Lower Mediastinal Lymph Node Metastasis Is an Independent Survival Factor of Siewert Type II and III Adenocarcinomas in the Gastroesophageal Junction

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We examined clinicopathological features and surgical outcomes in patients with adenocarcinoma in the gastroesophageal junction (GEJ), while also analyzing the survival factors that have a prognostic impact. Between 1991 and 2009, 61 patients with tumors in the GEJ (Siewert type II and III) underwent primary surgical resection. Thirty of 61 patients had type II tumors (49.2%) and 31 had type III tumors (50.8%). The tumor size was larger in type III tumors than type II tumors ($P = 0.0026$). The overall 5-year survival rates in patients with type II tumors and type III tumors were 44.2 per cent and 41.4 per cent, respectively, with no significant differences ($P = 0.1888$). The independent survival factors were lower mediastinal lymph node metastasis ($P = 0.0323$) and a noncurative resection ($P = 0.0442$). The independent survival factors for patients who underwent curative resections were the tumor size ($P = 0.0422$), M category ($P = 0.0489$), and lower mediastinal lymph node metastasis ($P = 0.0482$). This study showed lower mediastinal lymph node metastasis to be an independent survival factor, and also suggested that lower mediastinal lymph node metastasis was associated with distant metastasis in patients with adenocarcinoma in the GEJ (Siewert type II and III). Therefore, the preoperative early detection of such metastasis is important to improve patient survival.

THERE IS AN INCREASED INCIDENCE of adenocarcinoma in the gastroesophageal junction (GEJ) in the Western world.[1–3] Adenocarcinoma in the GEJ is an aggressive disease with early lymphatic and hematogenous dissemination, and many patients present with recurrence within 2 years after resection.[4–6] Therefore, it is associated with a poor prognosis.[7–9] Tumor-Node-Metastasis (TNM) cancer staging systems are survival factors of adenocarcinoma in the GEJ,[4, 6, 10–12] but new survival factors should be examined to develop a new therapeutic strategy.

The GEJ represents the border between the esophagus and the stomach, thus the choice of surgical procedure for adenocarcinoma in the GEJ is still discussed controversially.[10, 13–18] The results of randomized controlled trials have been reported.[19, 20] Hulscher et al.[19] performed a prospective randomized controlled trial to elucidate the optimal surgical approach for Siewert type I and II tumors in GEJ, and suggested that an extended transthoracic resection be recommended only for patients with type I tumors, however, not for patients with type II tumors. A meta-analysis comparing surgical treatment for lower esophageal carcinoma showed a higher morbidity for transthoracic resection than for transhiatal resection, but a similar survival.[21] A Japanese group conducted a randomized controlled trial to compare the effect of the left thoracoabdominal approach (LTA) and the transhiatal approach (TH) in cancer of the cardia or subcardia with esophageal invasion of 3 cm or less.[20] They reported that the LTA does not improve survival after the TH and it leads to increased morbidity in patients with cancer of the cardia or subcardia, and the LTA is therefore not justified to treat these tumors. However, there is no evidence of surgical therapy using the LTA for adenocarcinoma in the GEJ with esophageal invasion of more than 3 cm. We have performed the LTA for patients with esophageal invasion of more than 3 cm. This study examined adenocarcinoma in the GEJ including esophageal invasion of more than 3 cm.

Most tumors in the GEJ in eastern Asian countries, including Japan, are Siewert type II and III.[22] This

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article examined that clinicopathological features and surgical outcomes in patients with adenocarcinoma in the GEJ (Siewert type II and III tumors), while also analyzing the survival factors that have a prognostic impact.

Patients and Methods

Patient Population and Classification

Sixty-one patients with adenocarcinoma in the GEJ underwent surgical resection at the Second Department of Surgery, Wakayama Medical University between January 1991 and December 2009. Adenocarcinoma in the GEJ was defined as tumors with centers within 5 cm of the anatomical GEJ.[23, 24] The location of the primary cancer was classified using Siewert's classification.[23] A tumor with a lesion with a center between 1 cm oral and 2 cm aboral of the anatomic EGJ was a type II cancer (true carcinoma of the cardia), whereas a tumor with a center more than 2 cm below the anatomic EGJ was a type III cancer (subcardial gastric carcinoma).[23] The location of the tumor center and Siewert's classification were determined retrospectively based on the photographic findings of the resected specimens.

Surgical Approach

The choice of surgical approach and procedure was based on the tumor location and the tumor stage, based on abdominal and thoracic CT scans, endoscopy, endoscopic ultrasonography, and a barium meal study.

We had performed LTA for patients with esophageal invasion of more than 3 cm, or those with lower mediastinal lymph nodes more than 1 cm in diameter at preoperative staging. LTA involved total gastrectomy or proximal gastrectomy via an oblique incision over the left thorax and the abdomen. In the thoracic cavity, lower mediastinal lymph nodes were dissected below the left inferior pulmonary vein with esophagectomy. En block lymphadenectomy of a formal D2 lymphadenectomy in addition to the dissection of the lower mediastinal lymph nodes was performed if the operation was curative. Only the periesophageal lymph nodes were dissected as lower mediastinal lymph nodes if the operation was not curative.

On the other hand, the TH included total gastrectomy or proximal gastrectomy with transhiatal resection of the distal esophagus for patients with esophageal invasion of less than 3 cm. En block lymphadenectomy of a formal D2 lymphadenectomy in addition to the periesophageal lymph nodes was performed if the operation was curative.

Total gastrectomy was the removal of the entire stomach and proximal duodenum with esophagojejunal reconstruction. Proximal gastrectomy was defined as the resection of the proximal stomach with either esophagogastric anastomosis or the interposition of the jejunum. An end-to-side esophagojejunostomy or esophagogastrostomy was performed using a circular stapler.

Postoperative complications, such as anastomotic leakage, pancreatic fistula, intra-abdominal abscess, pyothorax, pneumonia, and mediastinitis were recorded as expected events. All in-hospital deaths and deaths within 1 month after surgery were defined as hospital mortality.

Histopathological Assessment

Resected specimens were assessed by experienced pathologists. All removed lymph nodes were counted, assessed separately, and identified according to their location. Hematoxylin and eosin–stained slides of paraffin-embedded tissue were used to determine tumor depth and the presence of lymph node metastases. Tumors were pathologically staged according to the TNM criteria for the stomach by using the 6th edition of the Cancer Staging Manual published by the American Joint Committee on Cancer.[25] Involvement of lower mediastinal lymph nodes (such as lower thoracic paraesophageal and supradiaphragmatic nodes) was classified as regional metastasis. Tumor histology and the location of regional lymph nodes were described according to the Japanese Classification of Gastric Carcinoma.[26]

Statistical Analysis

Data are presented as the prevalence or means (± standard deviation). The frequency distributions between the two groups were evaluated by the χ^2 test, Fisher's exact test, or the Mann-Whitney U test. Overall survival curves were estimated by the Kaplan-Meier method and the survival factors were assessed by log-rank test and Cox regression analyses. A P value < 0.05 was considered to be significant.

Results

Thirty of the 61 patients with resected adenocarcinoma of the GEJ had type II tumors (49.2%), and 31 had type III tumors (50.8%). A comparison of the clinicopathological features showed the tumor size to be larger in type III tumors than in type II tumors (P = 0.0026, Table1).

Table 1 shows the distribution of the surgical procedures. LTA was performed in 46.7 per cent of patients with type II tumors and 29 per cent of patients with type III tumors. On the other hand, TH was performed in 53.3 per cent of patients with type II tumors, and 71 per cent of patients with type III tumors. Patients with type II tumors underwent more LTA than patients with type III tumors, but no significant difference was observed in the distribution of the surgical procedures.

Table 2 shows histopathological characteristics of the resected specimens. There were no significant differences in TNM stage, histological type, or R category between type II tumors and III tumors. Moreover, the frequencies of metastasis in each lymph node station in patients who underwent curative resections were quite similar between the two groups (Table 3).

As shown in Table 4, postoperative morbidity was 17.4 per cent in patents with LTA, 21.1 per cent in patents with TH, and there were no significant differences.

TABLE 1. *Clinicopathological Features and Surgical Procedures of Siewert II/III Gastric Cancer Patients*

Classification	Type II (n = 30)	Type III (n = 31)	*P* value
Age (mean ± SD)	66.0 ± 11.1	64.8 ± 10.0	NS
Male:female ratio	2:1	2.1:1	NS
Macroscopic type			
Well-defined/Ill-defined	10/20	10/21	NS
Superficial type	1 (3.3%)	8 (25.8%)	
Borrmann 1	3 (10%)	1 (3.2%)	
Borrmann 2	6 (20%)	1 (3.2%)	
Borrmann 3	19 (63.3%)	17 (54.8%)	
Borrmann 4	1 (3.3%)	3 (9.7%)	
Unclassifiable	0	1 (3.2%)	
Maximum tumor size (mm, mean ± SD)	49 ± 20	74 ± 38	*P* = 0.0026
Approach			NS
Left thoracoabdominal approach	14 (46.7%)	9 (29%)	
Transhiatal approach	16 (53.3%)	22 (71%)	
Type of gastrectomy			NS
Distal esophagectomy and total gastrectomy	26 (86.7%)	24 (77.4%)	
Distal esophagectomy and proximal gastrectomy	4 (13.3%)	7 (22.6%)	

SD, standard deviation.

