

Factors Predicting Recurrence in Patients with Siewert Type II Carcinoma Treated with Curative Resection

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Abstract. Aim: To evaluate the recurrence risk for Siewert type II esophagogastric junction carcinoma treated with curative resection. Patients and Methods: We retrospectively analyzed clinicopathological and recurrence-free survival (RFS) data of 52 patients after curative resection for Siewert type II carcinoma focusing on the role of lymph node metastasis around the greater curvature or parapyloric area. Results: Recurrence was observed in 21 (40%) patients; the median time-to-recurrence was 11 months (range=3-33 months). According to multivariate Cox proportional hazard regression analysis, involvement of nodes no. 4sa, 4sb, 4d, 5 and/or 6 (odds ratio (OR)=6.62; 95% confidence interval (CI)=1.27-41.1; $p=0.04$) and younger age (OR=2.10; 95% CI=1.25-3.82; $p<0.01$) were significant independent risk factors affecting RFS. Conclusion: Involvement of no. 4-6 nodes appears to predict recurrence of Siewert type II carcinoma treated with curative resection. Patients with this risk factor may benefit from effective use of perioperative chemotherapy.

The incidence of adenocarcinoma of the esophagogastric junction (EGJ) has recently increased in both Western and Eastern countries (1). Adenocarcinomas centered within 5 cm of the EGJ are classified into three distinct entities, Siewert types I, II and III according to the location of the tumour centre (2, 3). Out of these, Siewert type II carcinomas are defined as those whose centers are within 1

cm above and 2 cm below the EGJ (true carcinomas of the cardia). The optimal treatment strategy for Siewert type II carcinoma is still unclear. With respect to the type of procedure (transthoracic esophagectomy or transhiatal total/proximal gastrectomy), two randomized clinical trials have reported that the transhiatal approach is preferable for survival benefit (4, 5). In terms of optimal lymphadenectomy, recent retrospective studies have reported that dissection of the paracardial and lesser curvature nodes yields the greatest potential therapeutic benefit, whereas dissection of the greater curvature, peripyloric and splenic hilar nodes is not beneficial for survival (6-9). Based on these findings, proximal gastrectomy with limited lymphadenectomy may suffice as an alternative to total gastrectomy with extended lymphadenectomy for Siewert type II carcinoma (6, 7). We have recently reported that proximal gastrectomy is not routinely recommended from the perspective of oncologic risk because involvement of the greater curvature and peripyloric nodes is an unfavourable prognostic factor in these patients (10). Although understanding the recurrence risk is helpful for determining the optimal treatment strategy, only limited information is available from previous studies (6-9). To evaluate the recurrence risk of Siewert type II carcinoma, we retrospectively examined clinicopathological and recurrence-free survival (RFS) data for patients who were treated with curative resection for this type of carcinoma and assessed the involvement of the greater curvature and peripyloric nodes.

Patients and Methods

This study was approved by the local ethics committee of Saitama Medical Center, Saitama Medical School.

Patients. We retrospectively reviewed a database of 52 patients with Siewert type II EGJ carcinoma (type II carcinoma) who had undergone curative resection at Saitama Medical Center, Saitama Medical University or Gunma Chuo Hospital between July 2005 and

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February 2014. Selection criteria for the type of surgical procedure and techniques were the same at the two institutions.

We performed tumour staging and histopathological grading according to the seventh edition of the Union for International Cancer Control pTNM staging guidelines for EGJ carcinoma (11). We numbered lymph node stations and described lymphatic or venous invasion according to the definitions of the Japanese Gastric Cancer Association (12). The symbols E (proximal segment) and G (distal segment) were used to denote the locations of each EGJ carcinoma according to the distance between the tumour centre and the EGJ. This resulted in three categories in which the dominant area of invasion is listed first, *i.e.* EG, E=G (both areas equally involved) and GE (12).

