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BRIEF ARTICLE

Lymph node metastasis in gastric cardiac adenocarcinoma in male patients

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Abstract

AIM: To reveal the clinicopathological features and risk factors for lymph node metastases in gastric cardiac adenocarcinoma of male patients.

METHODS: We retrospective reviewed a total of 146 male and female patients with gastric cardiac adenocarcinoma who had undergone curative gastrectomy with lymphadenectomy in the Department of Surgery, Xin Hua Hospital and Rui Jin Hospital of Shanghai Jiaotong University Medical School between November 2001 and May 2012. Both the surgical procedure and extent of lymph node dissection were based on the recommendations of Japanese gastric cancer treatment guidelines. Univariate and multivariate analyses of lymph node metastases and the clinicopathological features were undertaken.

RESULTS: The rate of lymph node metastases in male patients with gastric cardiac adenocarcinoma was 72.1%. Univariate analysis showed an obvious correlation between lymph node metastases and tumor size, gross appearance, differentiation, pathological tumor depth, and lymphatic invasion in male patients. Multivariate logistic regression analysis revealed that tumor differentiation and pathological tumor depth were the independent risk factors for lymph node metastases in male patients. There was an obvious relationship between lymph node metastases and tumor size, gross appearance, differentiation, pathological tumor depth, lymphatic invasion at pN_1 and pN_2, and nerve invasion at pN_3 in male patients. There were no significant differences in clinicopathological features or lymph node metastases between female and male patients.

CONCLUSION: Tumor differentiation and tumor depth were risk factors for lymph node metastases in male patients with gastric cardiac adenocarcinoma and should be considered when choosing surgery.

Key words: Gastric neoplasm; Lymph node metastasis; Risk factors; Gastrectomy; Lymphadenectomy

Core tip: There is an obvious correlation between lymph node metastases and tumor size, gross appearance, differentiation, pathological tumor depth and lymphatic invasion in male patients. Tumor differentiation and

pathological tumor depth were independent risk factors for lymph node metastases in male patients. There was an obvious relationship between lymph node metastases and tumor size, gross appearance, differentiation, pathological tumor depth, lymphatic invasion at pN_1 and pN_2, and nerve invasion at pN_3 in male patients. There were no significant differences in clinicopathological features or lymph node metastases between female and male patients.

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INTRODUCTION

Although its incidence and mortality have declined over the past 50 years, gastric cancer (GC) remains the fourth most common cancer and the second most frequent cause of cancer death worldwide[1-3]. In China, GC is the second most common malignancy and the third most frequent cause of cancer-related death, with an annual age-adjusted mortality rate of 24.34 deaths per 100000 people[4]. As GC incidence declines, the frequency of proximal gastric and gastroesophageal junctional adenocarcinomas continues to rise, and has become a significant clinical challenge[5-7]. The reasons for this rapid increase in aggressive proximal malignancies remain unclear. Tumors in the upper third of the stomach might spread *via* the lymphatic system through the lower esophageal channel to the mediastinum, through the suprapancreatic channel to the abdomen, or through the abdominal para-aortic channel to the retroperitoneum. Surgery is currently the only treatment that can lead to a cure. However, the optimal surgical strategy for tumors in the cardiac area of the stomach, especially tumors invading the lower esophagus, remains controversial[6]. The development of effective therapeutic strategies for these tumors requires information on patient characteristics, patterns of lymph node metastasis, and the efficacy of lymph node dissection. Adenocarcinoma of the cardia generally has a low curative resection rate and a poor prognosis; worse than carcinoma of the other regions of the stomach, mainly because the disease is at a more advanced stage at diagnosis[6-8]. The 5-year survival rate in resected cases is $\leqslant$ 20%[9].

The role of lymphadenectomy in GC surgery has been hotly debated during the past three decades. Although there is still no standard approach, it is obvious that an adequate lymphadenectomy, removing all the possible metastatic nodes, remains a milestone in GC surgery[10]. The most recent edition of the tumor, node, metastasis (TNM) classification states that at least 15 lymph nodes must be examined to form an accurate evaluation of the node status. The optimal extent of lymphadenectomy (D2) for this cancer has been defined in the Japanese Classification of Gastric Carcinoma[11], based on the retrospective historical data of the involved nodes in patients with gastric carcinoma. The optimal extent of lymph node dissection for Siewert type Ⅱ esophagogastric junction (EGJ) carcinoma is poorly defined in this classification. Rüdiger Siewert *et al*[12] uncovered the distribution of metastatic nodes in patients with type Ⅱ adenocarcinoma. In their cohort of 186 patients, they found that the disease mainly involved the paracardial and lesser curve nodes, followed in frequency by the nodes in the lower mediastinum, and suprapancreatic nodes and nodes along the greater curve were involved in patients with Siewert type Ⅱ EGJ cancers. Furthermore, they found positive parapyloric nodes in three of their patients, which lends support to their recommended strategy of extended total gastrectomy for type Ⅱ EGJ carcinoma.

Therefore, in the present study, we revaluated retrospectively the clinicopathological features and distribution of metastatic nodes in a two-center cohort of 146 patients with gastric cardiac adenocarcinoma. Univariate and multivariate analyses were applied to confirm the clinicopathological factors associated with lymph node metastases, and to provide a basis for choosing the optimal surgical treatment and for determining the appropriate range of lymph node dissection.

MATERIALS AND METHODS

Patients

Data were collected from a prospectively maintained database of patients with histologically confirmed gastric cardiac carcinoma who had curative gastrectomy (R0) with lymphadenectomy in the Department of Surgery, Xin Hua Hospital and Rui Jin Hospital of Shanghai Jiaotong University Medical School between November 2001 and May 2012. The clinicopathological characteristics and lymph node metastasis of gastric cardiac adenocarcinoma were compared in male and female patients (Table 1).

Surgery

All operations were performed with curative intent. Curative surgery was defined as the removal of all gross tumor and the demonstration of tumor-negative surgical margins by microscopic examination of the entire circumference. Subtotal or total gastrectomy was performed according to the tumor size, tumor location, and the status of the resection margins. Proximal gastrectomy involved resection of the proximal half of the stomach *via* an abdominal or thoracic approach, with an esophagogastric anastomosis. Following total gastrectomy with D2 lymph node dissection, an esophagojejunostomy was used routinely for Roux-en-Y reconstruction. Proximal resection margins were evaluated intraoperatively to confirm freedom from disease. Resection of adjacent organs was undertaken to achieve clear margins when deemed necessary. Both the surgical procedure and the extent of

Table 1 Demographics and clinicopathological features of gastric cardiac adenocarcinoma

Factors	Total (n = 146)	Sex		P value
		Female (n = 35)	Male (n = 111)	
Age (yr)				0.668
< 60	46	10	36	
⩾ 60	100	25	75	
Type of gastrectomy				0.776
Total	53	12	41	
Proximal gastrectomy	93	23	70	
Splenectomy				0.102
Presence	8	0	8	
Absence	138	35	103	
Tumor size (cm)				0.717
< 2	2	0	2	
2-5	93	23	70	
> 5	51	12	39	
Gross appearance				0.931
Type 0	6	2	4	
Type 1	13	3	10	
Type 2	105	26	79	
Type 3	13	2	11	
Type 4	9	2	7	
Tumor differentiation				0.389
Differentiated	76	16	60	
Undifferentiated	70	19	51	
Lymph nodes retrieved	22.88 ± 9.162	23.06 ± 9.449	22.78 ± 9.089	0.602
Pathological tumor depth				0.729
T1	8	2	6	
T2	16	2	14	
T3	4	1	3	
T4	118	30	88	
Node status (TNM)				0.665
pN_0	43	11	32	
pN_1	27	4	23	
pN_2	29	8	21	
pN_3	47	12	35	
pTNM staging				0.445
Ⅰ	15	2	13	
Ⅱ	37	11	26	
Ⅲ	94	22	72	
Ⅳ				
Lymphatic invasion				0.694
Positive	24	5	19	
Negative	122	30	92	
Venous invasion				0.393
Positive	5	2	3	
Negative	141	33	108	
Nerve invasion				0.350
Positive	22	7	15	
Negative	124	28	96	
Esophageal involvement				0.497
Presence	31	6	25	
Absence	115	29	86	

TNM: Tumour, node, metastasis.

lymph node dissection were based on the recommendations of the Japanese GC treatment guidelines[13]. No patient received neoadjuvant chemotherapy or postoperative radiotherapy.

Pathological examination

In both hospitals, the surgical team immediately examined the lymph nodes macroscopically, which were then divided and classified into lymph node stations, as defined by the Japanese Classification of Gastric Carcinoma[14]. No size limitation was imposed for lymph node harvesting. Specimens were fixed in formalin, stained with hematoxylin and eosin, and sent for histopathological evaluation, following which the number of histologically confirmed lymph nodes was recorded for each lymph node station. Each lymph node was embedded in paraffin and at least two sections were taken. Immunhistochemistry for micrometastasis was not performed.

