Original Paper

Significance of Surgical Treatment in Multimodal Therapy for Stage IV Highly Advanced Gastric Cancer

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ABSTRACT

Background/Aims: The purpose of this study was to evaluate the efficacy of surgical treatment following a response to chemotherapy to improve stage IV gastric cancer and to identify the factors contributing to survival benefit. **Methodology:** In total, 148 patients with cStage IV gastric cancer were treated with S-1 and CDDP. We retrospectively evaluated the factors contributing to a survival benefit and the significance of surgical treatment. **Results:** The 148 cStage IV patients included 107 males with a median age of 61 years. The overall response rate was 54.7%. After chemotherapy, 97 patients underwent surgery. R0 resection was successfully performed in 51 (52.6%) patients. The overall median survival time (MST) of the patients was 16.8 months, with a 5YSR of 16.4%. The MST of patients who went on to receive surgery was 22.5 months and the 5YSR was 19.6%. In the multivariate analysis of 97 patients who underwent surgery, R0 resection, lymph node dissection of D2/D3 and obtaining a CR/PR from chemotherapy were the only independently prognostic factors. **Conclusions:** The use of multi-modal treatment, including surgical treatment, at an appropriate time was well tolerated and effective for patients with stage IV gastric cancer.

Key Words: Gastric cancer; cStage IV; Surgical treatment; Multimodal therapy.

INTRODUCTION

Currently, gastric cancer treatment incorporating individualization is being explored to improve the performance of new multimodal treatments including a combination of chemotherapy, radiation therapy and surgery. Postoperative chemoradiotherapy in the United States (1), and peri-operative ECF (epirubicin, cisplatin (CDDP), 5-FU) in Europe (2) are the standard treatments for adenocarcinoma of the stomach or gastroesophageal junction. On the other hand, adjuvant S-1 chemotherapy followed by D2 surgery has been established as a standard treatment in Japan (3). Nonetheless, the prognosis for stage III/IV tumors is not satisfactory in any of these regions, and evidence has not been established for stage IV gastric cancer (4). This retrospective study evaluated the significance of surgical treatment as part of multimodal therapy for cStage IV gastric cancer, and the factors contributing to a survival benefit were analyzed.

METHODOLOGY

Patients

Between October 2000 and April 2009, 236 consecutive patients underwent S-1+CDDP combination chemotherapy as the initial treatment for far advanced gastric cancer at our institution, and we have previously reported their outcomes (5). Among these patients were those who underwent surgical resection with curative intent after chemotherapy. As a result, we began to experience some cases of long-term survival. Of the 236 patients given S-1 + CDDP combination therapy, 148 patients with cStage IV gastric cancer were retrospectively reviewed to compare the outcomes between surgical and non-surgical treatments and to determine the appropriate timing of surgery and the optimal extent of resection.

Treatment schedule

All patients received systemic chemotherapy consisting of S-1 and CDDP. S-1 was orally administered at a dose of 80mg/m2 for 21 consecutive days, followed by 14 days of rest. CDDP was administered intravenously on day 8 at a dose of 60mg/m2 with hydration. The treatment was repeated every 5 weeks (6) and administered for at least two cycles. An objective measurable tumor response was evaluated using the response evaluation criteria in solid tumors (RECIST) version 1.0 (7) on the basis of the CT findings. The primary lesion, was not considered to be measurable by the RECIST criteria and was assessed by a barium contrast study and/or endoscopic examinations according to the Japan Gastric Cancer Association (JGCA) clinical criteria for response assessment of chemotherapy and radiotherapy (8). The pretreatment stage was diagnosed according to the JGCA staging system (8) on the basis of the CT, upper GI series, endoscopy and staging laparoscopic findings. Surgery after chemotherapy was indicated when diagnostic imaging confirmed a reduction or disappearance of the primary lesion or massive nodal metastases in response to chemotherapy, and when extended resection or combined resection with curative intent was considered possible. Patients who continued to have clear evidence of unresectable disease and those who did not respond to the chemotherapy were discouraged from receiving surgery. Surgery with intent to cure was performed 3 to 4 weeks after the final cycle of chemotherapy. The standard surgical procedure was gastrectomy with D2 nodal dissection. For an R0 resection, a para-aortic nodal dissection (D3), splenectomy and/or distal pancreatectomy, or a partial hepatectomy was attempted if the cytological findings were negative. Most patients were treated with S-1 monotherapy as adjuvant therapy after surgery. S-1 (80mg/m2/day, days 1-14) was administered every 3 weeks for 1 year. The treatments after R2 resection or upon detection of recurrent disease were decided at the discre-

Hepato-Gastroenterology 2013; 60:00-00 doi 10.5754/hge12653

tion of each physician. The postoperative final tumor status was diagnosed comprehensively based on the clinical, surgical and pathological findings according to the criteria provided by the JGCA classification (8).

Statistical analysis

The terms used here are based on the Japanese classification of gastric carcinoma (8). Variables were expressed as the means ±SD. Comparisons between groups were performed using Student's t-test, the $\chi 2$ test and the Mann-Whitney U non-parametric test. The univariate and multivariate analyses using Cox's proportional hazards model were performed to identify independent prognostic factors. The median survival time (MST) and the 5-year survival rate (5YSR) were calculated from the time of initiation of chemotherapy to death. The survival analysis was performed using the Kaplan-Meier method. The log-rank test was used to calculate the statistical significance of the differences in the survival rates between the groups. A bilateral $p<0.05$ was considered to be significant.

Figure 1. Overall survival (n = 148)

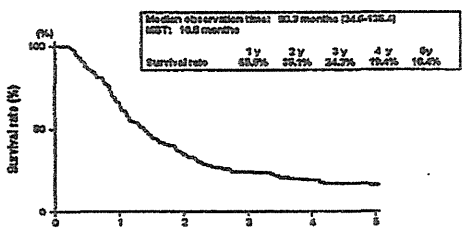

FIGURE 1. With a median follow-up of 80.3 months, the overall MST of the patients was 16.8 months, with a 5YSR of 16.4%.

Figure 2. Overall survival in the surgery and no-surgery groups as estimated by the Kaplan-Meier method

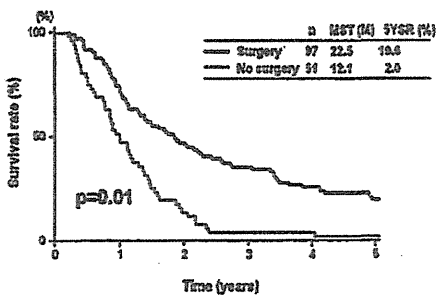

FIGURE 2. The MST of patients who went onto receive surgery was 22.5 months and the 5YSR was 19.6%. There was a statistically significant difference in the survival between these patients and those who did not receive a gastrectomy.

RESULTS

Patient demographics

The characteristics of the 148 cStage IV patients are shown in Table 1. There were 107 males and 41 females with a median age of 61 years. The distribution of the cStage IV factors included liver metastasis in 20 patients, peritoneal metastasis in 78 patients (including 36 POCY1 patients), involvement of abdominal para-aortic lymph nodes in 76 patients and locally advanced and potentially unresectable gastric cancer (cT4N2) in 14 patients. There were overlapping cases, i.e. 1 factor in 120 patients, 2 factors in 26 patients and 3 factors in 2 patients.

TABLE 1. Patient demographics (n=148)

Value	No. of cases
Age median (range)	61(32-83)
Gender	male/female 107/41
PS	0/1/2 80/50/158
Location	L,M,U/LMU 114/34
Macroscopic type	1,2/3,4 29/119
Histology	diff./undiff. 56/90
cT	T2/T3/T4 3/131/14
cN	N0,N1/N2,N3 42/106
cH	H0/H1 128/20
cP	P0/P1 106/42
CY	0/1/X 22/65/61
Resection	Yes/No 97/51

TABLE 2. Clinical response to chemotherapy

	No. of case	CR	PR	SD	PD	NE	RR(%)	DCR(%)
Overall	148	1	80	53	13	1	54.7	90.5
Metastatic focus								
Lymph node	123	4	62	49	6	2	53.7	95.1
Liver	22	1	7	9	4	1	36.4	77.3
Peritoneum	63	0	9	50	2	2	14.9	96.8
Primary lesion	148	2	73	69	3	1	50.7	97.3

Clinical response to chemotherapy

Measurable lesions were confirmed in 141 patients. The objective response rate for these lesions, according to the RECIST, was 46.1%. As shown in Table 2, the overall response rate (ORR) was 54.7%. There were 81 responders (one complete response (CR) and 80 partial responses (PR)). The response rates for regional/para-aortic lymph nodes, liver metastases, peritoneal metastases and primary gastric tumors were 53.4% (66/123), 36.4% (8/22), 14.9% (9/63) and 50.7% (75/148), respectively. Fifty-four other patients (36.5%) had stable disease (SD) and only 13 patients (8.8%) had progressive disease (PD). Of the 81 responders, the residual tumor was completely resected in 32 (39.5%) patients. Out of the 88 patients who underwent staging laparoscopy, 69 were found to have peritoneal metastasis; of these, complete remission of the peritoneal dis-

ease was confirmed at surgery in 20 (29.0%) patients.

