

Analysis of Lymph Node Metastases of 1,526 Cases with Thoracic Esophageal and Cardiac Carcinomas: A Random Sampling Report from the Fourth Hospital of Hebei Medical University from 1996 to 2004

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OBJECTIVE To summarize the regular pattern and state of lymph node metastasis of patients with esophageal and cardiac carcinomas, so as to analyze factors influencing lymph node metastasis.

METHODS Clinical data collected from 1,526 thoracic esophageal and cardiac carcinoma patients who were admitted in the Fourth Hospital of Hebei Medical University during a period from January 1996 to December 2004, were randomly selected and an Access Database of the patient's information was set up. Eight clinico-pathologic factors, including the patient's age, tumor location and size, pathological classification, the depth of tumor invasion, vascular tumor embolus (VTE), the state of surrounding organ encroachment and the status of tumor residues, were identified. A correlation between these factors and metastases was statistically analyzed using SPSS13.0 software.

RESULTS Lymph node metastatic sites from esophageal carcinomas included the thoracic and abdominal cavity. Lymph node metastasis from the superior esophageal carcinomas mainly occurred in the neck and thoracic cavity. There was a two-way lymph node metastasis in the patients with the middle esophageal carcinoma. The inferior esophageal carcinomas mainly metastasized to the paraesophageal, paragastric cardia, and left gastric artery lymph nodes. The rate and degree of the metastasis from the inferior esophageal carcinomas were significantly higher compared to those of the superior and the middle esophageal carcinomas ($P < 0.0125$).

The degree of abdominal lymph node metastasis from carcinomas of the gastric cardia was significantly higher compared with that of esophageal carcinomas. In the group with carcinoma of the gastric cardia, the rate and degree of the lymph node metastases in the paragastric cardia and left gastric artery were significantly higher compared to the group with esophageal carcinoma ($P < 0.05$). Paraesophageal lymph node metastasis from carcinomas of the gastric cardia in the thoracic cavity frequently occurred, too, and the degree of the metastasis was similar to that of esophageal carcinoma. There was no significant difference in the rate and degree of the paraesophageal lymph-node metastasis between the group with carcinoma of the gastric cardia compared to those with esophageal carcinoma ($P > 0.05$). Multifactorial logistic regression analysis showed that the tumor size, depth of tumor encroachment, VTE, and tumor residues could all bring about obvious impact on lymph-node metastases ($P < 0.05$).

CONCLUSION Lymph node metastasis from superior esophageal carcinomas mainly occurs in the neck and thoracic cavity. The middle esophageal carcinomas presented a two-way lymph-node metastasis (both the upwards and the downwards), and the lymph node metastasis from inferior esophageal carcinomas mainly occurred in the thoracic and abdominal

cavities. The metastases of carcinoma of the gastric cardia were most commonly found in the abdominal cavity, with frequent paraesophageal lymph-node metastasis. The sufficient attention should be paid to neck lymph node clearance in cases of esophageal carcinoma. What is of the greatest concern is the clearance of the left gastric artery lymph nodes, and also in cases of gastric cardia carcinoma, clearance, the paraesophageal lymph nodes. With an increase in the tumor size and depth of tumor encroachment, and occurrence of VTE and tumor residual cells, the risk of lymph node metastasis is significantly raised ($P < 0.05$).

KEY WORDS: esophageal carcinoma, cardiac carcinoma, lymph node metastasis, Logistic regression model.

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Introduction

China is a high-risk area for esophageal carcinoma. Over the past years, the incidence of malignant carcinoma of the gastric cardia, which is connected with the inferior segment of the esophagus, has been showing a rising tendency. Lymph nodes are one of the main sites for metastases from both esophageal carcinoma and carcinoma of the gastric cardia. A reasonable lymph node clearance will be helpful to improve the curative effect of surgery and postoperative quality of life, and can concurrently reduce the incidence of postoperative complications. In our study, clinical data from 1,526 patients undergoing surgery on esophageal cancer and gastric cardia carcinoma treated in the 4th Hospital of Hebei Medical University were randomly collected, and the state of lymph node metastasis was retrospectively analyzed. Our goal was to investigate the regular patterns and factors that influence metastasis.