Tumor size was recorded as the maximum diameter. The depth of infiltration was measured at the deepest point of penetration of the cancer cells. In this study, we referred to the classifications established by the Japanese Classification of Gastric Carcinoma: 3rd English edition[14], which define T1 as a tumor confined to the mucosa (M) or submucosa (SM); T2 as a tumor that invades the muscularis propria (MP); T3 as a tumor that invades the subserosa (SS); and T4 as tumor invasion that is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI). The macroscopic type was classified as type 0 (superficial), type 1 (mass), type 2 (ulcerative), type 3 (infiltrative ulcerative), type 4 (diffuse infiltrative) or type 5 (unclassifiable). We evaluated the tumor histology according to the classification established by the Japanese Research Society for GC[11]. Well-and moderately differentiated tubular adenocarcinoma, and papillary adenocarcinoma were classified as differentiated-type carcinomas; and poorly differentiated adenocarcinoma, signet ring cell carcinoma and mucinous carcinoma were classified as undifferentiated-type carcinomas.

The nodal classification was classified into four groups: pN_0, no metastasis; pN_1, one or two positive regional lymph nodes; pN_2, 3-6 positive regional lymph nodes; and pN_3, ⩾ 7 positive regional lymph nodes. We conducted the tumor staging according to the Japanese Classification of Gastric Carcinoma: 3rd English edition[14]. The ratio of lymph node metastasis was calculated by determining the number of patients with a metastasized lymph node in a particular station divided by the number of patients who underwent dissection of that lymph node. The metastatic incidence is the ratio of metastatic nodes to the total number of dissected nodes and was recorded for each nodal station for all regional lymph nodes.

Ethics

This study was carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The Institutional Review Board of Shanghai Jiaotong University gave ethical approval for this study. All patients provided written informed consent.

Statistical analysis

Descriptive data are presented as the mean ± SD. For between group comparisons, continuous variables were analyzed using Student's t test, and categorical variables with the χ^2 test. Factors found to be significant (P <

Table 2 Univariable analysis of lymph nodes metastasis in gastric cardiac cancer and clinicopathological factors

Factors	Total (n = 146)			Female (n = 35)			Male (n = 111)		
	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value
Age (yr)			0.927			0.134			0.353
< 60	33	13		5	5		28	8	
⩾ 60	71	29		19	6		52	23	
Tumor size (cm)			0.011			0.554			0.011
< 2	0	2		0	0		0	2	
2-5	62	31		15	8		47	23	
> 5	42	9		9	3		33	6	
Gross appearance			0.000			0.211			0.000
Type 0	0	6		0	2		0	4	
Type 1	5	8		2	1		3	7	
Type 2	82	23		19	7		63	16	
Type 3	10	3		2	0		8	3	
Type 4	7	2		1	1		6	1	
Tumor differentiation			0.000			0.150			0.000
Differentiated	44	32		9	7		35	25	
Undifferentiated	60	10		15	4		45	6	
Pathological tumor depth			0.000			0.051			0.000
T1	1	7		0	2		1	5	
T2	8	8		2	0		6	8	
T3	3	1		0	1		3	0	
T4	92	26		22	8		70	18	
Lymphatic invasion			0.001			0.102			0.003
Positive	24	0		5	0		19	0	
Negative	80	42		19	11		61	31	
Venous invasion			0.659			0.324			0.832
Positive	4	1		2	0		2	1	
Negative	100	41		22	11		78	30	
Nerve invasion			0.966			0.856			0.972
Positive	15	6		5	2		11	4	
Negative	88	36		19	9		69	27	
Esophageal involvement			0.192			0.912			0.131
Presence	25	6		4	2		21	4	
Absence	79	36		20	9		59	27	

0.05) in univariate analysis were included in subsequent multivariate logistic regression analysis, to identify independent variables associated with lymph node metastases. All statistical analyses were undertaken using SPSS for Windows, version 18.0 (SPSS, Chicago, IL, United States). For all analyses, $P < 0.05$ was considered statistically significant.

RESULTS

Demographics and clinicopathological features of gastric cardiac adenocarcinoma

The clinicopathological characteristics of gastric cardiac cancer are illustrated in Table 1. Among the 146 patients, there were 111 men and 35 women, ranging in age from 16 to 84 years (mean 63.9 ± 11.6 years). Surgical procedures comprised 93 proximal gastrectomies and 53 total gastrectomies. Splenectomy was required in 8 (5.5%) of the 146 patients undergoing curative resections. The total splenectomy patients were all male. Mean tumor length was 5.54 cm. Of the 146 patients, 6 (4.1%), 13 (8.9%), 105 (71.9%), 13 (8.9%) and 8 (5.8%) were type 0, 1, 2, 3 and 4, respectively. Tumors were differentiated in 76 patients and undifferentiated in 70. The number of lymph nodes retrieved was 22.88 ± 9.16, and 104 patients had positive lymph node metastases (71.2%). There were eight cases with a T1 tumor, 16 with a T2 tumor, 4 with a T3 tumor tumor, and 118 with a T4 tumor. Lymph node involvement according to the Japanese Classification of Gastric Carcinoma: 3rd English edition[14] included 43 patients with N0 disease, 27 with N1 disease, and 76 with N2-3 disease (Table 2). Evidence of lymphatic invasion, venous invasion and neural invasion was seen in 24 (16.4%), 5 (3.4%) and 22 patients (15.1%), respectively, On pathological examination, the tumors of 31 patients (21.2%) were found to have invaded the lower esophagus. None of the clinicopathological factors, such as age, type of gastrectomy, tumor size, gross appearance, tumor differentiation, pathological tumor depth, node status, pTNM staging, lymphatic invasion, venous invasion, nerve invasion and esophagus involvement were different between male and female patients ($P > 0.05$).

Univariate analysis of lymph node metastasis in gastric cardiac cancer and clinicopathological factors

Univariate analysis was performed on the relationship between lymph node metastases and clinicopathological factors. The findings revealed a close relationship between

Table 3 Univariate analysis of lymph node metastases in gastric cardiac adenocarcinoma and clinicopathological factors for sex differance

Factors	Female LN+ (n = 24)	Male LN+ (n = 80)	P value
Age (yr)			0.191
< 60	15.20%	84.80%	
⩾ 60	26.80%	73.20%	
Tumor size (cm)			0.743
< 2	0.00%	0.00%	
2-5	24.20%	75.80%	
> 5	21.40%	78.60%	
Gross appearance			0.961
Type 0	0.00%	0.00%	
Type 1	40.00%	60.00%	
Type 2	23.20%	76.80%	
Type 3	20.00%	80.00%	
Type 4	14.30%	85.70%	
Tumor differentiation			0.587
Differentiated	20.50%	79.50%	
Undifferentiated	25.00%	75.00%	
Pathological tumor depth			0.627
T1	0.00%	100.00%	
T2	25.00%	75.00%	
T3	0.00%	100.00%	
T4	23.90%	76.10%	
Lymphatic invasion			0.766
Positive	20.80%	79.20%	
Negative	23.80%	76.20%	
Venous invasion			0.192
Positive	50.00%	50.00%	
Negative	22.00%	78.00%	
Nerve invasion			0.399
Positive	31.30%	68.70%	
Negative	21.60%	78.40%	
Esophageal involvement			0.335
Presence	16.00%	84.00%	
Absence	25.30%	74.70%	

tumor size, gross appearance, differentiation, pathological depth, lymphatic invasion and lymph node metastases in all patients (P = 0.011, P = 0.000, P = 0.000, P = 0.000 and P = 0.001, respectively) and in male patients (P = 0.011, P = 0.000, P = 0.000, P = 0.000 and P = 0.003, respectively). However, there was no obvious correlation between lymph node metastases and clinicopathological features in female patients, nor between male and female patients (Table 3).

Multivariate analysis of lymph node metastases in gastric cardiac cancer for the entire study population and male patients

Multivariate analysis revealed that only tumor differentiation was an independent risk factor for lymph node metastases in gastric cardiac cancer for the entire study population (P = 0.001). Tumor size, gross appearance, pathological depth and lymphatic invasion had no significant effect on nodal involvement rates (Table 4). Multivariate analysis revealed that tumor differentiation and pathological depth were independent risk factors for lymph node metastases in gastric cardiac cancer for male patients (P = 0.001, P = 0.020). Tumor size, gross appearance and lymphatic invasion had no significant effect on nodal involvement rates (Table 4).

Relationship between sex and number of metastatic lymph nodes

There was no significant difference between female and male patients in terms of the number of retrieved lymph nodes, using the independent sample t test (P = 0.878). The number of metastatic lymph nodes in female patients was higher than that in male patients (6.20 ± 7.49 *vs* 4.84 ± 5.44). However, the difference was not significant (P = 0.243).

