The pattern and prevalence of lymphatic spread in thoracic oesophageal squamous cell carcinoma

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Abstract

Background: Oesophageal squamous cell carcinoma (SCC) is a common type of cancer in China. The knowledge of its pattern of lymphatic metastasis would be of clinical value for surgical and radiation oncologists to treat this disease. Material and methods: A large series of 1850 thoracic oesophageal SCC was retrospectively analysed after extended oesophagectomy with three-field lymphadenectomy (3FL). Specimens were assessed for pattern of lymphatic spread. Result: Of the 1850 patients, 1081 (58.4%) developed mediastinal, cervical and/or abdominal node metastases. The lymphatic metastasis rates were 35.6%, 22.2%, 26.5%, 6.1% and 26.5%, respectively, for the cervical, upper, middle, lower mediastinal nodes and abdominal nodes. The adjacent mediastinal node metastasis alone occurred in 5.5% of patients, and the multiple level or skip node spread accounted for 20.9% and 73.6% of patients with node metastases. Upward lymphatic spread developed in 46.4% of patients, both up- and downward in 33.2%, and the downward, 20.5%. For the upper oesophageal SCC, the most common node metastasis was in the cervical (49.5%) and followed by the upper mediastinal (28.7%), middle mediastinal (11.4%), abdominal (8.0%) and lower mediastinal (1.4%) nodes. For the middle oesophageal SCC, the highest incidence of node spread was also in the cervical (35.0%) and similar rates in the middle mediastinal (29.8%), abdominal (27.2%) and upper mediastinal (22.4%) nodes, but the least in the lower mediastinal (6.0%) node. For the lower oesophageal SCC, more node metastasis occurred in the abdominal (51.7%), and followed by the middle mediastinal (25.6%), cervical (17.2%), lower mediastinal (13.9%) and upper mediastinal (10.0%). However, the lymphatic metastasis rates of the upper, middle and lower thoracic oesophageal SCC were similar. The unfavourable factors for lymphatic metastasis were long oesophageal lesion (p < 0.000), late T stage (p < 0.000) and poor differentiation of tumour cells (p < 0.000). Conclusion: The prevalence was: (1) lymphatic spread prone to the upward in the upper oesophageal SCC, downward in the lower one and both up- and downward in the middle one with in favour of the upward and (2) multiple level and skip node metastases were very often seen. The unfavourable factors for long lymph node spread were poor differentiation of tumour cells, late T stage and poor differentiation of tumour cells.

Keywords: Thoracic oesophageal squamous cell carcinoma; Three-field lymphadenectomy; Lymphatic spread pattern and prevalence

1. Introduction

Oesophageal carcinoma is one of the most common cancers in China, especially in the northern China [1]. Lymphatic metastasis is a common pathway for the spread of cancer, and becomes a focus of investigation because it has been demonstrated as an important prognostic predictor in oesophageal carcinomas [2–7]. The knowledge of lymphatic spreading pattern and its prevalence will be of great value in a clinic, which would provide the evidence for determination of the extent of surgical resection and irradiation target for postoperative radiotherapy. Little information is available about the lymphatic spread of thoracic oesophageal squamous cell carcinoma (SCC). In an attempt to obtain an accurate postoperative staging and to improve the surgical results, extended oesophagectomy with three-field lymphadenectomy (3FL) has been proposed and performed in the Cancer Hospital of the Fujian Medical University (CHFMU) since 1993. This retrospective study aimed to analyse the data accumulated in the past 14 years and evaluate the pattern and its prevalence of lymphatic spread as well as the frequencies of lymph node metastasis in a large group of patients with thoracic oesophageal SCC.
2. Material and methods

2.1. Patient inclusion and exclusion criteria

The patient inclusion criteria were as follows: (1) SCC of thoracic oesophagus was confirmed by histology; (2) no supraclavicular, or cervical, node or abdominal node metastases had been detected by physical, ultrasound and computed tomography (CT) examination at staging work-up prior to surgery; (3) patient had not undergone any treatment prior to surgery; (4) an extended oesophagectomy with 3FL had been performed; (5) the number of lymph nodes removed by 3FL was ≥15; and (6) all data of patient medical history, record of surgery, pathological report and follow-up were available.