TABLE 2. *Histopathological Characteristics of Siewert II/III Gastric Cancer Patients*

Classification	Type II (n = 30)	Type III (n = 31)	*P* value
TNM stage			NS
I/II	16 (53.3%)	12 (38.7%)	
III/IV	14 (46.7%)	19 (61.3%)	
Histological type			NS
Differentiated	17 (56.7%)	19 (61.3%)	
Undifferentiated	13 (43.3%)	12 (38.7%)	
R category			NS
R0	25 (83.3%)	25 (80.6%)	
R1/2	5 (16.7%)	6 (19.4%)	
Proximal margin			NS
Positive	0	1 (3.2%)	
Negative	30 (100%)	30 (96.8%)	
Lower mediastinal lymph node metastasis	3 (10%)	3 (9.7%)	NS
Para-aortic lymph node metastasis	4 (13.3%)	4 (12.9%)	NS

TABLE 3. *Frequencies of Lymph Node Metastasis Stratified by the Siewert Type in Patients who Underwent a Curative Resection*

Classification	Type II (n = 25)	Type III (n = 25)	*P* value
Paracardial	17 (68%)	9 (36%)	0.0235
Along the lesser curvature	14 (56%)	15 (60%)	NS
Along the greater curvature	1 (4%)	5 (20%)	NS
Suprapyloric	2 (8%)	2 (8%)	NS
Infrapyloric	1 (4%)	3 (12%)	NS
Along the LGA	6 (24%)	6 (24%)	NS
Along the CHA	2 (8%)	2 (8%)	NS
At the splenic hilum	2 (8%)	1 (4%)	NS
Along the SA	6 (24%)	5 (20%)	NS
Lower mediastinal	3 (12%)	0	NS
Para-aortic	3 (12%)	3 (12%)	NS

LGA, left gastric artery; CHA, common hepatic artery; SA, splenic artery.

TABLE 4. *Postoperative Morbidity and Mortality after the Left Thoracoabdominal Approach and the Transhiatal Approach*

	LTA (n = 23)	TH (n = 38)	*P* value
Non-surgical complication			
Pneumonia	1 (4.3%)	0	NS
MRSA enterocolitis	2 (8.7%)	0	NS
Surgical complication			
Intra-abdominal abscess	0	1 (2.6%)	NS
Postoperative ileus	0	1 (2.6%)	NS
Anastomotic leakage	0	3 (7.9%)	NS
Leakage of pancreatic juice	1 (4.3%)	3 (7.9%)	NS
Morbidity	4 (17.4%)	8 (21.1%)	NS
Hospital mortality	0	0	NS

MRSA, methicillin-resistant *Staphylococcus aureus*.

No hospital mortality occurred in the patients with either approach. The overall 5-year survival rates in patients with type II tumors and type III tumors were 44.2 per cent and 41.4 per cent, respectively, and no significant differences were observed ($P = 0.1888$, Fig. 1).

A univariate analysis of the patients with resected adenocarcinoma of the esophagogastric junction revealed that tumor size (>7 cm, $P = 0.0039$), macroscopic appearance (ill-defined, $P = 0.0153$), histological type (undifferentiated, $P = 0.0143$), T category (T3/4, $P = 0.0007$), N category (N1/2/3, $P = 0.0141$), M category (M1, $P < 0.0001$), lymphatic invasion (present, $P = 0.0401$), lower mediastinal lymph node metastasis (present, $P = 0.0008$), and curability (noncurative, $P = 0.0002$) were survival factors (Table 5). The multivariate analysis showed lower mediastinal lymph node metastasis (present, $P = 0.0323$) and a noncurative resection (R1/2 resection, $P = 0.0442$) to all be independent survival factors (Table 5). The median survival time (MST) for patients with and without lower mediastinal lymph node metastases were 193 ± 45.5 days and 864 ± 70.4 days, respectively. The MST for patients with these metastases was significantly shorter than the MST for patients without these metastases ($P = 0.0008$) (Fig. 2).

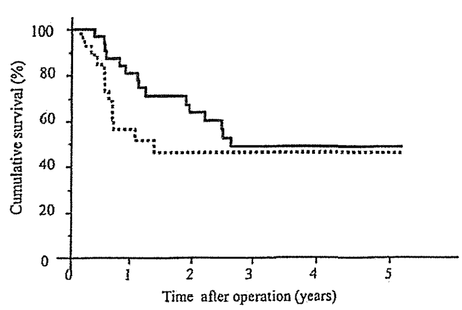

FIG. 1. Overall survival curves by Siewert's classification. The overall 5-year survival rates in patients with type II tumors — and type III tumors ···· were 44.2 per cent and 41.4 per cent, respectively; there was no significant difference ($P = 0.1888$).

A multivariate analysis of the patients who underwent curative resections showed tumor size (>7 cm, $P = 0.0422$), M category (M1, $P = 0.0489$), and lower mediastinal lymph node metastasis (present, $P = 0.0482$) to be independent survival factors (Table 6). All patients with an M1 status who underwent curative resections demonstrated paraaortic lymph node metastasis.

Discussion

Lower mediastinal lymph node metastasis was an independent survival factor of adenocarcinoma in the GEJ in the current series (Siewert type II and III tumors). In fact, the survival of patients with lower mediastinal lymph node metastasis was shorter than the survival of patients without this metastasis. The occurrence of lower mediastinal lymph node metastasis from Siewert type II and III tumors is reported to be 10 to 40 per cent.[27–33] Adenocarcinomas in the GEJ are staged in the same manner as that for gastric cancer by some authors,[7, 8, 22, 34, 35] but more like esophageal tumors by others.[36, 37] Lower mediastinal lymph node metastasis is considered to extend beyond regional for gastric cancer, but is classified as regional lymph node for esophagogastric junction cancer.[25] The current results suggest that lower mediastinal lymph nodes should be classified as distant metastasis with respect to Siewert II and III tumors. Taken together, the dissection of lower mediastinal lymph nodes was not effective for patients with lower mediastinal lymph node metastasis.

The present study compared the clinicopathological features and surgical outcomes of Siewert type II and III adenocarcinoma of the GEJ. There was a significant difference between type II and III adenocarcinoma regarding the maximum tumor size; however no significant difference was seen for other clinicopathological features, surgical procedures, and overall survival. Moreover, the distribution of lymph node metastases was quite similar between types II and

TABLE 5. *Univariate and Multivariate Survival Factors for Siewert Types II and III GEJ Cancer*

Clinicopathological Variable	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender (male)	0.794 (0.365–1.726)	0.5601		
Age (> 65 years)	1.119 (0.533–2.349)	0.7699		
Siewert (type II)	0.608 (0.287–1.287)	0.1888		
Tumor size (> 7 cm)	2.862 (1.357–6.038)	***0.0039***	1.280 (0.481–3.401)	0.6210
Esophageal invasion (> 3 cm)	1.968 (0.927–4.178)	0.0725		
Macroscopic appearance (ill-defined)	3.130 (1.185–8.268)	***0.0153***	1.446 (0.483–4.327)	0.5096
Histological type (undifferentiated)	2.491 (1.171–5.299)	***0.0143***	0.950 (0.347–2.600)	0.9208
T category (T3/4)	3.564 (1.635–7.769)	***0.0007***	1.736 (0.615–4.898)	0.2975
N category (N1/2/3)	5.053 (1.198–21.309)	***0.0141***	2.459 (0.257–23.497)	0.4345
M category (M1)	5.515 (2.334–13.033)	***<0.0001***	2.010 (0.666–6.068)	0.2154
Lymphatic invasion (present)	3.770 (1.844–13.757)	***0.0401***	1.431 (0.076–26.914)	0.8106
Venous invasion (present)	1.487 (0.631–3.507)	0.3615		
Lower mediastinal lymph node metastasis (present)	4.993 (1.767–14.109)	***0.0008***	3.621 (1.115–11.758)	***0.0323***
Approach (transthoracic resection)	1.576 (0.750–3.311)	0.2255		
Postoperative morbidities (present)	2.061 (0.949–4.477)	0.0618		
Curability (noncurative)	4.634 (1.924–11.158)	***0.0002***	2.605 (1.025–6.618)	***0.0442***
Neoadjuvant chemotherapy (absent)	0.692 (0.204–2.346)	0.5516		
Adjuvant chemotherapy (absent)	0.547 (0.220–1.360)	0.1944		

CI, confidence interval.

III for patients who underwent a curative resection. There is no consensus regarding whether type II tumors should be treated like type I tumors by thoracotomy, or type II tumors should be treated like type III tumors by TH. We considered that type II tumors should be treated in the same way as type III tumors, and the length of esophageal invasion was useful for selecting the surgical approach in patients with type II and III tumors.