Surgery

After chemotherapy, 97 patients underwent surgery, and a gastrectomy was performed in all patients. The remaining 51 patients were not treated surgically, generally because of persistent metastatic disease after chemotherapy. The median number of chemotherapy courses, median number of cStage IV factors, and response rates significantly differed between patients with and without surgery (2 vs. 4, 1 vs. 2 and 58.8% vs. 49.0%, respectively; $p<0.05$). The patients who underwent surgery included 73 males and 24 females, with a median age of 61 years. The surgical procedure was a total gastrectomy in 56 patients and a distal gastrectomy in 41 patients. Fourteen patients underwent extended lymphadenectomy, and gastrectomy with D0/D1 resection was performed in 31 patients, and a total of 64 patients received a combined resection. The median hospital stay, duration of surgery and blood loss were 14 days, 200 minutes and 310mL, respectively. R0 resection was successfully performed in 51 (52.6%) patients. Postoperative complications were recognized in 19 patients. The pathological response rate was 40.2%. The distribution of the pStage was as follows; 1 patient in pathological CR, 14 patients in pStage I/II, 16 in pStage III and 66 in pStage IV. Downstaging was obtained in 31 (32.0%) patients (Table 3).

TABLE 3. Demographics of surgery group (n=97)

Value	
Total gastrectomy	56
Distal gastrectomy	41
Lymph node dissection	
D1	31
D2	52
D3	14
Combined resection*	
Spleen	32
Pancreas	11
Diaphragm	11
Liver	6
Others	37
Surgical stress median (range)	
Hospital stay (days)	14(9-195)
Duration of surgery (minutes)	200(90-406)
Blood loss (mL)	310(20-2460)
Residual tumor	
R0	51
R1	18
R2	28
R0 resection rate	52.60%
Complications	
Pancreatic fistel	8
Ileus	6
Abdominal abscess	2
Leakage	2
Pneumonia	1
Mortality	0
Pathological response	
Grade	
3	1
2	13
1b	25
1a	57
0	1
Pathological stage	
Pathological CR	1
p Stage	
I	8
II	6
III	16
IV	66

**Include overlapping cases.*

Survival and analysis of prognostic factors

With a median follow-up of 80.3 months, the overall MST of the patients was 16.8 months, with a 5YSR of 16.4% (Figure 1). The MST of patients who went on to receive surgery was 22.5 months, and the 5YSR was 19.6%. There was a statistically significant difference in the survival between these patients and those who did not receive a gastrectomy (Figure 2). For all 148 patients included in the multivariate analysis, undergoing surgery (hazard ratio 0.373, $p<0.01$), obtaining a CR/PR following chemotherapy (0.307, $p<0.01$), and having one stage IV factor (0.359, $p<0.05$) were predictive of the overall survival (Table 4). In the univariate analysis of 97 patients who underwent surgery, a PS of 1 or less, 2 courses or fewer of chemotherapy, CY0 at surgery, cH0, obtaining a CR/PR following chemotherapy, lymph node dissection of D2 or more, pN1 or less, R0 and histological effects of 1b or more, were identified as significant prognostic determinants (Table 5). In the multivariate analysis of 97 patients who underwent surgery, R0 resection (0.109, $p<0.01$), lymph node dissection of D2/D3 (0.170, $p<0.05$) and obtaining a CR/PR from chemotherapy (0.221, $p<0.05$) were the only independently prognostic factors (Table 6).

DISCUSSION

According to the data of the Japanese stomach cancer registry in 2001, the 5YSR of patients with stage IV is extremely poor, at 15.8% (9), and the efficacy of surgery for stage IV patients is unknown (10,11). Further improvements in radical surgical techniques are unlikely to lead to any notable progress in the outcome (12,13). Thus, the present guidelines recommend the use of chemotherapy and other non-surgical treatments (4), and the development of an effective multimodal strategy has been sought. In recent years, the development of new anticancer drugs has improved the treatment outcomes. Chemotherapy performed in patients with hepatic metastasis, peritoneal dissemination, or distant lymph node metastasis resulted in a reduction of their tumor size or disappearance of metastatic foci, which often allows R0 surgery to be performed (14,15). Although chemotherapy is the standard of care for cStage IV metastatic gastric cancer, it does not cure the disease. However, if chemotherapy makes it possible to perform a R0 resection during the treatment process, it will be easier to control the dose and rest periods for the anticancer drugs that will be continuously required as postoperative adjuvant chemotherapy. Therefore, surgery remains an important option as a part of multimodal therapy for patients with resectable metastases. Nakajima et al. (16) reported that FLEP

therapy (5-FU, Leucovorin, etoposide, CDDP) yielded survival times of 12.7 months and 4.7 months in responders and non-responders, respectively. Gallard-Rincon et al. (17) reported that the survival time was 13.3 months in responders and 7.46 months in non-responders with combination therapy using CDDP, etoposide, leucovorin and 5-FU. Furthermore, Schumacher et al. (18) reported that when EAP therapy (etoposide, doxorubicin, CDDP) was administered to patients with stage III-IV disease, the survival time was 7.6 months in patients with non-curative resection, compared to 28.4 months in patients who were able to undergo curative resection. With regard to other types of cancer, surgical therapy performed at an appropriate time after chemotherapy is also useful for the treatment of hepatic metastases from colorectal cancer or recurrent GIST (19,20). In Japan, S-1 plus CDDP combination therapy is currently the first-line chemotherapy for unresectable/recurrent gastric cancer based on the results of the SPIRITS trial (21).The MST in the patients treated with S-1 plus CDDP was 13.0 months, and the RR obtained with this regimen was 54% in the present study. We have used this S-1 plus CDDP combination therapy regimen for unresectable/recurrent gastric cancer for several years. The advent of molecular-targeted drugs will contribute to further increase the response rate and/or the histological CR rate (22). An R0 resection is reported to be one of the most reliable prognostic indicators for patients after preoperative chemotherapy (23,24). Postoperative S-1 alone has proven to be beneficial for treating stage II and III gastric cancer (3). Hence, one of the potentially favorable multimodal treatments for stage IV gastric cancer would be a combination of preoperative administration of S-1 plus CDDP, subsequent gastrectomy with D2 or more lymphadenectomy to achieve R0, and postoperative S-1 administration. In the present study, the multi-modal treatment including surgery also showed good results in patients with poor-prognosis, highly advanced gastric cancer (stage IV). If curative resection is obtained by performing D2 or more dissection for chemotherapy responders, more favorable treatment outcomes will be obtained. The results of the present study indicate that the multi-modal treatment including surgical treatment at an appropriate time was well tolerated and effective for patients with stage IV gastric cancer.

TABLE 4. The results of the multivariate analysis of 148 patients.

Variables	hazard ratio	95% confidence limits	*p* value
Surgery/No surgery	0.373	(0.204-0.683)	0.001
Response (CR,PR/SD,PD)	0.307	(0.128-0.734)	0.004
No. of stage IV factors (~1/2)	0.359	(0.158-0.811)	0.013

TABLE 5. The results of the univariate analysis of the surgery group (n=97)

Variables	n	MST(M)	5YSR (%)	*p* value
PS				
0,1	83	23.0	22.2	
2	14	12.4	7.4	0.0324
No. of courses				
<2	67	18.3	18.2	
>2	30	26.1	23.3	0.0156
Location				
L,M,L	69	24.5	22.1	
LMU	28	13.7	14.3	0.0997
CY				
CY0	68	27.8	25.8	
CY1	29	13.5	3.4	0.0008
cH				
cH0	85	24.5	22.6	
cH1	12	10.0	0.0	0.0411
Response				
CR/PR	57	26.9	22.8	
SD/PD	40	16.0	15.4	0.0472
Dissection				
D0,1	31	13.4	6.5	
D2,3	66	26.9	26.2	0.0037
pN				
pN0,1	42	40.8	35.7	
pN2,3	55	14.0	7.4	0.0006
Residual tumor				
R0	48	41.8	38.3	
R1,2	49	13.4	2.0	<0.0001
Pathological response				
1a	59	16.9	20.7	
~1b	38	27.8	18.4	0.0434

TABLE 6. The results of the multivariate analysis of the surgery group (n=97)

Variables	Hazard ratio	95% confidence limits	*p* value
Residual tumor (R0,R1,2)	0.109	(0.028-0.429)	0.004
Dissection (D2,3/D0,1)	0.170	(0.039-0.739)	0.014
Response (CR,PR/SD,PD)	0.221	(0.056-0.817)	0.029)

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Surg Today
DOI 10.1007/s00595-013-0773-4

ORIGINAL ARTICLE

Comparison of the surgical treatment strategies for Siewert type II squamous cell carcinoma in the same area as esophagogastric junction carcinoma: data from a single Japanese high-volume cancer center

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Received: 8 July 2013 / Accepted: 3 September 2013

Abstract

Purpose Siewert type II esophagogastric junction adenocarcinoma (ADC) and squamous cell carcinoma (SCC) existing in the same area have distinct clinicopathological characteristics. The objective of this study was to examine differences in the surgical treatment and survival data, according to the histological subtype, in a single high-volume cancer center.

