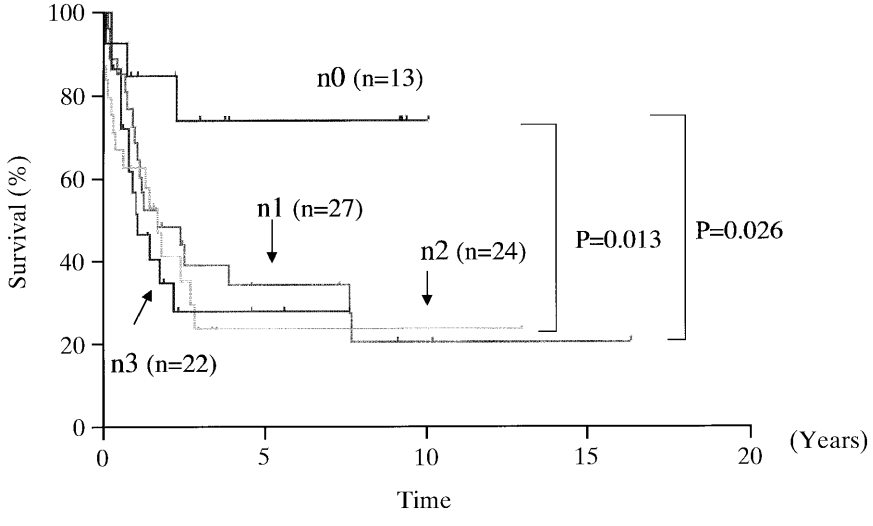

Fig. 5. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to extent of lymph node metastasis according to the Japanese classification)

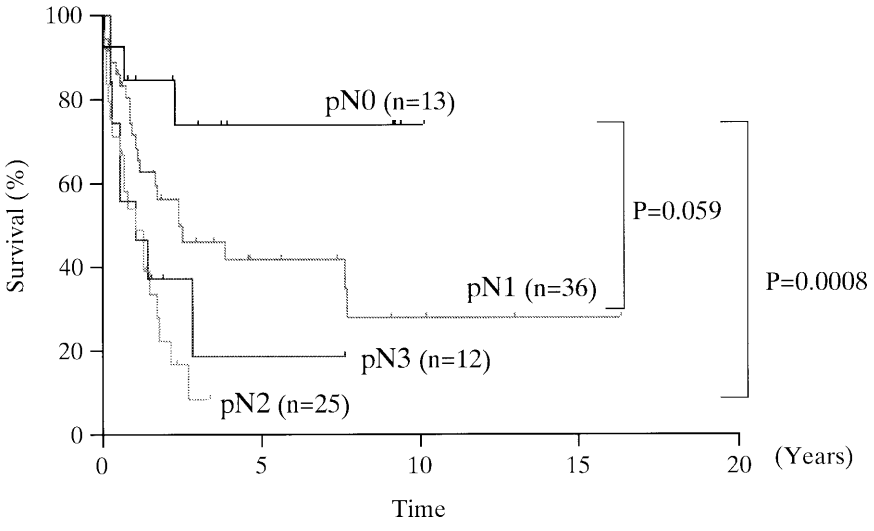

Fig. 6. Cumulative survival rate of 86 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to grade of lymph node metastasis according to modified TNM classification)

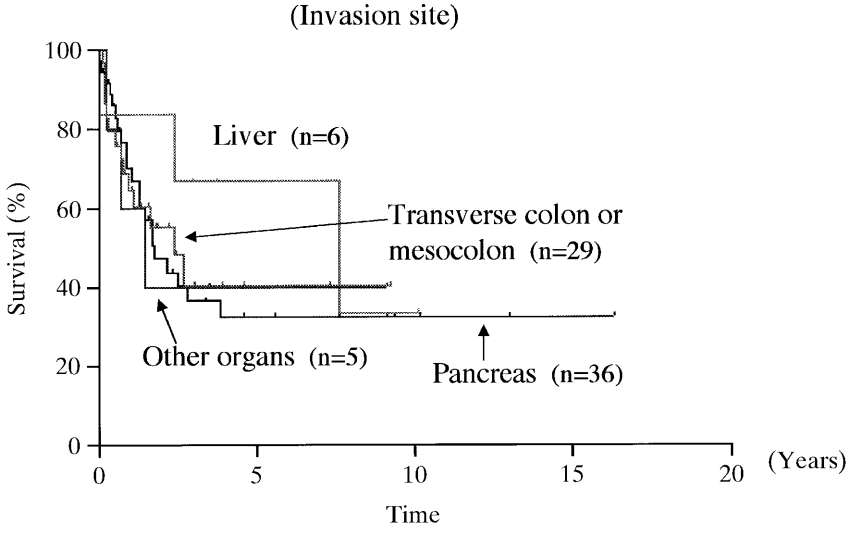

Fig. 7. Cumulative survival rate of 76 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for macroscopic invasion (in relation to invasion site in patients with one invaded organ)

other organs (40.0%; $n = 5$), but the differences were not significant (Fig. 7).