In some cases, no. 4sa, 4sb and 4d nodes (along the greater curvature), no. 5 nodes (suprapyloric) and no. 6 nodes (infrapyloric) can be dissected. In this study, we simplified the nomenclature by denoting at least one histologically proven node in any of these regions (no. 4sa, 4sb, 4d, 5 and/or 6) as involvement of no. 4-6 nodes.

Assessment of recurrence. Recurrent disease was assessed by physical examination, histological findings, clinical follow-up and imaging (*i.e.*, computed tomography, magnetic resonance imaging, ultrasonography, bone scintigraphy and ^{18}F -fluorodeoxyglucose positron emission tomography) (13). If no recurrent disease was diagnosed histologically, in clinical follow-up or by radiologic imaging, these investigations were repeated within 6 months. The first site of recurrence was recorded. The time to recurrence was defined as the period from the date of surgery until detection of the first recurrence. The mode of recurrence was classified as haematogenous metastasis (liver, lung, bone, skin, brain and adrenal), lymphatic metastasis (cervical, mediastinal and abdominal para-aortic) or dissemination (peritoneal and pleural).

Statistical analysis. Continuous variables are expressed as median and range. Patients' characteristics were compared using the χ^2 test, Fisher exact probability test and Mann-Whitney test, as appropriate. We calculated the cumulative survival rate by the Kaplan-Meier method and compared survival curves with the log-rank test. To assess the independence of prognostic factors, we subjected significant variables from the log rank test with *p*-values less than 0.05 to a multivariate Cox proportional hazard regression analysis. In the multivariate analysis, we calculated odds ratios (ORs) with a 95% confidence interval (CI). All statistical analyses were performed with the JMP 5.0 software (SAS Institute Inc., Cary, NC, USA) and *p*-values less than 0.05 were considered statistically significant.

Results

Patients' characteristics. The characteristics of 52 patients with type II carcinoma are presented in Table I. There were 45 male and 7 female patients with a median age of 69 years (range=40-84 years). The tumors were located in the GE region in the majority of patients (43/52). All patients had undergone curative resection through right thoracic plus abdominal (n=3), left thoracoabdominal (n=18) and transhiatal (n=31) approaches. Splenectomy had been performed in 20 patients. The median number of dissected and involved nodes was 36 (range=9-106) and 2 (range=0-

25), respectively. Twenty-two patients had received adjuvant chemotherapy, predominantly with S-1 agents.

Recurrence. The 5-year overall survival (OS) rate of the entire cohort was 53% with a median follow-up time of 23 months (range=6-85 months). Recurrence was observed in 21 (40%) patients and haematogenous, lymphatic and peritoneal recurrences were observed in 10, 7 and 4 patients, respectively. Almost 95% of recurrences were confirmed with computed tomography findings. The median time-to-recurrence was 11 months (range=3-33 months) and the cumulative rate of recurrence at 2 and 3 years was 60% and 53%, respectively. More than 85% of recurrences occurred within 2 years. We selected the following 16 factors for Kaplan-Meier analysis using the 2-year RFS rate: age (<69 years *vs.* ≥ 69 years), sex (male *vs.* female), location (EG *vs.* E=G/GE), tumor size (<50 mm *vs.* ≥ 50 mm), histological type (G1 *vs.* G2/G3), tumor depth (T1-3 *vs.* T4), nodal stage (N0-2 *vs.* N3), TNM stage (I-III *vs.* IV), esophageal invasion (<20 mm *vs.* ≥ 20 mm), gastric invasion (<33 mm *vs.* ≥ 33 mm), splenectomy (yes *vs.* no), type of approach (thoracotomy plus laparotomy *vs.* laparotomy alone), lymphatic invasion (ly0, ly1 *vs.* ly2, ly3), venous invasion (v0, v1 *vs.* v2, v3), adjuvant chemotherapy (yes *vs.* no) and involvement of nodes no. 4-6 (yes *vs.* no).