Methods We retrospectively examined data from a total of 123 patients. Seventy-two patients with Siewert type II ADC and 51 patients with SCC in the same area.

Results In terms of the clinicopathological factors, the SCC patients had more advanced stage disease and thoracotomy was more frequently performed than in the ADC patients. The 5-year overall survival (OS) rates did not differ significantly between SCC and ADC, regardless of whether or not mediastinal, splenic hilum and para-aortic lymph node dissection was performed. Based on the calculated index for the frequency of nodal metastasis and the five-year OS rate for involvement at each level, only node nos. 1, 2, 3 and 7 had a high index (>5) in both groups. The multivariate Cox regression analysis showed that only age (<65), the pN category and residual tumor classification were independently associated with the outcome.

Conclusions Differences in the histological type of esophagogastric junction cancer were not independent prognostic factors for survival, and there appears to be a benefit to dissecting the number 1, 2, 3 and 7 lymph nodes.

Keywords Siewert type II · Squamous cell carcinoma · Surgical treatment

Introduction

In recent years in Western countries, the dominant histological subtype of carcinoma found in the lower esophagus and esophagogastric junction (EGJ) has shifted from squamous cell carcinoma (SCC) to adenocarcinoma (ADC) [1, 2]. While SCC still accounts for the majority of these malignancies in Japan, the current availability of *Helicobacter pylori* eradication therapy is anticipated to change the proportions of these cancers, giving rise to a trend similar to that observed in Western countries [3].

At the 2nd International Gastric Cancer Congress held in Munich in 1997, a consensus was reached to classify ADC in the EGJ into three subtypes according to the Siewert classification [4]. Using the anatomical classification of the esophagus, ADC of the EGJ was defined as ADC with esophageal invasion with the epicenter of a tumor within 5 cm of the EGJ in the TNM Classification of Malignant Tumors 7th Edition [5] In Japan, Nishi's classification system is also used to classify carcinoma of the gastric cardia, and cancer at the EGJ is defined as a tumor with the epicenter within 2 cm proximal and distal to the EGJ, regardless of its histological subtype [6–8].

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Published online: 29 October 2013

As described above, EGJ carcinoma comprises two histological subtypes, ADC and SCC. ADC and SCC have distinct predisposing risk factors and clinicopathological features. However, the carcinoma subtypes were not distinguished in some of the previous clinical trials, and it is unclear whether the optimal treatments differ among these subtypes [9]. For example, the most appropriate surgical procedures and extents of lymph node dissection for ADC and SCC [10], considered separately in the ESMO Clinical Practice Guidelines for the diagnosis, treatment and follow-up, as well as in the NCCN Clinical Practice Guidelines in Oncology, have not yet been established. It is of the utmost importance to investigate the biological characteristics of ADC and SCC, and to identify the optimal treatment strategies for these distinct EGJ carcinomas [11].

Type II tumors, carcinomas of the true cardia, with the epicenter within an area 1 cm above and 2 cm below the cardia, in particular, are most likely to contain both ADC and SCC. Histologically specific treatment strategies, like those used in lung cancer and urinary bladder carcinoma, may be an important clinical issue, especially for SCC occurring at the same site as ADC. The objectives of this study were to examine the differences between SCC and ADC in terms of the surgical treatment, lymph node metastasis status and survival data, based on the histological subtype, in a single Japanese high-volume cancer center.

Methods

We diagnosed type II EGJ carcinoma if the epicenter was within 1 cm proximal and 2 cm distal to the anatomical EGJ based on a photograph of the resected specimen [12]. Between January 1985 and December 2008, a total of 6356 patients, 5658 patients with gastric carcinoma and 698 with esophageal carcinoma, underwent surgery at the Division of Surgery, Niigata Cancer Center Hospital, Niigata, Japan. We retrospectively examined the data from a total of 123 of these patients (72 with Siewert type II carcinoma undergoing at least D1 lymph node dissection and 51 patients with SCC in the same area with the lesion extending to the esophagus and stomach).

The tumor staging and nodal classification were performed according to the International Union Against Cancer (UICC) TNM staging system for EGJ cancer [5]. The lymph node levels were numbered according to the definition established by the Japanese Gastric Cancer Association and Japanese Esophageal Society [7, 8].

Surgical procedures

In principle, proximal or total gastrectomy without splenectomy via the abdominal approach was carried out for cT1 carcinoma, and thoracic esophagectomy or total gastrectomy with or without splenectomy via the thoracic or abdominal approach was carried out for cT2–T4 carcinoma. All procedural decisions were made by the primary surgeon.

Statistical analysis

Variables were expressed as the mean ± SD. Comparisons between groups were performed with Student's t test, the χ^2 test and the Mann–Whitney U nonparametric test. The multivariate analyses using Cox's proportional hazards model were performed to identify independent prognostic factors. The calculated mean survival time (MST) and the 5-year overall survival (OS) rates were calculated from the initiation of surgery until death. A survival analysis was performed using the Kaplan–Meier method. The log-rank test was used to calculate the statistical significance of the differences in OS rates between groups. A two-tailed value of $p < 0.05$ was considered to indicate a statistically significant difference. We evaluated the therapeutic benefit obtained by node dissection at each lymph node level, based on the index of the estimated benefit of lymph node dissection calculated by multiplying the incidence of metastasis by the 5-year OS rate of patients with metastasis at each node level [13].

Results

Patient backgrounds and surgical procedures

With regard to the clinicopathological factors, SCC had more invasive characteristics, including more extensive esophageal invasion, deeper tumor invasion and more advanced pathological stages, than ADC. Furthermore, the intestinal type was more frequently observed in SCC patients (Table 1).

Thoracic esophagectomy via right thoracotomy or a left thoracoabdominal (TA) approach was more frequently performed in SCC patients, whereas total gastrectomy with caudal pancreatectomy and splenectomy via the abdominal-transhiatal (TH) approach were the most common procedures for ADC (Table 1).

Treatment results and survival

The median follow-up was 9.0 years (range 3.8–24.8). The MST was 48.8 months, and the 5-year OS rate was 45.1 % for the SCC patients. The corresponding values for the ADC patients were 60.2 months and 47.2 %. Thus, there were no significant survival differences between the SCC and ADC patients (Fig. 1).

Table 1 Demographics and surgical procedures of the 123 patients with EGJ carcinoma

	SCC (51)	ADC (72)	*p* value
Tumor size (cm)	5.8 ± 2.0	5.3 ± 2.7	0.2839
Length of esophageal invasion (cm)	3.1 ± 1.8	1.8 ± 1.2	<0.0001
Macroscopic type			
Borrmann Type 1, 2	47 (92.2)	42 (58.3)	
Borrmann Type 3, 4	4 (7.8)	30 (41.7)	<0.0001
Histological type			
Differentiated type	37 (72.5)	48 (66.7)	
Undifferentiated type	14 (27.5)	24 (33.3)	0.5392
Depth of tumor invasion			
pT1/2	6 (11.8)	37 (51.4)	
pT3/4	45 (88.2)	35 (48.6)	<0.0001
Lymph node metastasis			
Negative	17 (33.3)	27 (37.5)	
Positive	34 (66.7)	45 (62.5)	0.5546
Peritoneal metastasis			
Negative	51 (100)	70 (97.2)	
Positive	0 (0.0)	2 (2.8)	0.2462
Liver metastasis			
Negative	51 (100)	70 (97.2)	
Positive	0 (0.0)	2 (52.8)	0.2462
Venous invasion			
Negative	25 (49.0)	29 (40.3)	
Positive	26 (51.0)	43 (59.7)	0.2550
Lymphatic invasion			
Negative	10 (19.6)	17 (23.6)	
Positive	41 (80.4)	55 (76.4)	0.6089
Stage			
I/II	18 (35.3)	37 (51.4)	
III/IV	33 (64.7)	35 (48.6)	0.0004
Residual tumor			
R0	46 (90.2)	67 (93.1)	
R1/2	5 (9.8)	5 (6.9)	0.6133
Length of operation (min)	249 ± 63	225 ± 88	0.3470
Blood loss (ml)	216 ± 150	259 ± 217	0.5095
Approaches			
Right thoracotomy	11 (21.6)	2 (2.8)	<0.0001
Left thoracophrenicolaparotomy	25 (49.0)	20 (27.8)	0.0035
Laparotomy	15 (29.4)	50 (69.4)	<0.0001
Combined resection			
Spleen	23 (43.1)	42 (58.3)	0.0474
Pancreas	5 (9.8)	21 (29.2)	0.0011

(); %

pT pathological depth of tumor invasion, *pT1* invasion of the mucosa or submucosa, *pT2* invasion of the muscularis propria, *pT3* invasion of the subserosa, *pT4* invasion of the serosa

The 5-year OS rates also did not differ significantly between SCC and ADC patients with/without dissection of the lower mediastinal lymph nodes, such as Nos. 108, 110, 111 and 112. There were no differences in the five-year OS rates between SCC and ADC patients with/without splenic hilum (No. 10) and para-aortic (No. 16) lymph node dissection.