All of the patients with lower mediastinal lymph node metastasis had more than 3 cm of esophageal invasion, and there was no recurrence of lower mediastinal lymph node in patients with invasion of 3 cm or less. Therefore, the length of esophageal invasion may be associated with lower mediastinal lymph node metastasis. TH is recommended to treat patients with Siewert type II or III tumors with esophageal invasion of 3 cm or less.[20] However, the prophylactic dissection of the lower mediastinal lymph nodes using LTA is unclear for patients with esophageal invasion of more than 3 cm. A randomized controlled trial is needed to examine whether LTA is useful for the treatment of these patients.

FIG. 2. Overall survival curve of patients with lower mediastinal lymph node metastases. The median survival time for patients with and without lower mediastinal lymph node metastases were 193 ± 45.5 days ···· and 0.864 ± 70.4 days —, respectively. The MST for patients with these metastases was significantly shorter than the MST for patients without these metastases (P = 0.0008).

A noncurative tumor resection (R1/2 resection) was also a strong independent survival factor in adenocarcinoma of the GEJ (Siewert type II and III tumors). The primary purpose of a surgical resection for this adenocarcinoma is the complete removal of both the primary tumors and lymph nodes. A microscopically positive proximal margin occurred in only one patient with TH, and no significant differences were observed in the postoperative morbidity and the hospital mortality between LTA and TH. Moreover, Lekakos et al.[38] report LTA offers satisfactory quality of life and surgical radicality. Therefore, LTA might be useful for obtaining a safe surgical margin for patients with esophageal invasion of more than 3 cm. However, some investigators report that transthoracic resections have higher morbidity and mortality rates than transhiatal resections.[20, 21] LTA is invasive and generally associated with considerable morbidity and mortality. In the future, LTA should be less invasive by using video-assisted surgery or thoracoscopic surgery.

In conclusion, lower mediastinal lymph node metastasis was an independent survival factor in patients with adenocarcinoma of the GEJ (Siewert types II and III). The results of this study suggest that lower mediastinal lymph node metastasis indicates the presence of distant metastasis. The early detection of lower

TABLE 6. *Univariate and Multivariate Survival Factors for Patients who Underwent a Curative Resection*

Clinicopathological Variable	Univariate Analysis		Multivariate Analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Gender (male)	0.693 (0.272–1.767)	0.4422		
Age (>65 years)	1.561 (0.627–3.884)	0.3384		
Siewert (type II)	0.557 (0.224–1.385)	0.2080		
Tumor size (>7 cm)	2.937 (1.185–7.275)	***0.0199***	2.737 (1.036–7.232)	***0.0422***
Esophageal invasion (>3 cm)	1.498 (0.569–3.947)	0.4134		
Macroscopic appearance (ill-defined)	2.998 (0.992–9.058)	0.0517		
Histological type (undifferentiated)	2.617 (1.059–6.470)	***0.0372***	1.489 (0.489–4.534)	0.4835
T category (T3/4)	3.252 (1.303–8.114)	***0.0115***	1.753 (0.615–4.999)	0.2939
N category (N1/2/3)	3.864 (0.892–16.737)	0.0707		
M category (M1)	5.707 (1.820–17.891)	***0.0028***	4.383 (1.007–19.079)	***0.0489***
Lymphatic invasion (present)	4.726 (0.631–35.427)	0.1307		
Venous invasion (present)	1.726 (0.570–5.223)	0.3338		
Lower mediastinal lymph node metastasis (present)	5.012 (1.090–23.053)	***0.0384***	6.360 (1.014–39.886)	***0.0482***
Approach (transthoracic resection)	1.039 (0.409–2.641)	0.9361		
Postoperative morbidities (present)	1.938 (0.735–5.107)	0.1810		
Neoadjuvant chemotherapy (absent)	0.179 (0.047–0.679)	0.0114	0.604 (0.110–3.316)	0.5621
Adjuvant chemotherapy (absent)	0.487 (0.160–1.478)	0.2038		

CI, confidence interval.

mediastinal lymph node metastasis is therefore important to improve the survival of patients with this type of metastasis.

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ORIGINAL ARTICLE

The evaluation of surgical treatment for gastric cancer patients with noncurative resection

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Abstract
Purpose This study aims to analyze the results of treatment in a series of 233 gastric cancer patients who underwent a noncurative resection.
Methods We performed a retrospective study of patients with noncurative treatment for advanced gastric cancer who were divided into three treatment groups: total gastrectomy (TG, n=150), distal gastrectomy (DG, n=44), and nonresection (NR, bypass procedure or chemotherapy only, n=39).
Results In multivariate analysis, surgical treatment (TG) and an absence of chemotherapy were significant independent prognostic factors for a poor survival. In the late period, the overall survival rate was significantly lower in the TG group than in the DG group (p=0.005) and was marginally lower than in the NR group (p=0.054). The resection group had a poorer compliance for chemotherapy than the NR group, and the TG group had a poorer compliance than the DG group (p<0.01). The morbidity rate was higher in the TG group than in the DG group (p<0.05).
Conclusions TG is considered to be inappropriate for the treatment of noncurative gastric cancer because of the poor prognosis, high morbidity rates, and poor compliance for chemotherapy associated with the procedure. However, noncurative DG was acceptable and postoperative chemotherapy should be used in selected patients.

Keywords Palliative gastrectomy · Noncurative resection · Adjuvant chemotherapy · Gastric cancer

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Abbreviations

TG	Total gastrectomy
DG	Distal gastrectomy
OS	Overall survival
MST	Median survival time
HR	Hazard ratio
CI	Confidence interval

Introduction

Gastric cancer is the second most common cancer in the world. Despite increasing emphasis on screening examinations, approximately 15% of patients with newly diagnosed gastric adenocarcinoma are clinical stage IV [1]. The prognosis of advanced gastric cancer patients with noncurative factors, such as hematogenous metastasis, peritoneal metastases, and lymphatic spread beyond the limit of gross surgical resection, is very poor, with a median survival time (MST) of approximately 8 months [2]. To further improve the outcome, multimodality therapy, such as radiotherapy and chemotherapy without surgery, has been reported in many studies, but these treatments have not been satisfactory for completely palliating the symptoms [3, 4]. On the other hand, there is no definitive evidence that noncurative gastrectomy has any survival benefits.

It is often difficult to decide whether a gastrectomy should be performed in patients with unexpected metastatic lesions encountered during surgical exploration. Several studies have demonstrated that palliative distal gastrectomy (DG) is well accepted as a palliative procedure because of its anatomical feasibility, but that a total gastrectomy (TG) should be avoided unless necessary to relieve obstruction or bleeding, owing to the expectation of much higher morbidity and mortality rates [5]. In contrast, there have been several studies showing that gastric cancer patients with a single noncurative factor may benefit from palliative resection [2]. The number of long-term survival cases after surgery has been increasing with the improvement of combination chemotherapy and with decreasing postoperative complications. Therefore, it is permissible to perform noncurative resection of gastric cancer [6].

Recently, in Japan and other Asian countries, S-1 has been considered to be the most important drug for metastatic or recurrent gastric cancer based on the results of several clinical trials [7]. Therefore, chemotherapy using S-1 might have some impact on the clinical usefulness of noncurative gastrectomy.

In this study, we retrospectively examined the prognostic factors of patients with gastric cancer who were unable to undergo curative resection and evaluated the survival benefits of noncurative gastrectomy. In addition, we performed an analysis dividing the patients into an early period (1991–1998) and a late period (1999–2007) because S-1 became available in Japan in 1999.

Methods

Patients

From September 1991 through December 2007, a total of 1,598 patients with gastric cancer were treated at Wakayama Medical University Hospital. This retrospective study included 233 patients with primary gastric cancer who underwent noncurative surgical treatment or chemotherapy. These 233 patients were followed up for at least 5 years or until death. The median follow-up interval for the patients was 88 months from the date of treatment. No patients received neoadjuvant chemotherapy.

Pretreatment evaluation

Patients routinely underwent pretreatment clinical assessment with computed tomographic (CT) scanning, endoscopy, and endoscopic ultrasonography. Then, we analyzed the clinicopathological characteristics and intraoperative parameters. In staging these cases, we used the 7th edition UICC-TNM classification [8]. Positive peritoneal cytology was classified as metastatic disease (M1). In the nonresection (NR) group, regional lymph nodes were considered to be involved by metastases if they were larger than 8 mm in short-axis diameter [9]. At baseline, lymph nodes will be categorized as follows: measurable lesions that can be accurately measured in at least one dimension [longest diameter to be recorded] as ≧20 mm with conventional techniques or as ≧10 mm with spiral CT scan.

Treatment

The indications for gastrectomy were judged individually by the operating surgeons based on the patients' general health, performance status, symptoms such as stenosis or bleeding, extent of disease, and feasibility of resection for those with extensive invasion to the retroperitoneum or for those with extensive peritoneal metastasis. Bypass surgery was performed as a palliative surgery when complete resection was impossible. An exploratory laparotomy was performed when preoperative imaging failed to detect nonresectable disease. Staging laparoscopy was not employed in this series. Patients who underwent R0 gastrectomy, but who were diagnosed with R1 resection postoperatively by histopathological examinations, were included in this study and were considered to be in the noncurative resection group. Chemotherapy was administered to patients with an inoperable status defined by noncurative factors, high-risk preoperative status, or personal preference. Patients did not undergo surgical treatment for palliation of local symptoms such as bleeding, stenosis, or perforation in the NR group. Since 1999, the oral dihydropyrimidine dehydrogenase inhibitor fluoropyrimidine, S-1, has been considered to be the first-choice treatment for advanced gastric cancer in Japan [7]. Before that, various anticancer drugs such as mitomycin C, adriamycin, 5-fluorouracil (5-FU), and cisplatin were used as single agents or in combination [10, 11].

