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Pattern of Lymphatic Metastasis and Influencing Factors in Thoracic Esophageal Carcinoma

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OBJECTIVE To explore the regular patterns of lymphatic metastasis in thoracic esophageal carcinoma (TEC) and the factors influencing these patterns.
METHODS Data of 229 TEC patients who underwent radical esophagectomy and thoracoabdominal 2-field lymphadenectomy were reviewed. Within this patient population, a total of 2458 lymph nodes were dissected during surgery. The distribution of the nodular metastasis rates (NMR) in various diseased regions in the esophageal carcinoma (EC) patients as well as factors influencing metastases such as the depth of tumor infiltration, tumor size, tumor morphology, and degree of tumor differentiation were analyzed.
RESULTS *i*) Lymphatic metastasis (LM) occurred in 102 EC cases, and the lymphatic metastasis rate (LMR) was 44.5% (102/229). The NMR was 9.5% (258/2458). *ii*) The NMRs were 19.0%, 6.7%, 9.8% and 12.2% in the superior, middle and inferior mediastinum, and abdominal cavity, respectively, in patients with EC in the superior thoracic segment; 26.1%, 7.4%, 11.8% and 11.9% in the same sites of the mediastinum, respectively, in those with middle thoracic-segment EC; and 0%, 1.6%, 5.3%, and 10.0%, respectively, in the same sites in those with inferior thoracic EC. *iii*) The LMRs of the EC patients in stage-T1, T2, T3 and T4 were 28.6%, 43.8%, 47.6% and 31.3%, respectively, and the NMRs of the patients were 7.9%, 10.8%, 10.7% and 10.8%, respectively. There were no significant differences between the LMR and the NMR of the EC patients in stage T1 to T4 ($\chi^2 = 2.733$, $P = 0.435$ and $\chi^2 = 0.686$, $P = 0.876$). *iv*) The LMR of the patients with the length of tumor ≤ 3 cm, > 3 cm and ≤ 5 cm, and > 5 cm were 45.2%, 43.4% and 46.2%, respectively, and the NMR according to the same range of the tumor size above were 9.1%, 11.6% and 11.7%, respectively. There were no significant differences between the groups ($\chi^2 = 0.094$, $P = 0.954$ and $\chi^2 = 3.933$, $P = 0.140$). *v*) The NMRs of the medullary, ulcerative, fungoid and sclerotic-type EC were 14.0%, 9.6%, 4.3% and 18.3%, respectively ($\chi^2 = 19.292$, $P = 0.000$), among which the NMR of the fungoid-type EC was the lowest. The LMRs were 42.5% and 75.0%, respectively in the cases with squamous cell carcinoma (SqCC) and poorly differentiated SqCC ($\chi^2 = 4.852$, $P = 0.028$), and the NMRs were 9.5% and 18.6% correspondingly in the 2 groups ($\chi^2 = 11.323$, $P = 0.001$). LM was commonly seen in the cases with poorly differentiated tumors.
CONCLUSION Lymph node metastases of TEC spreads widely and can involve many regions. Metastasis can even be found in early stages of EC. Morphologic type and the degree of tumor differentiation are the main factors affecting the LM.

KEY WORDS: esophageal carcinoma/thoracic segment, lymphatic metastasis, surgery.

Introduction

Esophageal carcinoma (EC) is one of the most frequently seen malignant tumors in China, and lymphatic metastasis (LM) is a main metastatic pathway in EC patients. Although there is a definite, regular pattern of LM in EC, the process and sites of LM are extremely complicated and have been the focus and a key point of clinical research. In our study, data from 229 TEC patients undergoing thoracoabdominal 2-field lymphatic dissection in the Thoracic Department of the 4th Hospital of Hebei Medical University, during a period from January 1997 to December 1999, were retrospectively analyzed, and the correlation factors affecting LM were discussed. The results of the study may help surgeons and radiotherapists in treating EC patients.

