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BRIEF ARTICLE

Prognostic factors of T4 gastric cancer patients undergoing potentially curative resection

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Abstract

AIM: To investigate the prognostic factors of T4 gastric cancer patients without distant metastasis who could undergo potentially curative resection.

METHODS: We retrospectively analyzed the clinical data of 71 consecutive patients diagnosed with T4 gastric cancer and who underwent curative gastrectomy at our institutions. The clinicopathological factors that could be associated with overall survival were evaluated. The cumulative survival was determined by the Kaplan-Meier method, and univariate comparisons between the groups were performed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model and a step-wise procedure.

RESULTS: The study patients comprised 53 men (74.6%) and 18 women (25.4%) aged 39-89 years (mean, 68.9 years). Nineteen patients (26.8%) had postoperative morbidity: pancreatic fistula developed in 6 patients (8.5%) and was the most frequent complication, followed by anastomosis stricture in 5 patients (7.0%). During the follow-up period, 28 patients (39.4%) died because of gastric cancer recurrence, and 3 (4.2%) died because of another disease or accident. For all patients, the estimated overall survival was 34.1% at 5 years. Univariate analyses identified the following statistically significant prognostic factors in T4 gastric cancer patients who underwent potentially curative resection: peritoneal washing cytology ($P < 0.01$), number of metastatic lymph nodes ($P < 0.05$), and venous invasion ($P < 0.05$). In multivariate analyses, only peritoneal washing cytology was identified as an independent prognostic factor (HR = 3.62, 95% CI = 1.37-9.57) for long-term survival.

CONCLUSION: Positive peritoneal washing cytology was the only independent poor prognostic factor for T4 gastric cancer patients who could be treated with potentially curative resection.

Key words: Gastric cancer; T4; Prognostic factors; Peritoneal cytology; Venous invasion

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INTRODUCTION

Although the incidence of gastric cancer has declined worldwide, this disease remains the second leading cause of cancer death because patients with an advanced form of gastric carcinoma still have a poor prognosis[1,2]. Depth of invasion, lymph node metastasis, or tumor di-

ameter are believed to be independent prognostic factors of gastric carcinoma[3,4]. Locally advanced gastric cancer defined as T4 in which the tumor perforates serosa (T4a) or invades adjacent structures (T4b)[5] often has a poor prognosis due to simultaneous distant metastasis such as peritoneal seeding, liver metastasis, and/or distant lymph node involvement. Even though distant metastasis is not apparent in T4 gastric cancer, curative surgery cannot always be performed because such cases sometimes show marked invasion to adjacent structures. Moreover, curative gastrectomy with combined resection of invaded adjacent organs has a reportedly high incidence of post-operative morbidity and mortality[6,7]. In fact, the overall survival rate for locally advanced gastric cancer patients is under 20% and is approximately 30% for those who can undergo surgical resection[8].

Nevertheless, a certain number of patients with locally advanced gastric carcinoma could survive curative gastrectomy and progress satisfactorily without tumor recurrence. In this study, we retrospectively studied surgical outcomes and prognostic factors for T4 advanced gastric carcinoma treated with potentially curative resection.

MATERIALS AND METHODS

From 2001 to 2009, 452 gastric cancer patients underwent surgical treatment at our institutions. Of these, 71 patients (15.7%) diagnosed with histological T4[5] gastric carcinoma and treated with potentially curative resection were selected for this study. All patients underwent D2gastrectomy. Surgery was considered potentially curative [tumor-nodes-metastases (TNM)-R0] or to be resection with curative intent when there was no gross residual tumor after surgery and the resection margins were histologically free from cancer cells. Patients with metastatic disease who had undergone palliative resection were excluded. The study patients comprised 53 men (74.6%) and 18 women (25.4%) aged 39-89 years (mean, 68.9 years). Sixty patients were included in the stage T4a group and 11 cases in the stage T4b group, according to TNM classification[5]. On histological examination, it was found that T4b gastric carcinomas exhibited invasions to the transverse colon in 5 patients, the pancreas in 3 patients, the diaphragm in 2 patients, and the liver in 1 patient. Of the 71 patients, 7 had tumors located in the upper third of the stomach, 28 had tumors in the middle third of the stomach, 21 had tumors in the lower third of the stomach, and 15 had tumors occupying the entire stomach. The tumor diameter ranged from 20 to 205 mm (mean, 84 mm). Proximal gastrectomy, distal gastrectomy, and total gastrectomy were performed in 3 patients (4.2%), 35 patients (49.3%), and 33 patients (46.5%), respectively. All the surgical procedures were based on the policy of curative resection, which meant complete removal of cancer tissue regardless of combined multi-organ resection with no residual tumor macroscopically.