Therefore, we divided the patients into two groups: an early period group (1991–1998; n=93) and a late period group (1999–2007; n=140). In the early period, most of the patients who received chemotherapy received two agents, predominantly cisplatin and a fluoropyrimidine (CS). In the late period, first-line chemotherapy with S-1 and cisplatin was used.

Postoperative outcomes

The survival period was calculated from the start of treatment to death or the latest followed up date. Hospital mortality was defined as death within 30 days or during the hospital stay. Postoperative complications were classified according to the Clavien–Dindo classification of surgical complications, and grades II, III, and IV were regarded as surgical morbidity [12].

Statistical analysis

The statistical analyses were performed using the SPSS Version 17.0 software program for Windows (SPSS Inc., Chicago, IL, USA). The chi-square and ANOVA tests were used to compare variables among the three treatment groups. Survival was estimated using the Kaplan–Meier method and was compared by nonparametric survival analyses using the log-rank test. A multivariate Cox proportional hazards analysis was performed on all variables found to be significant by a univariate analysis. Prognostic factors with a univariate $p<0.1$ were included in the multivariate analysis. A p value ≤0.05 was considered to be significant.

Results

Clinicopathological characteristics

The baseline characteristics of eligible patients in the resection (R) group and the NR group are presented in Table 1. One hundred ninety-four patients (83.3%) underwent a gastrectomy (R group), while the other 39 patients (16.7%) did not undergo a gastrectomy (NR group). The tumor size of the NR group was significantly larger than that of the R group ($p<0.001$). The incidence of N2–3 disease was significantly higher in the R group than in the NR group ($p<0.001$). The administration of chemotherapy in the NR group was more feasible than postoperative chemotherapy for the R group ($p<0.001$). In fact, the rate of patients who underwent second-line chemotherapy was 53.8% in the NR group and 7.7% in the R group, and there was a significant difference between the groups ($p<0.001$). In addition, the rate of patients who underwent third-line chemotherapy was 10.3% in the NR group and 1.0% in the R group (data was not shown). There were no significance differences in the age, Borrmann classification, histological grade, depth of invasion, or distant metastasis between the two groups.

Table 1 Patient characteristics of the 233 patients undergoing treatment

Characteristics	Number (percent)		p value
	Resection (n=194)	Nonresection (n=39)	
Age (years)			0.095
<65	91 (46.9)	24 (61.5)	
≧65	103 (53.1)	15 (38.5)	
Tumor size			<0.001
<8 cm	88 (45.4)	3 (7.7)	
≧8 cm	106 (54.6)	36 (92.3)	
Borrmann classification			0.296
Type 1	7 (3.6)	0 (0.0)	
Type 2	19 (9.8)	2 (5.1)	
Type 3	101 (52.1)	24 (61.5)	
Type 4	57 (29.4)	13 (33.3)	
Undetermined	10 (5.2)	0 (0.0)	
Histopathological grading			0.353
G1, G2	75 (38.3)	12 (30.8)	
G3, G4	119 (61.3)	27 (69.2)	
Depth of invasion[a]			0.289
T2	1 (5.0)	0 (0.0)	
T3	14 (7.2)	2 (5.1)	
T4a	118 (60.8)	30 (76.9)	
T4b	61 (31.4)	7 (17.9)	
Lymph node metastasis[a]			<0.001
N0–1	16 (8.2)	16 (41.0)	
N2–3	178 (91.8)	23 (59.0)	
Distant metastasis[a]			0.349
M0	24 (12.4)	7 (17.9)	
M1	170 (87.6)	32 (82.1)	
Chemotherapy			<0.001
Yes, previous period	61 (31.4)	3 (7.7)	
Yes, late period	59 (30.4)	35 (89.7)	
No	74 (28.2)	1 (2.6)	

Data are presented as the number (percent) of patients

[a] According to the TNM classification system of malignant tumors [8]

The demographic characteristics of the patients in the R group are shown according to the type of resection in Table 2. Forty-four patients underwent a distal gastrectomy (DG group) and 150 patients underwent a total gastrectomy (TG group). Differences were found between these two groups in the tumor size, blood loss, blood transfusion, type of tumor, histological grade, depth of invasion, and lymph node status. The TG group was associated with significantly higher rates of a tumor size over 8 cm ($p=0.037$), blood loss over 800 ml ($p=0.017$), blood transfusion ($p=0.027$), Borrmann type 4 ($p=0.012$), poorly differentiated type ($p=0.002$), T4a–4b ($p<0.001$), and N2–3 ($p<0.001$) disease when compared with the DG group. The distribution of R1 resections among the respective procedures was nine cases (6%) in the TG group and six cases (13.6%) in the DG group. There was no significant difference between two groups (data was not shown).

Survival data

A total of 184 patients were dead and 49 patients were alive at the time of this report. The MST of all patients was 8.0 months, and the 1- and 3-year overall survival (OS) rates were 38.7% and 10.0%, respectively (Fig. 1a). In addition, we examined the OS according to the treatment periods. There was a significant difference in the Kaplan–Meier survival curves between the early period and the late period ($p<0.001$) (Fig. 1b). The survival was closely related to the treatment period.

The univariate and multivariate Cox analyses of prognostic factors

The univariate and multivariate analyses for survival were calculated by the Cox proportional hazards regression model. The univariate analysis indicated that the lymph node status (N3, $p=0.001$), surgical treatment (TG, $p=0.012$),

Table 2 Patient characteristics of the 194 patients undergoing gastrectomy

Characteristics	Number (percent)		*p* value
	DG (*n*=44)	TG (*n*=150)	
Age (years)			0.901
<65	21 (47.7)	70 (46.7)	
≧65	23 (52.3)	80 (53.3)	
Tumor size			0.037
<8 cm	26 (59.1)	62 (41.3)	
≧8 cm	18 (40.9)	88 (58.7)	
Blood loss			0.017
<800 ml	34 (77.3)	86 (57.3)	
≧800 ml	10 (22.7)	64 (42.7)	
Blood transfusion			0.027
Done	14 (31.8)	76 (50.7)	
None	30 (68.2)	74 (49.3)	
Borrmann classification			0.012
Type 1	1 (2.3)	6 (4.0)	
Type 2	10 (22.7)	9 (6.0)	
Type 3	22 (50.0)	79 (52.7)	
Type 4	8 (18.2)	49 (32.7)	
Undetermined	3 (6.8)	7 (4.7)	
Histopathological grading			0.002
G1, G2	26 (59.1)	49 (32.7)	
G3, G4	18 (40.9)	101 (67.3)	
Depth of invasion[a]			<0.001
T2	1 (2.3)	0 (0.0)	
T3	9 (20.5)	5 (3.3)	
T4a	21 (47.7)	97 (64.7)	
T4b	13 (29.5)	61 (31.4)	
Lymph node metastasis[a]			<0.001
N0–1	14 (31.8)	2 (1.3)	
N2–3	30 (68.2)	148 (98.7)	
Distant metastasis[a]			0.452
M0	40 (90.9)	130 (86.7)	
M1	4 (9.1)	20 (13.3)	
Chemotherapy			0.465
Yes, previous period	8 (18.2)	53 (35.3)	
Yes, late period	18 (40.9)	41 (27.3)	
No	18 (40.9)	56 (37.3)	

Data are presented as the number (percent) of patients

[a] According to the TNM classification system of malignant tumors [8]

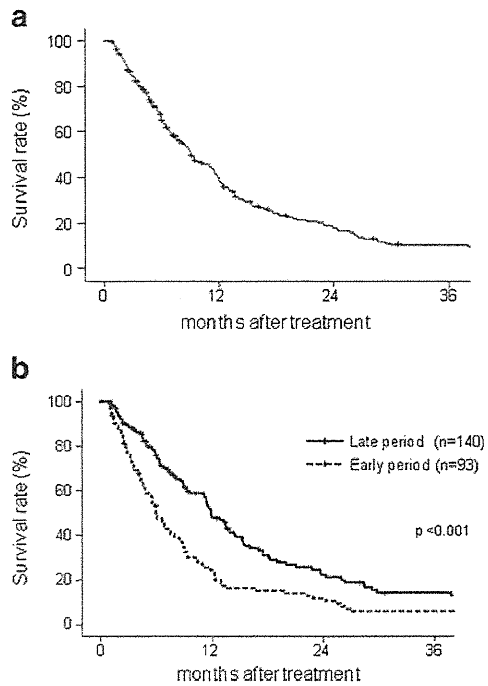

Fig. 1 **a** The OS curve of 233 patients with gastric cancer who could not undergo curative resection (MST, 8 months; 1-year OS, 38.7%; 3-year OS, 10.0%). **b** A comparison of the OS curves between patients in the early and late periods. The OS was significantly higher in the late group than in the early group ($p<0.001$)

absence of chemotherapy ($p=0.001$), and number of noncurative factors (≧2, $p=0.003$) predicted decreased OS. On the other hand, the depth of invasion (T4a–4b), tumor size (≤8 cm), Borrmann type (type 4), distant metastasis, and histopathologic grade (G3, G4) did not have a significant influence on the OS (Table 3). The multivariate analysis identified that the surgical treatment (hazard ratio [HR], 1.947; 95% confidence interval [CI], 1.321–2.870; $p=0.001$), absence of chemotherapy (HR, 1.529; 95% CI, 1.111–2.103; $p=0.009$), and number of noncurative factors (HR, 1.599; 95% CI, 1.155–2.213; $p=0.005$) were significant independent prognostic factors.

