

ORIGINAL ARTICLE

Is resection indicated in gastric cancer deemed curable preoperatively but found to be advanced intraoperatively?

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Summary

Purpose: This study was designed to evaluate the value of resection and to analyze clinicopathologic data on gastric cancer patients who were evaluated as curable preoperatively but diagnosed as advanced intraoperatively.

Methods: A retrospective analysis was performed on clinical, surgical, and pathological data of 264 patients who had undergone surgery for gastric cancer between January 2008 and October 2012. The patients who were diagnosed in advanced stages during surgical exploration were accepted into the study group. Patients were categorized into the following two groups: non-resection group (NRG) and resection group (RG). We compared the clinicopathologic features of the two groups and investigated the prognostic factors by performing univariate and multivariate analyses.

Results: A total of 79 patients diagnosed with advanced

disease in surgical exploration were evaluated. There were 40 patients (50.6%) in the NRG and 39 patients (49.4%) in the RG. The difference in median overall survival between the NRG and the RG was statistically significant (1.7 vs 5 months; $p=0.001$). In multivariate analysis, age less than 70 years, gastric resection, adjuvant chemotherapy, and male gender were found to be favorable significant independent prognostic factors for overall survival.

Conclusion: Resection seems to be associated with improved overall survival in patients who were diagnosed as advanced intraoperatively. Therefore, patient and tumor-related factors should be taken into consideration before planning resection. Randomized controlled studies are required.

Key words: gastrectomy, gastric cancer, prognosis, survival

Introduction

Gastric cancer is the fourth most common cancer after lung, breast, prostate, and colorectal cancer and it is the second most common cause of cancer-related death worldwide in both sexes [1]. In gastric cancer staging, TNM staging was accepted in 2002 and revised in 2010 by the American Joint Committee on Cancer (AJCC) and the International Union Against Cancer (UICC) [2]. According to this staging system, the term "advanced gastric cancer" is used for patients in stage 3 and 4.

Surgery is the major curable treatment modality for gastric cancer. Curative treatment means complete resection of the tumor with ad-

jacent lymph nodes and adequate margins in patients who have no peritoneal or distant metastases. Patients with extensive local invasion (celiac trunk and hepatic artery invasion, retroperitoneal fixation, hepatoduodenal ligament invasion, extensive duodenal infiltration), peritonitis carcinomatosa, diffuse liver metastases, or distant lymph node metastases are considered incurable [3]. There are conflicting results in the literature about the outcomes of palliative resection performed for advanced gastric cancer. Some studies emphasize that palliative resection improves the quality of life and survival and helps in the palliation of symptoms due to obstruction or bleeding

[4-6]. However, some authors report that palliative resection increases morbidity, prolongs hospital stay, and impairs the quality of life with no survival benefit, especially in patients with high-grade peritoneal seeding and high tumor load [7,8].

This study aimed to compare patients with gastric cancer who were evaluated as curable preoperatively but determined to be advanced intraoperatively. The analysis was based on the following clinicopathological variables and parameters which may have impact on the survival of these patients: age, gender, ASA score, tumor location, tumor size, operation type, histology, and extent of the tumor.

Methods

The study was approved by our institutional ethics committee. We reviewed the clinical, surgical, and pathological data of 264 patients who had undergone surgery for gastric cancer between January 2008 and October 2012. Routine blood tests, plain lung x-rays, endoscopic findings, biopsies, and abdominopelvic CT scans of the patients were evaluated.

Exclusion/inclusion criteria

The tumors were staged according to the AJCC TNM (7th edition) classification system. Patients who were operated on for gastric lymphoma and gastrointestinal stromal tumor, those who had received neoadjuvant chemoradiotherapy, and those who had previously undergone gastric surgery were excluded from the study. Patients who were detected to be in advanced stages in surgical exploration were retrospectively accepted as the study group.