According to the log-rank test, the following seven risk factors were significantly associated with RFS: age <69 years (*p*=0.02), tumor size ≥ 50 mm (*p*=0.05), increased tumor depth (*p*=0.05), increased nodal stage (*p*<0.01), thoracotomy (*p*=0.02), adjuvant chemotherapy (*p*=0.02) and involvement of no. 4-6 nodes (*p*<0.01). According to the multivariate Cox regression analysis, age <69 years (OR=2.10; 95% CI=1.25-3.82; *p*<0.01) and involvement of no. 4-6 nodes (OR=6.62; 95% CI=1.27-41.1; *p*=0.04) were significant independent risk factors for RFS (Table II).

Profile of patients with involvement of nodes no. 4-6. Four (80%) out of 5 patients with involvement of nodes no. 4-6 had recurrence and the affected organs were liver, peritoneum and mediastinal or abdominal para-aortic nodes. All patients with involvement of nodes no. 4-6 were male and their median age was 70 years (range=52-76 years). The median size of their tumors was 73 mm (range=35-105 mm), all tumors were located in the GE and all were staged greater than pT3 and pN2 (Table III).

Discussion

Our data clearly show that involvement of no. 4-6 nodes and younger age are independent risk factors for recurrence in patients with type II carcinoma who have undergone curative resection. Effective perioperative chemotherapy appears to be required for these patients with a high risk of recurrence.

Table I. Demographics of 52 patients with Siewert type II carcinoma.

Age (years)		Esophageal invasion (mm)	
Median (range)	69 (40-86)	Median (range)	20 (1-45)
Gender, n		Gastric invasion (mm)	
Male	45	Median (range)	33 (4-90)
Female	7	Lymphatic invasion, n	
Location, n		ly0, 1	32
EG	5	ly2, 3	20
E=G	4	Venous invasion, n	
GE	43	v0, 1	22
Tumor size (mm)		v2, 3	30
Median (range)	50 (5-105)	Approach, n	
Histological type, n		Right thoracic+abdominal	3
Differentiated (G1, 2)	27	Left thoracoabdominal	18
Undifferentiated (G3)	25	Transhiatal	31
Tumor depth, n Type of gastrectomy		Total	41
T1	8	Proximal	11
T2	5	Splenectomy, n	
T3	22	Yes	20
T4	17	No	32
Nodal stage, n		Dissected nodes, n	
N0	21	Median (range)	36 (9-106)
N1	7	Involved nodes, n	
N2	12	Median (range)	2 (0-25)
N3	12	Involvement of no. 4-6 nodes, n	
TNM stage, n		Yes	5
I	11	No	47
II	10	Adjuvant chemotherapy, n	
III	26	Yes	22
IV	5	No	30

The symbols E (proximal segment) and G (distal segment) are used to denote the locations of each esophagogastric junction (EGJ) carcinoma according to the distance between the tumour centre and the EGJ.

Siewert *et al.* reported the distribution of metastatic nodes in patients with type II adenocarcinoma treated with surgical resection (14). In patients with this type of tumor, they found involvement of predominantly the paracardial and lesser curve nodes, followed by those in the lower mediastinum and along the greater curve. However, they also found several positive parapyloric nodes, which they believed justified their recommended strategy of extended total gastrectomy. Recent retrospective studies have reported that dissection of the paracardial and lesser curvature nodes, but not the greater curvature, peripyloric and splenic hilar nodes, is beneficial to survival (6-9). Limited lymphadenectomy attained in proximal gastrectomy might be an adequate alternative and has a therapeutic benefit equivalent to that of extended lymphadenectomy with total gastrectomy for type II carcinoma (6, 7). However, we recently reported that proximal gastrectomy is not routinely recommended because metastasis around the greater curvature and peripyloric nodes is an unfavourable prognostic factor in these patients (10). Although the survival benefit for type

II carcinoma has been widely discussed, the recurrence risk should also be evaluated to determine the optimal treatment.