The exclusion criteria included: (1) histological diagnosis was mixed SCC with other histological types; (2) patient had been found to have supraclavicular, or cervical, node or abdominal node metastases prior to surgery; (3) patient had been treated with preoperative chemotherapy or irradiation; (4) the surgery procedure was other than the extended oesophagectomy with 3FL; (5) the number of lymph nodes removed by 3FL was <15 nodes; and (6) patient had suffered from other malignancies before oesophageal SCC.

2.2. Lymph node mapping

Lymphatic nodes were named according to the guideline of the Japanese Society for Esophageal Diseases (JSED) (Table 1) [8], and were divided into three groups: cervical, thoracic and abdominal lymph nodes. The cervical nodes included cervical para-oesophageal lymph nodes (101), deep cervical lymph nodes (102), retropharyngeal lymph nodes (103) and supraclavicular lymph nodes (104). The thoracic nodes were further grouped into three subgroups: the upper, middle and lower thoracic mediastinal. The upper mediastinal nodes were upper para-oesophageal lymph nodes (105) and thoracic paratracheal lymph nodes (106). The middle mediastinal nodes included subcarinal lymph nodes (107), middle para-oesophageal lymph nodes (108), hilar lymph nodes (109) and posterior mediastinal lymph nodes (112). The lower mediastinal nodes contained lower para-oesophageal lymph nodes (110) and diaphragmatic lymph nodes (111). For abdominal nodes, there were 16 subgroups, but in this study the nodes from #8 to #16 were grouped and named as #8 with ‘R’ indicating the right side and ‘L’ the left side.

2.3. The definition of oesophageal lesion location

In order to describe the location of oesophageal SCC, the thoracic oesophagus can be classified into the upper, middle and lower according to the 1997 UICC stage classification [9] (Fig. 1).

2.4. The pattern of lymphatic spread

The following definitions were applied in the current study to describe the pattern of lymphatic spread. The extent of the lymphatic metastasis was categorised into three: (1) adjacent node metastasis occurring in the same segment as the oesophageal lesion (e.g., middle oesophageal SCC metastasising to the middle mediastinal node only); (2) multiple levels of node metastasis occurring in adjacent as well as other nodes, including mediastinal nodes, cervical or abdominal; and (3) skip node metastasis in which the primary tumour did not continuously spread to the adjacent nodes, but skipped to far node levels, missing one or more than one node level.

For patients with multiple level or skip node metastases, three classifications were further made based on the node metastasis direction: (1) upward lymphatic spread towards the cranial direction (e.g., supramediastinal, or supraclavicular, or cervical node metastases from the middle and lower oesophageal SCC), (2) downward lymphatic spread towards the caudal direction (e.g., lower mediastinal node involvement from upper oesophageal SCC, or abdominal node,
metastases) and (3) both upward and downward lymphatic spread.