Retrieved lymph nodes, lymph node metastases, lymph node metastasis ratios and incidence for involved lymph nodes at each station in gastric cardiac adenocarcinoma

Lymph nodes (n = 3340, median 22.88; range 15-62) were removed from the 146 patients and examined, and 754 (median 5.16; range 0-30) were metastatic. For female patients, 807 (median 23.06; range 15-61) lymph nodes were examined and 217 (median 6.20; range 0-30) contained metastases. For male patients, 2533 (median 22.82; range 15-62) lymph nodes were examined and 537 (median 4.84; range 0-26) contained metastases (Table 5).

According to the Japanese Classification of Gastric Carcinoma: 3rd English edition[14], 103 cases (70.5%) were at N1, 23 cases (15.8%) at N2, 15 cases (10.3%) at N3, and four cases (2.7%) at M. A direct skip to N3, without moving through N2, occurred in 10 cases (6.8%). There were no skips to N2 without going through N1. Nodal metastases were frequent in the abdominal nodes, followed in frequency by involvement of the No. 3 (59.6%), No. 1 (26.7%), No. 2 (18.5%), and No. 4 (16.4%) nodes, and thereafter by mediastinal lymph nodes, which were affected only in a small number in our series (No. 110, 0.7%). The frequency of the metastatic involvement of the supra- and infra-pyloric nodes was low (4.1% and 3.4%, respectively), and no cases with metastasis to Nos. 13-15 were found. Only four patients received station No. 16 lymph node dissection, and three of them had metastasis (Table 5).

The extent of metastases in female cases was as follows: 24 cases were at N1 (16.4%, 24/146), representing a metastatic rate of 68.6% (24/35); 5 cases were at N2 (3.4%, 5/146), with a metastastic rate of 14.3% (5/146); and 4 cases were found at N3 (2.7%, 4/146), with a metastatic rate of 11.4% (4/146). The extent of metastases in male patients was as follows: 79 cases (54.1%) occurred at N1, with a metastatic rate of 71.2%; 18 cases occurred at N2 (12.3%), with an incidence of 16.2%; and 11 cases occurred at N3 (7.5%), with an incidence of 9.9% (Table 5).

Correlation between lymph node metastases at pN_1, pN_2 and pN_3 and clinicopathological factors, using the Japanese GC association classification for the entire study population and between male and female patients

Univariate analysis of variance revealed a close relationship between tumor size, gross appearance, differentiation, pathological depth and lymphatic invasion and

Table 4 Multivariate analysis of lymph node metastases in gastric cardiac cancer for the entire study population

Multivariate analysis	B	SE	χ^2 value	*P* value	OR	95%CI	
						Lower	Upper
Entire study population							
Tumor size	0.010	0.528	0.000	0.985	0.010	0.359	2.843
Gross appearance	-0.169	1.166	0.021	0.885	0.845	0.086	8.302
Tumor differentiation	1.806	0.522	11.981	0.001	6.084	2.188	16.912
Tumor depth	0.464	0.299	2.400	0.121	1.590	0.884	2.858
Lymphatic invasion	20.207	7720.675	0.000	0.998	5.967E8	0.000	
Constant	-3.181	1.664	3.656	0.056	0.042		
Male patients							
Tumor size	0.594	0.707	0.705	0.401	1.810	0.453	7.233
Gross appearance	-1.420	1.442	0.969	0.325	0.242	0.014	4.085
Tumor differentiation	2.525	0.749	11.375	0.001	12.493	2.880	54.199
Tumor depth	0.838	0.359	5.448	0.020	2.313	1.144	4.676
Lymphatic invasion	20.295	8351.751	0.000	0.998	6.514E8	0.000	
Constant	-5.010	2.212	5.132	0.023	0.007		

Table 5 Number of retrieved lymph nodes, lymph node metastases, lymph node metastasis ratios, and incidence at each station

Node station	pN category	Number of dissected nodes			Number of metastasis nodes			Incidence of lymph node metastasis			Ratio of lymph node metastasis		
		T	F	M	T	F	M	T	F	M	T	F	M
No. 1	pN_1	448	111	337	100	31	69	22.30%	26.90%	20.50%	26.70%	31.40%	24.30%
No. 2	pN_1	249	67	182	54	12	42	21.70%	17.90%	23.10%	18.50%	20.00%	18.00%
No. 3	pN_1	1308	334	974	404	100	304	30.90%	29.90%	31.20%	59.60%	60.00%	59.50%
No. 4	pN_1	589	136	453	87	45	42	14.80%	33.10%	9.30%	16.40%	22.90%	14.40%
No. 5	pN_3	39	9	30	11	7	4	28.20%	77.80%	13.30%	4.10%	5.70%	3.60%
No. 6	pN_3	146	33	113	13	9	4	8.90%	27.30%	3.50%	3.40%	8.60%	1.80%
No. 7	pN_2	176	49	127	32	8	24	18.20%	16.30%	18.90%	11.60%	8.60%	12.60%
No. 8	pN_2	108	26	82	13	3	10	12.00%	11.50%	12.20%	4.10%	5.70%	3.60%
No. 9	pN_2	39	8	31	15	2	13	38.50%	25.00%	41.90%	4.10%	2.90%	4.50%
No. 10	pN_2	37	11	26	8	0	8	21.60%	0.00%	30.80%	1.40%	0.00%	1.80%
No. 11	pN_2	36	6	30	5	0	5	13.90%	0.00%	16.70%	2.70%	0.00%	3.60%
No. 12	pN_2	45	6	39	5	0	5	11.10%	0.00%	12.80%	1.40%	0.00%	1.80%
No. 13	M	8	0	8	0	0	0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
No. 14	M	30	2	28	0	0	0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
No. 15	M	13	5	8	0	0	0	0.00%	0.00%	0.00%	0.00%	0.00%	0.00%
No. 16	M	32	0	32	6	0	6	18.80%	0.00%	18.80%	2.10%	0.00%	2.70%
No. 110	M	37	4	33	1	0	1	2.70%	0.00%	3.00%	0.70%	0.00%	0.90%
Total		3340	807	2533	754	217	537	22.70%	26.90%	21.30%			

lymph node metastases at pN_1 in all patients ($P = 0.020$, $P = 0.000$, $P = 0.000$, $P = 0.000$ and $P = 0.001$, respectively) and male patients ($P = 0.021$, $P = 0.000$, $P = 0.001$, $P = 0.001$ and $P = 0.002$, respectively) (Table 6). However, there was no obvious correlation between lymph node metastases and clinicopathological features in female patients (Table 6) and between male and female patients (Table 7).

There was obvious relationship between the lymphatic invasion and lymph node metastases at pN_2 in all patients ($P = 0.048$) and male patients ($P = 0.046$) (Table 6). There was no significant correlation between clinicopathological features and the presence of lymph node metastases at pN_2 in female patients (Table 6) nor between male and female patients (Table 7).

There was an obvious relationship between lymphatic invasion and nerve invasion and lymph node metastases at pN_3 in all patients ($P = 0.009$, $P = 0.001$) (Table 6). There was a significant correlation between lymphatic invasion in female patients (Table 6) and neural invasion in male patients (Table 6) and the presence of lymph node metastases at pN_3. There was no significant correlation between clinicopathological features and the presence of lymph node metastases at pN_3 between male and female patients (Table 7).

DISCUSSION

According to some clinicians, true carcinoma of the cardia may be considered a distinct clinical entity, with different biological behavior and a more aggressive natural history than subcardial gastric carcinoma[15-17]. Strangely enough, the location, extent and even the existence of the gastric cardia are controversial[18]. Anatomists have applied the term cardia to that part of the stomach that lies around the orifice of the tubular esophagus. The American Joint Committee on Cancer describes the EGJ as the first part of the stomach, which is located immediately below the diaphragm and is often called the cardia[19]. The definition of the cardia commonly employed in Japan is

Table 6 Correlation between lymph node metastases at pN_1, pN_2 and pN_3 and clinicopathological factors