Materials and Methods

Clinical data

Clinical case files were collected from the patients with esophageal carcinoma and gastric cardia carcinoma, who received surgical treatment in our hospital during a period from January 1996 to December 2004. Sorting of the cases was conducted based on the patient's ID numbers ranging from small to large, and the sampling was based on selecting 1 patient out of 4 (1,526 of 6,104 cases). A total of 1,526 cases were collected, and an Access Database of the patient's clinical data was set up, with a collection of the case files of 1,414 patients with esophageal carcinoma and carcinoma of the gastric cardia who underwent radical surgery. There were 1,020 males and 394 females among the 1,414 cases, with a male-female

ratio of 2.6:1. The patient's age ranged from 24 to 80 years, with an average age of 58.2.

Evaluation criterion

The segmenting and staging of the esophageal carcinomas and carcinomas of the gastric cardia and lymph node grouping were as follows: the segmenting and the TNM staging of esophageal carcinoma were conducted referring to the 1997 UICC segmenting standards. As for the regional lymph node grouping of esophageal carcinoma, all cleared lymph nodes of the neck were classified as one group, with a common name of the Neck Lymph node Group. For a grouping of the intrathoracic lymph nodes, the 1997 AJCC-UICC methods were utilized, totally 14 groups. Eight groups were involved in the intrathoracic lymph node grouping, among which both the superior and the inferior paratracheal lymph node groups were jointly called the the Paratracheal Lymph node Group.

The TNM staging of the gastric cardia carcinoma referred to the 1987 UICC Gastric Cancer Staging. For the regional lymph node grouping of this carcinoma, the lymph nodes were divided into 16 groups of the 3 stations based on the routine methods of gastric cancer treatment, among which the lymph nodes of the left and the right gastric cardias were collectively called the Paragastric Cardia Lymph Nodes.

As to the patients undergoing a radical surgery, the rate and degree of the metastasis was calculated. Based on a computation by Zhang et al.^[1], the metastatic rate equaled the number of cases with a pathologically confirmed lymph-node metastasis, or with lymph node dissection in a group. The degree of metastasis equaled the number of pathologically proven lymph node metastasis, or the number of the dissected lymph nodes in a group.

Statistical analysis

Eight clinicopathologic factors were chosen, i.e. the age, tumor location, tumor size, pathological types, depth of tumor infiltration, vascular tumor embolus (VTE), surrounding encroachment, and tumor residues, with further detailed classification of each factor. An analysis for the correlation between lymph node metastasis and the clinico-pathological factors was performed (Table 1). A SPSS13.0 package was used. The chi-square test with two rates of sample was employed for numeration data. The partition of chi-square was used for comparisons among multiple rates of the sample, and Logistic regression analysis was utilized for correlation between lymph node metastasis and the clinicopathologic factors. The $\alpha = 0.05$ was used as the significant level of a statistical test. When the method of multiple comparisons of the rates was used for comparing three different sample rates, the significant level of a statistical test was $\alpha = 0.0125$.

Table 1. Clinical data of the patients undergoing radical surgery of esophageal carcinoma and carcinoma of the gastric cardia.

Classifications	Cases	Constituent ratio (%)
Tumor locations		
Superior thoracic segment	107	7.6
Middle thoracic segment	644	45.5
Inferior thoracic segment	135	9.6
Gastric cardia carcinoma	528	37.3
Tumor size (cm)		
≤ 3	268	19.0
3.1~5	587	41.5
5.1~7	333	23.6
> 7	223	15.8
Pathological types		
SqCa	839	59.3
Adenocarcinoma	471	33.3
Undifferentiated small cell carcinoma	39	2.8
Mucinous adenocarcinoma	36	2.6
Others	28	2.0
Depth of tumor encroachment		
Cancer in situ	41	2.9
Encroachment of the lamina propria, submucosa	74	5.2
Encroachment of the superficial muscular layer	98	6.9
Encroachment of the deep muscular layer	170	12.0
Encroachment of the fibrous membrane	542	38.3
Encroachment of the surrounding soft tissue	484	34.2
Clinical stages		
0~I	141	10.0
II	542	38.3
III	528	37.3
IV	197	13.9
VTE		
Negative	1348	95.3
Positive	62	4.4
Surrounding invasion		
Negative	1197	84.65
Positive	216	15.3
Tumor residues		
Negative	1321	93.42
Positive	89	6.3

Exclusive of data depletion

Results

General review for lymph node metastasis of the patients with radical surgery (Table 2)

Lymph node metastases were found only in 561 (39.7%) of the total cases of the group. A total of 8,413 lymph nodes were cleared during surgical treatment, with an average clearance of 6/per case. The number of positive lymph nodes was 1,596 and the degree of metastasis

19%. A total of 5,916 lymph nodes were cleared during surgical operation of the esophageal carcinomas, with an average of 6.7/per case. The number of positive lymph nodes was 821 and the degree of metastasis 13.9%. During surgical treatment of gastric cardia carcinoma, 2,497 lymph nodes were cleared, average 4.7 per case. The number of positive lymph nodes reached 775, and the degree of metastasis 31%.