Materials and Methods

Clinical data

From January 1997 to December 1999, 229 TEC patients received radical excision of EC and thoracoabdominal 2-field lymphatic dissection with clearance of more than 8 nodes in each case in the Thoracic Surgery Department of our hospital. Among the patients, there were 166 males and 63 females, with the age ranging from 30 to 72 years and a median age of 55. In these cases, carcinoma occurred in the superior thoracic segment in 16 patients, in middle thoracic segment in 174 patients and in the inferior thoracic segment in 39. Based on tumor morphology, 69 of the cases were the medullary type, 132 the ulcerative, 13 the fungoid, 6 the sclerotic and 9 were the anabrosis type. In the 229 cases, 219 were squamous cell carcinoma (SqCC), 6 were adenocarcinoma, 3 were small cell carcinoma, and 1 was basal cell carcinoma. The patients were staged using the pathologic TNM classification (UICC, 2002) as follows: 3 at stage 0, 5 at stage I, 134 at stage II, and 87 at stage III.

Definition of the LM terms

Lymphatic metastasis rate (LMR) = (number of the cases with pathologically confirmed LM/total number of the cases) × 100%; nodular metastasis ratio (NMR) = (number of the pathologically confirmed LM/total number of the cleared nodes) × 100%.

LM zoning

Zoning of the nodes to be cleared was conducted based on the intrathoracic lymph nodes zoning standard of the American Thoracic Society Nodal Staging System. In accordance with the definition of anatomic sites for the nodes to be cleared, in our study the clearance of the superior mediastinum included the nodes in the Zone 2 (next to the superior part of trachea) and Zone 4 (adjacent to the inferior part of trachea). The clearance of the middle mediastinum included Zone 5 (aortic pulmonic window), Zone 7 (inferior tracheal protuberance) and Zone 10 (tracheobronchial) nodes, while that of the inferior mediastinum included Zone 8 (paraesophageal) and Zone 15 (diaphragmatic) nodes. Clearance of the abdominal cavity included Zone 16 (cardia), Zone 17 (left side of the stomach), Zone 18 (hepatic hilum), Zone 19 (hilum of spleen), and Zone 20 (abdominal paraaortic) nodes.

Statistical analysis

SPSS11.5 software was used in the statistical analysis of our study, and the χ^2 test was used for comparison among the intergroup rates.

Results

General condition of LM

LM occurred in 102 of the 229 EC cases, with the LMR of 44.5% (102/229). A total of 2458 nodes were cleared during all of the surgeries, and the number of lymph nodes cleared ranged from 8 to 23 in each of the patients, with an average of 11. LM was found in 258 of the total nodes cleared, and the NMR was 10.5% (258/2458).

Diseased region and LM

Extensive LM could be found in various diseased regions in the TEC patients. In these regions, LM in the superior mediastinum was commonly seen in the patients with EC at the superior and middle thoracic segments, and LM in the abdominal cavity was frequently seen in those with EC at the inferior thoracic segment (Table 1).

Table 1. Distribution of NMR in various diseased regions in TEC patients.

Sites of LM	NMR%		
	Superior thoracic segment	Middle thoracic segment	Inferior thoracic segment
Superior mediastinum	19 (4/21)	26.1 (12/46)	0 (0/2)
Middle mediastinum	6.7 (3/45)	7.4 (35/474)	1.6 (1/61)
Inferior mediastinum	9.8 (4/41)	11.8 (68/574)	5.3 (7/131)
Abdominal cavity	14.2 (9/63)	11.9 (93/779)	10 (22/221)
Total	11.8 (20/170)	11.1 (208/1873)	7.2 (30/415)

Depth of tumor infiltration and LM

No LM was found in the EC patients with stage-Tis. LM occurred in the EC patients with stage-T1-T4. There were no significant differences in the comparison between the LMR and NMR in the patients with TEC ranging from Stage T1 to T4 (χ^2 = 2.733, P = 0.435 and χ^2 = 0.686, P = 0.876, Table 2).

Tumor size and LM

After fixation of EC specimens, the specimens were divided into 3 groups according to the size of tumor, i.e. the sizes of ≤ 3 cm, > 3 cm and ≤ 5 cm, and > 5 cm. There were no significant differences between LMR and NMR among different size groups (χ^2 = 0.094, P = 0.954 and χ^2 = 3.933, P = 0.140, Table 3).

Tumor morphology and LM

Based on the tumor morphology after the pathologic examination of the specimens, middle-late stage EC was divided into the medullary, ulcerative, fungoid and sclerotic types, and early stage EC was classified as the anabrosis type. For the effect of morphologic type of the tumor on LM, see Table 4. The χ^2 test showed that there were no statistical differences in comparison of LMRs among the pathologic types of middle-late stage EC (χ^2 = 3.769, P = 0.288). However, there were statistically significant differences in comparison of the NMR among different pathologic types (χ^2 = 19.292, P = 0.000), among which the NMR of fungoid-type EC was very low.