Characterists	pN_1									pN_2									pN_3								
	Total			Female			Male			Total			Female			Male			Total			Female			Male		
	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value	LN+	LN-	*P* value
Age (yr)			0.830			0.134			0.287			0.066			0.541			0.082			0.670			0.179			0.769
< 60	33	13		5	5		28	8		11	35		2	8		9	27		4	42		0	10		4	32	
⩾ 60	70	30		19	6		51	24		12	88		3	22		9	66		11	89		4	21		7	68	
Tumor size (cm)			0.020			0.554			0.021			0.151			0.191			0.314			0.095			0.068			0.345
< 2.0	0	2		0	0		0	2		0	2		0	0		0	2		0	2		0	0		0	2	
2.0-5.0	62	31		15	8		47	23		11	82		2	21		9	61		6	87		1	22		5	65	
> 5.0	41	10		9	3		32	7		12	39		3	9		9	30		9	42		3	9		6	33	
Gross appearance			0.000			0.211			0.000			0.674			0.513			0.748			0.395			0.428			0.560
Type 0	0	6		0	2		0	4		0	6		0	2		0	4		0	6		0	2		0	4	
Type 1	5	8		2	1		3	7		1	12		0	3		1	9		0	13		0	3		0	10	
Type 2	81	24		19	7		62	17		19	86		4	22		15	64		13	92		3	23		10	69	
Type 3	10	3		2	0		8	3		2	11		1	1		1	10		2	11		1	1		1	10	
Type 4	7	2		1	1		6	1		1	8		0	2		1	6		0	9		0	2		0	7	
Tumor differentiation			0.000			0.150			0.001			0.071			0.782			0.054			0.324			0.855			0.215
Differentiated	44	32		9	7		35	25		8	68		2	14		6	54		6	70		2	14		4	56	
Undifferentiate	59	11		15	4		44	7		15	55		3	16		12	39		9	61		2	17		7	44	
Pathological tumor depth			0.000			0.051			0.001			0.360			0.808			0.406			0.265			0.861			0.363
T1	1	7		0	2		1	5		0	8		0	2		0	6		0	8		0	2		0	6	
T2	8	8		2	0		6	8		1	15		0	2		1	13		0	16		0	2		0	14	
T3	3	1		0	1		3	0		1	3		0	1		1	2		0	4		0	1		0	3	
T4	91	27		22	8		69	19		21	97		5	25		16	72		15	103		4	26		11	77	
Lymphatic invasion			0.001			0.102			0.002			0.048			0.693			0.046			0.009			0.030			0.074
Yes	24	0		5	0		19	0		7	17		1	4		6	13		6	18		2	3		4	15	
No	79	43		19	11		60	32		16	106		4	26		12	80		9	113		2	28		7	85	
Venous invasion			0.637			0.324			0.861			0.791			0.137			0.440			0.466			0.601			0.169
Yes	4	1		2	0		2	1		1	4		1	1		0	3		1	4		0	2		1	2	
No	99	42		22	11		77	31		22	119		4	29		18	90		14	127		4	29		10	98	
Nerve invasion			0.792			0.856			0.679			0.734			1.000			0.669			0.001			0.111			0.001
Yes	15	7		5	2		10	5		4	18		1	6		3	12		7	15		2	5		5	10	
No	88	36		19	9		69	27		19	105		4	24		15	81		8	116		2	26		6	90	
Esophageal involvement			0.165			0.912			0.108			0.109			0.272			0.205			0.587			0.658			0.691
Yes	25	6		4	2		21	4		2	29		0	6		2	23		4	27		1	5		3	22	
No	78	37		20	9		58	28		21	94		5	24		16	70		11	104		3	26		8	78	

the area within 2 cm above and below the EGJ, and tumors whose center is situated in this area are considered to be cancer of the cardia; such cancers are distinguished from upper GCs. Siewert *et al*[20] proposed a topographical classification for cardiac carcinomas. In contrast to the previously described classification system, Siewert and Stein[20] attempted to resolve the problem of splitting up EGJ tumors into esophageal and gastric tumors by creating a third entity. These tumours show a high rate of early lymphatic dissemination and lymph node metastases[12,15,21] and are usually related to poorer prognosis[12,22]. The reasons for this sudden increase of gastric cardia carcinomas are not clear, but changing risk factors such as smoking, alcohol use, presentation at a more advanced stage, salty foods, pollution and increases in gastroesophageal reflux diseases might explain it partially[5,7,23].

Table 7 Correlation between lymph node metastases at pN1, pN2 and pN3 and clinicopathological factors for sex difference

Clinicopathological factors	pN1			pN2			pN3		
	Female LN+	Male LN+	*P* value	Female LN+	Male LN+	*P* value	Female LN+	Male LN+	*P* value
Age (yr)			0.179			0.692			0.159
< 60	5 (15.2)	28 (84.8)		2 (18.2)	9 (81.8)		0 (0.0)	4 (100.0)	
⩾ 60	19 (27.1)	51 (72.9)		3 (25.0)	9 (75.0)		4 (36.4)	7 (63.6)	
Tumor size (cm)			0.792			0.692			0.475
< 2.0	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
2.0-5.0	15 (24.2)	47 (75.8)		2 (18.2)	9 (81.8)		1 (16.7)	5 (83.3)	
> 5.0	9 (22.0)	32 (78.0)		3 (25.0)	9 (75.0)		3 (33.3)	6 (66.7)	
Gross appearance			0.960			0.472			0.423
Type 0	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Type 1	2 (40.0)	3 (60.0)		0 (0.0)	1 (100.0)		0 (0.0)	0 (0.0)	
Type 2	19 (23.5)	62 (76.5)		4 (21.1)	15 (78.9)		3 (23.1)	10 (76.9)	
Type 3	2 (20.0)	8 (80.0)		1 (50.0)	1 (50.0)		1 (50.0)	1 (50.0)	
Type 4	1 (14.3)	6 (85.7)		0 (0.0)	1 (100.0)		0 (0.0)	0 (0.0)	
Tumor differentiate			0.555			0.782			0.634
Differentiated	9 (20.5)	35 (79.5)		2 (25.0)	6 (75.0)		2 (33.3)	4 (66.7)	
Undifferentiate	15 (25.4)	44 (74.6)		3 (20.0)	12 (80.0)		2 (22.2)	7 (77.8)	
Pathological tumor depth			0.624			0.738			
T1	0 (0.0)	1 (100.0)		0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	NS
T2	2 (25.0)	6 (75.0)		0 (0.0)	1 (100.0)		0 (0.0)	0 (0.0)	
T3	0 (0.0)	3 (100.0)		0 (0.0)	1 (100.0)		0 (0.0)	0 (0.0)	
T4	22 (24.2)	69 (75.8)		5 (23.8)	16 (76.2)		4 (26.7)	11 (73.3)	
Lymphatic invasion			0.744			0.567			0.634
Positive	5 (20.8)	19 (79.2)		1 (14.3)	6 (85.7)		2 (33.3)	4 (66.7)	
Negative	19 (24.1)	60 (75.9)		4 (25.0)	12 (75.0)		2 (22.2)	7 (77.8)	
Venous invasion			0.198			0.052			0.533
Positive	2 (50.0)	2 (50.0)		1 (100.0)	0 (0.0)		0 (0.0)	1 (100.0)	
Negative	22 (22.2)	77 (77.8)		4 (18.2)	18 (81.8)		4 (28.6)	10 (71.4)	
Nerve invasion			0.247			0.862			0.733
Positive	5 (35.7)	9 (64.3)		1 (25.0)	3 (75.0)		2 (33.3)	4 (66.7)	
Negative	19 (21.6)	69 (78.4)		4 (21.1)	15 (78.9)		2 (25.0)	6 (75.0)	
Esophageal involvement			0.321			0.435			0.930
Presence	4 (16.0)	21 (84.0)		0 (0.0)	2 (100.0)		1 (25.0)	3 (75.0)	
Absence	20 (25.6)	58 (74.4)		5 (23.8)	16 (76.2)		3 (27.3)	8 (72.7)	

It is crucial that the therapeutic strategy for gastric cardiac adenocarcinoma be clarified through evaluation of both the pattern of lymph node metastasis and the efficacy of lymph node dissection in this region. According to Siewert *et al*[20], metastases already exist in 72.0% of the cases at the time of surgery on tumors of the distal esophagus and the cardia. Lymphogenous metastases were present in 73.5% of the cases in our study. The cause of the frequent invasion of lymph nodes is the density of the lymph duct supply both to the stomach and to the lower esophagus, such that the cancers at the EGJ invade the regional lymph nodes concerned at an early stage[24].

Previous studies have proved that the number of lymph nodes retrieved has a significantly impact in pN category, which resulted in a "stage-migration" phenomenon[25-27]; therefore, in the present study the quality of lymphadenectomy was adequate because the median number of resected lymph nodes was clearly more than 15, as recommended by the Japanese Classification of Gastric Carcinoma: 3rd English edition[14]. Furthermore, the median number of 23 lymph nodes in our study is comparable with other prospective studies on the treatment of GC[27,28]. The number of dissected lymph nodes is closely associated with the pathological stages and prognosis. A population-based study by Bouvier *et al*[29] showed that the error rate was 47.1% if the pathological stages were classified according to the identical TNM stages for the patients with < 10 or > 15 detected lymph nodes. Thus, the pathological stages are not reliable for patients with < 10 detected lymph nodes in GC surgery. On TNM stages, Union for International Cancer Control version 5 states that the number of dissected lymph nodes in advanced GC must be ⩾ 15 to ensure the reliability of pathological stages and prognosis judgment. In a study reported by Karpeh *et al*[30], 27 patients with GC classified as stage Ⅱ and Ⅲ disease, and having < 15 lymph nodes examined, had significantly lower 5-year survival rates than those who had ⩾ 15 lymph nodes examined. In a similar analysis, Bouvier *et al*[29] concluded that > 10 lymph nodes should be analyzed per specimen to allow for valid N staging.