2.5. Surgical approach

All patients underwent resection through a right thoractomy, followed by laparotomy, bilateral cervical collar incision and en bloc oesophagectomy with cardiectomy, partial gastrectomy and advancing a greater curvature gastric tube to the neck for an oesophago gastric anastomosis. The dissection of 3FL was carried out as follows. In the thorax, a right fourth intercostal thoractomy was performed, and then the tumour-bearing oesophagus was removed en bloc within an envelope of the adjoining tissues that included both pleural surfaces laterally, the pericardium anteriorly and all lymphovascular tissues wedged dorsally between the oesophagus and the spine. The thoracic lymphatic duct was resected in the en bloc resection throughout its course in the posterior mediastinum, which meant a complete dissection of the middle and lower mediastinal nodes, including the peri-oesophageal, parahiatal, subcarinal and aortopulmonary window nodes. In the abdomen, the upper abdominal and retroperitoneal lymph nodes were removed, which contained coeliac, splenic, common hepatic, left gastric, lesser curvature and parahiatal nodes. Lastly, clearance of superior mediastinal and cervical lymph nodes was performed by a collar incision. The nodes removed were those along the right and left laryngeal recurrent nerves throughout their mediastinal course, the upper thoracic para-oesophageal nodes, both right and left tracheobronchial nodes, pretracheal nodes, the deep nodes in lower cervical area located posterior and lateral to the carotid sheath and supraclavicular nodes.

2.6. Histopathological assessment of the removed specimen and lymph nodes

The lymph nodes were picked up from the surgical specimen and each group of nodes was assigned a special number indicating its localisation. The specimens associated with nodes were fixed in 10% of formalin and embedded in paraffin, and stained by haematoxylin and eosi n (HE). Two experienced gastrointestinal pathologists read all slides to evaluate the depth of primary tumour invasion and node involvement. If there were discrepancies between two pathologists, they would discuss it together to reach an agreement. Finally, the numbers of positive and negative node as well as their locations were recorded. Specimen analysis was performed in a standardised fashion with prospective documentation of all assessed parameters.

2.7. Statistics

All evaluated parameters were prospectively documented throughout the study period in a dedicated database. The clinical features were distributed by mean/standard deviation or percentage. The standard chi-square test was used to compare the difference between two groups. All tests were two sided; a p value of less than 0.05 was considered significant. All analyses were performed using the statistical package SPSS for Windows (release 11.5; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Study population

From January 1993 to November 2006, 2389 patients with thoracic oesophageal SCC had been treated with surgery in CHFMU. A total of 539 patients was excluded due to the preoperative chemotherapy or irradiation (231 cases), the number of nodes removed of <15 (233 cases) and the mixed histology of SCC and others (75 cases). The remained 1850 patients were eligible for further analysis. The patient population included 1351 males and 499 females with a median age of 55.0 years (range: 27–84 years). The oesophageal lesions were located in the upper thoracic region in 289 patients, the middle in 1381 and the lower in 180. The pathological stages were stage I in 86, stage IIa in 595, stage IIb in 78, stage III in 363 and stage IV in 728. Their clinical and pathological characteristics were shown in Table 2.

3.2. Frequencies of lymphatic spread

A total of 47 470 nodes had been removed from 1850 patients with a mean of 26 nodes (range: 15–71) per patient. The lymph node metastasis rate was 9.2% (4350/47470), and 58.4% (1081/1850) of patients suffered lymphatic metastases (Table 3). The frequencies of lymph node metastasis in the subgroups of node are listed in Table 4 (JSED) and Table 5 (Fig. 1). The cervical lymph node metastasis rate was 35.6%, with a higher frequency of 28.1% in right neck and 14.5% in...

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**Table 2**
The clinical and pathologic characteristics of 1850 patients of thoracic oesophageal squamous cell carcinoma.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Median age, years</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>55.0 (27–84)</td>
</tr>
<tr>
<td>II</td>
<td>55.0 (27–84)</td>
</tr>
<tr>
<td>III</td>
<td>595</td>
</tr>
<tr>
<td>IV</td>
<td>78</td>
</tr>
<tr>
<td>V</td>
<td>363</td>
</tr>
<tr>
<td>VI</td>
<td>728</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessel involvement</th>
<th>No</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1569</td>
<td>281</td>
<td></td>
</tr>
</tbody>
</table>
the left neck ($p < 0.05$). The node metastasis rates were 22.2%, 26.5%, 6.1% and 26.5%, respectively, for the upper, middle and lower mediastinal nodes as well as abdominal nodes in 1850 patients.

