

Postoperative Follow-up of Patients with Gastric Cancer According to Nodal Status

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Abstract. *Background: The aim of the present study was to determine the suitable postoperative management of patients with gastric cancer. Patients and Methods: A total of 161 patients with gastric cancer who developed recurrence after curative resection were reviewed retrospectively to investigate the clinicopathological characteristics of recurrence in subgroups classified according to the Japanese Classification of Gastric Cancer (JCGC) staging system. Results: Survival analysis of recurrent cases alone demonstrated significant differences in disease-free survival (DFS) among groups according to the pN stage ($p=0.0009$); however, there was no significant difference among groups according to the pT stage ($p=0.39$). Eighty percent of recurrences developed within 32, 25, and 15 months in the N0, N1/2 and N3 groups, respectively. Conclusion: The present study demonstrated that DFS and post-recurrent survival significantly differed among groups according to pN stage. These findings may provide useful information for maximizing the efficiency of postoperative follow-up.*

The incidence of gastric cancer is still one of the highest among various malignancies (1), and is the second most frequent cause of cancer-related death worldwide. Recent advances in diagnostic techniques and the spread of medical screening examinations have increased early detection of gastric cancer (2). However, some patients develop early recurrence and consequently demonstrate extremely poor survival rates (3).

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Key Words: Postoperative follow-up, gastric cancer, nodal status, DFS, recurrence.

Therefore, periodic follow-up is generally performed for early detection of recurrence, although the Japanese Gastric Cancer Association (JGCA) guidelines do not propose a specific postoperative follow-up program. The diagnosis for recurrent disease relies largely on conventional serum tumor markers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9, ultrasonography, and computed tomography (CT). These diagnostic tools, however, lack sufficient sensitivity and specificity for the early detection of recurrent gastric cancer; other information on the characteristics of recurrence, such as “when” and “where,” might be useful for clinical practice. Therefore, a postoperative management program should be determined for each individual patient with gastric cancer based on the risk, frequency pattern, and time of recurrence.

In the present study, we investigated the clinicopathological characteristics of recurrence in subgroups of patients with gastric cancer classified according to the Japanese Classification of Gastric Carcinoma (JCGC) staging system. We also determined suitable management options for the postoperative program of patients with gastric cancer.

Patients and Methods

Patients. Between 1997 and 2011, a total of 1,587 patients with gastric cancer underwent surgical resection at the Kyoto Prefectural University of Medicine Hospital. Out of these, 161 patients (10.1%) who developed recurrence after curative gastrectomy (R0) with D1-plus or D2 lymph node dissection (Japanese-style radical lymph node dissection) were enrolled in the present retrospective study. Patients with distant metastases and multiple primary cancers were excluded. Patients treated with preoperative chemotherapy were also excluded from the study. The clinicopathological characteristics of patients with recurrent gastric cancer, such as the timing and pattern of recurrence, were reviewed retrospectively using the hospital database of patients with gastric cancer, and the features of subgroups with recurrence were classified according to the staging system. The degrees of venous invasion and lymphatic invasion were divided into four grades according to the JCGC staging system, and other histological features were also classified according to the JCGC (4) and the tumor-node-metastasis staging system (5).

Follow-up consisted of blood examinations, including serum tumor markers CEA and CA19-9, radiological examinations of the gastrointestinal tract, endoscopic procedures, CT, and ultrasonography. Follow-up procedures were performed every three months for at least two years, and were continued periodically for at least five years.

Recurrences were grouped by pattern, such as lymphatic, peritoneal, or hematogenous. Recurrence was considered to have been histologically proven if it was documented by surgical biopsy, needle biopsy, or by cytology of the appropriate fluid. Radiological proof of recurrence was specifically reviewed in the context of clinical presentation and commonly required sequential imaging to demonstrate the progression of metastatic lesions. In rare situations, such as progressing subcutaneous nodules or obvious diffuse peritoneal recurrence, a specific recurrence was detected by clinical examination alone.

Statistical analysis. The chi-square test was performed to explore the distribution of interval scaled data. Survival rates were calculated by the Kaplan-Meier method, with the date of gastrectomy as the starting point. Differences in survival were examined by the log-rank test. Multivariate analysis of prognostic factors related to survival was performed using the Cox proportional hazard model. A value of $p < 0.05$ was regarded as significant.