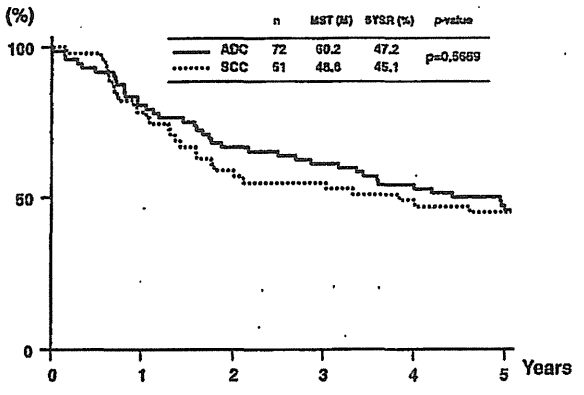

Fig. 1 Overall survival after resection of esophagogastric junction carcinoma according to histologic subtype

Distributions of the metastatic nodes and the index of estimated benefit from lymph node dissection

As shown in Table 2, nodal metastases frequently involved the abdominal lymph nodes, followed in frequency by node Nos. 1, 3, 2 and 7 in both ADC and SCC patients. Mediastinal lymph node dissection was performed in a total of 84 patients, and the metastatic rate was 22.9 % in SCC patients and 13.9 % in ADC patients. The metastatic rate of the No. 10 lymph node was low, at 0 % in SCC and 7.0 % in ADC patients. Only 31 patients underwent No. 16 lymph node dissection, and the metastatic rate was 28.6 % in SCC and 20.8 % in ADC cases (Table 2). Extended lymph node dissection was performed for regions where metastasis was suspected based on the preoperative clinical imaging findings.

Table 2 Distribution of the metastatic nodes and index of the estimated benefit from lymph node dissection

Lymph node station	SCC (51)					ADC (72)				
	Dissected cases	Metastasis cases	Metastatic rate	5YSR of metastasis cases	Index	Dissected cases	Metastasis cases	Metastatic rate	5YSR of metastasis cases	Index
1	49	20	40.8	27.8	11.3	72	33	45.8	24.2	11.1
2	49	9	18.4	33.3	6.1	72	16	22.2	37.5	8.3
3	49	17	34.7	33.3	11.6	72	29	40.3	27.6	11.1
4s	37	0	0	–	0.0	57	1	1.8	0	0.0
4d	35	0	0	–	0.0	66	2	3.0	50	1.5
5	31	0	0	–	0.0	60	1	1.7	0	0.0
6	36	1	2.8	0	0.0	63	3	4.8	33.3	1.6
7	47	9	19.1	33.3	6.4	71	20	28.2	20	5.6
8a	44	1	2.3	0	0.0	66	5	7.6	20	1.5
9	45	4	8.9	0	0.0	69	11	15.9	9.1	1.4
10	24	0	0	–	0.0	43	3	7.0	33.3	2.3
11p	39	5	12.8	20.0	2.6	64	6	9.4	16.7	1.6
11d	30	0	0	–	0.0	40	0	0	–	0.0
12a	6	1	16.7	0	0.0	36	0	0	–	0.0
16	7	2	28.6	0	0.0	24	5	20.8	20	4.2
a2lat	6	1	16.7	0	0.0	21	5	23.8	20	4.8
a2int	1	1	100	–	0.0	3	1	33.3	0	0.0
b1lat	4	1	25.0	0	0.0	10	1	10.0	0	0.0
b1int	0	0	0	–	0.0	6	0	0	–	0.0
ML	48	15	31.3	9.1	2.1	36	5	13.9	20	2.8
108	21	1	4.8	50.0	2.4	9	0	0	–	0.0
110	46	14	30.4	14.7	4.5	34	4	11.7	25	2.9
111	36	3	8.3	0	0.0	32	0	0	–	0.0
112	12	1	8.3	0	0.0	8	1	12.5	0	0.0

An index of the benefit gained by the dissection of each station was calculated by multiplication of the frequency of metastasis at the station by the 5-year survival rate of patients with metastasis at that station; metastatic rate × 5-year OS/100

Table 3 The total number of cases with lymph node metastasis with and without mediastinal lymph node metastasis

	All $n = 84$	SCC $n = 48$	ADC $n = 36$
Mediastinal LN metastasis (+)	6.7 ± 5.8	5.3 ± 3.5	9.8 ± 8.8
Mediastinal LN metastasis (−)	2.5 ± 3.6	2.0 ± 3.1	3.0 ± 4.1
p value	0.0003	0.0047	0.0063

Table 4 The number of patients with each site of first recurrence

	SCC	ADC	Total
Hematogenous	10	15	25
Liver	8	9	17
Lung	0	3	3
Bone	2	1	3
Brain	0	1	1
Skin	0	1	1
Lymphatic	11	3	14
Para-aortic	5	1	6
Mediastinal	3	0	3
Cervical	2	1	3
Other abdominal	1	1	2
Peritoneal	1	8	9
Local	1	0	1

Based on the index calculated employing the frequency of nodal metastasis and the 5-year OS rate for involvement at each lymph node level, only node Nos. 1, 2, 3 and 7, in both SCC and ADC patients, had a high index (>5). Although the estimated therapeutic index of lymph node dissection was 5 or less, the dissection of No. 110 in SCC and dissection of No. 16a2 lat in ADC patients were found to be effective (Table 2).

Lymph node metastasis status, recurrence sites and the results of the multivariate cox regression analysis

In 16 patients with mediastinal lymph node metastasis, the average total number of metastatic lymph nodes was 6.7, which was significantly higher than that (2.5) in the 68 patients who were positive for metastasis to only the abdominal lymph nodes. Similar results were obtained when metastases were examined according to the histological subtypes of SCC and ADC (Table 3).

Hematogenous metastasis was noted in 25 (10 SCC and 15 ADC) patients, and liver metastasis accounted for 17 of these patients. Lymphatic metastasis was observed in 14 (11 SCC and 3 ADC) patients; No. 16 lymph node metastasis in six patients, and mediastinal and cervical lymph node metastases in three patients each (Table 4).

Table 5 The results of the multivariate Cox regression analysis for the overall survival in patients with EGJ carcinoma ($n = 123$)

Variables	Hazard ratio	95 % confidence limits	p value
Age (< 65/≥ 65)	0.365	(0.215–0.618)	<0.01
Lymph node metastasis (n (−)/n (+))	0.370	(0.205–0.666)	<0.01
D-number (D0/D1, D2)	0.398	(0.158–0.998)	<0.01

A multivariate Cox regression analysis showed that only the age (<65 years), pN category (pN0) and residual tumor classification (R0) were independently associated with the outcome. Neither the histological subtype nor lower mediastinal, No. 10 and 16 node dissections were independently associated with the outcomes (Table 5).

Discussion

No standard procedure has yet been established for the surgical treatment of EGJ carcinoma in terms of the presence/absence of the need for thoracotomy, extent of esophageal and gastric resection, extent of mediastinal and abdominal lymph node dissection and the need for splenectomy. In the present study, we identified clear differences in the clinicopathological factors, approaches and surgical procedures used for SCC and ADC in our center.

A Dutch trial involving patients with Siewert type I/II carcinoma, treated in two high-volume centers, examined the superiority of two-field lymphadenectomy via the right TA over D1 lymphadenectomy via the TH approach [14]. It was recommended that right TA be performed for patients with type I tumors and TH for those with type II carcinoma based on a subsequent subset analysis [15].

In Japan, a randomized controlled trial (RCT) was conducted by the Stomach Cancer Study Group of the Japan Clinical Oncology Group to compare the left TA approach with the abdominal-TH approach in patients with Siewert Type II/III carcinoma (JCOG9502) [16]. The results failed to demonstrate the superiority of the left TA approach in terms of the OS. Accordingly, it was concluded that the abdominal-TH approach with para-esophageal lymph node dissection to a feasible extent should be recommended for Siewert Type II/III tumors.

Moreover, based on a study involving 1,002 patients, Siewert et al. [17] justified applying right TA for type I carcinoma of the esophagus and the abdominal-TH approach and D2 dissection of abdominal lymph nodes for type II and III gastric tumors. In addition, Yamashita et al.