The sex distribution in this study showed an absolute male predominance (3.2:1) in gastric cardiac adenocarcinoma, which is similar to previous studies[23,31,32]. The sex ratio for cancer of the pylorus is only 1.5[33]. Although the exact reason for the male predominance of this type of cancer remains unknown, it seems to be a definite feature of this type of tumor, irrespective of the origin of the population[7,34]. Some scholars pointed out that this

may be because sex hormones such as estrogen affect the incidence rate of GC[35,36]. In our group, 98.6% of patients had tumors > 2 cm. Larger tumors have higher rates of lymph node metastases. Of the 104 cases with lymph node metastases, all the tumor sizes were > 2 cm, accounting for all metastases. Morphological classification was mainly of the ulcerative type (71.9%). Otherwise, type 0, 1, 3 and 4 accounted for 4.1%, 8.9%, 8.9% and 5.5%, respectively. Histologically, there were slightly more undifferentiated tumors (52.1%) than differentiated tumors (47.9%), and > 83.6% of patients had T3 or T4 tumors.

Toward the latter, the seventh edition of the TNM classification of malignant tumors defines rules for classifying carcinomas arising within the vicinity of the EGJ to end the imprecise regulation of earlier editions, where carcinomas around the EGJ could be staged according to either the classification of esophageal carcinomas or the classification of gastric carcinomas. However, neither of the two staging systems has proven to be clearly superior to the other, and neither of them is perfect for so-called cardiac adenocarcinomas. For the N classification of the so-called cadiac adenocarcinomas, both schemes are monotone and distinct, with continuously decreasing and significantly different prognosis with an increasing number of lymph node metastases[37]. Huang[38] pointed out that the Version 7 manual would predict the prognosis of patients more effectively than the Version 6 manual according to the staging of GC. The staging of lymph nodes (pN) can predict the prognosis better than the invasion depth of cancer tissue (pT), while the lymph node status in the axial area of the celiac artery is particularly critical. The Version 7 manual defined the EGJ-involved gastric cardia cancer staging improperly and this should be corrected. Of course, their research results are to be updated and verified with more large-sample studies. Huang *et al*[39] postulated that type Ⅱ EGJ adenocarcinomas are more adequately staged as GC by the seventh edition of the American Joint Committee on Cancer classification.

Many researchers have attempted to investigate the relationship between nodal involvement and clinicopathological factors. The factors related to lymph node metastasis include age, sex, clinical staging of tumor, pathological tissue type, invasion depth of lesion, tumor size, and typing. As expected, we found tumor characteristics such as tumor size, gross appearance, differentiation, pathological depth and lymphatic invasion were associated with lymph node metastases in all patients and male patients, and could represent a selection indicator of lymph node dissection. However, there was no obvious correlation between lymph node metastases and clinicopathological features in female patients. In gastric cardiac adenocarcinoma, the clinicopathological features and lymph node metastasis patterns did not differ significantly between male and female patients. These results were similar to those reported by previous studies[40]. Male patients had lymph node metastasis in 72.1%; slightly higher than that in female patients. The present study discovered that the metastasis rate of lymph nodes increased with the maximum diameter of the lesion; nevertheless, it is not advisable to simply take the tumor size as the correlation factor for predicting the lymph node metastasis because of variations in the period of tumor growth. Borrmann typing is also related to lymph node metastasis. The metastasis rate of lymph nodes in type Ⅲ and Ⅳ GC was significantly higher than in type Ⅰ and Ⅱ in this paper. This could be explained by the main invasion growth of the former types and the limited growth of the later types, because weak or strong invasion ability may lead to differences in the metastasis rate of lymph nodes. Histological type is closely related to nodal status. In our group, the rate of lymph node metastases in undifferentiated tumors was higher than that observed in differentiated cancer: 85.7% (60/70) and 67.9% (44/76), respectively. The tumor differentiation extent decides the biological behavior of GC. A larger extent of cell differentiation possibly causes a larger metastasis rate of lymph nodes. Some scholars have found that poorly differentiated GC cells produced more type Ⅳ collagenase, which can degrade the basilar membrane, reduce the ability to resist cancer cell infiltration, and cause the rate of lymph node metastasis to be higher than that for differentiated adenocarcinoma. Moreover, there is an increasing rate of node involvement as the T stage increases; in our series, 12.5% of T1, 50.0% of T2, 75.0% of T3 and 78.0% of T4 cases had positive nodes. This suggests a correlation between T stage factor and the presence of positive nodes. The results of this study showed that lymphatic duct invasion is closely related to the lymph node metastasis; the metastasis rate of lymph nodes was up to 100% in the LVI (+) group, but 0% in the LVI (-) groups. Many studies have shown that metastasis of lymphatic duct invasion occurs before lymph node metastasis. The presence of lymphatic duct invasion or cancer cells indicates the prophase of lymph node metastasis or a manifestation of lymph node metastasis. The above factors should be the focus of preoperative gastric cardia treatment options. The appropriate degree of lymph node dissection must selected to improve the surgical efficacy in gastric cardia cancer.

In this study, multivariate analysis revealed that tumor differentiation was the only independent risk factor for lymph node metastases in all patients, and revealed that tumor differentiation and pathological depth were independent risk factors for lymph node metastases in male patients. By logistic methods, Liu *et al*[41] also confirmed that the tumor length, invasion depth, blood vessel invasion and specimen stump had a significant effect on lymph node metastasis. With the increase of tumor length and invasion depth, the appearance of blood vessel invasion and specimen stump cancer cells, the risk of lymph node metastasis increased significantly.

The new nodal staging in the 7th TNM classification is based on the number of metastatic nodes. In our group, all 146 cases of gastric cardiac adenocarcinoma

received radical gastrectomy. Postoperatively, 3340 regional lymph nodes were located. Seven hundred and fifty-four lymph nodes were found in 104 cases with lymph node metastases - an average of 7.25 per case. It had been considered that all the regional nodes of the stomach were potentially involved in metastasis in patients with adenocarcinoma of the gastric cardia[42]. Lymphogenous metastasis by cancer of the cardia frequently affects the lymph nodes at the greater and lesser curvature of the stomach. Less frequent involvement of the lymph nodes at right cardial and left cardial lymph nodes has been observed[39,43,44]. In line with previous findings[12,45,46], the Mine *et al*[47] confirmed that nodal station numbers 3 (lesser curvature), 1 (right cardia), 2 (left cardia) and 7 (left gastric artery) were most frequently involved in type Ⅱ junctional cancers. The study of Hosokawa *et al*[40] came to a similar conclusion. The present study discovered that the perigastric lymph nodes (in Groups 3, 1, 4 and 2) in patients with the cardia cancer ranked the top four positions by metastasis rate, suggesting that the cardiac lymph node is a key dissection object in the reasonable radical operation.

Even after a precise anatomical-topographical differentiation of this tumor entity, Siewert *et al*[20] found a small number of patients with parapyloric node metastasis in their cohort with type Ⅱ adenocarcinoma. Consistent with their finding, in our patient series we found 4.1% of patients with suprapyloric node metastasis and 3.4% with infrapyloric node metastasis. Wang *et al*[48] reported that the pathological examination after total gastrectomy showed metastasis rates of lymph nodes in No. 5 and No. 6 of 9.1%-13.6%. They believed that it was difficult to remove all tumor tissues (including metastatic lymph nodes) without total gastrectomy.

Yamashita *et al*[34] clearly indicated that dissection of the paracardial and lesser curve lymph nodes offered significant therapeutic benefit, suggesting that these lymph nodes were possibly peritumoral. Furthermore, the number of metastatic nodes in these stations and the total number of metastatic nodes in all stations were equally predictive of the clinical outcome. Dissection of other perigastric nodes, such as Nos. 4sb, 4d, 5, and 6, offered only marginal therapeutic benefit as determined by calculating the index of estimated benefit of nodal dissection. Thus, involvement of the lymph nodes in these stations appeared to represent distant rather than locoregional metastasis[34]. Therefore, both esophagectomy with gastric tube reconstruction and gastrectomy with Roux-en-Y reconstruction seem to be valid procedures clinically.