Parameters assessed

In CT evaluation, no distant metastasis was detected preoperatively. All operations were performed with curative intent. Patients were categorized into the following two groups: NRG and RG. Demographic findings, ASA scores, operation types (exploratory surgery, feeding jejunostomy, bypass surgery, and subtotal or total gastrectomy), tumor location, tumor size, tumor histology, length of hospital stay, hospital mortality, and overall survival rates were analyzed. Tumors were classified into two groups based on histology: differentiated (papillary, well, or moderately differentiated) and undifferentiated (poorly differentiated or undifferentiated adenocarcinoma, signet ring cell carcinoma, and mucinous adenocarcinoma). Adjuvant chemotherapy was administered based on the patient performance status and patient preference. All patients were followed up until October 2013 (cut-off date) or until death. Survival rates were obtained by calling the

patients' families, or by examining the civil population registry records. The length of overall survival was calculated from the day of surgical resection until the time of death or last follow-up.

Statistics

Statistical analyses were performed using the IBM SPSS Statistics for Windows 20.0 statistical package (Chicago, IL, 2011). To analyze the categorical variables of the groups, the chi-square or Fisher's exact test were used. For non-categorical variables, the Student's t-test and the Mann-Whitney U tests were used. For survival analysis and comparison of groups, the Kaplan-Meier method with log-rank test were used. Independent prognostic factors in multivariate survival analysis were evaluated by using the Cox's proportional hazards regression model. A p value <0.05 was considered to be statistically significant.

Results

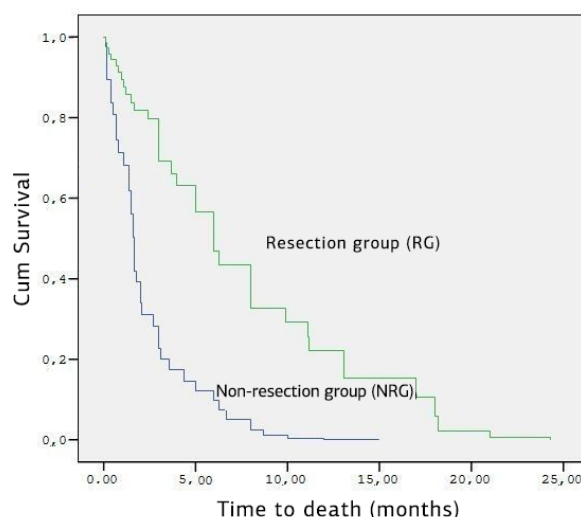
Two hundred and sixty-four patients were operated on for gastric cancer between January 2008 and October 2012. There were 183 male (69.3%) and 81 female (30.7%) patients, with a median age of 67.2 years (range 27-91). According to the operative and pathological findings, 92 (35%) patients were accepted as having advanced disease. After the exclusion criteria for the patients in advanced stage were applied, the data of the remaining 79 patients who underwent operation for advanced gastric cancer were reviewed. The median follow-up time was 90 days (range 3-730). There were 52 male (65.8%) and 27 (34.2%) female patients with median age 69 years (range 35-90). Forty patients (50.6%) belonged to the NRG and 39 (49.4%) to the RG. The mean patient age of the RG was lower than the NRG (63±13 vs 70±11 years, p=0.009). The demographics and tumor characteristics of the patients are shown in Table 1. In the NRG, the number of patients with tumor size greater than 5 cm was significantly higher than in the RG (p=0.003). Additionally, the number of patients with local invasion and peritoneal dissemination in the NRG was greater than in the RG (p=0.020, p<0.0001, respectively). In the NRG, feeding jejunostomy was performed in 22 (55%) patients with obstructive complaints, gastroenterostomy was performed in 13 (32%) patients, and laparotomy only was performed in 5 (13%) patients. In the RG, total gastrectomy (TG) was performed in 24 (62%) patients and subtotal gastrectomy (SG) in 15 (38%) patients. The median hospital stay of the patients in the NRG and the RG were 6 (range 2-25) and 11 (range 3-37)