The 5-year cumulative survival rates according to the type of gastrectomy were 51.7% after distal gastrectomy ($n = 31$), 28.6% after proximal gastrectomy ($n = 7$), and 27.1 after total gastrectomy ($n = 48$), and there was no significant differences between these groups.

Multivariate analysis. To determine the prognostic factors of the patients with T4 gastric cancer treated by potentially curative surgery, the following items were examined as variables for multivariate analysis (Cox's proportional hazard model, stepwise selection method): sex (male, female), age (years), maximum dimension of tumor (Borrmann type 4, other types), location of tumor (lower- or middle-third of the stomach, upper-third of the stomach, whole stomach), maximum dimension of the tumor (less than 90 mm, 90 mm or more), number of invaded organs (one, two or more), histological depth of invasion (pT2, pT3, pT4), histological type (differentiated, poorly differentiated), extent of lymph node metastasis according to the Japanese classification (n0, n1, n2 or more), grade of lymph node metastasis according to the modified TNM classification (pN0, pN1, pN2 or more) and lymph node dissection (D2, D3).

When the extent of lymph node metastasis according to the Japanese classification was used, location of the tumor, followed by histological depth of invasion, lymph node dissection, and lymph node metastasis, were identified as significant prognostic factors (Table 2). When the grade of lymph node metastasis according to the modified TNM classification was used, lymph node metastasis, followed by histological depth of invasion, location of tumor, and lymph node dissection were identified as significant prognostic factors (Table

Table 2. Prognostic factors, determined by multivariate analysis (Cox's proportional hazard model, stepwise selection), in patients with advanced gastric cancer with combined resection of adjacent organs for macroscopic invasion[a]

Variable	Relative risk	95% CI	*P* value
Location of tumor			0.0015
Lower- or middle-third of the stomach	1		
Upper-third of the stomach	2.837	1.403–5.735	0.0037
Whole stomach	4.150	1.800–9.569	0.0008
Histological depth of invasion			0.0056
pT4	1		
pT3	0.374	1.189–0.741	0.5419
pT2	0.264	0.087–0.807	0.0194
Lymph node dissection			
D2	1		
D3	0.488	0.251–0.943	0.0328
Lymph node metastasis (JC)[a]			0.0504
n0			
n1, n2	3.238	0.940–11.150	0.0626
n3	4.511	1.327–15.334	0.0158

CI, Confidence interval
[a] Extent of lymph node metastasis was assessed using the Japanese classification (JC)

Table 3. Prognostic factors, determined by multivariate analysis (Cox's proportional hazard model, stepwise selection), in patients with advanced gastric cancer with combined resection of adjacent organs for macroscopic invasion[a]

Variable	Relative risk	95% CI	*P* value
Lymph node metastasis (TNM)[a]			0.0011
pN0	1		
pN1	2.733	0.806–9.265	0.1066
pN2, 3	7.811	2.189–27.888	0.0015
Histological depth of invasion			0.0013
pT4	1		
pT3	0.341	0.172–0.674	0.2823
pT2	0.182	0.057–0.587	0.0043
Location of tumor			0.0025
Lower- or middle-third of the stomach	1		
Upper-third of the stomach	3.323	1.640–6.730	0.0009
Whole stomach	2.700	1.133–6.432	0.0250
Lymph node dissection			
D2	1		
D3	0.494	0.259–0.945	0.0331

[a] Grade of lymph node metastasis was evaluated using modified TNM classification

3). Although similar prognostic factors were selected regardless of the classification of the lymph node metastasis, the grade of lymph node metastasis by the TNM classification was a stronger prognostic factor than the extent of lymph node metastasis by the Japanese classification.

Prognostic factors in patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for microscopic invasion

Multivariate analysis. Multivariate analysis was performed in 46 pT4 patients with radical surgery. When lymph node metastasis according to the Japanese classification was used, only location of tumor was detected as a significant prognostic factor (Table 4). When lymph node metastasis according to the modified TNM classification was used, lymph node metastasis (TNM classification) and location of tumor were identified as significant prognostic factors (Table 5).