Results

Clinicopathological characteristics. The mean age of patients with recurrence was 67.1 years (range=28-89 years), and the male-to-female ratio was 2.2:1.0. The median tumor size was 60 mm (range=10-220 mm). The mean and median duration between gastrectomy and recurrence were 1.28 years (range=0.10-5.23 years) and 0.97 years (range=0.10-5.23 years), respectively. Other clinicopathological factors are summarized in Table I. Eighty-five patients (53%) developed a clinically-apparent recurrence within one year, and 128 patients (79%) had such a recurrence within two years postoperatively. The 161 patients who developed a recurrence were classified into subgroups according to the JCGC staging system: 10 patients as pT1, 11 as pT2, 46 as pT3, and 94 as pT4; and 26 patients as pN0, 26 as pN1, 36 as pN2, and 73 as pN3. The final stage was I in eight patients, II in 28, and III in 125.

Recurrence timing. To determine the characteristics of recurrence timing, we analyzed the survival of recurrent cases only. Figure 1 shows the disease-free survival (DFS) curves patients with recurrence for each group classified according to the pathological depth of tumor (pT stage) and pathological nodal status (pN stage). There were significant differences in DFS among groups according to the pN stage ($p=0.0009$); however, no significant difference was found among groups according to the pT stage ($p=0.39$). Because the survival curves of patients were similar in the N1 and N2 groups, and the N3a and N3b groups, a re-analysis was performed by combining them into three groups: N0, N1/2,

Table I. Clinicopathological factors of patients with node-negative and those with node-positive disease who developed recurrence.

Variable	Node-negative recurrence (%)	Node-positive recurrence (%)	p-Value*
Total	26	135	
Gender			
Male	18 (69.2)	93 (68.9)	0.9725
Female	8 (30.8)	42 (31.1)	
Age			
<65 years	10 (38.5)	55 (40.7)	0.8279
≥65 years	16 (61.5)	80 (59.3)	
Location			
Upper third	8 (30.8)	46 (34.1)	0.7423
Middle/Lower third	18 (69.2)	89 (65.9)	
Macroscopic appearance			
Localized	11 (42.3)	47 (34.8)	0.4701
Diffuse	15 (57.7)	88 (65.2)	
Histology			
Diff.	12 (46.2)	50 (37.0)	0.3855
Undiff.	14 (53.8)	85 (63.0)	
Size			
<30 mm	3 (11.5)	12 (8.9)	0.6785
>30 mm	23 (88.5)	123 (91.1)	
Depth			
T1	3 (11.5)	7 (5.2)	0.1636
T2/T3	12 (46.2)	45 (33.3)	
T4	11 (42.3)	83 (61.5)	
Lymphatic invasion			
0	11 (42.3)	17 (12.6)	<0.001
1/2/3	15 (57.7)	118 (87.4)	
Venous invasion			
0	15 (57.7)	48 (35.6)	0.0364
1/2/3	11 (42.3)	87 (64.4)	
Lymphatic invasion			
Hematogenous	7 (26.9)	31 (23.0)	0.1573
Lymphatic	7 (26.9)	38 (28.1)	
Peritoneal	12 (46.2)	62 (45.9)	
Unknown	0 (0)	4 (3.0)	

and N3 (Figure 2). There was no significant difference in DFS among the groups according to the pathological stage (I-III) (data not shown).

The median time of recurrence (median DFS) was 19.7 months in node-negative (N0) patients, 16.1 months in N1/2 patients, and 8.5 months in N3 patients.

Moreover, the post-recurrence survival in patients with node-negative disease was longer than that of those with node-positive disease ($p=0.0079$); however, there was no significant difference in the post-recurrence survival among groups according to pT stage ($p=0.3385$) (Figure 3).