Survival according to the independent prognostic factors

The MST of the TG group was 7.5 months, that of the DG group was 13.5 months, and that of the NR group was 12.9 months. The OS rate during the entire study period was significantly lower in the TG group than in the DG group ($p=0.002$) as well as that in the NR group ($p=0.003$) (Fig. 2). The survival of the NR group improved in the late period. In the early period, the OS rate was significantly lower in the TG group than in the DG group ($p=0.038$) and was similar to that in the NR group (Fig. 3a). In contrast, in the late period, the OS rate was significantly lower in the TG group than in the DG group ($p=0.005$) and was marginally lower than that in the NR group ($p=0.054$) (Fig. 3b).

The compliance for the chemotherapy

Figure 4 shows the distribution of the length of chemotherapy for these three treatment groups. Although 97.4% of the patients in the NR group underwent chemotherapy, about 40% of the R group did not undergo postoperative

Table 3 Univariate and multivariate analysis (Cox regression) of the factors influencing survival in 223 gastric cancer patients

Univariate analysis				Multivariate analysis			
Variable		HR (95% CI)	*p* value	Variable		HR (95% CI)	*p* value
Age	≧65/>65	0.739 (0.419–1.301)	0.294				
Tumor size	≦8 cm/>8 cm	1.067 (0.796–1.143)	0.667				
Depth of invasion[a]	T4a–4b/T2–3	0.681 (0.242.1.919)	0.468				
Lymph node metastasis[a]	N3/N1–2	2.515 (1.481–4.272)	0.001	Lymph node metastasis	N3/N1–2	1.217 (0.796–1.859)	0.365
Borrmann classification	Type 4/others	1.209 (0.657–2.223)	0.542				
Histopathological grading	G2, G3/G1, G2	1.209 (0.721–2.316)	0.468				
Distant metastasis[a]	M1/M0	0.964 (0.617–1.507)	0.874				
Surgical treatment	TG/others	2.103 (1.178–3.756)	0.012	Surgical treatment	TG/others	1.947 (1.321–2.870)	0.001
Chemotherapy	No/yes	1.660 (1.227–2.247)	0.001	Chemotherapy	No/yes	1.529 (1.111–2.103)	0.009
Number of noncurative factors	≧2/1	1.595 (1.176–2.163)	0.003	Number of noncurative factors	≧2/1	1.599 (1.155–2.213)	0.005

CI confidence interval, *TG* total gastrectomy

[a] According to the TNM classification system of malignant tumors [8]

chemotherapy. The reasons for discontinuation of or failure to initiate the treatment in the R group were postoperative complications, a poor nutritional status, the adverse effects of chemotherapy, and early disease progression. In the R group, chemotherapy was performed for more than 4 months in 22 of 41 patients (53.7%) in the DG group, while only 27 of 121 patients (22.9%) underwent chemotherapy for more than 4 months in the TG group. The compliance for chemotherapy was significantly better in the DG group than in the TG group ($p<0.01$).

Postoperative complications

The postoperative complications, which were classified as grade II and/or severe according to the Clavien–Dindo system, are listed in Table 4 [12]. In the TG group, 40 patients (26.6%) had complications, and in the DG group, 5 patients (11.4%) had complications. There was a significant difference in terms of the morbidity rate between the two groups ($p<0.05$). The most common complications were anastomotic leakage and pancreatic fistulas. In the DG group, 1 patient (2.3%) had pancreatic fistula, and in the TG group, 12 patients (8.0%) had complications. In ten patients, the cause of pancreatic fistulas was pancreatic tail resection and, in three patients, the cause was lymphadenectomy around the splenic artery. There were no statistically significant differences in the incidence of each complication, such as anastomotic leakage, wound infection, pneumonia, hemorrhage, and pancreatic fistula between the two treatment groups. Hospital mortality occurred in one patient in the both the DG group (2.2%) and the TG group (0.7%) due to tumor progression. There was no significant difference in the total mortality rates between the two groups.

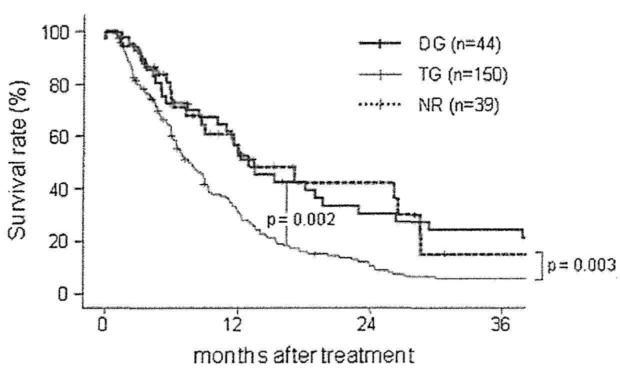

Fig. 2 A comparison of the survival curves among patients who received the three different treatments. *Thick solid line* 44 patients who underwent a DG, *thin solid line* 150 patients who underwent a TG, and *dashed lines* 39 patients who did not undergo a resection (NR). The OS rates was significantly lower in the TG group than in the DG group ($p=0.002$) and in the NR group ($p=0.003$)

Discussion

Surgical resection may be the current mainstay of treatment for patients with gastric cancer who are unable to undergo curative resection; however, the survival benefit for such resection is controversial because of the lack of prospective data. It was necessary to assess the patient population in which an acceptable outcome could be obtained after noncurative gastrectomy.

Our study demonstrated one major finding regarding the surgical treatment for noncurative gastric cancer. TG was found to be inappropriate for the treatment of these patients

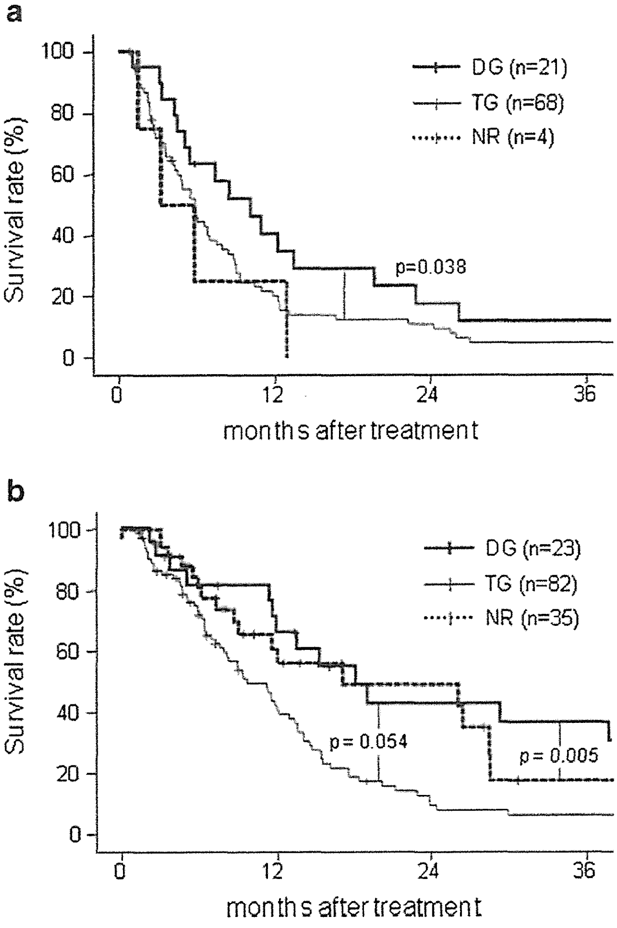

Fig. 3 **a** A comparison of the survival curves of patients who were treated with DG, TG, and NR in the early period. The OS of the patients who underwent a TG was significantly inferior to those who underwent a DG (p=0.038) and was similar to the NR group. **b** In the late period, the OS of the patient who underwent TG was significantly inferior to that of patients who underwent DG (p=0.005) and was marginally inferior to that of those who underwent NR (p=0.054)

because the survival rate of the TG group was significantly lower than that of the NR group. A multivariate analysis showed that TG is an independent poor prognostic factor, and its HR was 1.52, which was similar to a lack of chemotherapy.

In general, there were higher rates of advanced stage, large tumors, and proximally located tumors in patients who underwent TG than in patients who underwent DG [1]. In fact, in this study, the rates of a large tumor size (≥8 cm), Borrmann type 4, undifferentiated histopathological type (G3, G4), deep tumor invasion, and severe lymph node metastasis (N2–3) were significantly higher in the TG group than in the DG group. However, a multivariate analysis showed that these factors were not prognostic factors, while on the other hand, the use of TG, as well as a lack of chemotherapy, was a significant independent prognostic factor.