Lymph node metastasis of the tumors of different sizes

Esophageal carcinoma

The lymph-node metastasis site of esophageal carcinomas included the thoracic and abdominal cavities, among which the metastatic degree of lymph nodes in the left gastric artery ranked the first, which was significantly higher than that of the paraesophageal and paragastric cardia lymph nodes ($P < 0.0125$). There was no significant difference in the metastatic degree between paragastric cardia and paraesophageal lymph nodes ($P > 0.0125$), and there was no significant difference in the metastatic rate between the paraesophageal, paragastric cardia, and left gastric-artery lymph nodes ($P > 0.0125$).

Superior esophageal carcinomas mainly metastasized to the neck and thoracic lymph nodes, with a low degree of metastasis towards the abdominal lymph nodes compared to the middle thoracic lymph nodes. The middle esophageal carcinoma presented an upward and downward lymph-node metastasis, with a similar degree of metastasis compared to both the superior thoracic and the inferior esophageal carcinomas. There was no significant difference in the degree of metastasis in the lymph nodes of the inferior tracheal protuberance between the middle thoracic and the inferior esophageal carcinomas ($P > 0.05$). There was no significant difference in the metastatic rate and degree in the paraesophageal and the paragastric cardia lymph nodes between the middle thoracic and the superior esophageal carcinomas ($P > 0.0125$). Also there was no significant difference in the rate of left gastric-artery lymph node metastasis between the middle thoracic and the superior esophageal carcinomas ($P > 0.0125$). Inferior esophageal carcinomas mainly metastasize to the para-

Table 2. Lymph node metastasis of the patients undergoing radical surgery.

Lymph node groups	Esophageal cancer (n = 886)					Carcinoma of the gastric cardia (n = 528)						
	Positive lymph nodes	Cleared lymph nodes	Degree of metastasis (%)	Positive cases	Detected cases	Metastasis rate (%)	Positive lymph nodes	Cleared lymph nodes	Degree of metastasis (%)	Positive cases	Detected cases	Metastasis rate (%)
Neck lymph node	29	59	49.15	15	27	55.56	0	0	-	0	0	-
Paratracheal	28	71	39.44	17	33	51.52	0	0	-	0	0	-
Pre-vascular and/or retrotracheal	36	114	31.58	28	65	43.08	1	8	12.50	1	4	25.00
Subaortic	10	61	16.39	5	26	19.23	0	0	-	0	0	-
Below the eminence	122	1519	8.03	80	556	14.39	0	49	0.00	0	18	0.00
Paraesophageal	212	1592	13.32	127	593	21.42	57	390	14.62	37	200	18.50
Inferior pulmonary ligament	15	338	4.44	11	177	6.21	10	189	5.29	7	104	6.73
Hilum of the lung	23	250	9.20	14	119	11.76	1	20	5.00	0	9	0.00
Paragastric cardia	87	601	14.48	58	353	16.43	196	537	36.50	98	214	45.79
Left gastric artery	245	1257	19.49	145	649	22.34	473	1172	40.36	218	423	51.54
Group A	3	24	12.50	1	10	10.00	15	55	27.27	10	30	33.33
Group B	6	17	35.29	4	12	33.33	10	43	23.26	7	31	22.58
Group C	5	13	38.46	2	14	14.29	12	34	35.29	7	19	36.84

esophageal, the paragastric cardia and the left gastric-artery lymph nodes, with a significantly higher rate and degree of metastasis than that of superior thoracic and middle esophageal carcinomas ($P < 0.0125$).

Gastric cardia carcinoma

The lymph node metastatic site of gastric cardia carcinoma was mainly in the abdominal cavity, where the rate and degree of metastasis of paragastric cardia and left gastric-artery lymph nodes was significantly higher compared to the esophageal carcinoma group ($P < 0.05$). There was no significant difference in the rate and degree of metastasis between the left gastric-artery and the paragastric cardia lymph nodes ($P > 0.0125$), but with a significantly higher metastasis compared to the paraesophageal lymph node group ($P < 0.0125$). The metastatic degree of thoracic paraesophageal lymph nodes in gastric cardia carcinoma was similar to that of esophageal carcinoma, and there was no significant difference in the metastatic rate and degree between the two groups ($P > 0.05$).