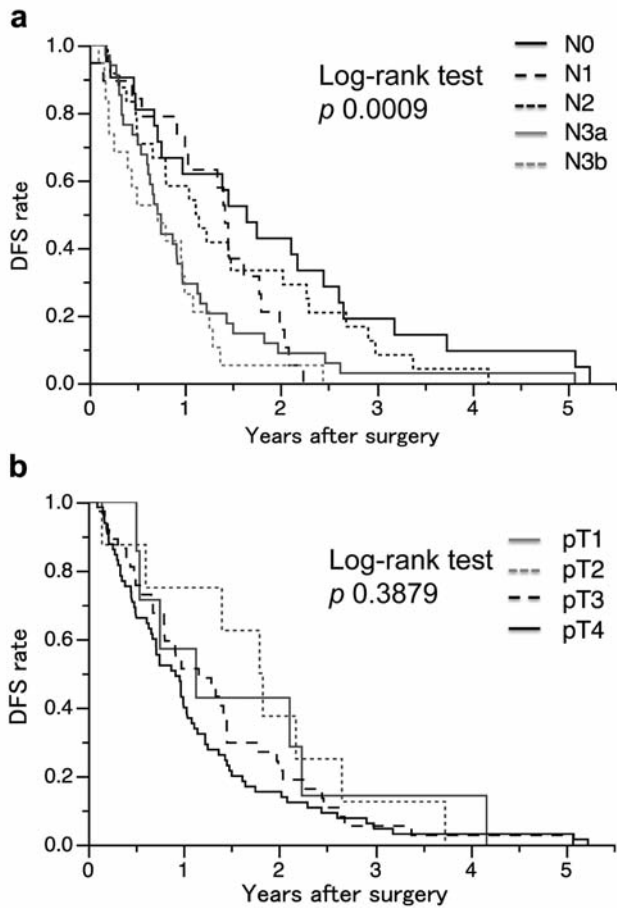


Figure 1. Disease-free survival (DFS) of patients who developed recurrence in the N0, N1, N2 and N3 groups (a), and in the T1, T2, T3 and T4 groups (b). The time of recurrence was significantly different among the groups ($p=0.0009$).

Comparison of clinicopathological factors between patients with node-negative and node-positive disease who developed recurrences. There was no significant difference in clinicopathological factors between node-negative and node-positive cases who developed a recurrence, except for lymphatic invasion and venous invasion. There was also no significant difference in the pattern of recurrence between these two groups (Table I).

Discussion

Although diagnostic and surgical techniques have progressed in recent years, recurrences are sometimes encountered in patients with gastric cancer (6, 7). Recurrence has generally been considered to arise from preoperative and/or intraoperative clinically occult metastasis (8, 9). Periodic postoperative surveillance is generally performed for the

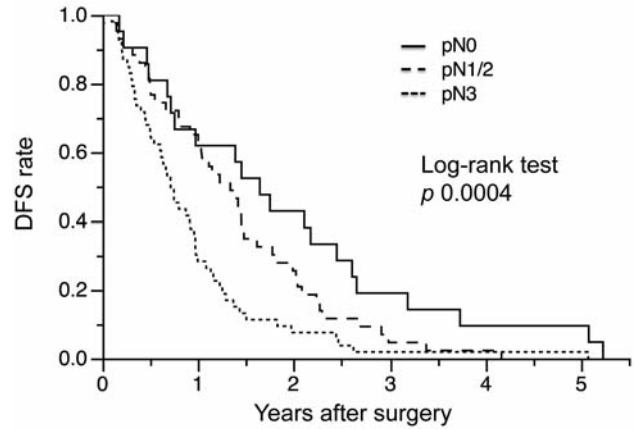


Figure 2. Disease-free survival (DFS) of patients who developed recurrence in the N0, N1/2 and N3 groups. The time of recurrence was significantly different among the groups ($p=0.0004$).