The cumulative survival rates of patients with advanced gastric cancer with microscopic invasion to adjacent organs, in relation to the location of the tumor and the grade of lymph node metastasis according to the modified TNM classification, are shown in Figs. 8 and 9, respectively.

Table 4. Prognostic factors, determined by multivariate analysis (Cox's proportional hazard model, stepwise selection), in patients with advanced gastric cancer with combined resection of adjacent organs for microscopic invasion[a]

Variable	Relative risk	95% CI	*P* value
Location of tumor			0.0118
Lower- or middle-third of the stomach	1		
Upper-third of the stomach	2.558	1.043–6.276	0.0253
Whole stomach	3.833	1.496–9.816	0.0846

[a] Extent of lymph node metastasis was evaluated using the Japanese classification

Table 5. Prognostic factors, determined by multivariate analysis (Cox's proportional hazard model, stepwise selection), in patients with advanced gastric cancer with combined resection of adjacent organs for microscopic invasion[a]

Variable	Relative risk	95% CI	*P* value
Lymph node metastasis (TNM)[a]			0.0494
pN0	1		
pN1	1.139	0.313–4.137	0.8430
pN2, 3	3.310	0.874–12.533	0.0781
Location of tumor			0.0504
Lower- or middle-third of the stomach	1		
Upper-third of the stomach	2.865	1.139–7.203	0.0253
Whole stomach	2.396	0.888–6.465	0.0846

[a] Grade of lymph node metastasis was evaluated using modified TNM classification

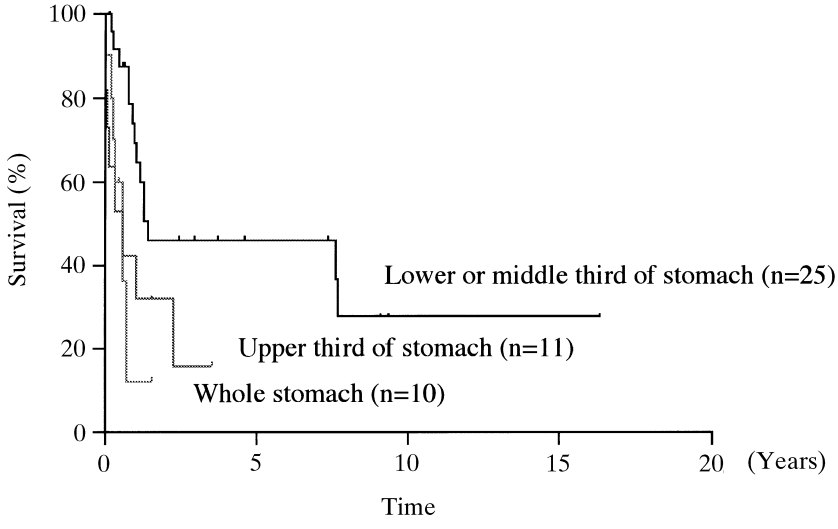

Fig. 8. Cumulative survival rate of 46 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for microscopic invasion (in relation to location of tumor)

Discussion

In the present study, the long-term outcome of T4 gastric cancer patients with combined resection of adjacent organs was better than that of patients with palliative gastrectomy (data not shown). These findings agree with those of previous studies [3–6]. According to these findings, surgeons should perform radical surgery with combined resection of invaded organs for T4 gastric cancer patients. In addition to this therapeutic principle, surgeons should be aware of the prognostic factors for these patients.

The most important characteristic of the present study was that the subjects were patients with macroscopic T4 gastric cancers. During surgery, when a gastric tumor was fixed to adjacent organs, it was difficult to judge histological invasion to these adjacent organs. Consequently, we performed resection of these organs in radical surgery.