Table 1. Comparison of demographics and tumor characteristics of the patients

Characteristics	NRG (N=40)	RG (N=39)	p-value
Age (years)			
70<	24	17	0.108
70≥	16	22	
Gender			
Female	13	14	0.468
Male	27	25	
ASA score			
≥3	23	20	0.371
<3	17	19	
Tumor location			
Upper 1/3	2	11	0.006
Middle 1/3	12	14	0.375
Lower 1/3	10	9	0.582
2/3 or more	16	5	0.006
Tumor size (cm)			
<5	1	10	0.003
≥5	39	29	
Chemotherapy			
Yes	12	19	0.070
No	28	20	
Tumor histology			
Differ.	25	23	0.464
Undiffer.	15	16	
Peritoneal dissemination			
Present	22	1	0.000
Liver metastasis			
Present	4	3	0.514
Adjacent organ invasion			
Present	19	9	0.020
DLM			
Present	37	32	0.145

NRG: non-resection group, RG: resection group, DLM: distant lymph node metastasis

days, respectively, and was significantly shorter in the NRG than in the RG ($p < 0.0001$). Hospital mortality occurred in 5 patients (12.5%) in the NRG and in 6 patients (15.3%) in the RG ($p = 0.482$). The Kaplan-Meier median overall survival of the NRG and the RG was 1.7 months (95% CI, 1.28-2.11 months) and 5 months (95% CI, 2.65-7.34 months), respectively, and it was significantly longer in the RG ($p = 0.001$) (Figure 1). In the RG, when patients were categorized into two groups as being greater or less than 70 years of age, there was no statistically significant difference between the groups in terms of hospital mortality ($p = 0.075$). In univariate analysis, the following were found to be related prognostic factors affecting overall survival:

**Figure 1.** Overall survival in the NRG and the RG (median 1.7 vs 5 months; $p = 0.01$).

al: age greater or less than 70 years ($p < 0.0001$), gender ($p = 0.023$), ASA score ($p = 0.008$), only laparotomy performed ($p = 0.007$), adjuvant chemotherapy administration ($p < 0.001$), subtotal gastrectomy performed ($p = 0.015$), and complete resection performed ($p = 0.001$) (Table 2). In multivariate analysis, significant independent prognostic factors affecting overall survival were identified as gender ($p = 0.003$), postoperative chemotherapy administration ($p = 0.000$), age over 70 years or less ($p = 0.001$), and resection ($p = 0.001$) (Table 3).

Discussion

Gastric cancer is usually detected in advanced stages except in countries such as Japan which have formal screening programs. Unfortunately, less than one third of the patients are candidates for surgical management worldwide. In our study, 35% of the patients were found to be in advanced stages intraoperatively. If the number of patients who were accepted in inoperable stages and surgical exploration was not considered, this rate may be higher than estimated. In addition, diagnostic laparoscopy is an effective method in staging gastric cancer and it can avoid unnecessary laparotomy for patients with advanced disease. In our clinic, staging laparoscopy for gastric cancer was started in 2013. For that reason, the patients who were staged with laparoscopy were not enrolled in the study.

In the present study, male gender and age less

Table 2. Univariate survival analysis for gastric cancer patients with advanced disease

Factors	No of patients N (%)	Mean (months)	Median (months)	p value
Age (years)				
<70	41 (51.9)	7.54	6	0.0001
≥70	38 (48.1)	3.02	1.7	
Gender				
Female	27 (34.2)	3.55	2	0.023
Male	52 (65.8)	6.30	3	
ASA score				
≥3	43 (54.4)	3.47	2.1	0.008
<3	36 (45.6)	7.25	5	
Tumor location				
Upper 1/3	13 (16.4)	5.31	5	0.947
Middle 1/3	26 (33.0)	5.53	3.1	0.785
Lower 1/3	18 (22.8)	6.17	1.7	0.550
2/3 or more	22 (27.8)	4.22	1.8	0.347
Tumor size (cm)				
<5	11 (13.9)	5.58	2.4	0.812
≥5	68 (86.1)	5.25	3	
Chemotherapy				
Yes	31 (32.2)	9.59	8	0.0001
No	48 (68.8)	2.62	1.6	
Histology				
Dif.	48 (68.8)	5.11	2.4	0.593
Undif.	31 (39.2)	5.77	5	
Peritoneal dissemination				
Present	23 (29.1)	3.83	1.8	0.182
Absent	56 (70.9)	5.90	3.6	
Liver metastasis				
Present	7 (8.90)	4.24	2.7	0.786
Absent	72 (91.1)	5.39	3	
Adjacent organ invasion				
Present	28 (35.4)	4.73	2	0.337
Absent	51 (64.6)	5.74	3	
Type of the operation				
L	22 (27.8)	2.74	1.60	0.007
GE	13 (16.5)	3.39	2	0.217
J	5 (6.30)	4.54	3.10	0.834
TG	24 (30.4)	6.27	5	0.384
SG	15 (19.0)	8.95	8	0.015
Resection of the primary tumor				
Resection	39 (49.4)	7.32	5	0.001
No resection	40 (50.6)	3.20	1.70	