Most series report 7%-40% of mediastinal nodal involvement for type Ⅱ and Ⅲ esophagogastric cancer even though abdominal nodes are more affected[49]. In our series, mediastinal lymph nodes were affected only in a small number (No. 110, 0.7%), lower than that reported in the literature[40,49,50]. The necessity of a prophylactic mediastinal nodal dissection remains controversial. Mine *et al*[47] suggested that lower mediastinal lymph nodes, and station numbers 16A2lat (left renal vein), 11 (splenic artery) and 9 (celiac axis) were the second most frequently involved, and positivity here influenced survival. Hiroharu's data[34] suggested that extensive mediastinal lymph node dissection *via* thoracotomy offers no survival benefit over para-periesophageal node clearance alone by the transhiatal approach, which is associated with a lower morbidity, consistent with Sasako' and Hulscher' finding[51,52]. Phase Ⅲ trials in The Netherlands (Dutch trial) and Japan (JCOG 9502) also suggested that an extended transthoracic resection was more hazardous surgery, in terms of morbidity, than a transhiatal esophagectomy. Extended surgery could not be recommended for patients with type Ⅱ tumors[52]. In addition, nodal recurrence was the most frequent in the para-aortic nodes, and less frequent in the mediastinal nodes in Hiroharu's series[34]. These results mostly consistent with another report[40] support the hypothesis that complete mediastinal nodal clearance is not essential for local control of this disease. Nevertheless, Reeh *et al*[53] showed that the presence of lower mediastinal lymph nodes in AOG(oesophagogastric junction) type Ⅱ suggests that at least a lower mediastinal dissection should be performed.

Lymph node Nos. 10 and 11 (splenic hilum and splenic artery) belong to pN_2 cardia cancer and a have a higher metastatic rate. The high risk factors include female sex, Borrmann type Ⅳ, tumor size > 5 cm, poorly differentiated adenocarcinoma, signet ring cell carcinoma, Lauren's diffuse type, vascular lymphatic invasion, and perineural invasion. Some authors believe that a splenectomy must be included for patients with the above high-risk factors[54]. Okajima *et al*[55] reported that the metastasis rates for lymph node Nos. 10 and 11 in cardia cancer were 15.5% and 12.1%, respectively, and Sakaguchi *et al*[56] estimated the rate at 24%. This reflects the status of lymph node metastasis; however, these data were derived from the pathological examination of surgical specimens, mostly based on the corresponding radical operation, and was subject to the understanding of radical surgical indications. Sakaguchi *et al*[56] believed that the lymph node metastasis of Nos. 10 and 11 in a larger tumor (> 4 cm), with deeper lesions (T3 and T4) and infiltrative lesions occurred easily. Thus, these clinical characteristics may provide a reference for understanding the indications for combined splenectomy. In our study, the metastasis rates for lymph node No. 10 lymph 1.4%, and for No. 11 it was 2.7%, which are lower than those reported in the literature[39,40,57]. Metastasis in these lymph nodes was mainly observed in advanced GC. Therefore, it would be prudent to select the combined resection of distal pancreatectomy and splenectomy for lymph node dissection in patients with cardia cancer[58,59].

The present study showed that the most common sites of the pN_1 lymph node metastasis were Nos. 1-4; the most common sites of the pN_2 lymph nodes were Nos. 7-9; and the most common sites of the pN_3 lymph nodes were Nos. 5 and 6. Lymph node metastasis occurred mostly in the abdominal cavity and lymph node

metastasis of cardia cancer is more similar to that seen for GC. The lymph node metastasis in cardia cancer observed in this study suggests that: (1) for lymph nodes Nos. 1-9, conditions must be focally examined in preoperative ultrasound endoscopic and computed tomography examination; and (2) the superior paragastric fatty tissues should be thoroughly removed in the radical operation for GC and the total lymph node should be dissected in the regions; the celiac trunk and common hepatic artery must be skeletonized and the left gastric artery must be cut to remove the Nos. 7-9 lymph nodes thoroughly.

One analysis showed that 32.9% of type Ⅱ tumors had involvement of the lymph nodes along the major branched arteries (the left gastric artery, common hepatic artery, splenic artery and celiac axis), and the rate was 50% in type Ⅲ tumors[60]. Siewert *et al*[61] also reported similar results; 25% nodal involvement in type Ⅱ tumors and 39% in type Ⅲ tumors. These reports clearly indicate that abdominal nodal metastases are frequently observed in adenocarcinoma of the esophagogastric junction type Ⅱ/Ⅲ tumors, as in true gastric cancer**.** Therefore, the extent of a nodal dissection for AEG type Ⅱ/Ⅲ should be same as that applied for GC, and an abdominal D2 lymphadenectomy is recommended for patients with type Ⅱ/Ⅲ tumors, unless D2 increases the surgical risk[32]. Siewert types Ⅱ and Ⅲ cancers could be removed safely with an abdominal approach[45]. Our results agree with the conclusion of Husemann, that carcinoma of the cardia is a type of carcinoma of the stomach that must be treated according to the criteria of GC surgery[50].

In our study, of 104 patients with lymph node metastases, all were N1, 23 were N2, and 15 were N3. Investigating the correlation between pN_1, pN_2 and pN_3 lymph node metastases and clinicopathological factors, we found that tumor size, gross appearance, differentiation, pathological depth and lymphatic invasion were associated with lymph node metastases in all patients and male patients at pN_1. There was an obvious correlation between lymph node metastases and lymphatic invasion in all patients at pN_2. Univariate analysis of variance revealed a close relationship between lymph node metastases and lymphatic invasion and neural invasion in all patients and lymphatic invasion in female patients at pN_3. Study of Di Leo *et al*[10] study of the treatment of advanced gastric cancer showed that T2 tumors were consistently associated with pN_2 stations nodal infiltration. Such behavior, although less frequent than in T3/4 tumors, does not allow conservative surgery in terms of nodal resection[10].

There were limitations to the present study. First, it was a retrospective study based on postoperative examination of resected specimens. Second, the number of patients was low. Thus, further study with a larger sample size should be carried out to confirm our results. Otherwise, the extent of nodal involvement was most likely underestimated. The lack of information of nodal status at specific remote sites in some cases also made the investigation of nodal stage migration impossible. The retrospective nature of this study meant that there was some selection bias, such as the surgeon's preference for a thoracoabdominal or transabdominal approach.

In conclusion, the findings in this study indicate that the clinicopathological features and risk factors for lymph node metastasis of male and female patients with gastric cardiac adenocarcinoma did not differ significantly. Therefore, the effect of male sex on the clinical course of gastric cardiac adenocarcinoma had a weak impact in comparison to female sex once a curative resection had been performed. However, further evaluations should be performed. The outcome should improve if male patients, as well as female patients, undergo careful diagnosis of malignancy and early multimodality treatment**.**

COMMENTS

Background

As gastric cancer incidence declines, the frequency of proximal gastric and gastroesophageal junctional adenocarcinomas continues to rise, and has become a significant clinical challenge. Adenocarcinoma of the cardia generally has a low curative resection rate and a poor prognosis; worse than carcinoma of other regions of the stomach, mainly because the disease is at a more advanced stage at diagnosis. It is crucial that the therapeutic strategy for gastric cardiac adenocarcinoma be clarified through evaluation of both the pattern of lymph node metastasis and the efficacy of lymph node dissection in this region.

Research frontiers

The optimal surgical strategy for tumors in the cardiac area of the stomach, especially tumors invading the lower esophagus, remains controversial. The development of effective therapeutic strategies for these tumors requires information on patient characteristics, patterns of lymph node metastasis, and the efficacy of lymph node dissection.

Innovations and breakthroughs

Univariate analysis showed an obvious correlation between lymph node metastases and tumor size, gross appearance, differentiation, pathological depth and lymphatic invasion in male patients. Multivariate logistic regression analysis revealed that tumor differentiation and pathological depth were independent risk factors for lymph node metastases in male patients. There was an obvious relationship between lymph node metastases and tumor size, gross appearance, differentiation, pathological depth, lymphatic invasion at pN_1, and lymphatic invasion at pN_2 and neural invasion at pN_3 in male patients. There were no significant differences in clinicopathological features or lymph node metastases between female and male patients.

Applications

Tumor differentiation and depth were risk factors for lymph node metastases in male patients with gastric cardiac adenocarcinoma and should be considered when choosing surgery.

Terminology

The definition of the cardia commonly employed in Japan is the area within 2 cm above and below the esophagogastric junction, and tumors whose center is situated in this area are considered to be cancer of the cardia; such cancers are distinguished from upper gastric cancers. Siewert and Stein proposed a topographical classification for cardiac carcinomas.

Peer review

Congratulate the authors for an excellent effort. As rightly highlighted, a future attempt in expanding the population size should hopefully provide further insights.