Histopathologic differentiation and LM

The degree of tumor differentiation correlated to LM as expected, and there were significant differences between LMR and NMR in the SqCa and poorly differentiated SqCa patients (χ^2 = 4.852, P = 0.028 and χ^2 = 11.323, P = 0.001, Table 5).

Table 2. Effect of different T stages of TEC on LM.

Depth of tumor infiltration	*n*	No. of LM cases	Total number of lymph nodes cleared	No. of LM	LMR %	NMR%
Tis	3	0	35	0	0 (0/3)	0 (0/35)
T1	7	2	76	6	28.6 (2/7)	7.9 (6/76)
T2	56	24	611	66	43.8 (24/56)	10.8 (66/611)
T3	147	71	1542	165	47.6 (71/147)	10.7 (165/1542)
T4	16	5	194	21	31.3 (5/16)	10.8 (21/194)

Table 3. Effects of various tumor sizes of TEC on LM.

Tumor size (cm)	*n*	No. of LM cases	No. of lymph nodes cleared	No. of LM	LMR %	NMR%
≤ 3	104	47	1105	99	45.2 (47/104)	9.1 (101/1105)
> 3 and ≤ 5	99	43	1071	134	43.4 (43/99)	11.6 (124/1071)
> 5	26	12	282	25	46.2 (12/26)	11.7 (33/282)

Table 4. Effect of different morphologic types of TEC on LM.

Macroscopic pathologic types	*n*	No. of LM cases	Sum total of lymph nodes cleared	No. of LM	LMR %	NMR%
Medullary	69	32	721	101	46.4 (32/69)	14 (101/721)
Ulcerative	132	61	1439	138	46.2 (61/132)	9.6 (138/1439)
Fungoid	13	3	138	6	23.1 (3/13)	4.3 (6/138)
Sclerotic	6	4	60	11	66.7 (4/6)	18.3 (11/60)
Anabrosis	9	2	100	2	22.3 (2/9)	2.0 (2/100)

Table 5. Effect of degree of tumor differentiation on LM.

Pathologic type	*n*	No. of LM cases	Sum total of lymph nodes cleared	No. of LM	LMR %	NMR%
SqCC	207	88	2217	210	42.5 (88/207)	9.5 (210/2217)
Poorly differentiated SqCC	12	9	129	24	75.0(9/12)	18.6 (24/129)

Discussion

Both the incidence and death rate of EC patients are high, and LM is the major pattern of metastases of EC. Jamieson et al.[1] summarized the literature they reviewed including 312 original articles, published during the period from 1990 to 2000, and found that the death rate of patients undergoing excision of EC was about 6.7%, and the 5-year survival rate was approximately 27.9%. The LM of EC was very high, and the prognosis was poor. This closely correlates to a distinctive characteristic in the anatomy of the esophagus, i.e. the rich capillary nodal networks. Owing to mutual substance exchange between the esophageal submucosa and the muscular layer through nodal networks, the extensive drainage of mediastinal lymph nodes may form, resulting in the meeting of the collateral vessels and lymphatic vessels in the neck and abdomen. Therefore, the LM of EC is usually involved in several regions, such as the neck, chest, and abdomen etc., and has the feature of extensive spreading. It was reported that the LMR of EC ranged from 45.3% to 69.0%[2-6], and the NMR approximately ranged from 10.3% to 15.2%[2,3,5,7]. The data from our group revealed that cancer metastasis occurred in 45% of EC patients when surgery was performed, with a NMR of 10.5%. These findings also indicated that very extensive LM might occur in the various diseased regions of TEC patients where LM was commonly seen, in the superior mediastinum in EC of the upper thoracic segment and in the abdomen in EC of the inferior thoracic segment. This is generally in conformity with the regularity of LM in EC, i.e., ascending LM occurring first in the upper thoracic EC, descending LM coming from the inferior thoracic EC; however, the opportunity for ascending or descending LM in the middle thoracic EC varies greatly. There were different results in various studies previously reported in the literature[3,4]. In our study, the NMR of middle thoracic EC was 26.1% in the superior mediastinum and was 11.9% in the abdomen, showing the feature of predominant ascending metastasis. Concurrently, NMR of inferior thoracic EC was 0% in the superior mediastinum. This was possibly related to the thoracicoabdominal 2-field lymphadenectomy used in the surgery, in which both the scope of the lymphatic clearance and the number of the lymph nodes cleared were limited, and as a result, failed to completely demonstrate the character of LM and the regularity of metastasis in the EC patients.

