

Is Gastric Tube Reconstruction the Optimal Surgical Procedure for Siewert Type II Esophagogastric Junction Carcinoma?

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Abstract. *Background/Aim:* To evaluate the potential risk of gastric tube reconstruction for Siewert type II esophagogastric junction carcinoma. *Patients and Methods:* We retrospectively analyzed clinicopathological and survival data of 41 patients who had undergone total gastrectomy for Siewert type II carcinoma, focusing on lymph node metastasis around the middle to lower greater curvature or parapyloric area. *Results:* Histological examination showed involvement of at least one lymph node in six patients (14%). Multivariate Cox proportional hazard regression analysis of seven clinicopathological variables showed that lymph node metastasis around the middle to lower greater curvature, or parapyloric area was the only significant independent unfavorable factor (odds ratio=6.62; 95% confidence interval=1.27-41.1; $p=0.03$) for survival. We identified no significant predictors of lymph node metastasis in analyzed patients. *Conclusion:* From an oncological point of view, we do not recommend routine gastric tube reconstruction for Siewert type II carcinoma.

Adenocarcinomas centred within 5 cm of the esophagogastric junction (EGJ) are classified into three distinct entities: Siewert types I, II and III, according to the location of the tumor center (1, 2). 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). Controversies concerning surgery for Siewert type II

carcinoma are two-fold. First controversy is about which type of procedure (transthoracic esophagectomy or transhiatal total/proximal gastrectomy) is optimal in terms of postoperative morbidity and survival, even though this issue has been, in part, clarified by two randomised clinical trials, both of which concluded that the transhiatal approach is preferable in terms of survival benefit (4, 5). The other controversy is with regard to whether gastric tube reconstruction is safe from an oncological point of view, because there are insufficient data on peri-gastric lymph node metastasis, especially metastasis around the middle to lower greater curvature and peripyloric area, regions that are technically impossible to dissect when performing gastric tube reconstruction. To evaluate the oncological risk of gastric tube reconstruction for Siewert type II carcinoma, we retrospectively examined clinicopathological and survival data on patients who had undergone total gastrectomy for this type of carcinoma, focusing on lymph node metastasis around the middle to lower greater curvature and peripyloric area.

Patients and Methods

Patients. We retrospectively reviewed a database of 41 patients with Siewert type II EGJ carcinoma (type II carcinoma) who had undergone total gastrectomy at the Saitama Medical Center, Saitama Medical University or Social Insurance Gunma Chuo General Hospital between January 2005 and July 2013. During the same period, proximal gastrectomies had been performed at these two Institutions on 11 selected patients who had disease of earlier clinical stages or were elderly; we excluded these patients from the study. Selection criteria for type of procedure (total or proximal gastrectomy) and surgical techniques were the same at the two institutions.

We performed tumor staging and histopathological grading according to the seventh edition of the Union for International Cancer Control pTNM staging guidelines for EGJ carcinoma (5). We numbered lymph node stations and described lymphatic or venous invasion according to the definitions of the Japanese Gastric Cancer Association (6). We used the symbols E (proximal segment) and G (distal segment) to denote the locations of each EGJ carcinoma,

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Key Words: Esophagogastric junction carcinoma, Siewert type II, gastric tube reconstruction.

Table I. *Demographics of 41 patients with Siewert type II carcinoma.*

Age (years)		TNM stage, n	
Median (range)	70 (40-84)	I	8
Gender, n		II	6
Male	37	III	21
Female	4	IV	6
Location, n		Esophageal invasion (mm)	
EG	4	Median (range)	19 (1-45)
E=G	2	Gastric invasion (mm)	
GE	35	Median (range)	32 (4-60)
Tumor size (mm)		Approach, n	
Median (range)	50 (5-105)	Left thoracoabdominal	12
Histological type, n		Transhiatal	29
Differentiated (G1, 2)	24	Splenectomy, n	
Undifferentiated (G3)	17	Yes	16
Tumor depth, n		No	25
T1	7	Dissected nodes, n	
T2	3	Median (range)	36 (9-106)
T3	15	Involved nodes, n	
T4	16	Median (range)	2 (0-25)
Nodal stage, n		Adjuvant chemotherapy, n	
N0	14	Yes	17
N1	7	No	24
N2	9		
N3	11		

naming the dominant area of invasion first, according to the distance between the tumour centre and the EGJ, first, resulting in three categories; namely, EG, E=G (both areas equally involved), or GE (6). When performing proximal gastrectomies with gastric tube reconstruction in patients with type II carcinoma, it is technically difficult to completely dissect No. 4sb nodes (nodes along the middle of the greater curvature), no. 4d nodes (along the lower greater curvature), no. 5 nodes (suprapyloric) and no. 6 nodes (infrapyloric); however, no. 4sa nodes (along the upper greater curvature) can be dissected in some cases. In this study, we simplified the nomenclature by denoting at least one histologically proven node in any of the regions no. 4sb, 4d, 5 and/or 6 as “involved no. 4sb–6 nodes”.