REFERENCES

1 **Brenner H**, Rothenbacher D, Arndt V. Epidemiology of stomach cancer. *Methods Mol Biol* 2009; **472**: 467-477 [PMID: 19107449 DOI: 10.1007/978-1-60327-492-0_23]

2 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents:

defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150 [PMID: 16682732 DOI: 10.1200/JCO.2005.05.2308]
3 **Parkin DM**, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74-108 [PMID: 15761078 DOI: 10.3322/canjclin.55.2.74]
4 **Zou XN**, Sun XB, Chen WQ, Zheng RS, Zhang SW, Dai Z, Liu WD. Analysis of incidence and mortality of gastric cancer in China in 2003-2007. *Zhongliu* 2012; **32**: 109-114
5 **Devesa SS**, Blot WJ, Fraumeni JF. Changing patterns in the incidence of esophageal and gastric carcinoma in the United States. *Cancer* 1998; **83**: 2049-2053 [PMID: 9827707]
6 **Kunisaki C**, Shimada H, Nomura M, Matsuda G, Otsuka Y, Ono H, Akiyama H. Surgical outcome in patients with gastric adenocarcinoma in the upper third of the stomach. *Surgery* 2005; **137**: 165-171 [PMID: 15674196 DOI: 10.1016/j.surg.2004.06.005]
7 **Bruno L**, Nesi G, Montinaro F, Carassale G, Lassig R, Boddi V, Bechi P, Cortesini C. Clinicopathologic findings and results of surgical treatment in cardiac adenocarcinoma. *J Surg Oncol* 2000; **74**: 33-35 [PMID: 10861606]
8 **Fontana MG**, La Pinta M, Moneghini D, Villanacci V, Donato F, Rindi G, Paparini S, Baronchelli C, Bertoli G, Alquati P. Prognostic value of Goseki histological classification in adenocarcinoma of the cardia. *Br J Cancer* 2003; **88**: 401-405 [PMID: 12569383 DOI: 10.1038/sj.bjc.6600663]
9 **Graham AJ**, Finley RJ, Clifton JC, Evans KG, Fradet G. Surgical management of adenocarcinoma of the cardia. *Am J Surg* 1998; **175**: 418-421 [PMID: 9600291]
10 **Di Leo A**, Marrelli D, Roviello F, Bernini M, Minicozzi A, Giacopuzzi S, Pedrazzani C, Baiocchi LG, de Manzoni G. Lymph node involvement in gastric cancer for different tumor sites and T stage: Italian Research Group for Gastric Cancer (IRGGC) experience. *J Gastrointest Surg* 2007; **11**: 1146-1153 [PMID: 17576611]
11 **Japanese Gastric Cancer Association**. Japanese Classification of Gastric Carcinoma - 2nd English Edition - *Gastric Cancer* 1998; **1**: 10-24 [PMID: 11957040 DOI: 10.1007/s101200100009]
12 **Rüdiger Siewert J**, Feith M, Werner M, Stein HJ. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/topographic classification in 1,002 consecutive patients. *Ann Surg* 2000; **232**: 353-361 [PMID: 10973385]
13 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; **14**: 113-123 [PMID: 21573742 DOI: 10.1007/s10120-011-0042-4]
14 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
15 **Ichikura T**, Ogawa T, Kawabata T, Chochi K, Sugasawa H, Mochizuki H. Is adenocarcinoma of the gastric cardia a distinct entity independent of subcardial carcinoma? *World J Surg* 2003; **27**: 334-338 [PMID: 12607062 DOI: 10.1007/s00268-002-6776-8]
16 **Kunisaki C**, Akiyama H, Nomura M, Matsuda G, Otsuka Y, Ono H, Shimada H. Surgical outcomes for early gastric cancer in the upper third of the stomach. *J Am Coll Surg* 2005; **200**: 15-19 [PMID: 15631915 DOI: 10.1016/j.jamcollsurg.2004.09.015]
17 **Saito H**, Fukumoto Y, Osaki T, Fukuda K, Tatebe S, Tsujitani S, Ikeguchi M. Distinct recurrence pattern and outcome of adenocarcinoma of the gastric cardia in comparison with carcinoma of other regions of the stomach. *World J Surg* 2006; **30**: 1864-1869 [PMID: 16983479 DOI: 10.1007/s00268-005-0582-z]
18 **Wijetunge S**, Ma Y, DeMeester S, Hagen J, DeMeester T, Chandrasoma P. Association of adenocarcinomas of the distal esophagus, "gastroesophageal junction," and "gastric cardia" with gastric pathology. *Am J Surg Pathol* 2010; **34**: 1521-1527 [PMID: 20871225 DOI: 10.1097/PAS.0b013e3181eff133]
19 **Kong SH**, Yoo MW, Kim JW, Lee HJ, Kim WH, Lee KU, Yang HK. Validation of limited lymphadenectomy for lower-third gastric cancer based on depth of tumour invasion. *Br J Surg* 2011; **98**: 65-72 [PMID: 20954197 DOI: 10.1002/bjs.7266]
20 **Siewert JR**, Stein HJ. Classification of adenocarcinoma of the oesophagogastric junction. *Br J Surg* 1998; **85**: 1457-1459 [PMID: 9823902]
21 **Mariette C**, Castel B, Toursel H, Fabre S, Balon JM, Triboulet JP. Surgical management of and long-term survival after adenocarcinoma of the cardia. *Br J Surg* 2002; **89**: 1156-1163 [PMID: 12190682 DOI: 10.1046/j.1365-2168.2002.02185.x]
22 **de Manzoni G**, Pedrazzani C, Pasini F, Di Leo A, Durante E, Castaldini G, Cordiano C. Results of surgical treatment of adenocarcinoma of the gastric cardia. *Ann Thorac Surg* 2002; **73**: 1035-1040 [PMID: 11996237 DOI: 10.1016/S0003-4975(01)03571-8]
23 **Hamabe Y**, Ikuta H, Nakamura Y, Kawasaki K, Yamamoto M. Clinicopathological features of esophageal cancer simultaneously associated with gastric cancer. *J Surg Oncol* 1998; **68**: 179-182 [PMID: 9701211]
24 **Casson AG**, Darnton SJ, Subramanian S, Hiller L. What is the optimal distal resection margin for esophageal carcinoma? *Ann Thorac Surg* 2000; **69**: 205-209 [PMID: 10654514 DOI: 10.1016/S0003-4975(99)01262-X]
25 **de Manzoni G**, Verlato G, Roviello F, Morgagni P, Di Leo A, Saragoni L, Marrelli D, Kurihara H, Pasini F. The new TNM classification of lymph node metastasis minimises stage migration problems in gastric cancer patients. *Br J Cancer* 2002; **87**: 171-174 [PMID: 12107838 DOI: 10.1038/sj.bjc.6600432]
26 **Wu CW**, Hsiung CA, Lo SS, Hsieh MC, Chen JH, Li AF, Lui WY, Whang-Peng J. Stage migration influences on stage-specific survival comparison between D1 and D3 gastric cancer surgeries. *Eur J Surg Oncol* 2005; **31**: 153-157 [PMID: 15698731]
27 **Barbour AP**, Rizk NP, Gonen M, Tang L, Bains MS, Rusch VW, Coit DG, Brennan MF. Lymphadenectomy for adenocarcinoma of the gastroesophageal junction (GEJ): impact of adequate staging on outcome. *Ann Surg Oncol* 2007; **14**: 306-316 [PMID: 17091329 DOI: 10.1245/s10434-006-9166-x]
28 **Hölscher AH**, Drebber U, Mönig SP, Schulte C, Vallböhmer D, Bollschweiler E. Early gastric cancer: lymph node metastasis starts with deep mucosal infiltration. *Ann Surg* 2009; **250**: 791-797 [PMID: 19809298 DOI: 10.1097/SLA.0b013e3181bdd3e4]
29 **Bouvier AM**, Haas O, Piard F, Roignot P, Bonithon-Kopp C, Faivre J. How many nodes must be examined to accurately stage gastric carcinomas? Results from a population based study. *Cancer* 2002; **94**: 2862-2866 [PMID: 12115373 DOI: 10.1002/cncr.10550]
30 **Karpeh MS**, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. *Ann Surg* 2000; **232**: 362-371 [PMID: 10973386 DOI: 10.1097/00000658-200009000-00008]
31 **Yoon HY**, Kim CB. Gastroesophageal junction adenocarcinoma of young patients who underwent curative surgery: a comparative analysis with older group. *Surg Today* 2011; **41**: 203-209 [PMID: 21264755 DOI: 10.1007/s00595-009-4228-x]
32 **Hasegawa S**, Yoshikawa T. Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies. *Gastric Cancer* 2010; **13**: 63-73 [PMID: 20602191 DOI: 10.1007/s10120-010-0555-2]
33 **Sterup K**, Mosbech J. Sex ratio of gastric cancer related to site of the tumour. *Scand J Gastroenterol Suppl* 1971; **9**: 87-89 [PMID: 4327215]
34 **Yamashita H**, Katai H, Morita S, Saka M, Taniguchi H, Fukagawa T. Optimal extent of lymph node dissection for