Logistic regression analysis between lymph node metastasis and clinicopathologic factors

Monofactorial logistic regression

Tumor location, tumor size, pathological types, depth of tumor infiltration, VTE and circumambient encroachment, as well as tumor residues all showed an obvious impact on the lymph node metastases ($P < 0.01$). Patient age showed no relationship ($P = 0.262$).

Multifactorial logistic regression analysis

Tumor size, depth of tumor infiltration, VTE and tumor residues all had a significant impact on the lymph node metastasis ($P < 0.05$). Compared to tumors with a length of ≤ 3 cm, when the length of the tumors reached a range from 3.1 cm to 5 cm, 5.1 cm to 7 cm, and over 7 cm, the risk of lymph node metastasis was respectively 1.8, 2.5 and 2.3 times higher. There was a significant difference in statistical analysis ($P < 0.01$).

Compared to cancer in situ, when the tumor invaded the lamina propria or submucosa, the risk of lymph node metastasis was 5.7 times higher, but with no statistical significance ($P = 0.112$). When encroachment of the superficial muscular layer, deep muscular layer, fibrous membrane and surrounding soft tissue occurred, the risk of lymph node metastasis was respectively 11.1, 16.0, 21.3 and 25.5 times higher, with a significant difference ($P < 0.05$). When the VTE was positive, the risk of lymph node metastasis was 4.3 times higher than that of negative VTE, showing a significant difference ($P < 0.01$). When the surgical tumor residue was positive, the risk of lymph node metastasis was 1.7 times that of a negative tumor residue. The difference was significant ($P < 0.05$).

Discussion

Concerning carcinoma of the gastric cardia, at the present time there is no firm consensus regarding how it is defined. However there are various definitions of gastric cardia carcinoma from different countries all over the world. In Japan, the gastric cardiac area is defined as a region 2 cm inside both the lower end of esophagus and the superior extremity of the stomach, while in the US, gastric cardia carcinoma is defined as a cancer with its focal center in a region 1 cm above and 2 cm below the borderline between the esophageal and gastric mucosa. In China, this cancer is defined as one which primarily occurs at or covers a region of 2 cm below the borderline between the esophageal and gastric mucosa. It has been suggested by most scholars that carcinoma of the gastric cardia is a disease individually classified apart from gastric cancer and esophageal carcinoma, but some have insisted that the disease should be in a category of esophageal carcinoma. Other authors have insisted that the disease is part of gastric cancer. In our study, gastric cardia carcinoma was investigated in combination with esophageal carcinoma, in order to observe the usual route of tumor lymph node metastasis.

There is no obvious specificity in segmenting the esophageal lymphatic drainage, as the lymph from each esophageal segment is usually emptied into the neighboring lymph nodes. Findings by Feng et al.^[2] indicated that superior esophageal carcinomas mainly metastasized towards the neck lymph nodes, middle esophageal carcinoma towards the neck, the mediastinal, and the abdominal lymph nodes, and inferior esophageal carcinoma towards the mediastinal and the abdominal lymph nodes. A summary from Li et al.^[3] suggested that: most metastases of superior esophageal carcinomas occurred in the neck, paraesophageal, and parabronchial lymph nodes; the metastases of middle esophageal carcinomas mainly were found in the vicinity of the tumor, in the left gastric-artery, paraesophageal, and paragastric cardia lymph nodes, as well as in the lymph nodes under the tracheal protuberance, and metastasis from inferior esophageal carcinomas occurred around the tumor, in the left gastric-artery and paragastric cardia lymph nodes, as well as in lymph nodes under the tracheal protuberance. The results of this study are consistent with previous reports.

Concerning lymph node clearance, there was a difference in the degree of lymph node clearance for the tumors of different sizes. More attention should be paid to neck lymph node clearance of esophageal carcinoma. Based on previous reports, the metastatic rate of the left gastric-artery lymph nodes from esophageal carcinomas was 15.2% to 35.7%. Therefore the clearance of the left gastric-artery lymph nodes is also one of the key factors in clearing lymph nodes, with an emphasis on those nodes of the neck, along with mediastinal and celiac nodes in the middle and inferior thoracic segments. In

treatment of inferior esophageal carcinoma, more attention should be paid to clearing the mediastinal and celiac nodes.