Dif: differentiated, Undif : undifferentiated, L: laparotomy alone, GE: gastroenterostomy, J: jejunostomy, TG: total gastrectomy, SG: subtotal gastrectomy

than 70 years emerged as positive prognostic factors for improved overall survival in multivariate

analysis. According to our results, the male/female ratio was 2.25/1 and this finding was consistent

Table 3. Cox regression multivariate analyses of overall survival in advanced stage gastric cancer patients

Factors	<i>p</i> value	HR	95%CI
Gender	0.003	2.166	1.302-3.603
Resection	0.001	2.437	1.444-4.115
Adjuvan chemotherapy	0.000	3.255	1.907-5.555
Age 70 \geq or lower	0.001	2.471	1.473-4.146

HR: hazard ratio, CI: confidence interval!

with previous studies [9]. In a study reported by Xiao et al. [10], it was stated that being older than 65 years and being female had negative effects on survival in gastric cancer patients (HR:1.962, 95% CI: 1.342-2.870, $p=0.001$ and HR:1.679, 95% CI:1.079-2.612, $p=0.022$, respectively). Consistent with these results, the present study found that overall survival was shorter in female patients and patients older than 70 years of age. In addition, Sato et al. [11] reported shorter overall survival for gastric cancer in female patients. They attributed this finding to late diagnosis in older patients with more diffuse histology types, and differences in following screening, medical examinations, or treatment for gastric cancer. In the present study, consistent with this finding, the overall survival was significantly shorter in female patients (HR:2.166, 95% CI: 1.302-3.603, $p=0.003$).

The incidence of gastric cancer increases with age and it is usually detected in the sixth and seventh decades of life. In the Dutch Gastric Cancer Trial, it was reported that palliative resection may be beneficial for patients less than 70 years [12]. Furthermore, previous studies including large numbers of patients have also supported this finding [13,14]. Consistent with these findings, it was found that being older than 70 years of age was an independent prognostic factor in advanced gastric cancer ($p=0.001$, HR:2.471, 95% CI: 1.473-4.146).

ASA score is another factor in patients with advanced gastric cancer, which may have an impact on postoperative mortality. Marriette et al. [6] reported that an ASA score of 3-4 ($p<0.001$) is a negative predictor of postoperative mortality. Similarly, in this study, ASA score of 3 or higher was found to be a negative predictor in univariate analysis, but not in multivariate analysis.

The resection type is another factor that may impact the OS. In a randomized study from Italy, it was reported that there was no statistically sig-

nificant difference in the 5-year survival between patients who underwent TG or SG with negative surgical margins (62.4 TG vs 65.3% SG) [15]. In contrast to this study, Sanchez-Bueno et al. [16] reported significantly longer overall survival rates in patients who underwent SG compared with TG (48.1 SG vs 18% TG). Similarly, Liang et al. [14] reported longer survival for patients who underwent SG. In our results with the log-rank test, overall survival was longer in patients who underwent SG ($p=0.016$). However, the operation type alone had no effect on survival according to the multivariate analysis.