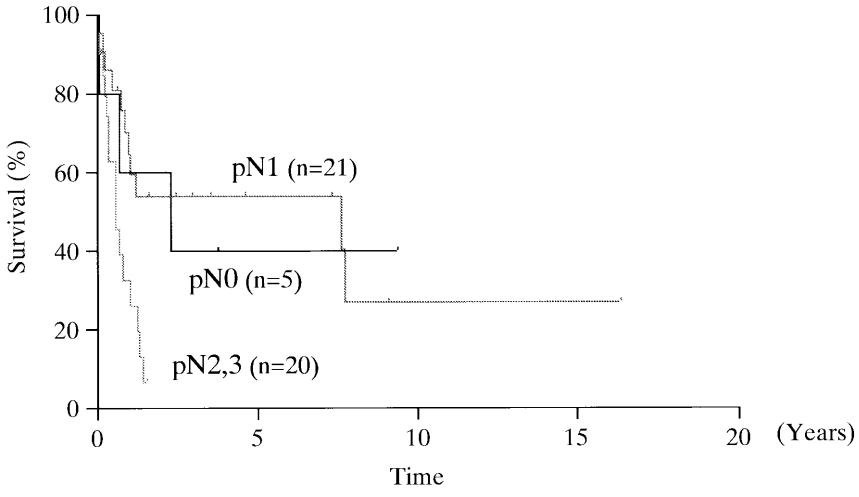

Fig. 9. Cumulative survival rate of the 46 patients with advanced gastric cancer treated by radical surgery with combined resection of adjacent organs for microscopic invasion (in relation to grade of lymph node metastasis according to modified TNM classification)

In the present study, univariate analysis demonstrated that the poorer prognostic factors of T4 gastric cancer patients with radical surgery were macroscopic type (Borrmann type 4), location of tumor (upper-third of the stomach, whole stomach), maximum dimension of the tumor (more than 90 mm), number of invaded organs (two or more), and lymph node metastasis. Kodama et al. [5] reported, by univariate analysis, that the best indication for en-bloc combined organ resection was invasion limited to only one other organ, grade of lymph node metastasis of not more than N2, no incurability factor, and any macroscopic type other than Borrmann type 4. The present findings with univariate analysis are consistent with their observations.

Multivariate analysis revealed that lymph node metastasis (modified TNM classification and Japanese classification), histological depth of invasion, location of tumor, and extent of lymph node dissection were significant prognostic factors in patients with gastric cancer with macroscopic invasion to adjacent organs, and that lymph node metastasis (modified TNM classification) and location of tumor were significant prognostic factors in the patients with gastric cancer with microscopic invasion to adjacent organs.

Lymph node metastasis was reported to be one of the important prognostic factors in patients with gastric cancer [10–12]. In patients with T4 gastric cancer, as well as patients with early gastric cancer [13] and those with T3 advanced gastric cancer [14], lymph node metastasis was an important prognostic factor. With regard to the classification of lymph node metastasis, we found that the grade of lymph node metastasis according to the TNM classification was a stronger prognostic factor than the extent of lymph node metastasis according to the Japanese classification [15]. Consequently, in patients with advanced gastric cancer with macroscopic or microscopic invasion to adjacent organs, the prognosis of those patients with a grade of lymph node metastasis limited to pN1 or less was significantly better than the prognosis in those with pN2 or greater. Katai et al. [16] reported, in an evaluation of the new International Union Against Cancer TNM staging for gastric carcinoma, that the survival of PT4/PN1 patients was significantly greater than that of other subgroups in stage IV. The present findings agree with theirs.

In the present study, location of the tumor was a prognostic factor by both multivariate analysis and univariate analysis in patients with gastric cancer with macroscopic and microscopic invasion. It was reported that gastric cancer located in the upper part of the stomach or the whole stomach had poorer prognosis than that located in the middle or lower part of the stomach [17]. In general, cancer of the gastric cardia has been regarded as a cancer for which it is difficult to achieve a cure. However, a reasonable explanation for these findings has not been reported.

With regard to the type of lymph node dissection, in the present study, superextended lymph node dissection (D3), including paraaortic lymph nodes, showed better prognosis for patients with macroscopic T4 gastric cancer on multivariate analysis, although the difference between D2 and D3 dissection was not significant either by univariate analysis or by multivariate analysis for patients with microscopic T4 gastric cancer. It remains unclear which factor is most important for curing T4 advanced gastric cancer; lymph node dissection or resection of involved organs, because we performed D2 or greater lymph node dissection in all patients with radical surgery. It was reported that paraaortic lymph node dissection improved the prognosis of patients with advanced gastric cancer [18–20]. However, the effectiveness of superextended lymph node dissection (D3), including the paraaortic lymph nodes, for ad-

vanced gastric remains unclear. A nationwide randomized control study is currently underway by the Japan Clinical Oncology Group (JCOG) Sasako Group.

In conclusion, for patients with macroscopic T4 gastric cancer located in the middle- or lower-third of the stomach, aggressive resection of invaded adjacent organs, with extended lymph node dissection, should be performed to improve long-term outcome.

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