Data regarding the patients' clinicopathological features, surgical outcomes including morbidity and mortality, and follow-up data were obtained from a clinical database. Histological classification and staging were principally based on the seventh edition of the International Union Against Cancer (UICC) TNM classification[5]. We evaluated clinicopathological factors of T4 gastric cancer patients that could be associated with overall survival. These parameters were age, gender, tumor diameter, histological type, lymph node metastasis, metastatic lymph node ratio (MLR), lymphatic invasion (ly), venous invasion (v), and peritoneal washing cytology (CY). For statistical analysis, the patients were grouped into 2 categories with respect to age [$\leqslant$ 68 years or > 68 years (mean value)], tumor diameter [$\leqslant$ 84 mm or > 84 mm (mean value)], histological type (differentiated or undifferentiated), number of metastatic lymph nodes (N0 or N1 *vs* N2 or N3)[5], MLR [$\leqslant$ 0.27 or > 0.27 (mean value)], and peritoneal washing cytology (CY0 or CY1) [5]. Similarly, the patients were divided into 2 groups with respect to lymphatic invasion (ly0 or ly1 *vs* ly2 or ly3) and venous invasion (v0 or v1 *vs* v2 or 3) according to the Japanese Gastric Cancer Association (JGCA) system[9]. Post-operative morbidity and mortality were defined as operation-related complications or death that occurred within 30 days after surgery.

The observation period ended on July 31, 2010. The median follow-up duration from the date of surgery was 24 mo (range, 1-89 mo). Fifty patients (70.5%) were given post-operative adjuvant chemotherapy using S-1 for 29 patients, UFT for 7 patients, paclitaxel for 7 patients, and others for 7 patients. The cumulative survival was determined by the Kaplan-Meier method, and univariate comparisons between the groups were performed using the log-rank test. Multivariate analysis was performed using the Cox proportional hazard model and a step-wise procedure. *P* value differences less than 0.05 were considered significant.

RESULTS

Sixty-one patients (85.9%) had lymph node metastasis, 9 (12.7%) had N1, 18 (25.4%) had N2, and 34 (47.9%) had N3 disease. Differentiated tumors were histologically revealed in 31 patients and undifferentiated tumors were seen in 40 patients. The degree of lymphatic invasion according to the JGCA system[9] were 0.0%, 23.9%, 45.1%, and 31.0% for ly0, ly1, ly2, and ly3, respectively. The degree of venous invasion according to the JGCA system[9] were 32.4%, 42.3%, 23.9%, and 1.4% for v0, v1, v2, and v3, respectively. Twenty-seven patients (38.0%) were positive for peritoneal washing cytology. Patient characteristics are presented in Table 1. Nineteen patients (26.8%) had postoperative morbidity. Pancreatic fistula occurred in 6 patients (8.5%) and was the most frequent complication, followed by anastomosis stenosis in 5 patients (7.0%). Three patients (4.2%) died of post-operative complications: 2 were due to multi-organ failure associated with pancreatic fistula, and 1 was due to acute gangrenous cholecystitis combined with peritonitis. These complications are listed in Table 2. Thirty-one patients (43.7%) died during the follow-up period. Of these, 28 were related to recurrence of gastric cancer, and 3 were due to another disease or accident. The estimated overall survival at 5 years and the median survival time (MST) for all patients

Table 1 Patient characteristics

Variables	*n* (%)
Age	
≤ 68	31 (43.7)
> 68	40 (56.3)
Gender	
Male	53 (74.6)
Female	18 (25.4)
Tumor location	
Upper 1/3	7 (9.9)
Middle 1/3	28 (39.4)
Lower 1/3	21 (29.6)
Tumor size (mean, mm)	20-205 (84)
Type of gastrectomy	
Proximal	3 (4.2)
Distal	35 (49.3)
Total	33 (46.5)
Lymph node involvement	
Positive	61 (85.9)
Negative	10 (14.1)
Histological type	
Differentiated	31 (43.7)
Undifferentiated	40 (56.3)

Table 2 Postoperative complications

	Patients (*n* = 71)	%
Morbidity	19	26.8
Pancreatic fistula	6	8.5
Anastomosis stricture	5	7.0
Anastomosis leakage	3	4.2
Cholecystitis	3	4.2
Abdominal abscess	2	2.8
Ileus	1	1.4
Mortality	3	4.2

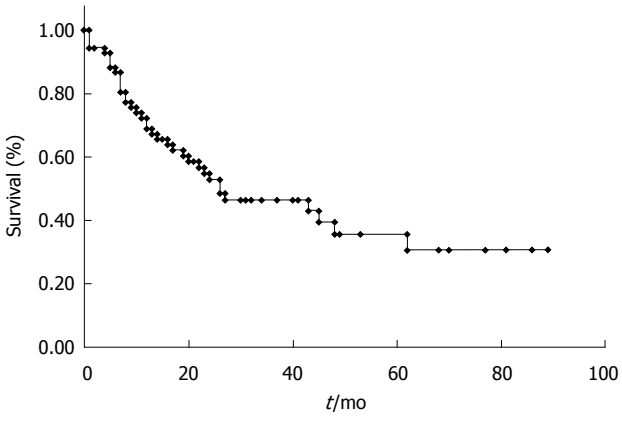

Figure 1 Kaplan-Meier survival curve of T4 gastric cancer patients.

were 34.1% (Figure 1) and 19 mo, respectively.

