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, and lymphatic invasion at pN1 and pN2, and nerve invasion at pN3 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.
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 pN1 and pN2, and nerve invasion at pN3 in male patients. There were no significant differences in clinicopathological features or lymph node metastases between female and male patients.

**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[8]. 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[9-11]. The 5-year survival rate in resected cases is ≤ 20%[12].

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[13]. 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[14], 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 esophagogastroduodenal carcinoma (EGJ) carcinoma is poorly defined in this classification. Rüdiger Siewert et al[15] 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 esophagogastrectomy. 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
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. Immunohistochemistry for micrometastasis was not performed.

**Tumor size** was scored 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[13]. 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: pN0, no metastasis; pN1, one or two positive regional lymph nodes; pN2, 3-6 positive regional lymph nodes; and pN3, ≥ 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 χ2 test. Factors found to be significant (P <
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, 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

| Factors                                      | Total (\(n = 146\)) | Female (\(n = 35\)) | Male (\(n = 111\)) |
|----------------------------------------------|----------------------|----------------------|---------------------|
| Age (yr)                                     |                      |                      |                     |
| < 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              |

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 node metastases 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, 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 (\(P > 0.05\)).
tumor size, gross appearance, differentiation, pathological depth, lymphatic invasion and lymph node metastasis 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).

**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 \( (6.20 \pm 7.49 vs 4.84 \pm 5.44)\). 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: \( 3^{rd} \) English edition, \( 103 \) cases (75.0%) were at N1, 25 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 metastatic 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 pN1, pN2 and pN3 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...
lymph node metastases at pN1 in all patients (P = 0.020, P = 0.000, P = 0.000, and P = 0.001, respectively) and male patients (P = 0.021, 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 an obvious relationship between the lymphatic invasion and lymph node metastases at pN3 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 pN3 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 pN3 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 pN3. There was no significant correlation between clinicopathological features and the presence of lymph node metastases at pN3 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[18-17]. 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<sub>i</sub>, pN<sub>e</sub> and pN<sub>s</sub> and clinicopathological factors

| Characteristics | Total | pN<sub>i</sub> | pN<sub>e</sub> | pN<sub>s</sub> |
|-----------------|-------|----------------|----------------|----------------|
|                 | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male | Female | Male |
| Age (yr)        | 0.850  | 0.134 | 0.287  | 0.066 | 0.541  | 0.082 | 0.670  | 0.179 | 0.769  | 0.32  | 0.32  | 0.32  |
|                  | < 60   | 33   | 5     | 28    | 5     | 8     | 2     | 9     | 27    | 4     | 42    | 0    | 10    | 4    |
|                  | ≥ 60   | 70   | 30    | 19    | 6     | 31    | 24    | 12    | 88    | 3     | 22    | 9    | 66    | 11   |
| Tumor size (cm) | 0.020  | 0.554 | 0.021  | 0.151 | 0.391  | 0.314 | 0.095  | 0.068 | 0.345  | 0.76  | 0.18  | 0.68  |
|                  | < 2.0  | 0    | 2     | 0     | 2     | 0     | 0     | 0     | 2     | 0     | 2     | 0    | 0     | 2    |
|                  | 2.0-5.0 | 62  | 31    | 15    | 8     | 47    | 23    | 11    | 82    | 2     | 21    | 9    | 61    | 6    |
|                  | > 5.0  | 41   | 10    | 9     | 3     | 32    | 7     | 12    | 39    | 3     | 9     | 30   | 9     | 42   |
| Gross appearance| 0.000  | 0.211 | 0.000  | 0.674 | 0.513  | 0.748 | 0.395  | 0.428 | 0.560  | 0.00  | 0.00  | 0.00  |
| Type 0          | 0     | 6    | 0     | 2     | 0     | 4     | 0     | 6     | 2     | 0     | 4    | 0    | 0     | 0    |
| Type 1          | 5     | 8    | 2     | 3     | 1     | 7     | 1     | 12    | 0     | 3     | 1    | 9    | 0     | 13   |
| Type 2          | 81    | 24   | 19    | 7     | 62    | 17    | 19    | 86    | 4     | 22    | 15   | 64   | 13   |
| Type 3          | 10    | 3    | 2     | 0     | 8     | 3     | 2     | 11    | 1     | 1     | 1    | 10   | 2    |
| Type 4          | 7     | 2    | 1     | 1     | 6     | 1     | 1     | 8     | 0     | 2     | 1    | 6    | 0     | 9    |
| Tumor differentiation | 0.000 | 0.150 | 0.001 | 0.071 | 0.782 | 0.054 | 0.324 | 0.855 | 0.215 |
| Differentiated  | 44    | 32   | 9     | 35    | 25    | 15    | 4     | 44    | 7     | 15    | 55   | 3     | 16   |
| Undifferentiate  | 59    | 11   | 15    | 4     | 44    | 7     | 15    | 55    | 3     | 16   | 12   | 39   | 9     |
| Pathological tumor depth | 0.000 | 0.051 | 0.001 | 0.014 | 0.808 | 0.406 | 0.265 | 0.861 | 0.363 |
| T1              | 1     | 7    | 0     | 2     | 1     | 5     | 0     | 8     | 2     | 0     | 6    | 0    | 0     |
| T2              | 8     | 8    | 2     | 0     | 6     | 8     | 1     | 15    | 0     | 2     | 1    | 13   | 0    |
| T3              | 3     | 1    | 0     | 1     | 3     | 0     | 1     | 3     | 0     | 1     | 1    | 2    | 0    |
| T4              | 91    | 27   | 22    | 8     | 69    | 19    | 21    | 97    | 5     | 25    | 16   | 72   | 15   |
| 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    |
| No              | 79    | 43   | 19    | 11    | 60    | 32    | 16    | 106   | 4     | 26    | 12   | 80   | 9    |
| 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     | 3    | 1    | 1    |
| No              | 99    | 42   | 22    | 11    | 77    | 31    | 22    | 119   | 4     | 29    | 18   | 90   | 14   |
| 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    |
| No              | 88    | 36   | 19    | 9     | 69    | 27    | 19    | 105   | 4     | 24    | 15   | 81   | 8    |
| Esophageal involvement | 0.165 | 0.912 | 0.018 | 0.012 | 0.272 | 0.205 | 0.587 | 0.658 | 0.691 |
| Yes             | 25    | 6    | 4     | 2     | 21    | 4     | 2     | 29    | 0     | 6     | 2    | 23   | 4    |
| No              | 78    | 37   | 20    | 9     | 58    | 28    | 21    | 94    | 5     | 24    | 16   | 70   | 11   |