With regard to gastric cardia carcinoma, there is, at present, no consensus for lymph node clearance. Li et al.^[4] suggested that carcinoma of the gastric cardia at first metastasized to the celiac lymph nodes, and then extended to thoracic nodes at an advanced stage cancer. However, the studies of Steup et al.^[5] showed that patients with thoracic metastasis from gastric-cardiac carcinoma achieved a survival rate of 5~10 years. This suggests that gastric cardia carcinoma should be included in Stage-N2 instead of the current classification of M1. Previous reports showed that paraesophageal lymph node metastasis from gastric cardia carcinoma was 11.9% to 30.0%^[6,7]. In our study, node clearance with this cancer should be conducted in the abdominal cavity, as well as with the paraesophageal lymph nodes.

Multiple factors influence lymph node metastasis, with previous reports focusing on the effect of the depth of tumor infiltration and tumor size, but the studies on the VTE and tumor residues have received less attention^[8,9]. Yuan et al.^[10] found that after tumor encroachment of the superficial muscular layer, the rate of lymph node metastasis significantly increased, while there was no significant difference related to the other neighboring layers. Concurrently, new AJCC TNM staging takes into account the depth of tumor infiltration as the key index for tumor staging, without considering the length of the tumor. Moreover it exists two different ideas on the relationship between the tumor size and lymph node metastasis. In our study, 8 clinicopathologic factors with a possible impact on lymph-node metastasis from esophageal carcinoma and gastric cardia carcinoma were selected for Logistic regression analysis. A monofactorial Logistic regression analysis showed that the tumor location, tumor size, pathological types, depth of tumor encroachment, VTE, surrounding invasion, and tumor residues all had a pronounced effect on lymph node metastasis, whereas age was not a factor. Further multifactorial Logistic regression analysis indicated that lymph node metastasis was influenced by tumor size, depth of tumor infiltration, VTE and tumor residues. The risk of lymph node metastasis significantly increased, with an increase in the tumor size and the depth of tumor encroachment, as well as occurrence of VTE and residual tumor cells. The authors believe that once tumor encroachment of the superficial muscular layer is found during surgery, careful regional lymph node clearance is very important. The dissection of the esophageal gastric cardia carcinoma with a scope of 5 cm beyond both the superior and the inferior margin of the tumor is not sufficient, and in principle most of the esophagus should be excised as much as possible to avoid the presence of positive tumor residues. Choice of postoperative treatment methods not only depends on the clinical stages, but the tumor size, VTE, and tumor residues should also

be taken into consideration.

Radical surgery is one of the major means for treating esophageal carcinoma and gastric cardia carcinoma, and systemic clearing of lymph nodes is a major surgical step. Igaki et al.^[11] found that the 5-year survival rate of the patients undergoing an extensive three-field lymph node clearance, including the esophageal neck, chest and abdomen, was significantly higher compared to the patients with a two-field (chest and abdomen) lymph node clearance. Nevertheless, the three-field lymph node clearance lacks a conclusive criterion for case selection, with negative factors, such as an excessive wide-bound operating field, major surgical trauma, high incidence of postoperative complications, damage to the recurrent laryngeal nerve, and a poor long-term quality of life, etc. In China the present major mode of operation for esophageal carcinoma is the two-field lymphadenectomy. Shao^[12] pointed out that neck anastomosis of a subtotal esophageal resection plus a concurrent two-field lymph node clearance resulted in a better curative effect. The lymph nodes of the inferior tracheal protuberance at the intra-thoracic mediastinum, the lesser gastric curvature of intra-abdominal paragastric cardia and, in the left gastric artery can be completely excised, and preoperative radiotherapy alone, or combined with chemotherapy can be conducted at the mediastinum above the tracheal protuberance (duct cancer) and the bilateral supraclavicular regions. Reports have shown that the 5-year survival rate of the patients with the combined therapy is not poorer compared to those with a three-field clearance. Up to the present time, no prognostic analysis has been conducted. In our study, however based on a regularity of the lymph node metastasis, the authors strongly recommend the two-field lymph node clearance for inferior esophageal carcinoma and carcinoma of gastric cardia. In the case of middle and superior thoracic carcinoma, extensive three-field lymph node dissection is recommended.

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