[18] examined the optimal extent of lymph node dissection for Siewert type II carcinoma in a study including 225 patients, and determined that dissection of the paracardial and lesser curvature nodes is essential for achieving the therapeutic benefit of surgery. However, all of these studies were conducted for ADC. Therefore, further studies are needed to investigate the effects of histological differences on the distribution of lymph node metastasis and outcomes. However, to the best of our knowledge, there have been no reports on the surgical procedures or survival data based on the tumor histology of EGJ carcinoma.

The survival data in our series included a MST of 60.2 months and a 5-year OS rate of 47.2 % for ADC patients. The index calculated employing the frequency of nodal metastasis and the 5-year OS rate for involvement at each lymph node level indicated that the only lymph nodes which should be dissected were Nos. 1, 2, 3 and 7 in ADC patients. The multivariate Cox regression analysis showed that age, the pN category and the residual tumor classification were independently associated with the outcome. These results are in good agreement with those obtained in other studies [14, 16–19]. Therefore, the data from our series are highly consistent with those of previous studies, indicating the reliability of our present investigation.

In our series, the clinicopathological background factors and surgical procedures differed between the SCC and ADC groups, while there were no significant differences in the outcomes or therapeutic benefits provided by lymph node dissection. However, only three of the 51 SCC patients did not undergo mediastinal lymph node dissection. Because of this possible bias in the data, we cannot directly assess the clinical significance of mediastinal lymph node dissection in SCC cases.

The rate of mediastinal lymph node metastasis in our series was 22.9 % (11/48) in SCC and 13.9 % (5/36) in ADC patients, which was not significantly different. In addition, the values of the index of estimated benefit from the mediastinal lymph node dissection were similar in SCC and AC cases (2.9–2.2).

In our series of 123 patients, none exhibited mediastinal lymph nodes metastasis alone, suggesting that metastasis to mediastinal lymph nodes basically occurs after that to abdominal lymph nodes. In 16 patients with mediastinal lymph nodes metastasis, the average total number of metastatic lymph nodes was 6.7, which was significantly higher than that (2.5) in the 68 patients who were positive only for metastasis to abdominal lymph nodes. Similar results were obtained when the metastases were examined according to the histological subtypes. These results indicate that metastasis of EGJ carcinoma of Siewert type II occurs first to the abdominal lymph nodes, and then to mediastinal lymph nodes, regardless of the histopathological subtype of the tumor. Thus, patients with mediastinal lymph node metastasis probably already have abdominal lymph node metastasis, and the total number of metastatic lymph nodes would inevitably be high. Consequently, the addition of mediastinal lymph node dissection with additional thoracotomy may not provide a meaningful clinical benefit.

Our examination of the recurrence sites revealed that hematogenous recurrence, mainly in the liver, accounted for the majority of relapses in both SCC and AC, followed by No. 16 lymph node recurrence. Only three SCC patients and none of the ADC patients had mediastinal lymph nodes recurrence. This revealed hematogenous metastasis to the liver to be common in EGJ carcinoma cases, an observation consistent with other studies [18, 20].

Perioperative chemo-radiotherapy for EGJ carcinoma, including SCC, reportedly improves the outcomes [9]. Since patients with EGJ carcinoma are potentially at high risk of hematogenous micrometastasis, prophylactic dissection of mediastinal lymph nodes would offer no apparent benefits in terms of the local control or prognostic improvement. Among our patients with mediastinal lymph nodes metastasis, one SCC patient with three metastatic nodes (one at No. 108 and two at No. 110), and only one ADC patient with one metastatic lymph node, at No. 110, survived longer than 5 years. Based on these findings, we speculated that the effectiveness of mediastinal lymph node dissection is nearly as low in SCC as it is in ADC.

Conclusions

Overall, taking the surgical invasiveness into account, it can be assumed that the appropriate procedures for both SCC and ADC include dissection of the abdominal lymph nodes, focusing on the paracardial area and the lesser curvature of the stomach, para-esophageal lymph nodes (No. 110) for SCC, and a part of the para-aortic lymph nodes (No. 16 a2 lat) for ADE via the abdominal-TH approach.

A multivariate Cox regression analysis showed that histological subtype (SCC and ADE) was not an independent prognostic factor.

In this study, two datasets for esophageal and gastric tumors treated in our center were integrated for the analysis. Thus far, patients with lesions on the esophageal side have undergone esophageal surgery performed by specialists, while those with lesions on the gastric side have been treated by surgeons specializing in gastric surgery. This historical background may have yielded apparently contradictory outcomes. Further evidence is needed to confirm the present findings and establish the outcomes of each of the skilled approaches used for SCC and ADC. Such evidence is needed to prepare for the anticipated increase in the number of patients with EGJ carcinoma.

Conflict of interest The authors have no conflicts of interest to declare.

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Uchiyama et al. World Journal of Surgical Oncology 2012, 10:115
http://www.wjso.com/content/10/1/115

WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH Open Access

Immunohistochemical consistency between primary tumors and lymph node metastases of gastric neuroendocrine carcinoma

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Abstract

Background: Gastric neuroendocrine carcinoma (G-NEC) is a rare, highly malignant tumor that exhibits aggressive growth leading to vascular invasion, distant metastasis and extremely poor prognosis. We studied the clinicopathological findings of seven patients at our institute to better under this disease.

Methods: Seven cases of G-NEC were identified among 1,027 cases of gastric carcinoma that underwent gastrectomy at Kansai Rousai Hospital between 2002 and 2010. We studied the pathological and immunohistochemical features of gastric neuroendocrine carcinomas at both the primary site and metastatic lymph nodes.

Results: The mean patient age was 73 years (range 63 to 86 years). There were no females in this series. The final staging was Stage I in one case, Stage II in two, Stage III in two and Stage IV in two. A total of 31 metastatic lymph nodes were found in these patients. This study revealed that the ratio of neuroendocrine cells was similar between the primary and metastatic sites, which tended to show the same expression patterns of neuroendocrine markers.

Conclusions: Metastatic lymph nodes showed heterogeneous immunohistochemical expression patterns similar to the primary sites. G-NEC is far advanced at diagnosis and rapidly reaches the lymph nodes retaining its heterogeneity, carrying a worse prognosis than common gastric cancer.

Mini abstract: G-NEC grows rapidly and metastasizes to the lymph nodes, retaining its pathological and immunohistochemical heterogeneity even at the metastatic sites.

Keywords: Ki67, Immunohistochemistry, Heterogeneity

Background

Gastric neuroendocrine carcinoma (G-NEC) is a rare tumor (0.1 to 0.2% of all gastric carcinomas) with highly malignant biological behavior exhibiting aggressive growth that leads to vascular invasion, distant metastasis and extremely poor prognosis. The 2010 WHO classification defines well-differentiated endocrine tumors/carcinomas as neuroendocrine tumors (NETs), and poorly differentiated endocrine carcinomas as neuroendocrine carcinomas (NECs). Compared with well-differentiated gastric NETs, G-NECs have highly malignant behavior and poor prognosis, but their prognostic markers and therapeutic strategies have not yet been defined.

A definite diagnosis of G-NEC is provided by immunohistochemical examination with neuroendocrine markers, such as synaptophysin (SYN), chromogranin A (CGA), CD56 and neuron-specific enolase (NSE). It has been proposed that care should be exercised in diagnosis because of the variation shown by G-NECs in both histological morphology and immunohistochemical expression. However, no reports have investigated the relationship between the expression pattern at the primary site and that at the metastatic sites as to both histological morphology and immunohistochemical expression. In this study, we examined the primary tumors and all metastatic lymph nodes, and reviewed the association

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of expression patterns by means of immunohistochemical examination.

Methods

Patients and specimens

Seven cases of G-NEC were identified among 1,027 cases of gastric carcinoma that underwent gastrectomy at Kansai Rousai Hospital between 2002 and 2010 (0.68%). All patients gave written informed consent for clinicopathological evaluation.

Table 1 lists the clinicopathological characteristics of these patients. The median age was 73 years (range 63 to 86 years). There were no females in this series. All patients underwent gastrectomy with regional lymph node dissection, and in Case 4, additional liver resection was performed for synchronous liver metastasis.

Immunohistochemical staining

All resected stomachs and lymph nodes were fixed in 10% neutral formalin, and then, the entire tumor was step-cut to a width of 4 to 5 mm. Specimens were embedded in paraffin, cut into 4-μm sections and stained with hematoxylin and eosin. An immunohistochemical procedure using the EnVision system (DakoCytomation, Glostrup, Denmark) was employed as previously established. Immunohistochemical staining was examined in all blocks of the maximum divided surface of the primary site and all blocks of the metastatic lymph nodes in each case. We reviewed the histology of the tumor on hematoxylin and eosin stains and evaluated the expression of SYN, CGA, CD56 and NSE. We examined not only the primary tumors but also 236 lymph nodes, from which we identified 31 metastatic lymph nodes derived from five patients. The immunohistochemical expression for each antibody was defined as follows: – (<5%), 1+ (5 to 9%), 2+ (10 to 49%) and 3+ (over 50%). The ratio of the tumor area with positivity of each marker was evaluated throughout the maximum dimension of the primary tumors and metastatic lymph nodes. Positivity was defined as a dimension ratio of expression exceeding 10% (over 2+). The following antibodies were used: anti-synaptophysin and anti-CD56 purchased from Novocastra Laboratories Ltd. (Newcastle upon Tyne, UK), and anti-chromogranin A and anti-NSE purchased from DakoCytomation (Glostrup, Denmark). The Ki67 labeling index was also estimated in the block including the deepest part of the primary tumor.