The clinicopathological records of the 71 patients and the 5-year survival rates are shown in Table 3. The statistically significant prognostic factors were peritoneal washing cytology ($P < 0.01$), number of metastatic lymph nodes ($P < 0.05$), and venous invasion ($P < 0.05$). The 5-year overall survival rate of the patients with positive peritoneal washing cytology was 15.2%, which was significantly decreased compared to patients with negative peritoneal washing cytology (47.6%). The 5-year overall survival rate of patients with N2 or N3 was 23.8%, which was significantly poorer than patients with N0 or N1 (67.4%). Similarly, the 5-year overall survival rate of patients with v2 or v3 was 9.7 %, which was significantly decreased compared to patients with v0 or v1 (45.7%). The tumor diameter, degree of lymphatic invasion, and histological classification were not significant prognostic factors according to the results of the univariate analysis. In multivariate analysis, only peritoneal washing cytology was identified as an independent prognostic factor (HR = 3.62, 95% CI = 1.37-9.57) for long-term survival (Table 4).

Table 3 Clinicopathological factors and univariate survival analyses

	n	5-yr survival (%)	*P*
Age (mean: 68.9)			
≤ 68	31	45.5	0.415 (NS)
> 68	40	26.2	
Gender			
Male	53	31.0	0.510 (NS)
Female	18	50.1	
Tumor diameter (mm, mean: 84)			
≤ 84	39	34.4	0.213 (NS)
> 84	32	33.9	
Histological type			
Differentiated	31	18.6	0.565 (NS)
Undifferentiaed	40	40.7	
Number of lymph node meta			
N0 or N1	19	67.4	< 0.05
N2 or N3	52	23.8	
MLR (mean: 0.27)			
≤ 0.27	46	38.9	0.083 (NS)
> 0.27	25	20.7	
Lymphatic invasion			
ly0 or ly1	17	49.3	0.453 (NS)
ly2 or ly3	54	29.7	
Venous invasion			
v0 or v1	53	45.7	< 0.05
v2 or v3	18	9.7	
Peritoneal washing cytology			
Negative (CY0)	44	47.6	< 0.01
Positive (CY1)	27	15.2	

NS: Not significant.

Table 4 Multivariate analysis

	Hazard ratio	95% CI	*P*
Number of LN meta	1.3104	0.4075-4.2137	0.6501
Venous invasion	0.9642	0.3335-2.7882	0.9464
Peritoneal washing cytology	3.6262	1.3743-9.5683	< 0.01

CI: Confidence interval.

DISCUSSION

Owing to the progression of surgical techniques and the

standardization of curative R0 resection, the prognosis of the patients with gastric cancer has been improved in recent years. Nevertheless, patients with advanced gastric carcinoma, especially serosa invading locally advanced tumor diagnosed as T4 in TNM classification[5], still have a poor prognosis[10]. The poor prognosis associated with T4 advanced gastric cancer may result from the presence of incurable factors including distant lymph node involvement, peritoneal metastasis, and hematogenous metastasis such as liver metastasis[11]. If a patient with T4 gastric carcinoma does not have the incurable factors mentioned above, a relatively better survival can be expected when curative surgery regardless of en-block multi-organ resection is achieved. Various T4 gastric carcinoma prognostic factors have been reported in the literature. Kunisaki *et al*[4] reported that tumor diameter (> 100 mm) and lymph node metastases (more than 7) are poor prognostic factors in T4 gastric cancer patients and concluded that curative surgery with multi-organ resection is indicated for patients with few metastatic lymph nodes (6 or less) and a relatively small tumor diameter (≤ 100 mm). Similarly, several reports suggested that tumor size in gastric cancer is a significant prognostic factor, and large gastric cancers with a diameter > 80 mm have more aggressive behavior and frequent peritoneal recurrences[12,13]. However, our study revealed that the tumor size was not a significant prognostic factor in T4 gastric carcinoma patients who could undergo potentially curative resection. The divergent conclusions of these reports[4,12,13] with ours might be explained by different patient populations.

Our study was limited to patients with T4 gastric carcinoma without distant metastasis and who were treated with potentially curative resection, whereas other studies[4,12,13] included patients with distant metastasis. Therefore, tumor size may not be a significant prognostic factor in T4 gastric carcinoma, if the patient does not have distant metastasis and can be treated with curative resection.