The size of the tumor is another prognostic indicator for gastric carcinoma. In a study carried out on 513 patients with gastric cancer, Wang et al. [17] classified the maximum tumor size into 4 subgroups and reported that the overall survival decreased when the tumor size increased. In contrast, Xiao et al. [10] reported that there was no relationship between tumor size and prognosis in a series of 431 patients (tumor size greater than 4 cm, RR:1.511, 95% CI, 0.890-2.566, $p=0.126$). In our study, there was no statistically significant survival difference between patients with tumor size less or greater than 5 cm in advanced gastric cancer ($p=0.812$).

Considerable controversy is found in the literature about the value of palliative resection for advanced-stage gastric cancer. In a previous study from Greece, Sougioultzis et al. [9] reported the results of 218 patients who had undergone palliative gastrectomy for stage IV gastric carcinoma. They reported that median survival was significantly higher in patients with previous palliative gastrectomy (53 vs 16 weeks). In a multicenter study from 21 French centers, Mariette et al. [6] compared the results of 677 patients who underwent resection and 532 patients who were not resected for advanced gastric cancer. They reported that median survival was significantly longer in

the resection group (11.9 vs 8.5 months, $p < 0.001$). Additionally, Amaral et al. [4] reported that palliative resection showed superiority in survival only for patients who had locally advanced disease. Besides this study, many other studies exist in the literature that advocate that there is no survival benefit with palliative resection in patients with two or more incurability criteria; these include hepatic metastasis, organ invasion, peritoneal dissemination, and lymph node involvement [7,18]. These conflicting results indicate that patient and tumor-related factors should be taken into consideration before a decision regarding resection in advanced gastric cancer is made.

Discussions regarding patients with advanced gastric cancer focused on whether palliative resection has a survival advantage for patients with peritonitis carcinomatosa or not. According to the study of Kikuchi et al. [19], which included 122 patients, it was suggested that palliative gastrectomy is suitable for patients with peritonitis carcinomatosa provided that there is no evidence of liver metastasis. Additionally, Lin et al. [20] reported that palliative gastrectomy combined with adjuvant chemotherapy improved overall survival in patients with stage IV gastric cancer, even in patients with incurability criteria such as liver metastasis, peritoneal dissemination, and lymph node metastasis. In contrast, some authors suggest that palliative resection has an advantage in patients with locally advanced disease or in patients with solitary metastasis [4,21]; no survival benefit, however, was reported in patients with peritonitis carcinomatosa [22]. In our study, it was seen that there was no impact of inoperability criteria (peritoneal dissemination, distant metastasis, or adjacent organ invasion) alone on overall survival according to the log-rank test results. However, resection was found to be a significant independent prognostic factor for OS according to

multivariate analysis results ($p = 0.001$, HR: 2.437, 95% CI 1.444-4.115).

In a more recent meta-analysis in 2013, Sun et al. [23] concluded that patients who received adjuvant chemotherapy had better survival benefit and they also added that synchronous metastectomy with gastric resection had improved survival. Many studies have affirmed the survival benefit with postoperative chemotherapy or chemoradiotherapy for gastric cancer [24-26]. In 2002, Panzini et al. [27] reported a meta-analysis of 17 phase 3 studies which included 3118 patients. According to the results of this meta-analysis, adjuvant chemotherapy had positive effects on overall survival. Consistent with these studies, our study also revealed that adjuvant chemotherapy prolonged survival as an independent prognostic factor ($p = 0.000$, HR: 3.255, 95% CI 1.907-5.555).

Our study has some limitations. It is a retrospective study and quality of life after resection was not evaluated. Our hospital is a tertiary regional hospital and we have no gastrointestinal surgery section. For that reason, surgical expertise may have played a role in the selection of patients who should undergo resection or not and this may result in bias. Additionally, patients with poor performance status did not receive chemotherapy.

In the present study, multivariate analysis revealed that age, gender, resection and chemotherapy were independent prognostic factors for overall survival. Therefore, patient and tumor-related factors should be taken into consideration while planning resection for advanced-stage patients. Randomized controlled studies are required.

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