For entire group of 1850 patients, adjacent mediastinal node metastasis alone was only 5.5%, and more common were the multiple level or skip node spread, which accounted for 20.9% and 73.6% of patients with node metastases,

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For entire group of 1850 patients, adjacent mediastinal node metastasis alone was only 5.5%, and more common were the multiple level or skip node spread, which accounted for 20.9% and 73.6% of patients with node metastases,
respectively (Table 6). With regard to the direction of the lymphatic spread, there were much higher incidences of the upward metastasis (46.4%) and both upward and downward (33.2%), compared to downward (20.5%) (p = 0.000).

3.3. The pattern of lymphatic spread as a function of oesophageal SCC location

When patients were categorised based on the different locations of oesophageal lesion, that is, the upper, middle and lower oesophageal, the lymphatic metastasis frequencies were quite similar, with 56.7%, 58.4% and 61.8%, respectively, but the spreading pattern differed slightly (Table 5 and Fig. 1). For the upper oesophageal SCC, the most common node metastasis was in the cervical (49.5%), followed by the upper mediastinal (28.7%), middle mediastinal (11.4%), abdominal (8.0%) and lower mediastinal (1.4%). For the middle oesophageal SCC, the highest frequency of node spread was also in the cervical (35.0%), and similar rates were noted in the middle mediastinal (29.8%), abdominal (27.2%) and upper mediastinal (22.4%), but the least in the lower mediastinal (6.0%) node. For the lower oesophageal SCC, more node metastasis occurred in the abdominal (51.7%), followed by the middle mediastinal (25.6%), cervical (17.2%), lower mediastinal (13.9%) and upper mediastinal (10.0%) nodes.

As shown in Table 6, overall, adjacent node metastasis alone occurred in less than 10% in all of the upper, middle and lower oesophageal SCC, whereas multiple levels of node metastasis developed more often with frequencies of 40.2%, 17.8% and 14.5%, respectively. Moreover, much higher frequencies of skip metastases were noticed, with 49.4%, 77.3% and 82.7%, respectively, for the upper, middle and lower oesophageal SCC. Regarding the node metastasis direction in patients with multiple node levels or skip node metastases, for the upper oesophageal SCC, the predominant metastasis was the upward (76.9%), and both of the upward and downward occurred in 20.4% and the downward in 2.7% (Table 6). However, for the lower oesophageal SCC, 33.6% and 13.1%, both upwards and downwards, and the upwards, respectively, and for the middle, node spreading was upwards (45.2%), downwards (35.5%), or both up and down (19.3%).

3.4. The risk factors for lymphatic spread

The invariable analysis indicated that three clinical and histological parameters were found as independent risk factors (Table 7). First, the length of oesophageal lesion correlated with node metastasis, the incidences being 50.3%, 61.8% and 71.1%, respectively, for length of <5 cm, 5 cm to <8 cm and ≥8 cm (p < 0.000). The second was T stage, and