The reasons why TG was a poor prognostic factor were not fully clear from our data; however, several reasons can be suggested. First, surgical stress may be related to the poor prognosis. TG is a more invasive procedure than DG, and there was a higher incidence of the resection of another adjacent organ, such as the spleen, colon, pancreas, etc., in these patients. Surgery itself is reported to increase the risk of recurrence by releasing tumor cells into the circulation, increasing growth factors, and causing immunosuppression [13, 14]. Surgery can also induce a lot of stress which may lead to increased reactive oxygen species being released from leukocytes through the action of cytokines, causing circulatory disturbance in organs as a result of the counteraction of nitric oxide [15, 16].

Second, hemorrhage and the use of blood transfusion have been shown to be associated with a poor prognosis [17, 18]. In fact, in this study, the incidence of blood loss of ≥800 ml and the need for a blood transfusion were higher in the TG group than in the DG group.

Third, TG is a more technically demanding procedure than subtotal gastrectomy and is more often associated with splenectomy, which has an adverse effect on postoperative complications and on the susceptibility to infections. Even

Fig. 4 The distribution of the compliance rates for chemotherapy for the three treatment groups: those who were not treated with chemotherapy (*open bar*), those treated with chemotherapy for <4 months (*light gray bars*), and those treated with chemotherapy for more than 4 months (*dark gray bars*). The data labels on top of each bar show the number of events/number at risk

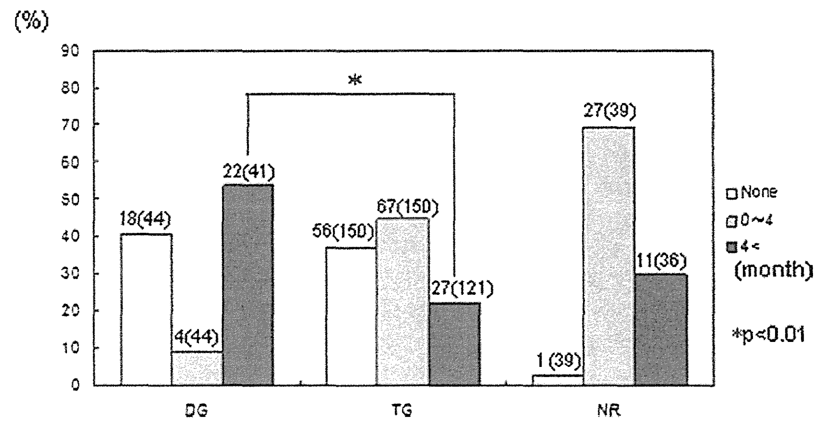

Table 4 Postoperative in-hospital complications among the patients undergoing gastrectomy

Complication	No. of complications (%)		p value
	DG (n=44)	TG (n=150)	
Morbidity			
Anastomotic leakage	2 (4.5)	9 (6.0)	0.71
Intra-abdominal abscess	0	5 (3.3)	0.22
Wound infection	0	5 (3.3)	0.22
Pneumonia	1 (2.3)	7 (4.7)	0.48
Hemorrhage	1 (2.3)	0	0.06
Pancreatic fistula	1 (2.3)	12 (8.0)	0.18
Others	0	2 (1.3)	0.19
Total	2 (11.4)	40 (26.6)	0.04
Mortality	1 (2.3)	1 (0.7)	0.35

Data are presented as the number (percent) of patients

in large-volume centers, noncurative gastrectomy is associated with substantial morbidity (38%) and mortality (12%) [2]. Fabio et al. reported that the incidence of postoperative complications was higher among patients who underwent palliative TG compared with patients who underwent potentially curative TG [19]. In fact, in this study, the postoperative complication rate of the TG group was 26.6%, which was higher than that of the DG group (p=0.04). The complications of TG have a considerable influence on prolonging hospital stays and markedly diminish the patient's quality of life [19]. The occurrence of postoperative complications was a major independent prognostic factor for long-term survival [20]. In addition, patients who underwent TG had a lower caloric intake and worse nutritional status in comparison with the patients who underwent a partial gastrectomy; this is also associated with impairment of immune function and with an increased rate of recurrence after surgery [21–23].

Recently, the effects of chemotherapy for patients with advanced gastric cancer have been remarkably improved. In fact, our study demonstrated that the survival curves demonstrated significant differences based on when the patients were treated (early period vs. late period, $p<$ 0.001). In the early period, 5-FU-based chemotherapy was the standard treatment for advanced gastric cancer, while in the late period, S-1-based chemotherapy was the standard treatment. Cisplatin- and fluorouracil-based chemotherapies have been most widely assessed, and novel agents, such as taxane derivatives, CPT-11, and oxaliplatin, are currently being explored [24–26]. Koizumi et al. reported that combination chemotherapy using S-1 and CDDP was effective, with an MST of 13 months in a phase III study in Asian countries [7]. Therefore, the feasibility of administering chemotherapy is important to achieve long-term survival. However, the compliance rate for chemotherapy after a gastrectomy is usually poor. Cunningham et al. reported in the MAGIC trial for gastroesophageal cancer that 34% of patients who completed preoperative chemotherapy and surgery did not begin postoperative chemotherapy, predominantly owing to early disease progression, the patient's request, or due to postoperative complications [26]. In this study, the compliance for receiving chemotherapy for more than 4 months in the TG group (22.3%) was poorer than in the DG group (65.9%), and the poor compliance may have been associated with the poor survival in the TG group. TG has been reported to significantly increase the maximum concentration (C_{max}) and the areas under the curves (AUC) of plasma fluorouracil and 5-chloro-2,4-dihydropyridine after oral administration of S-1 compared to the preoperative value [27]. Statistically significant relationships have been observed between S-1-induced adverse effects and the AUC, C_{max}, and plasma concentration of 5-FU [28, 29]. In addition, Takahari et al. reported that early dose reduction was necessary for the recovery from surgery for patients receiving postoperative adjuvant S-1 plus cisplatin in comparison with the original protocol, based on the results of a feasibility study, and he amended the protocol so that the first cycle consisted of S-1 monotherapy [30].

Conclusions

TG was concluded to be inappropriate for patients with incurable gastric cancer, considering the poor prognosis, high morbidity rates, poor compliance for postoperative chemotherapy, and worse nutritional status, unless it is necessary to palliate specific symptoms that cannot not be addressed by nonsurgical modalities. In contrast, noncurative DG is acceptable because the compliance for postoperative chemotherapy was still relatively high and some of the patients who received postoperative chemotherapy could achieve long-term survival. However, this study has several limitations, including that the characteristics of the patients were significantly different among the DG, TG, and NR groups, and moreover, a selection bias may have been introduced in favor of operating on patients with a good performance status. Therefore, this conclusion should be interpreted cautiously. In order to accurately define the role of palliative gastrectomy, it will be necessary to perform a well-designed randomized trial, comparing surgical treatment vs. chemotherapy. The role of gastrectomy in the management of patients with incurable advanced gastric cancer has been now investigated by the Japan Clinical Oncology Group 0705, and we are currently awaiting the results [31].

Conflicts of interest None.

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ORIGINAL ARTICLE

The impact of abdominal shape index of patients on laparoscopy-assisted distal gastrectomy for early gastric cancer

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Abstract
Purpose The aim of this study was to explore the effects of the abdominal shape index on gastric cancer patients' short-term surgical outcomes of laparoscopy-assisted distal gastrectomy (LADG) in both genders.
Methods This retrospective study included 231 consecutive patients with early gastric cancer who underwent LADG with Billroth I anastomosis between 1998 and 2009. The abdominal shape index of patients was calculated using preoperative abdominal computed tomography scans and the Fat Scan software program.
Results In male patients, the duration of surgery was longer in patients with a body mass index ≥25 kg/m^2 (P=0.016), with the anterior to posterior diameter ≥200 mm (P<0.0001), with the transverse diameter (TD) ≥300 mm (P=0.030), with the waist ≥85 cm (P=0.039), and with the visceral fat area (VFA) ≥100 cm^2 (P=0.029). The intraoperative blood loss was higher in the large TD group (P=0.049), in the high waist group (P=0.006), and in the large VFA group (P=0.007). In female patients, the correlations between these surgical outcomes and this abdominal shape index were not found. No significant relationships between each body shape index and the number of lymph nodes retrieved were found in either gender. Postoperative complications were not associated with the fat volume and abdominal shape index.
Conclusions Accumulation of fat did not affect short-term surgical outcomes except for the duration of surgery and intraoperative blood loss in male patients.