Siewert type II esophagogastric junction carcinoma. *Ann Surg* 2011; **254**: 274-280 [PMID: 21772128 DOI: 10.1097/SLA.0b013e3182263911]
35 **Harrison JD**, Jones JA, Ellis IO, Morris DL. Oestrogen receptor D5 antibody is an independent negative prognostic factor in gastric cancer. *Br J Surg* 1991; **78**: 334-336 [PMID: 2021850 DOI: 10.1002/bjs.1800780321]
36 **La Vecchia C**, D'Avanzo B, Franceschi S, Negri E, Parazzini F, Decarli A. Menstrual and reproductive factors and gastric-cancer risk in women. *Int J Cancer* 1994; **59**: 761-764 [PMID: 7989115 DOI: 10.1002/ijc.2910590609]
37 **Gertler R**, Stein HJ, Loos M, Langer R, Friess H, Feith M. How to classify adenocarcinomas of the esophagogastric junction: as esophageal or gastric cancer? *Am J Surg Pathol* 2011; **35**: 1512-1522 [PMID: 21934477 DOI: 10.1097/PAS.0b013e3182294764]
38 **Huang Q**. Definition of Gastric-esophageal junctional area and progress of tumor classification and staging. *Zhonghua Xiaohua Neijing Zazhi* 2011; **28**: 121
39 **Huang Q**, Shi J, Feng A, Fan X, Zhang L, Mashimo H, Cohen D, Lauwers G. Gastric cardiac carcinomas involving the esophagus are more adequately staged as gastric cancers by the 7th edition of the American Joint Commission on Cancer Staging System. *Mod Pathol* 2011; **24**: 138-146 [PMID: 20852593 DOI: 10.1038/modpathol.2010.183]
40 **Wayman J**, Bennett MK, Raimes SA, Griffin SM. The pattern of recurrence of adenocarcinoma of the oesophago-gastric junction. *Br J Cancer* 2002; **86**: 1223-1229 [PMID: 11953876 DOI: 10.1038/sj.bjc.6600252]
41 **Liu W**, Hao XS, Chen Y, Li HX, Wang SJ, Wang PZ, Fan Q, Jin Y, Guan LY, Song LN, Ping YM, Meng XL, Wang R, Liu JF, Wang XL. Analysis of lymph node metastasis in 1526 cases with thoracic esophageal cancer and cardia cancer (attached with random sampling report of the Fourth Hospital of Hebei Medical University from 1996 to 2004). *Zhongguo Zhongliu Linchuang* 2008; **35**: 601-605
42 **Papachristou DN**, Fortner JG. Adenocarcinoma of the gastric cardia. The choice of gastrectomy. *Ann Surg* 1980; **192**: 58-64 [PMID: 7406565 DOI: 10.1097/00000658-198007000-00010]
43 **Sons HU**, Borchard F. Cancer of the distal esophagus and cardia. Incidence, tumorous infiltration, and metastatic spread. *Ann Surg* 1986; **203**: 188-195 [PMID: 3947155 DOI: 10.1097/00000658-198602000-00013]
44 **Ielpo B**, Pernaute AS, Elia S, Buonomo OC, Valladares LD, Aguirre EP, Petrella G, Garcia AT. Impact of number and site of lymph node invasion on survival of adenocarcinoma of esophagogastric junction. *Interact Cardiovasc Thorac Surg* 2010; **10**: 704-708 [PMID: 20154347 DOI: 10.1510/icvts.2009.222778]
45 **Fang WL**, Wu CW, Chen JH, Lo SS, Hsieh MC, Shen KH, Hsu WH, Li AF, Lui WY. Esophagogastric junction adenocarcinoma according to Siewert classification in Taiwan. *Ann Surg Oncol* 2009; **16**: 3237-3244 [PMID: 19636628 DOI: 10.1245/s10434-009-0636-9]
46 **Pedrazzani C**, de Manzoni G, Marrelli D, Giacopuzzi S, Corso G, Minicozzi AM, Rampone B, Roviello F. Lymph node involvement in advanced gastroesophageal junction adenocarcinoma. *J Thorac Cardiovasc Surg* 2007; **134**: 378-385 [PMID: 17662776 DOI: 10.1016/j.jtcvs.2007.03.034]
47 **Mine S**, Sano T, Hiki N, Yamada K, Nunobe S, Yamaguchi T. Lymphadenectomy around the left renal vein in Siewert type II adenocarcinoma of the oesophagogastric junction. *Br J Surg* 2013; **100**: 261-266 [PMID: 23180514 DOI: 10.1002/bjs.8967]
48 **Wang LS**, Wu CW, Hsieh MJ, Fahn HJ, Huang MH, Chien KY. Lymph node metastasis in patients with adenocarcinoma of gastric cardia. *Cancer* 1993; **71**: 1948-1953 [PMID: 8443744]
49 **Dresner SM**, Lamb PJ, Bennett MK, Hayes N, Griffin SM. The pattern of metastatic lymph node dissemination from adenocarcinoma of the esophagogastric junction. *Surgery* 2001; **129**: 103-109 [PMID: 11150040 DOI: 10.1067/msy.2001.110024]
50 **Husemann B**. Cardia carcinoma considered as a distinct clinical entity. *Br J Surg* 1989; **76**: 136-139 [PMID: 2702444 DOI: 10.1002/bjs.1800760210]
51 **Sasako M**, Sano T, Yamamoto S, Sairenji M, Arai K, Kinoshita T, Nashimoto A, Hiratsuka M. Left thoracoabdominal approach versus abdominal-transhiatal approach for gastric cancer of the cardia or subcardia: a randomised controlled trial. *Lancet Oncol* 2006; **7**: 644-651 [PMID: 16887481 DOI: 10.1016/S1470-2045(06)70766-5]
52 **Hulscher JB**, van Sandick JW, de Boer AG, Wijnhoven BP, Tijssen JG, Fockens P, Stalmeier PF, ten Kate FJ, van Dekken H, Obertop H, Tilanus HW, van Lanschot JJ. Extended transthoracic resection compared with limited transhiatal resection for adenocarcinoma of the esophagus. *N Engl J Med* 2002; **347**: 1662-1669 [PMID: 12444180 DOI: 10.1056/NEJMoa022343]
53 **Reeh M**, Mina S, Bockhorn M, Kutup A, Nentwich MF, Marx A, Sauter G, Rösch T, Izbicki JR, Bogoevski D. Staging and outcome depending on surgical treatment in adenocarcinomas of the oesophagogastric junction. *Br J Surg* 2012; **99**: 1406-1414 [PMID: 22961520 DOI: 10.1002/bjs.8884]
54 **Shin SH**, Jung H, Choi SH, An JY, Choi MG, Noh JH, Sohn TS, Bae JM, Kim S. Clinical significance of splenic hilar lymph node metastasis in proximal gastric cancer. *Ann Surg Oncol* 2009; **16**: 1304-1309 [PMID: 19241107 DOI: 10.1245/s10434-009-0389-5]
55 **Okajima K**, Isozaki H. Splenectomy for treatment of gastric cancer: Japanese experience. *World J Surg* 1995; **19**: 537-540 [PMID: 7676696 DOI: 10.1007/BF00294715]
56 **Sakaguchi T**, Sawada H, Yamada Y, Fujimoto H, Emoto K, Takayama T, Ueno M, Nakajima Y. Indication of splenectomy for gastric carcinoma involving the proximal part of the stomach. *Hepatogastroenterology* 2001; **48**: 603-605 [PMID: 11379363]
57 **de Manzoni G**, Verlato G, Guglielmi A, Laterza E, Tomezzoli A, Pelosi G, Di Leo A, Cordiano C. Classification of lymph node metastases from carcinoma of the stomach: comparison of the old (1987) and new (1997) TNM systems. *World J Surg* 1999; **23**: 664-669 [PMID: 10390583 DOI: 10.1007/PL00012365]
58 **Kunisaki C**, Makino H, Suwa H, Sato T, Oshima T, Nagano Y, Fujii S, Akiyama H, Nomura M, Otsuka Y, Ono HA, Kosaka T, Takagawa R, Ichikawa Y, Shimada H. Impact of splenectomy in patients with gastric adenocarcinoma of the cardia. *J Gastrointest Surg* 2007; **11**: 1039-1044 [PMID: 17514409 DOI: 10.1007/s11605-007-0186-z]
59 **Holdsworth RJ**, Irving AD, Cuschieri A. Postsplenectomy sepsis and its mortality rate: actual versus perceived risks. *Br J Surg* 1991; **78**: 1031-1038 [PMID: 1933181]
60 **Hasegawa S**, Yoshikawa T, Cho H, Tsuburaya A, Kobayashi O. Is adenocarcinoma of the esophagogastric junction different between Japan and western countries? The incidence and clinicopathological features at a Japanese high-volume cancer center. *World J Surg* 2009; **33**: 95-103 [PMID: 18958523 DOI: 10.1007/s00268-008-9740-4]
61 **Siewert JR**, Stein HJ, Feith M. Adenocarcinoma of the esophago-gastric junction. *Scand J Surg* 2006; **95**: 260-269 [PMID: 17249275]

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