<table>
<thead>
<tr>
<th>Node level Total (1850 patients)</th>
<th>Upper oesophageal (289 patients)</th>
<th>Middle oesophageal (1381 patients)</th>
<th>Lower oesophageal (180 patients)</th>
<th>χ² value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of patients with lymphatic metastasis</td>
<td>58.4 (1081/1850)</td>
<td>56.7 (164/289)</td>
<td>58.4 (807/1381)</td>
<td>61.1 (110/180)</td>
<td>0.870</td>
</tr>
<tr>
<td>Lymphatic level with node metastasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjacent alonea</td>
<td>5.5 (59/1081)</td>
<td>10.4 (17/164)</td>
<td>4.8 (39/807)</td>
<td>2.7 (3/110)</td>
<td>8.737</td>
</tr>
<tr>
<td>Multiplea</td>
<td>20.9 (226/1081)</td>
<td>40.2 (66/164)</td>
<td>17.8 (144/807)</td>
<td>14.5 (16/110)</td>
<td>36.381</td>
</tr>
<tr>
<td>Skipa</td>
<td>73.6 (796/1081)</td>
<td>49.4 (81/164)</td>
<td>77.3 (624/807)</td>
<td>82.7 (91/110)</td>
<td>59.995</td>
</tr>
<tr>
<td>χ² value</td>
<td>1243.23</td>
<td>61.482</td>
<td>1084.851</td>
<td>184.609</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td></td>
</tr>
<tr>
<td>Spread directionb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Upwardc</td>
<td>46.4 (474/1022)</td>
<td>76.9 (113/147)</td>
<td>45.2 (347/768)</td>
<td>13.1 (14/107)</td>
<td>103.095</td>
</tr>
<tr>
<td>Downwardc</td>
<td>20.5 (209/1022)</td>
<td>2.7 (4/147)</td>
<td>19.3 (148/768)</td>
<td>53.3 (57/107)</td>
<td>99.910</td>
</tr>
<tr>
<td>Both upward and downwardd</td>
<td>33.2 (339/1022)</td>
<td>20.4 (30/147)</td>
<td>35.2 (273/768)</td>
<td>33.6 (36/107)</td>
<td>12.768</td>
</tr>
<tr>
<td>χ² value</td>
<td>154.623</td>
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</tr>
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</table>

a Adjacent alone: Metastasis occurred only in adjacent mediastinal nodes, which located in the same segment as oesophageal lesion; Multiple: Besides adjacent nodes, other nodes, including other level nodes in mediastinum, cervical or abdominal nodes were involved; Skip: Primary tumour did not continuously spread into the adjacent node, but skipped to far node levels, missing one or more than one node level.

b For 1022 patients with multiple level and skip node metastases.
c Upward: Node spreading was towards up to the cranial; Downward: Node metastases were downward to the caudal; Both upward and downward: lymphatic spread was toward to up and down.

d Node spreading was towards up or down.

* Denominator: the number of total patients; numerator: the number of patients with node metastasis.
as the T stage increased, higher node metastasis frequencies followed with 21.1%, 49.1%, 62.3% and 73.0%, respectively, in patients with T1 to T4 \( (p < 0.000) \). The third was the tumour cell differentiation, which showed the highest node metastasis in poor differentiation SCC (72.1%), the lowest in good differentiation SCC (41.4%), and the middle in between in moderate differentiation SCC (59.8%) \( (p < 0.000) \).

4. Discussion

Oesophageal carcinoma is one of the most common cancers in China, whereas it is not common in North America and European countries. There are differences in clinical and histological characteristics between the East and the West as well. In China, SCC accounts for 95% of oesophageal cancer and is located predominantly in thoracic oesophagus \[10\], but in the West there are higher incidences of oesophageal adenocarcinoma and are predominantly located in the gastric and oesophageal junction. Probably, there are differences in biological behaviour between adenocarcinoma and SCC, and so does the prevalence and pattern of lymphatic spread \[4,11\]. Therefore, the current study was designed to retrospectively investigate the characteristics of lymphatic spread in oesophageal carcinoma, focussing on SCC in thoracic oesophagus.

Lerut et al. \[12\] have shown lymph node metastasis to be a significant prognostic factor using the multivariate analysis, and Baba et al. \[13\] have emphasised the ratio of invaded to removed lymph nodes as an important independent prognostic factor. To diagnose lymphatic node metastasis in oesophageal cancer, the common diagnostic methods were CT \[14,15\], magnetic resonance imaging (MRI) \[16\], endoscopic ultrasonography (EUS) \[17,18,19\], F-fluorodeoxyglucose-positron emission tomography (F-FDG-PET) \[14,15\], which produced the diagnostic accuracy of 73—78%, 64%, 67.6—77.5% and 63—84%, respectively. However, there were still quite high false-positive or false-negative rates in the modern image diagnoses. It is a frequent phenomenon that enlarged nodes are not metastatic, but normal-sized nodes are. Therefore, to investigate the prevalence and pattern of lymphatic spread in oesophageal SCC, the modern image technology has its limitation.