Results

Gross findings and staging

Five tumors were located in the middle of the stomach, and the remaining two were in the lower stomach (Table 1). One case was a T1b (submucosa) tumor, four cases were T3 (subserosa), one was T4a (penetration of serosa) and one was T4b (invasion to adjacent structures) (Table 2). Lymph node metastasis was found in five cases. The final staging was Stage IA in one case, Stage IIA in one, Stage IIB in one, Stage IIIA in one, Stage IIIB in one and Stage IV in two, according to the seventh American Joint Committee on Cancer (AJCC) TNM staging classification. The tumors had grown to a median size of 6 cm (range 2 to 13 cm) in the greatest dimension. Grossly, the tumor was Type 3 in three cases, Type 2 in three and Type 5 in one.

Expression of immunohistochemical staining between the primary and metastatic sites

Only three cases were correctly diagnosed as G-NEC preoperatively. We summarized the varied histological patterns of the primary tumors and lymph nodes in Table 3. According to the WHO classification, five of the seven tumors were large-cell subtypes and the others were small-cell subtypes. They were classified into five pure neuroendocrine carcinomas and two tumors combined with adenocarcinoma. We examined a total of 236 lymph nodes obtained from seven patients. Among them, 31 positive nodes included 12 nodes showing pure adenocarcinoma, 3 showing both adenocarcinoma and neuroendocrine

Table 1 Patients' characteristics

Patient No.	Age	Location	Gross type	Tumor size (cm)	Preoperative diagnosis	Operation	R
1	63	L	3	13	tub2	Distal gastrectomy	R2
2	71	M	2	2	por1 > tub2	Total gastrectomy	R0
3	71	M	3	13	NEC	Distal gastrectomy	R1
4	86	M	2	3	tub2 > por1 > por2	Distal gastrectomy + Hepatectomy	R1
5	74	M	2	9	NEC	Distal gastrectomy	R0
6	69	L	3	3	tub2	Distal gastrectomy	R0
7	77	M	5	6	NEC	Distal gastrectomy	R0

NEC, neuroendocrine carcinoma; por1, poorly differentiated adenocarcinoma, solid type; por2, poorly differentiated adenocarcinoma, non-solid type; R, Resectability; tub2, moderately differentiated tubular adenocarcinoma.

Table 2 Clinicopathological findings of primary tumor and resected lymph node

Pt No	Pathological Stage							Metastatic ratio of dissected lymph nodes		Histology of lymph node metastases					
										Ad		Concomitant Ad and NEC		NEC	
								n	(%)	n	(%)	n	(%)	n	(%)
1	T4b	N3a	M0	H0	P0	CY1	IV	8/16	(50)	0	(0)	0	(0)	8	(100)
2	T3	N2	M0	H0	P0	CY0	IIIA	5/26	(19)	0	(0)	0	(0)	5	(100)
3	T3	N0	M0	H0	P0	CY0	IIA	0/42	(0)	-		-		-	
4	T3	N1	M0	H1	P0	CY0	IV	1/31	(3)	0	(0)	0	(0)	1	(100)
5	T3	N1	M0	H0	P0	CY0	IIB	2/52	(4)	0	(0)	0	(0)	2	(100)
6	T4a	N3b	M0	H0	P0	CY0	IIIC	15/25	(60)	12	(80)	3	(20)	0	(0)
7	T1b	N0	M0	H0	P0	CY0	IA	0/44	(0)	-		-		-	

carcinoma, and 16 showing pure neuroendocrine carcinoma. While the cases with pure NEC had lymph node metastasis of pure NEC (for example, Case 1 shown in Figures 1 and 2), the two remaining cases with both adenocarcinoma cells and neuroendocrine carcinoma cells had varied lymph node metastasis. Case 4 had pure NEC, and Case 6 had both pure adenocarcinoma nodes and concomitant nodes. In addition, we verified the primary and lymph node subtypes by staining for neuroendocrine markers, and all primary tumors were strongly stained by SYN and CD56. Most cases showed varied expression patterns that were similar in both the primary and metastatic sites. The accordance of positivity between the primary sites and lymph nodes was extremely high: 80% in SYN, 100% in CGA, 60% in CD56 and 80% in NSE. Furthermore, the Ki67 labeling index was high, over 20% in all cases.

Clinical course

Adjuvant chemotherapy, including S-1, was introduced to all cases but one at an early stage. The median treatment duration was 8.1 months (range 0.9 to 24.5 months). During the treatment course, there were two recurrences (Cases 1 and 4) and one death three months after incurative surgery (Case 1). The major site of relapse was the liver, followed by the peritoneum. Chemotherapy was introduced after liver recurrence in Case 4. The patient responded well to the therapy and achieved long, overall survival, 21 months, despite his advanced stage. The three-year disease-free survival rate was 64.3%, and the three-year overall survival rate was 83.8% after surgery.

Discussion

NECs are classified into pure tumors and composite tumors admixing adenocarcinomatous differentiation [1,2]. Criteria for classification in NEC categories is that over 30% of the cells display the features of neuroendocrine differentiation [2]. NECs have aggressive biological behavior and exhibit rapid proliferation. [1-7]

Table 3 Histology and immunohistochemical findings of both primary tumor and metastatic lymph nodes

Patient no.	Primary tumor						Lymph node metastases					Ki-6 7 labeling index (%)	Mitotic counts (/10HPF)
	Histology	Ratio of neuroendocrine cell (%)	Expression of neuroendocrine markers				Histlogy	Expression of neuroendocrine markers					
			SYN	CGA	CD56	NSE		SYN	CGA	CD56	NSE		
1	SC	100	3+	-	3+	3+	SC	3+	-	3+	3+	60	60 to 70
2	LC	100	3+	3+	2+	1+	LC	1+	3+	1+	2+	20	20
3	LC	100	3+	-	2+	3+						80	80 to 90
4	LC > tub2	90	3+	3+	3+	-	LC	3+	3+	2+	-	30	80 to 90
5	LC	100	3+	-	3+	-	LC	3+	-	3+	-	70	100 to 110
6	LC > tub2 > por1	60	3+	3+	3+	1+	pure Ad	2+	-	-	-	70	20
							LC + Ad	3+	2+	1+	-		
7	SC	100	3+	-	2+	3+						80	100 to 110

Expression positivity was defined as follows; - (<5%), 1+ (5 to 9%), 2+ (10 to 49%), and 3+ (over 50%). Ad, adenocarcinoma; CGA, chromogranin A; HPF, high power fields; LC, large cell; NSE, neuron-specific enolase; SC, small cell; SYN, synaptophysin.

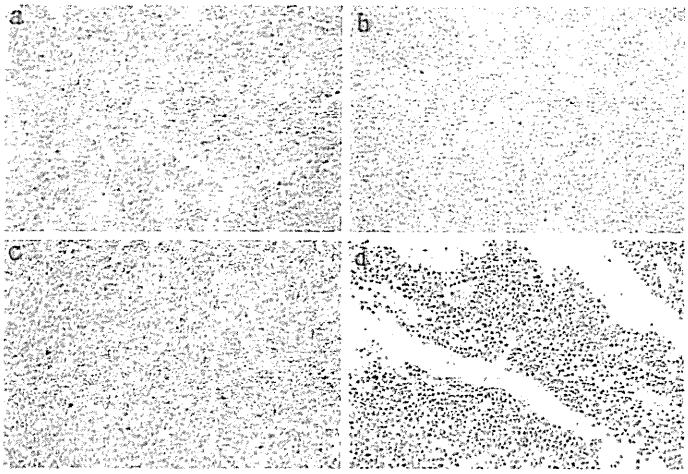

Figure 1 Immunohistochemical expression for neuroendocrine markers in primary tumor (Case 1). a) Synaptophysin, b) chromogranin A, c) CD56, d) neuron-specific enolase. Tumor cells variably expressed neuroendocrine markers.

We studied the characteristics of G-NECs by means of pathological and immunohistochemical examination of both the primary sites and metastatic lymph nodes. In this study, we found an admixed population of pure neuroendocrine cells, adenocarcinoma cells and their intermediate cells that have the morphological features of adenocarcinoma with positivity to neuroendocrine markers. Other studies have reported that NEC shows strong staining for neuroendocrine markers, such as CGA, SYN, NSE and CD56 [1-3,5,7]. In our series, the positivity rate for CGA, SYN, NSE and CD56 was 42.9%, 100%, 85.7% and 72.7%, respectively. Among these markers, tumors showed the highest positivity for SYN and lowest positivity for CGA. CGA is a marker for neuroendocrine granules and an indicative factor of differentiation to neuroendocrine cells. The poor differentiation in our cases prevented sufficient expression of granules.