Keywords Laparoscopy-assisted distal gastrectomy · Gastric cancer · Abdominal shape index · Body mass index · Fat Scan software

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Introduction

Gastric cancer remains the second leading cause of cancer-related death worldwide, and it is the most common malignancy in Japan, Asia, South America, and Eastern Europe [1, 2]. In Japan, because endoscopic screening has been adopted, the proportion of early gastric cancer (EGC) cases is increasing and now includes more than 50% of all gastric cancer patients [3]. Most patients with EGC have a good prognosis and may be completely cured by surgery alone. Therefore, surgeons are focusing on the short-term outcomes and quality of life after surgery in these patients, and as a result, laparoscopic surgery is being increasingly used to treat a subset of EGC patients [4–6]. Indeed, laparoscopy-assisted distal gastrectomy (LADG) represents a less invasive surgical technique in terms of reduced postoperative morbidity, rapid return of gastrointestinal function, shortened hospital stay after surgery, reduced adhesions, and better cosmetic results [7, 8]. Several randomized clinical trials have already proven its feasibility based on surgical outcomes [9, 10]. The Japanese guideline allows LADG for EGC as investigational treatment, considering patients' performance status [3, 11]. However, a nationwide survey of LADG for gastric cancer showed that the total number of patients who were treated with the laparoscopic technique has increased and that the increase was especially pronounced in the patients with cT1N0, cT1N1, and cT2N0 tumors [3, 12].

Obesity and overweight has been generally regarded as a risk factor for surgical complications. Indeed, in our institute, being overweight, with a body mass index (BMI) of more than 25 kg/m^2, increased the risk of postoperative complications in gastric cancer patients undergoing open gastrectomy [13]. Abdominal shape may also influence accessibility in patients receiving LADG. A large amount of abdominal fat may make it more difficult to access the abdominal cavity in patients undergoing LADG, particularly in obese male patients. Many surgeons feel that an excess of intra-abdominal visceral fat accumulation increases the difficulty of LADG. We hypothesized that indicators of obesity, such as visceral fat area (VFA) accumulation, a higher BMI, a large waist, or a large anterior to posterior diameter (APD), are associated with technical difficulty and the postoperative outcomes of LADG. Some reports of LADG have suggested that obesity is a key risk factor for predicting postoperative complications [14, 15]. On the other hand, several reports have shown the feasibility and safety of LADG for gastric cancer in obese patients [6, 10, 16, 17]. However, there have been very few reports on the effect of obesity on the technical feasibility and postoperative outcomes of LADG in terms of a detailed abdominal shape of patients indicated by the VFA, subcutaneous fat, or body size. We therefore conducted this study to explore the effects of abdominal shape on gastric cancer patients' short-term surgical outcomes after LADG in both genders, in terms of surgical outcomes, retrieved lymph node numbers, and morbidities.

Materials and methods

Patients

Between January 1, 1998 and December 31, 2009, a total of 1,832 patients underwent surgery for gastric adenocarcinoma at Wakayama Medical University Hospital. During that period, a total of 273 patients received LADG due to early gastric adenocarcinoma. We performed LADG when the lesion was located in the antrum or the body of the stomach. In Japan and Asia, D2 gastrectomy is the standard and optimal surgical procedure for patients with advanced gastric cancer [18], and any patient with gastric cancer infiltrating the muscularis layer was excluded from undergoing this procedure at our institute [11]. In our institute, lesions with a preoperative endoscopic diagnosis of differentiated type intramucosal cancer without ulcer findings, differentiated type intramucosal cancer no larger than 3 cm in diameter with ulcer findings, and differentiated type minute invasive submucosal (less than 500 μm below the muscularis mucosa) cancer no larger than 3 cm in diameter are considered as expanding indications for endoscopic resection [19]. Therefore, patients suitable for endoscopic resection were also excluded. LADG with D1+α lymph node (nos. 1, 3, 4 d, 4sb, 5, 6, plus 7; Japanese Research Society for Gastric Cancer, JRS-GC) [11] dissection was selected for tumors restricted to the mucosa but not suitable for endoscopic resection. D1+β lymph node (nos. 1, 3, 4 d, 5, 6, plus 7, 8a, and 9) dissection was selected for the remaining EGC tumors. We preoperatively assessed the depth of invasion using upper gastrointestinal radiography, endoscopy, and endoscopic ultrasonography. In this retrospective study, we reviewed the outcomes of 231 consecutive patients who underwent LADG with the Billroth I (B-I) anastomosis during that period. In our institute, the standard B-I anastomosis was chosen. We excluded from the study patients who had received LADG with Roux-en-Y reconstruction. Follow-up data were obtained from a database, which included the background of the patients, surgical data, and their tumor characteristics. Tumor invasion and lymph node status were classified by UICC criteria [12]. Informed consent was obtained from all of the patients in accordance with the guidelines of the Ethical Committee on Human Research of Wakayama Medical University Hospital.

Body shape index

The medical records and the abdominal computed tomography (CT) scans of 231 patients who underwent LADG were reviewed. The CT scans were performed within 4 weeks before surgery. The abdominal APD, transverse diameter (TD), subcutaneous fat area (SFA), and VFA at the umbilicus level were calculated using preoperative abdominal CT scans and the Fat Scan software program version 3 (N2 systems Inc., Osaka, Japan) [14, 20, 21]. Waist circumference was measured preoperatively in centimeters via tape measure at the widest point between the lower border of the right costal margin and the top of the iliac crest [22]. The cutoff value for VFA was 100 cm^2. The cutoff value for the male waist was 85 cm and for females 90 cm. These values are equivalent to that used in Japan for the diagnosis of metabolic syndrome by the Japan Society of the Study of Obesity [22]. Patient height and body weight were measured preoperatively, and the BMI was calculated as the weight in kilograms divided by the square of the height in meters as recommended by the National Institutes of Health (NIH) Consensus Development Conference in 1985 as an accurate index for the prediction of medically significant obesity [23]. Patients with a BMI greater than 25 kg/m^2 were classified as overweight by the World Health Organization (WHO) criteria [24]. According to NIH criteria, a BMI of 25 to 29.9 kg/m^2 was classified as overweight, and a BMI of 30 kg/m^2 or greater was classified as obesity [25]. In this study, the patients were assigned to two groups according to their BMI: BMI less than 25 and BMI greater than 25. The cutoff values for other parameters were calculated using the median (rounded up). The cutoff value for the male APD was 200 mm and for females 180 mm. The cutoff value for TD was 300 mm. The cutoff value for the male SFA was 100 cm^2 and for females 150 cm^2.

Surgical procedures

The anatomical distribution and numbering of regional lymph nodes was based on the JRS-GC [11]. In our institute, LADG has been performed since 1993 [26]. Since then, we have improved on our original method. Briefly, the patient was placed in a supine position under general anesthesia. Initially, an umbilical trocar (12 mm; camera port) was inserted via the open surgical method, and five trocars were introduced under laparoscopic guidance to the midline (12 mm), the right upper quadrant (12 mm), the left upper quadrant (12 mm), the right middle quadrant (5 mm), and the left middle quadrant (5 mm). During pneumoperitoneum induced by a pressure of 10 mmHg, the greater omentum was sealed up to the inferior portion of the spleen using laparoscopic coagulating shears, a harmonic scalpel (EthiconEndo-Surgery, Inc., Cincinnati, OH, USA), and/or the LigaSure™ vessel sealing device (Valleylab, Boulder, Co, USA). The left gastroepiploic vessels were dissected at the point before the first branch (nos. 4 d, 4sb). After completion of the omentectomy, the root of the right gastroepiploic vein and artery were isolated and sealed using the harmonic scalpel with clips (no. 6). The duodenum around the pylorus ring was isolated and transected using an Echelon™ 60 ENDOPATH (Ethicon). The root of the right gastric artery was isolated in the hepatoduodenal ligament and resected with clips (no. 5). The lesser omentum along the liver edge to the esophagogastric junction was also resected. The perigastric lymph nodes were dissected along the upper lesser curvature up to the esophagocardial junction (nos. 1 and 3). For laparoscopic D1 + α lymph node dissection, the root of the left gastric vein and artery were isolated and sealed using a harmonic scalpel with clips or ligated using a laparoscopic knot pusher (no. 7). For laparoscopic D1 + β lymph node dissection, the lymph nodes along the common hepatic artery were dissected (no. 8a), and the lymph nodes around the celiac trunk and the proximal part of the splenic artery were similarly dissected (no. 9), and successively, the root of the left gastric vein and artery were dissected (no. 7). The lymph node dissection was completed intracorporeally.

The upper midline trocar incision was extended to 4~5 cm vertically, and a small wound retractor (ALEXIS wound retractor S, Applied Medical, Santa Margarita, CA, USA) was inserted. The stomach was pulled out extracorporeally, resected 4 cm from the greater curvature using scissors, and divided using an Echelon™ 60 ENDOPATH at the 5 cm proximal side of the tumor. A purse-string suture was placed in the duodenal stump, and the anvil head of an end-to-end anastomosis (CDH, EthiconEndo-Surgery) was inserted. A 29-mm aperture CDH was then inserted through the gastrotomy incision of the greater curvature side, and the center rod was passed through the posterior wall of the stomach. The CDH was fired after the center rod and the anvil were connected, and a side-to-end gastroduodenostomy was completed.