In the present study, the rate of recurrence of type II carcinoma was 40%, which is similar to the rate for esophageal carcinoma (37%) but higher than that for gastric carcinoma (14%) reported in our previous studies (13, 15). The median time to recurrence of type II carcinoma was 11 months, which is similar to that of esophageal (11 months) and gastric (10 months) carcinoma (13, 15). Multivariate analysis showed that involvement of no. 4-6 nodes and younger age are significant independent risk factors for recurrence after curative resection. Younger age has been identified as a favourable prognostic factor in other studies, in contrast to being a recurrence risk factor in this study, whereas younger age is significantly correlated with any clinicopathological variables. Involvement of no. 4-6 nodes, which is significantly correlated with nodal stage (data not shown), is a risk factor predicting not only survival (10) but also recurrence. These findings suggest that involvement of no. 4-6 nodes would be helpful for predicting postoperative

Table II. Univariate and multivariate predictors of recurrence in 52 patients with Siewert type II carcinoma after curative resection.

Variables	Univariate			Multivariate	
	Number	2-year RFS rate (%)	p-Value	Odds ratio (95% CI)	p-Value
Age (median: years)			0.02	2.10 (1.25-3.82)	<0.01
<69	26	38.8			
≥69	26	74.0			
Tumor size (median: mm)			0.05	2.14 (0.67-7.51)	0.20
<50	22	73.6			
≥50	30	44.3			
pT category			0.05	1.32 (0.43-4.23)	0.63
T1-3	35	69.5			
T4	17	33.9			
pN category			<0.01	1.22 (0.38-3.68)	0.72
N0-2	40	64.5			
N3	12	21.4			
Thoracotomy			0.02	1.30 (0.36-4.69)	0.69
Yes	21	27.2			
No	31	75.1			
Adjuvant chemotherapy			0.02	2.45 (0.70-8.62)	0.16
Yes	22	29.8			
No	30	75.7			
Involvement of no. 4-6 nodes			<0.01	4.86 (1.09-20.3)	0.04
Yes	5	0			
No	31	61.4			

RFS: Recurrence-free survival; 95% CI: 95% confidence interval.

Table III. Characteristics and recurrence pattern of 5 patients with involvement of no. 4-6 nodes.

Case	Age	Gender	Location	Tumor size (mm)	Tumor depth	Nodal status/nodes no. 4-6 (number)	Recurrence organ
1	52	Male	GE	35	pT3	pN3a (13)/4sa (3)	Liver
2	73	Male	GE	40	pT3	pN3b (16)/5 (2)	Peritoneum
3	64	Male	GE	75	pT3	pN2 (5)/6 (2)	Mediastinal nodes
4	70	Male	GE	105	pT4a	pN3a (13)/4sa (2), 4sb (2), 4d (2)	None
5	76	Male	GE	73	pT4a	pN3b (25)/4d (2)	Abdominal para-aortic nodes

recurrence, although patients with involvement of these nodes did not have consistent recurrence patterns.

Identification of involvement of no. 4-6 nodes during surgery may indicate more extensive lymphatic system spread of cancer cells and distant, rather than locoregional, metastasis suggesting that dissection alone may not prevent recurrence (10). Although curative surgery is the primary treatment modality for type II carcinoma, the rate of prevention of recurrence in patients with advanced carcinoma, including those with involvement of no. 4-6 nodes, is still unsatisfactory. In this study, the major regimen for advanced carcinoma patients receiving adjuvant chemotherapy was S-1 agents according to the AGCT-GC trial (16). Further perioperative chemotherapy may prevent recurrence in such

patients; indeed, a phase III trial of perioperative chemotherapy for advanced gastric or EGJ carcinoma has demonstrated significant improvement in PFS (17).

Although this was a retrospective study with a small sample size, our data indicate that involvement of no. 4-6 nodes predicts recurrence in patients with type II carcinoma after curative resection. Because dissection-alone may not prevent recurrence in patients with advanced carcinoma, including those with involvement of no. 4-6 nodes, effective perioperative chemotherapy is required for these patients with a high risk of recurrence. A prospective study with a larger series of cases is, therefore, required to determine the optimal perioperative chemotherapy for patients with Siewert type II carcinoma treated with curative resection.

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