The clinicopathologic factors affecting the LM of TEC mainly include the degree of tumor infiltration, tumor size, the morphologic type and the degree of differentiation of the cancer cells[8]. In general, the infiltration depth of EC closely correlates to LM[2,3,4,6], and the area where the tumor cells penetrate the submucosa, the LM will obviously be increased[9,10]. Gotohda et al.[10] analyzed 65 early TEC cases undergoing neck, chest and abdomen 3-field lymphadenectomy, among which no LM occurred in cases with intra-mucosal cancer (0/13), or the LMR reached up to 44% (23/52) when the cancer cells invaded the muscularis mucosa or submucosa. Stein et al.[11] reported the regularity of LM in 290 cases with early EC, in which the LMR attained 2.1% (2/96) in the intramucosal carcinoma cases, but the LM was 20.7% in submucosal squamous cell carcinoma and 36.4% in submucosal adenocarcinoma cases. In our study, there was no LM in intramucosal carcinomas (Tis stage), nevertheless, LM occurred in other cases with T1-T4 stage carcinoma, and there were no significant differences between LMR and NMR in the T1-T4 stage EC cases. These findings indicate that cancer metastases may occur in early EC, and that the tumor cells can spread extensively along the abundant network of lymphatic vessels in the deep layer of the mucosa once the cells break through the basal membrane, until reaching the mucosal layer.

Tumor size was regarded as the sole standard of non-surgical pathologic staging of EC (Yangquan Staging 1976) in China, i.e., tumor size of < 3 cm was defined as the early change, the size of 3-5 cm as intermediate affection, and the size of > 5 cm as advanced affection. However, at present, the evidence is not sufficient. Over the past few years, many researchers have felt that there were no apparent correlations between the tumor size and LM[2,5,7,12,13], so the clinical stage of EC should not be determined by tumor size. Nevertheless, whether or not tumor size correlates with LM remains controversial. Studies by some researchers have shown that the longer the lesion is, the higher the LMR[14]. In our study, the length of the lesion was divided into 3 groups after the formalin fixation of the EC specimen, i.e., the group with the affection length of ≤ 3 cm, with the length ranging from > 3 cm and ≤ 5 cm, and with the length of > 5 cm. The results also indicated that there were no obvious differences between the LMR and NMR in EC at different tumor sizes, which was in conformity with most results of other studies.

Our study revealed that the LMRs of the ulcerative, medullary and sclerotic-type EC were all high, while the LMR of fungoid-type EC was relatively low, which was possibly related to biological characteristics of the fungoid-type EC, such as intraluminal growth and tumor infiltration limited to shallow layers. The findings in the study done by Siewert et al.[15] show that the differentiation of EC cells was also an independent influencing factor of LM, and that the higher the differentiation, the less LM occurs. A similar conclusion was also made by Wang et al.[2] and Wang et al.[16] from China. Our study also indicated that both LMR and NMR were lower in the poorly differentiated SqCa cases than in the well and moderately differentiated SqCa cases, suggesting that the lower the degree of tumor differentiation, the more likely LM may occur.

In conclusion, we believe that although the pattern of LM in TEC demonstrates definite regularity, it involves many sites and can spread extensively. In addition, cancer metastasis can occur in early stages of TEC. The LM of EC is related to the macroscopic morphology and tumor differentiation, but it has no obvious correlation with the tumor size. However, in our study, the thoracoabdominal 2-field lymphadenectomy was performed in patients, but the scope of lymph node clearance in the surgical procedure was limited; therefore, it failed to completely demonstrate the features and regularity of LM in the EC patients. The special histologic features and complexity of lymphatic drainage in EC demonstrate the significance of our study on the regulation of LM of EC. Further, the findings of the study may supply the theoretical basis for standardizing the clearance scope of the mediastinal lymph node drainage area of EC and guide postoperative radiotherapy towards precise exposure in the scope of the radiation, in order to improve the survival of patients.

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