Postoperative complications

Leakage at the anastomosis site was defined as the leakage of contrast medium by upper gastrointestinal graphy after surgery. Intra-abdominal abscess was defined as intra-abdominal fluid collection with positive cultures identified by ultrasonography or CT, associated with persistent fever and elevations of white blood cells and serum C-reactive protein. The International Study Group of Pancreatic Surgeons (ISGPF) has proposed a consensus definition and clinical grading for postoperative pancreatic fistula, which were defined as follows: grade A, called "transient fistula," has no clinical impact; grade B, required a change in management or adjustment in the clinical pathway; and grade C, a major change in clinical management or deviation from the normal clinical pathway [27]. In this study, grades B and C were regarded as clinically significant pancreatic fistula. The diagnosis of postoperative pneumonia was made via CT and hematological tests. Anastomotic bleeding was defined as any anastomotic bleeding occurring in the early postoperative period (within 14 days). Anastomotic stenosis was defined as the requirement for endoscopically guided balloon dilation against anastomotic stenosis. Postoperative deterioration of liver function was defined as patients with a serum aspartate aminotransferase (AST) level greater than two times the upper limit of the normal serum AST level within postoperative day (POD) 14. Postoperative wound infection was defined as the presence of moderate seropurulent or frank purulent discharge with or without systemic symptoms. Surgical mortality included in-hospital deaths within POD30.

Statistical analysis

The StatView 5.0 software package (Abacus Concepts, Inc, Berkeley, CA, USA) was used for all statistical analyses.

Table 1 Clinicopathological characteristics of the patients

	Male	Female	*P* value
Age, years (median, range)	66 (31–86)	65 (32–85)	0.931
Tumor size, mm (median, range)	20 (5–50)	18 (3–50)	0.053
TNM stage (IA / IB / II)	144 / 7 / 2	72 / 6 / 0	0.381
Operation time, min (median, range)	282 (165–469)	267 (180–500)	0.021
Blood loss, ml (median, range)	110 (10–615)	93 (10–480)	0.694
Lymph node dissection (D1+α / β)	76 / 77	36 / 42	0.677
D1+α	18 (0–43)	23 (4–59)	0.010
D1+β	26 (3–66)	28 (13–63)	0.517

Quantitative results are expressed as the median and range. Statistical comparisons between two groups were performed with χ^2 statistics or the Mann–Whitney *U* test. A *P* value of less than 0.05 was considered to be statistically significant. Univariate and multivariate logistic regression analyses were performed to identify risk factors influencing postoperative complications. Risk factors with a univariate $P<0.10$ were included in the multivariate analysis. Risk factors with a multivariate $P<0.05$ were defined as independent risk factors.

Results

Clinicopathological characteristics of the patients

In our study, 153 patients were males, and 78 patients were females. Patient characteristics, disease, and surgical records were stratified according to the distinction of sex. There were no differences between the genders in terms of age, tumor size, or distribution of tumor stage. The duration of surgery was longer in male patients than in female patients ($P=0.021$; Table 1). The blood loss was similar in both genders. The ratio of D1+α to β on lymph node dissection was similar in the two groups. The numbers of resected lymph nodes for D1+β dissections did not significantly differ between the two groups, although the numbers for D1+α dissection were higher in the female patients than in the male patients ($P=0.010$; Table 1).

Body shape index of the patients

We stratified the body shapes of the patients according to their sex, as shown in Table 2. There were no differences between the two groups in their BMI, TD of the abdomen, or waist. Male patients had a higher APD of the abdomen and VFA than female patients (APD, $P=0.014$; VFA, $P<0.0001$). On the other hand, female patients had a higher SFA than male patients ($P<0.0001$).

The relationship between the duration of surgery and body shape index

Table 3 shows the length of the surgery for each of the body shape indices in both genders. Patients were assigned to one of two groups according to their body shape index. In male patients, the duration of surgery was longer in the patients with a BMI ≥25 kg/m^2 than in those with a BMI <25 kg/m^2 ($P=0.016$), in the APD ≥200-mm group than in the APD <200-mm group ($P<0.0001$), in the TD ≥300-mm group than in the TD <300-mm group ($P=0.030$), in the waist ≥85-cm group than in the waist <85-cm group ($P=0.039$), and in the VFA ≥100-cm^2 group than in the VFA <100-cm^2 group ($P=0.029$). On the other hand, in female patients, no correlations between the length of surgery and the body shape index were found ($P>0.05$).

Blood loss and body shape index

In male patients, the intraoperative blood loss was higher in the TD ≥300-mm group than in the TD <300-mm group ($P=0.049$), in the waist ≥85-cm group than in the waist <85-cm group ($P=0.006$), and in the VFA ≥100-cm^2 group than in the VFA <100-cm^2 group ($P=0.007$) (Table 4). On the other hand, in female patients, no correlations between the

Table 2 Body shape index of the patients

Parameters	Male	Female	*P* value
BMI, kg/m^2	22.2 (14.2–30.5)	22.4 (14.9–29.2)	0.847
APD, mm	185 (132–286)	175 (136–222)	0.014
TD, mm	285 (183–375)	281 (202–342)	0.425
Waist, cm	81 (54–114)	78 (51–100)	0.063
SFA, cm^2	100 (27–235)	142 (56–1065)	<0.0001
VFA, cm^2	110 (20–334)	68 (16–142)	<0.0001

BMI body mass index, *APD* anterior–posterior diameter, *TD* transverse diameter, *SFA* subcutaneous fat areas, *VFA* visceral fat areas

Table 3 Operation time according to body shape index

Male (n=153)				Female (n=78)			
Parameters	Patient numbers	Operation time	P value	Parameters	Patient numbers	Operation time	P value
BMI>25 kg/m^2	25	312 (200–435)	0.016	BMI>25 kg/m^2	18	262 (180–450)	0.762
BMI<25	128	276 (165–469)		BMI<25	60	269 (180–500)	
APD>200 mm	49	319 (226–439)	<0.0001	APD>180 mm	31	262 (180–450)	0.996
APD<200	104	265 (165–469)		APD<180	47	270 (180–500)	
TD>300 mm	49	296 (190–439)	0.030	TD>300 mm	25	265 (180–500)	0.661
TD<300	104	276 (165–469)		TD<300	53	268 (180–451)	
Waist>85 cm	56	297 (190–439)	0.039	Waist>90 cm	11	282 (195–500)	0.495
Waist<85	97	274 (165–469)		Waist<90	67	265 (180–480)	
SFA>100 cm^2	59	282 (187–439)	0.908	SFA>150 cm^2	27	269 (190–500)	0.549
SFA<100	94	282 (165–469)		SFA<150	51	266 (180–480)	
VFA>100 cm^2	71	293 (187–439)	0.029	VFA>100 cm^2	14	254 (180–355)	0.805
VFA<100	82	273 (165–469)		VFA<100	64	270 (180–500)	

BMI body mass index, *APD* anterior-posterior diameter, *TD* transverse diameter, *SFA* subcutaneous fat areas, *VFA* visceral fat areas

intraoperative blood loss and their body shape index were found (P>0.05, Table 4).

The relationship between the number of retrieved lymph nodes and the body shape index

In male patients, lymph node dissection of D1+α vs. D1+β was performed in 76 vs. 77 of the 153 patients. To evaluate the influences of fat volume and abdominal shape on the number of retrieved lymph nodes, we studied the relationships between each body shape index, as determined by BMI, APD, TD, waist circumference, SFA and VFA, and the number of lymph nodes retrieved. As shown in Table 5, no significant relationships for the numbers of retrieved lymph nodes were found for either the D1+α dissection group or D1+β dissection group (P>0.05). Similarly, in female patients, no significant relationships between the body shape indices and the number of lymph nodes retrieved were found for either the D1+α dissection group or D1+β dissection group (P>0.05) (Table 5).

Postoperative complications

Details of the major postoperative complications are listed in Table 6. Regarding surgical complications, anastomotic leakage was not found in any of the patients in our series. Intra-abdominal abscess was observed in two of the 153 male patients. A pancreatic fistula was observed in one male patient. Regarding systemic complications, pneumonia was observed in two male patients and one of the 78 female

Table 4 Blood loss according to body shape index

Male (n=153)				Female (n=78)			
Parameters	Patient numbers	Blood loss	P value	Parameters	Patient numbers	Blood loss	P value
BMI>25 kg/m^2	25	148 (10–605)	0.156	BMI>25 kg/m^2	18	130 (10–480)	0.131
BMI<25	128	102 (10–615)		BMI<25	60	82 (10–460)	
APD>200 mm	49	132 (10–605)	0.094	APD>180 mm	31	109 (10–480)	0.102
APD<200	104	99 (10–615)		APD<180	47	83 (10–460)	
TD>300 mm	49	127 (10–475)	0.049	TD>300 mm	25	93 (10–460)	0.983
TD<300	104	102 (10–615)		TD<300	53	93 (10–480)	
Waist>85 cm	56	141 (10–615)	0.006	Waist>90 cm	11	134 (50–480)	0.074
Waist<85	97	92 (10–530)		Waist<90	67	83 (10–390)	
SFA>100 cm^2	59	127 (10–605)	0.101	SFA>150 cm^2	27	113 (10–480)	0.212
SFA<100	94	99 (10–615)		SFA<150	51	83 (10–390)	
VFA>100 cm^2	71	144 (10–615)	0.007	VFA>100 cm^2	14	105 (10–195)	0.070
VFA<100	82	80 (10–300)		VFA<100	64	91 (10–480)	

BMI body mass index, *APD* anterior–posterior diameter, *TD* transverse diameter, *SFA* subcutaneous fat areas, *VFA* visceral fat areas