Statistical analysis. We have expressed continuous variables as the median and range. We compared patient characteristics by using the χ^2 test, Fisher exact probability test and Mann–Whitney test as appropriate. We calculated 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 the significant variables in 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 with 95% confidence interval (95% CI). We performed all statistical analyses with JUMP 5.0 software (SAS Institute Inc., Cary, NC, USA). We considered *p*-values less than 0.05 to be statistically significant.

Results

Patients' characteristics. The characteristics of 41 patients with type II carcinoma are presented in Table I. There were 37 male and four female patients with a median age of 70 years (range=

40-84 years). The tumours were located in the GE region in the majority of patients (35/41). All patients had undergone total gastrectomy, plus distal esophagectomy through left thoracoabdominal and transhiatal approaches in 12 and 29 patients, respectively. Splenectomy had been performed in 16 patients. The median number of dissected and involved nodes was 36 (range= 9-106) and 2 (range= 0-25), respectively. Seventeen patients had received adjuvant chemotherapy, mainly with S-1 or other fluoropyrimidine agents. Thirty-four patients had undergone R0 resection and seven R1 or R2 resection.

Profile of patients with involved nodes no. 4sb-6. Six patients (14%) had involved nodes no. 4sb-6. All these patients were males with a median age of 72 years (range=64-78 years). The median size of their tumors was 55 mm (range=40-105 mm), all tumours were located in the GE and all were staged greater than pT3 and pN2.

Survival analysis. The 5-year overall survival (OS) rate of the entire cohort was 59.2%, with a median duration of follow-up of 22 months (range=1-77 months). We selected the following 17 factors for the Kaplan–Meier analysis: age (<70 years *vs.* ≥70 years), gender (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 (<30 mm *vs.* ≥30 mm), splenectomy (yes *vs.* no), type of approach (left thoracoabdominal *vs.* transhiatal),

Table II. Characteristics of 6 patients with involved nodes no. 4sb-6.

Case	Age	Gender	Location	Tumor size (mm)	Tumor depth	Nodal status (number)	Nodal station of lymph nodes (number)
1	78	Male	GE	60	pT4a	pN3a (14)	6 (4)
2	73	Male	GE	40	pT3	pN3b (16)	5 (2)
3	64	Male	GE	75	pT3	pN2 (5)	6 (2)
4	76	Male	GE	73	pT3	pN3b (25)	4d (2)
5	64	Male	GE	70	pT4a	pN3a (14)	4d (3)
6	70	Male	GE	105	pT4a	pN3a (13)	4sb (2), 4d (2)

Table III. Univariate and multivariate predictors of overall survival in 41 patients with Siewert type II carcinoma undergoing total gastrectomy.

Variables	Univariate			Multivariate	
	Number	5-Year OS rate (%)	p-Value	Odds ratio (95% CI)	p-Value
Tumor size (median: mm)			0.04	3.58 (0.63-30.5)	0.16
<50	18	82.1			
≥50	23	43.3			
pT category			0.01	1.60 (0.29-8.23)	0.57
T1-3	26	75.4			
T4	16	36.9			
pN category			<0.01	2.46 (0.43-12.8)	0.29
N0-2	30	71.7			
N3	11	17.9			
pStage			<0.01	2.88 (0.22-48.1)	0.41
I-III	35	72.4			
IV	6	0			
Residual tumor classification			<0.01	1.42 (0.07-24.5)	0.80
R0	34	71.9			
R1, 2	7	0			
Lymphatic invasion			<0.01	1.43 (0.21-12.0)	0.75
ly0, 1	20	84.0			
ly2, 3	21	36.0			
Involvement of no. 4sb-6 nodes			<0.01	6.62 (1.27-41.1)	0.03
Yes	6	70.0			
No	35	0			

OS: Overall survival; 95% CI: 95% confidence interval.

residual tumour (R0 vs. R1, 2), lymphatic invasion (ly0, ly1 vs. ly2, ly3), venous invasion (v0, v1 vs. v2, v3), adjuvant chemotherapy (yes vs. no) and involved nodes no. 4sb-6 (yes vs. no).

According to the log rank test, the following seven factors were significantly associated with worse OS: tumor size ≥50 mm ($p=0.04$), increased tumor depth ($p=0.01$), increased nodal stage ($p<0.01$), advanced TNM stage ($p<0.01$), residual tumor (R1, 2) ($p<0.01$), lymphatic invasion (ly2, ly3) ($p<0.01$) and involvement of no. 4sb-6 nodes ($p<0.01$). According to the multivariate Cox regression analysis, involvement of no. 4sb-6 nodes (odds ratio=6.62; 95% CI=1.27-41.1; $p=0.03$) was the only significant independent prognostic indicator for survival (Table II).