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.\cite{20} proposed a topographical classification for cardiac carcinomas. In contrast to the previously described classification system, Siewert and Stein\cite{23} 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\cite{12,15,21} and are usually related to poorer prognosis\cite{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\cite{5,23}.
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., 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.

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; 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. Furthermore, the median number of 23 lymph nodes in our study is comparable with other prospective studies on the treatment of GC. The number of dissected lymph nodes is closely associated with the pathological stages and prognosis. A population-based study by Bouvier et al. 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 Karpch et al., 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. 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. The sex ratio for cancer of the pylorus is only 1.5. 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. Some scholars pointed out that this...
may be because sex hormones such as estrogen affect the incidence rate of GC. 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 41%, 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 cardiac adenocarcinomas, both schemes are monotone and distinct, with continuously decreasing and significantly different prognosis with an increasing number of lymph node metastases. Huang 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 cardiac 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 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. 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 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 re-
gional 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 fre-
cently 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\(^{[30,43,44]}\). In line with previous
findings\(^{[32,45,46]}\), the Mine \textit{et al}\(^{[37]}\) confirmed that nodal sta-
tion 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 Ho-
sokawa \textit{et al}\(^{[34]}\) 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, suggest-
ning that the cardiac lymph node is a key dissection object
in the reasonable radical operation.

Even after a precise anatomical-topographical dif-
erentiation of this tumor entity, Siewert \textit{et al}\(^{[26]}\) found a
small number of patients with parapyloric node metastas-
is in their cohort with type II adenocarcinoma. Consis-
tent 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 \textit{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 \textit{et al}\(^{[20]}\) 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 esophage-
tomy with gastric tube reconstruction and gastrectomy
with Roux-en-Y reconstruction seem to be valid proce-
dures clinically.

Most series report 7%-40% of mediastinal nodal
involvement for type II and III esophageogastric can-
er even though abdominal nodes are more affected\(^{[39]}\). In
our series, mediastinal lymph nodes were affected only in
a small number (No. 110, 0.7%), lower than that reported
in the literature\(^{[20,49,50]}\). The necessity of a prophylactic
mediastinal nodal dissection remains controversial. Mine
\textit{et al}\(^{[37]}\) suggested that lower mediastinal lymph nodes,
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[30]. Siewert et al[30] 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[33]. Siewert types II and III cancers could be removed safely with an abdominal approach[30]. 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[30].

In our study, of 104 patients with lymph node metastases, all were N1, 23 were N2, and 15 were N3. Investigating the correlation between pN1, pN2 and pN3 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 pN1. There was an obvious correlation between lymph node metastases and lymphatic invasion in all patients at pN2. 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 pN3. Study of Di Leo et al[38] study of the treatment of advanced gastric cancer showed that T2 tumors were consistently associated with pN3; stations nodal infiltration. Such behavior, although less frequent than in T3/4 tumors, does not allow conservative surgery in terms of nodal resection[34].

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 pN1, and lymphatic invasion at pN3 and neural invasion at pN3 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.

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