We found that the tumors varied in immunohistochemical expression. In one tumor, while some cells with high CGA expression showed negativity for other markers, some cells with no CGA expression showed diffuse high positivity for other markers. In addition, besides neuroendocrine cells positive for SYN, some adenocarcinoma cells showed positivity for SYN among composite-type tumors.

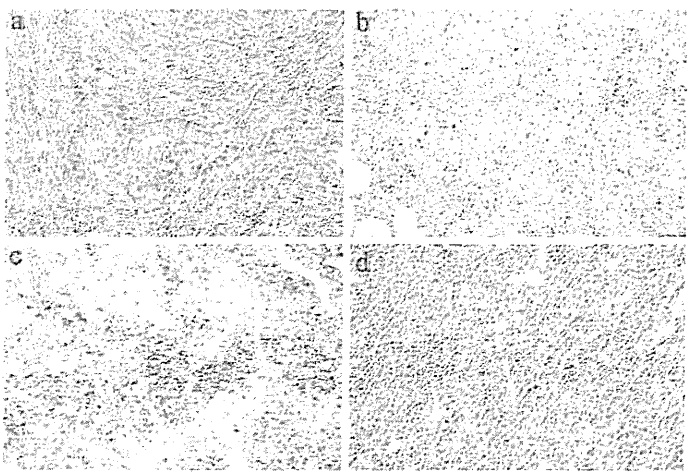

Figure 2 Immunohistochemical expression for neuroendocrine markers in metastatic tumor cells in lymph nodes (Case 1). a) Synaptophysin, b) chromogranin A, c) CD56, d) neuron-specific enolase. Expression patterns of neuroendocrine markers in metastatic tumors were similar to those in the primary tumor.

This indicates histological and immunophenotypical continuity between the adenocarcinoma component and the NEC component.

Furthermore, focusing on lymph nodes, we found that cases with pure neuroendocrine primary sites had metastatic lymph nodes with pure neuroendocrine cells (Table 3). The variation in immunohistochemical expression patterns of the primary site was maintained even in the metastatic pure endocrine cells. In Case 6, one of the two cases with combined primary tumors, composite metastasis of NEC and adenocarcinoma was seen in some lymph nodes, and pure adenocarcinoma metastasis was seen in other nodes. The tumor showed consistency in both histological type and immunohistochemical expression between the primary site and the metastatic lymph nodes. This result led to a hypothesis as to the manner of metastasis. That is, clustered cells, including adenocarcinoma and neuroendocrine cells with varied immunophenotypes, spread to the lymph nodes and coexisted there. Additionally, lymph nodes of composite-type tumors expressed a slightly different staining pattern. Cells not undergoing sufficiently mature differentiation in primary sites may differentiate into neuroendocrine cells or develop varied immunohistochemical expression. In this series, there was no clear association between immunohistochemical expression and clinical outcome. Cases with low Ki67 labeling indices had a good prognosis. For example, Case 2, for which the Ki67 labeling index was 20%, achieved the longest survival term, 55 months. Case 4, for which the Ki67 labeling index was 30%, was successfully treated with surgery and chemotherapy and survived for 21 months despite distant metastasis. Limitations of this study include short duration of follow-up and small sample size mostly composed of pure types. Therefore, large-scale and long-term studies are needed to draw a definitive conclusion.

Conclusion

In summary, we reported the pathological and immunohistochemical features of neuroendocrine carcinomas at both the primary sites and metastatic lymph nodes. The cells grow rapidly and metastasize to the lymph nodes retaining their heterogeneity even at the metastatic sites.

Abbreviations

G-NEC: Gastric neuroendocrine carcinoma; NETs: neuroendocrine tumors; NECs: neuroendocrine carcinomas; SYN: synaptophysin; CGA: chromogranin A; NSE: neuron-specific enolase; por1: poorly differentiated adenocarcinoma, solid type; por2: poorly differentiated adenocarcinoma, non-solid type; R: Resectability; tub2: moderately differentiated tubular adenocarcinoma; AJCC: American Joint Committee on Cancer; Ad: adenocarcinoma; HPF: high power fields; LC: large cell; SC: small cell.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CU and ST conceived of the study. ST and SN supervised the manuscript writing. SN performed the pathological and immunohistochemical evaluation and scoring. AT, HM, TK, SN, RS, KN, YT and TK collected the cases and clinical information. CU performed the literature review and wrote the manuscript. AT and SN performed the statistical analysis. All authors read and approved the final manuscript.

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Received: 13 February 2012 Accepted: 10 May 2012
Published: 22 June 2012

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doi:10.1186/1477-7819-10-115
Cite this article as: Uchiyama *et al.*: Immunohistochemical consistency between primary tumors and lymph node metastases of gastric neuroendocrine carcinoma. *World Journal of Surgical Oncology* 2012 10:115.

Hindawi Publishing Corporation
International Journal of Surgical Oncology
Volume 2011, Article ID 748745, 8 pages
doi:10.1155/2011/748745

Review Article

Lymph Node Dissection in Curative Gastrectomy for Advanced Gastric Cancer

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Received 15 January 2011; Accepted 29 March 2011

Academic Editor: Michael Hünerbein

Gastric cancer is one of the most common causes of cancer-related death worldwide. Surgical resection with lymph node dissection is the only potentially curative therapy for gastric cancer. However, the appropriate extent of lymph node dissection accompanied by gastrectomy for cancer remains controversial. In East Asian countries, especially in Japan and Korea, D2 lymph node dissection has been regularly performed as a standard procedure. In Western countries, surgeons perform gastrectomy with D1 dissection only because D2 is associated with high mortality and morbidity compared to those associated with D1 alone but does not improve the 5-year survival rate. However, more recent studies have demonstrated that western surgeons can be trained to perform D2 lymphadenectomies on western patients with a lower morbidity and mortality. When extensive D2 lymph node dissection is preformed safely, there may be some benefit to D2 dissection even in western countries. In this paper, we present an update on the current literature regarding the extent of lymphadenectomy for advanced gastric cancer.

1. Introduction

Gastric cancer is one of the most common causes of death worldwide [1]. Although the prognosis of patients with advanced gastric cancer has improved with the introduction of effective chemotherapy [2] or adjuvant radiotherapy [3], surgical resection remains the primary therapeutic modality for curable advanced cancer. With regard to surgical procedure, dissection of regional LN is regarded an important part of en bloc resection for gastric cancer. However, there are significant differences in the extent of lymphadenectomy preformed by surgeons in different countries.

In Japan, D2 dissection has been recommended as standard practice since the 1960s [4]. East Asian surgeons, especially Japanese and Korean surgeons, routinely performed gastrectomy with D2 dissection. However, most Western surgeons perform gastrectomy with only D1 dissection, because D1 was associated with less mortality and morbidity than D2 in prospective randomized trials preformed in the Netherland and the UK concluded that there was no survival benefit for D2 over D1 lymph node dissection [5, 6]. However, there were significant problems with these studies, including a high morbidity and mortality rate in the D2 group associated with inadequate surgical training, with inadequate dissection of D2 and with the frequent performance of distal pancreatectomy and splenectomy in the D2 group, which is now considered unnecessary [7].

More recent studies have demonstrated that western surgeons at experienced centers can be trained to perform D2 gastrectomy for selected western patients with low morbidity and mortality [8–10]. There may be some benefits to D2 gastrectomy when performed safely, but this assertion requires further validation to establish the global standard in gastrectomy.

In this paper, we describe an update on the current literature regarding the extent of lymphadenectomy for advanced gastric cancer.

2. Grouping of Lymph Nodes

The lymph nodes of the stomach have been arranged into a very useful classification by the Japanese Gastric Cancer Association (JGCA) [11, 12] (Table 1, Figure 1).

Table 1: Regional lymph nodes.