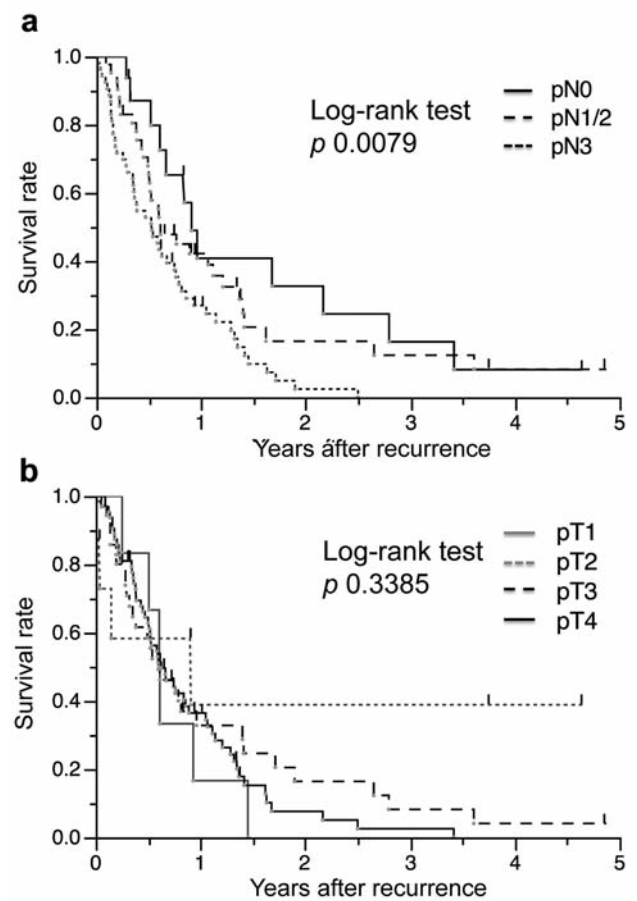


Figure 3. The survival time after recurrence for each stage. The survival time after recurrence in node-negative patients was longer than that in node-positive patients ($p=0.0079$).

early detection of recurrence. However, several reports have demonstrated that routine follow-up after gastrectomy does not contribute to early detection of cancer recurrence nor has any survival benefit (10, 11). If there was additional information concerning the timing and pattern of recurrence for each patient with gastric cancer, an intensive follow-up program could be scheduled for early detection and treatment of recurrence. These facts prompted us to investigate the clinical characteristics of recurrence in patients with gastric cancer classified according to the clinical stage, and also to determine suitable management options for the postoperative program of patients with node-negative gastric cancer.

In the present study, pN stage was found to be a prognostic factor even in patients with recurrent gastric cancer, but pT stage was not. Not only DFS, but also post-recurrence survival differed significantly among groups classified according to pN stage. We found that 80% of recurrences developed within 32, 25, and 15 months in the N0, N1/2, and N3 groups, respectively (Figure 1a), which indicated that almost all of the patients with high N stage developed recurrence within two years. These findings on the average timing of recurrence according to the pN stage have yielded valuable information for maximizing the efficiency of follow-up programs and alleviating patients' anxieties during the postoperative follow-up period.

Another notable finding is that some patients with node-negative cancer developed a recurrence more than three years after surgery, although patients with node-positive disease seldom developed a postoperative recurrence after three years. Node-negative disease generally comes with a good prognosis; however, our previous study demonstrated that lymphatic invasion can provide additional useful information in identifying patients with node-negative disease at high risk for recurrence (12). Therefore, node-negative cases with lymphatic invasion might be candidates for a longer-than-usual postoperative follow-up period.

In addition, we investigated the clinicopathological characteristics of recurrence in node-negative disease by comparison with those of node-positive cases. There was no significant difference in the recurrence pattern between node-negative and node-positive cases, except for frequent multiple recurrences in those with node-positive cancer. Metastasis of gastric cancer falls into three main categories: peritoneal dissemination, lymphatic spread, and hematogenous spread, all of which consist of a highly complex series of mechanisms that are somewhat related to one another. Other recent reports have demonstrated that there is considerable communication between lymphatic and venous vessels (13), and that peritoneal dissemination sometimes develops in patients without serosal tumor invasion (14). These findings, which indicate the complexity of cancer metastasis, can explain the apparently unusual

finding of no significant difference in recurrence pattern between patients with node-negative disease and those with node-positive disease.

These findings may provide useful information for the clinical management of patients with gastric cancer. The reasons for these prognostic differences are not exactly known; however, there are possible explanations. The first possibility is that a larger number of clinically occult cancer cells may remain as distant lymph node metastases or arise from intraoperative spillage from lymphatic vessels in the advanced nodal stage than in the N0 stage, even after apparent curative gastrectomy with extended lymph node dissection. An alternative possibility is that the cancer cells themselves have more aggressive properties, including proliferative and metastatic potential, in the advanced nodal stage than in the N0 stage. In the present study, prognosis was significantly worse in patients with advanced nodal stage disease than in those with N0 stage, even after the diagnosis of recurrence. These findings may support the latter hypothesis, although the exact mechanisms are not yet known.

Conclusion

The present study demonstrates that DFS and post-recurrence survival significantly differed among groups according to pN stage. These findings may provide useful information for maximizing the efficiency of postoperative follow-up.

Conflicts of Interest

None.

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Received August 20, 2013

Revised September 16, 2013

Accepted September 17, 2013