Lymph node metastasis is a commonly reported prognostic factor for poor outcome in patients with T4 gastric carcinoma[4,11,14]. Saito *et al*[14] reported that infiltrative type and lymph node metastasis were independent poor prognostic factors in curatively resected patients with T4 gastric carcinoma, and stated that multi-organ resection does not seem to be effective even when curative resection is performed in infiltrating tumors with lymph node metastasis. Jeong *et al*[11] revealed that lymph node metastasis (greater than pN3) was an independent poor prognostic factor for patients with T4 gastric carcinoma who underwent curative surgery, and concluded that curative resection does not seem to be effective in patients with extensive lymph node metastasis (more than N3). In our study, although patients with more extensive lymph node metastasis (N2 or N3) had a significantly poorer prognosis compared to patients in whom lymph node metastasis was limited (N0 or N1) according to the results of univariate analysis, multivariate analysis revealed that lymph node metastasis was not an independent prognostic factor for T4 gastric cancer patients who underwent potentially curative resection. Although the degree of lymph node metastasis influences surgical outcomes in patients with T4 gastric carcinoma, a relatively good prognosis can be expected with curative R0 resection followed by adjuvant chemotherapy even if the patient has extensive lymph node metastasis (N2 or N3).

In this study, positive peritoneal washing cytology was identified as the only independent prognostic factor for T4 gastric cancer patients who underwent potentially curative resection. Several reports[15-21] have emphasized the prognostic significance of intra-peritoneal free cancer cells for potentially curable serosa-invaded gastric carcinoma. Intraperitoneal free cancer cells which may be exfoliated mainly from the serosal surface of the stomach penetrated by the primary tumor, are closely related to peritoneal dissemination[18]. Therefore, detection of intra-peritoneal free cancer cells that might have already seeded at the time of operation but cannot be found macroscopically is a key point for influencing the prognosis of T4 gastric cancer patients and for adjuvant treatment planning for those patients. Euanorasetr *et al*[17] reported that all patients with positive peritoneal washing cytology developed peritoneal recurrence, with no patient surviving more than 5 years, and that the sensitivity of peritoneal washing cytology in predicting peritoneal recurrence was only 61% regardless of its high specificity (100%). In addition, the sensitivity of peritoneal washing cytology was previously reported as relatively low, ranging from 14% to 70%[16,22-25]. The relatively high false-negative rate might arise from technical flaws such as incomplete sampling during the lavage process[17]. Recently, the real-time quantitative polymerase chain reaction (PCR) technique has made it possible to detect the presence of only a few cancer cells in the abdominal cavity and this technique is more sensitive than traditional peritoneal lavage cytology[26,27]. Katsuragi *et al*[18] reported that the prognosis of patients with isolated tumor cells in the peritoneal lavage fluid detected by PCR-based identification was significantly poorer than the prognosis for PCR-negative patients in T4 gastric cancer. Therefore, detection of intraperitoneal free cancer cells should be the most important and useful way to infer surgical outcome and prognosis of T4 gastric cancer patients. According to the results, T4 gastric cancer patients with positive peritoneal washing cytology might be treated in the same way as for the patients with peritoneal metastasis. More aggressive adjuvant chemotherapy such as S-1 plus cisplatin[28] or DCF[29] should be indicated for patients with T4 gastric cancer with positive peritoneal washing cytology that could undergo potentially curative resection to improve prognosis.

COMMENTS

Background

Although the incidence of gastric cancer has declined particularly in Western countries, the disease remains the fourth most common cancer and continues to be the second leading cause of cancer death worldwide. The therapeutic strategy for advanced gastric carcinoma, such as T4 locally advanced gastric carcinoma, is to improve the prognosis of all gastric cancer patients, since surgical results for early stage gastric carcinoma are satisfactory.

Innovations and breakthroughs

In this study, patients included were limited to T4 advanced gastric carcinoma without distant metastasis who could be treated with potentially curative resec-

tion. Various clinicopathological factors including peritoneal washing cytology that could be associated with overall survival of T4 gastric cancer patient were evaluated on univariate analysis using the Kaplan-Meier method and on multivariate analysis using a Cox proportional hazard model and a step-wise procedure.

Applications

Aggressive adjuvant chemotherapy should be indicated for the patients with T4 gastric carcinoma with positive peritoneal washing cytology to improve the prognosis, even if the tumor can be resected without no residual tumor macroscopically. Thus, identification of effective adjuvant chemotherapy for advanced gastric carcinoma with positive peritoneal cytology for patients who could undergo potentially curative resection will be the problem in the near future.

Peer review

This is an interesting work that underlines the prognostic value of peritoneal cytology in curatively resected T4 gastric carcinomas. The text is well-organized and the key points are clearly described.

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