Profile of patients with lymph node metastasis around the middle to lower greater curvature or parapyloric area. There were significant differences between patients with and without involvement of no. 4sb-6 nodes in nodal stage ($p<0.01$), number of involved nodes including or excluding no. 4sb-6 ($p<0.01$) and lymphatic invasion ($p=0.01$) (Table III). According to the multivariate logistic regression analysis, these variables were not predictors of involvement of no. 4sb-6 nodes (data not shown).

Discussion

We have clearly shown that involvement of no. 4sb-6 nodes is an independent unfavorable factor in patients with type II carcinoma who have undergone total gastrectomy and that gastric tube reconstruction with proximal

Table IV. Clinicopathological characteristics according to the status of no. 4sb-6 nodes.

Variable	Involvement of no. 4sb-6 nodes		p-Value
	Yes (n=6)	No (n=35)	
Age, years			0.67
<70	2	17	
≥70	4	18	
Gender, n			0.38
Male	6	31	
Female	0	4	
Location, n			0.57
EG, E=G	0	6	
GE	6	29	
Tumor size (mm)			0.21
<50	1	17	
≥50	5	18	
Histological type, n			0.21
Differentiated (G1, 2)	2	22	
Undifferentiated (G3)	4	13	
Tumor depth, n			0.19
T1-3	2	23	
T4	4	12	
Nodal stage, n			<0.01
N1-2	1	29	
N3	5	6	
Involved nodes (mean±SD)	14.5±1.9	3.4±0.8	<0.01
(Involved nodes except no.4sb-6)	11.2±2.0		<0.01
Dissected nodes (mean±SD)	32.2±8.3	38.2±3.4	0.52
TNM stage, n			0.21
I-III	4	31	
IV	2	4	
Lymphatic invasion, n			0.02
Ly0, 1	0	20	
Ly2, 3	6	15	
Vessel invasion, n			0.75
v0, 1	3	20	
v1, 2	3	15	

SD: Standard deviation.

gastrectomy is carefully performed based on the incidence or survival of these patients.

Siewert *et al.* reported the distribution of metastatic nodes in 186 patients with type II adenocarcinoma (7). They found that mainly the paracardial and lesser curve nodes, followed in frequency by those in the lower mediastinum and along the greater curve, are involved in patients with this type of tumor. However, they found positive parapyloric nodes in 3/186 patients, which they believed supported and justified their recommended strategy of extended total gastrectomy. They neither precisely described the greater curve nodes, nor assessed associations between incidence of nodal involvement at the various node stations and outcomes; thus, this remains to be clarified.

Recent retrospective studies have reported that limited lymphadenectomy attained in proximal gastrectomy may be an adequate alternative, with a therapeutic benefit equivalent to that of extended lymphadenectomy with total gastrectomy and abdominal lymphadenectomy for type II EGJ carcinoma (8, 9). However, in our study, 6/41 patients (14%) had involvement of no. 4sb-6 nodes; this incidence (4.0%) out of dissected no. 4sb-6 nodes (data not shown) is relatively high compared with that (range=0.8-2.0%) of previous studies (8-10). In only one of these recent studies did all patients undergo total gastrectomy; thus, only in this study is the incidence of involvement of no. 4sb-6 nodes likely to be accurate (9). These researchers reported that age and nodal stage are independent prognostic factors after total gastrectomy (9).

In the present study, the 5-year OS rate was 59.2%, which is similar to that of recently reported studies (37-60%). The multivariate analysis showed that involvement of no. 4sb-6 nodes is an independent prognostic factor after total gastrectomy. Moreover, there were significant differences between patients with and without involvement of no. 4sb-6 nodes in the nodal stage, and number of involved nodes including or excluding no. 4sb-6. These findings seem to be helpful preoperatively for assessing the risk of involvement of no. 4sb-6 nodes; however, multivariate analysis did not identify any significant predictors of involvement of these nodes, probably because of the small sample size.

Identification of involvement of no. 4sb-6 nodes during surgery may indicate more extensive lymphatic system spread of cancer cells, and that dissection alone may not improve the survival rate. Although radical surgery is the primary modality for treatment of type II EGJ carcinoma, long-term survival of patients with advanced carcinoma, including those with involvement of no. 4sb-6 nodes, is still unsatisfactory. Perioperative chemotherapy may improve prognosis of such patients: phase III trials of perioperative chemotherapy for gastric cancer have demonstrated significant improvement in survival (11, 12).

Although this was a retrospective study with a small sample size, the incidence or predictor of involvement of no. 4sb-6 nodes suggests that routine gastric tube reconstruction with proximal gastrectomy is not the optimal surgical procedure for type II carcinoma. A prospective study with a larger series of cases is needed to clarify the optimal surgical procedure for this type of carcinoma.

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Received December 6, 2013

Revised December 21, 2013

Accepted December 23, 2013