Fortunately, the extended oesophagectomy with 3FL has continuously been carried out to treat operable thoracic oesophageal SCC in the CHFMU, which provided an opportunity to investigate the lymphatic spread of oesophageal SCC. From the current data, lymphatic metastasis in oesophageal SCC was quite often with a frequency of 58.4% for the entire group and 56.7%, 58.4% and 61.1%, respectively, for the upper, middle and lower thoracic oesophageal SCC. Adjacent mediastinal node metastasis alone accounted for only 5.5% in 1081 patients with node spread, whereas multiple level and skip node metastasis occurred much more often (20.9% and 73.6%, respectively). It indicated that thoracic oesophageal SCC was a carcinoma that easily metastasised through lymphatic vessels along the oesophageal axis to multiple level nodes or to the nodes distant from the primary lesion. With regard to the lymphatic spread direction, overall, the trend was upward (46.4% for the upward only and 33.2% for both up- and downward), but the downward accounted for 20.5% \( (p = 0.000) \).

However, the prevalence of lymphatic metastasis differed for the different locations of oesophageal SCC. For the upper thoracic oesophageal SCC, node spread was prone to metastasise upward, whereas it was downward for the lower one. While, for the middle thoracic oesophageal SCC, it could metastasise both up- and downward, but more node metastasis was upward. In terms of node metastasising mode, skip spreading occurred at much higher rate in the middle (77.3%) and lower (82.7%) oesophageal SCC than in the upper (49.4%) alone \( (p < 0.000) \). Another tendency drawing attention towards the upper oesophageal SCC was that the node involvement rates decreased in order from the highest in the cervical (49.5%) down to the lowest in the lower mediastinal (1.4%) and the abdominal (8.0%) nodes. In contrast, for the lower oesophageal SCC, the highest incidence of node metastasis was in the abdominal (51.7%) node, much higher than that in other node areas \( (p < 0.000) \).

Most of the findings from the current analysis were consistent with that reported by Ando et al. \[6\] and Akiyama et al. \[7\]. The prevalence of multiple level lymphatic metastasis and skip spreading in distant node levels demonstrated again that 3FL was necessary for oesophageal SCC to treat the disease. In addition, postoperative irradiation to cervical and supraclavicular areas would probably be the indication for oesophageal SCC after two-field lymphadenectomy. In curative irradiation for early stages of oesophageal SCC, it could also be the rationale to irradiate the lymphatic levels with high frequencies of node metastases. Thus, the data shown in the current study would be of clinical value in treating oesophageal SCC for surgical and radiation oncologists.

As regards the risk factor for lymphatic metastasis in oesophageal SCC, several publications in the literature report that the depth of tumour invasion \[19\], T stage \[11\], tumour cell differentiation \[17\] and lesion length \[20\] correlated to the lymphatic metastases. This study also elucidated the independent prognostic factors for the high risk of node metastasis, including long oesophageal lesion \( (p = 0.000) \), late T stage \( (p = 0.000) \) and poor differentiation of tumour cells \( (p = 0.000) \). Those unfavourable risk factors should be taken into account when the probability of node spreading was evaluated in the treatment of oesophageal SCC.

In summary, this study reported the frequencies of lymphatic metastasis in a large series of 1850 thoracic oesophageal SCC after extended oesophagectomy and 3FL, which showed that 58.4% of patients developed mediastinal, cervical and/or abdominal node metastases. The prevalence was: (1) lymphatic spread was prone upward in the upper oesophageal SCC, downward in the lower and both up- and downward in the middle ones, but in favour of the upward; (2) multiple level and skip node metastases are very often seen. The unfavourable factors for node spread were long oesophageal lesion, late T stage and poor differentiation of tumour cells.

References