No. 1	Right paracardial LN
No. 2	Lest paracardial LN
No. 3a	LN along the left gastric vessels
No. 3b	LN along the right gastric vessels
No. 4sa	LN along the short gastric vessels
No. 4sb	LN along the left gastroepiploic vessels
No. 4d	LN along the right gastroepiploic vessels
No. 5	Suprapyloric LN
No. 6	Infrapyloric LN
No. 7	LN along the left gastric artery
No. 8a	LN along the common hepatic artery (anterosuperior group)
No. 8b	LN along the common hepatic artery (posterior group)
No. 9	LN along the celiac artery
No. 10	LN at the splenic hilum
No. 11p	LN along the proximal splenic artery
No. 11d	LN along the distal splenic artery
No. 12a	LN in the hepatoduodenal ligament (along the hepatic artery)
No. 12b	LN in the hepatoduodenal ligament (along the bile duct)
No. 12p	LN in the hepatoduodenal ligament (behind the portal vain)
No. 13	LN on the posterior surface of the pancreatic head
No. 14v	LN along the superior mesenteric vein
No. 14a	LN along the superior mesenteric artery
No. 15	LN along the middle colic vessels
No. 16a1	LN in the aortic hiatus
No. 16a2	LN around the abdominal aorta (from the upper margin of the celiac trunk to the lower margin of the left renal vein)
No. 16b1	LN around the abdominal aorta (from the lower margin of the left renal vein to the upper margin of the inferior mesenteric artery)
No. 16b2	LN around the abdominal aorta (from the upper margin of the inferior mesenteric artery to the aortic bifurcation)
No. 17	LN on the anterior surface of the pancreas head
No. 18	LN along the inferior margin on the pancreas
No. 19	Infradiaphragmatic LN
No. 20	LN in the esophageal hiatus of the diaphragm
No. 110	Paraesophageal LN in the lower thorax
No. 111	Supradiaphragmatic LN
No. 112	Posterior mediastinal LN

According to this classification, lymph nodes surrounding stomach are divided into 20 stations and these are classified into three groups depending upon the location of the primary tumor. This grouping system is based on the results of studies of lymphatic flow at various tumor sites, together with the observed survival associated with metastasis to each nodal station [13]. In this grouping system, the most perigastric LNs (stations nos. 1–6) are defined as group 1, whereas the nodes along the left gastric artery (station no. 7), common hepatic artery (station no. 8), celiac axis (station no. 9), splenic artery (station no. 11) and proper hepatic artery (station no. 12) are defined as group 2. Minor modifications of this grouping system are necessary according to the location of the primary tumor. D1 gastrectomy is defined as dissection of all the Group 1 nodes, and D2 is defined as dissection of all the Group 1 and Group 2 nodes.

Recently, new Japanese Classification of Gastric Carcinoma [12] and guideline for Diagnosis and Treatment of Carcinoma of the Stomach [14] edited by the Japanese Gastric Cancer Society were published in May and October, 2010 to match to the standard of TNM classification of UICC [15, 16] (Tables 2 and 3).

Table 2: Depth of tumor invasion (T)—Japanese classification and TNN.

Depth of tumor invasion (T)	Japanese classification (JC: 13th edition)	TNM classification (6th edition)	JC (14th edition)/TNM (7th edition)
Mucosa and/or muscularis mucosa (M)	T1 (M)	Tis/T1	Tis/T1a
Submucosa (SM)	T1 (SM)	T1	T1b
Muscularis propria (MP)	T2 (MP)	T2a	T2
Subserosa (SS)	T2 (SS)	T2b	T3
Penetration of serosa (SE)	T3	T3	T4a
Invasion of adjacent structures (SI)	T4	T4	T4b

Table 3: Extent of lymph node metastasis (*N*)—Japanese classification and TNN classification.

N category	Japanese classification (JC: 13th edition)	TNM classification (6th edition)	JC (14th edition)/TNM (7th edition)
N_0	No evidence of LN metastasis	No evidence of LN metastasis	No evidence of LN metastasis
N_1	Metastasis to only Group 1 LN	Metastasis in 1 to 6 regional LNs	Metastasis in 1 to 2 regional LNs
N_2	Metastasis to Group 2 LN, but no metastasis to Group 3 LN	7–15 nodes	3–6 nodes
N_3	Metastasis to Group 3 LN	16 or more nodes	7 or more nodes N3a: 7–15 nodes N3b: 16 or more nodes

LN: lymph node.

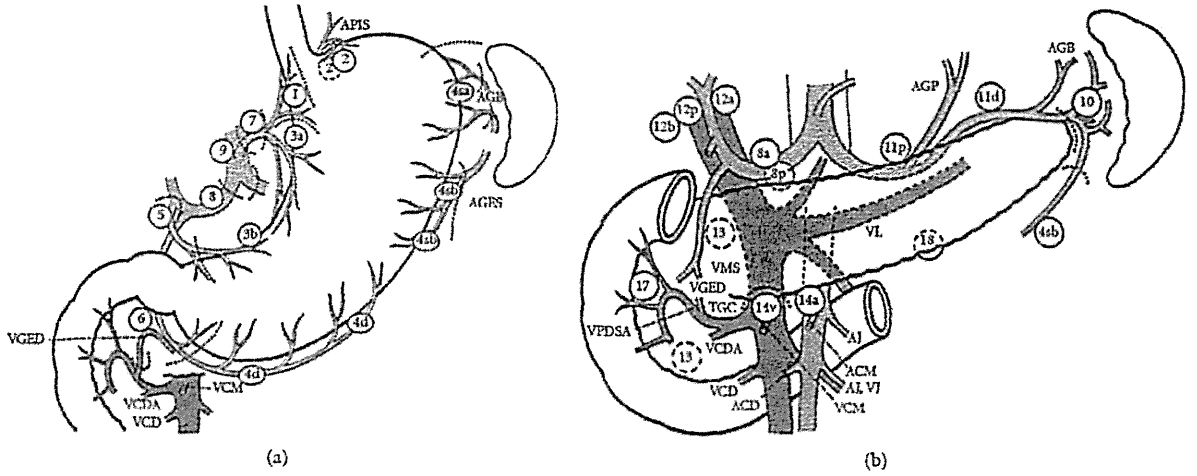

FIGURE 1: Lymph node station numbers according to the Japanese classification of gastric cancer of the 14th edition reproduced form [12] with permission.

In this classification, the extent of LN metastasis is divided into three groups according to the number of metastatic LN, not to the *N*-number of the extent of LN metastasis.

Moreover in this guideline, the main modification about lymph node dissection is that selection of D1 or D2 dissection is prescribed by the kind of gastrectomy, for example, total gastrectomy or distal gastrectomy, not by the location of the primary tumor. It is provided that D1 gastrectomy includes the dissection of the nodes along the left gastric (station no. 7) as well as the perigastric lymph nodes (stations nos. 1–6), regardless of the location of tumor. LNs along the superior mesenteric vein (station no. 14v) are eliminated from D2 dissection for tumor in the lower third of the stomach.

In other words, D1 distal gastrectomy consists of LN dissection of station nos. 1, 3, 4sb, 4d, 5, 6, and 7 and D1 total gastrectomy includes station nos. 1–6 and 7 (Figure 2).

In Japan, although the surgical procedure is performed according to the new guidelines, standard surgery for cN1 or T2 and more cases is defined as gastrectomy with D2 dissection.

3. D1 versus D2

In Japan, D2 dissection was introduced in the 1960's and gastrectomy with D2 dissection has been regarded as a safe surgical procedure and performed regularly in ordinary general hospitals [4]. Therefore, in Japan, a clinical trial comparing D1 versus D2 would be considered unethical today.

However, whether D2 LN dissection in radical gastrectomy should be routinely performed is still unclear in the world.

Based on the results of several RCTs comparing D1 and D2/D3 dissection performed in western countries, D2 dissection is not recommended because D2 is associated with high morbidity and mortality rate.

Two large-scale RCTs wereperformed by the Dutch Gastric Cancer Group [5, 17–19] and Medical Research Council Gastric Cancer Surgical Group [6, 20] (Table 4). The RCT by the Dutch group was performed between 1989 and 1993 and involved 711 patients from 80 hospitals but excluded 285 patients who had received palliative treatment [5]. The RCT by the British group was performed between 1987 and 1994 and involved 400 patients but excluded 337 patients based on staging laparoscopy demonstrating advanced disease [6].

The stage distribution in the Dutch RCT was slightly less advanced than that in the British study; UICC stage I tumors comprised 43% and 35% of the total, respectively, and T3 tumors comprised 44 and 27%.

In the Dutch trial, D2 patients demonstrated higher postoperative morbidity (43% versus 25% for D1: $P < .001$) and higher morbidity (10% versus 4% for D1: $P < .004$). Overall 5-year survival rates were similar in the D1 and D2 groups (45% for D1 and 47% for D2).

The hazard ratio (HR) comparing the risk of death within 5 years after D2 surgery to that of 5 years after D1 surgery was 1.00 (95% confidence interval (95% CI), 0.82–1.22) [5]. However, at 11 years, survival rates were 30% for D1 and 35% for D2 ($P = .53$). When hospital deaths were excluded, survival rates were 32% for D1 ($n = 365$) and 39% for D2 ($n = 299$) and the relative risks of these patients favored the D2 surgery group ($P = .07$) [17].

Low-quality surgery due to a very low hospital volume could explain why D2 surgery was not beneficial, along with high hospital mortality in that series. About 50% of the patients in the D2 group did not undergo lymph node dissection at all stations that should have been resected. However, 6% of the patients in the D1 group underwent dissection of more stations that would not been resected in D1 surgery. These factors could have led to the limited difference in outcomes, between D1 and D2 surgery [18].