DETERMINING THE LYMPH NODE CLINICAL TARGET VOLUME OF UPPER ESOPHAGEAL CARCINOMA WITH COMPUTED TOMOGRAPHY

MINGHUAN LI1, YUHUI LIU2, BINGJIE FAN1 and JINMING YU1

1 Department of Radiation Oncology, Shandong Tumor Hospital and Institute, Key Laboratory of Radiation Oncology of Shandong Province, Jinan 250117, Shandong Province, China
2 Department of Radiology, Shandong Tumor Hospital and Institute, Jinan 250117, Shandong Province, China

Abstract - Radiation is an important modality for cervical and upper-thoracic esophageal squamous cell carcinoma (ESCC). Delineating the lymph node clinical target volume (CTVn) for EC remains a challenging task. The present paper retrospectively analyzes the distribution of affected lymph nodes of cervical and upper thoracic ESCC on CT images to provide a reference for determination of CTVn. The cases of untreated cervical or upper-thoracic ESCC patients with regional lymph node metastases at diagnosis were retrospectively analyzed. CT scans were done to assess the extent of circumferential involvement and the local-regional lymph node status. Based on the CT criteria (cervical, mediastinal and upper abdominal lymph nodes were considered to be positive for malignancy when they were larger than 8-12 mm in short-axis diameter according to different station respectively). Detailed lymph node stations were recorded for every case and the distribution information of loco-regional node metastasis for these patients was analyzed. A total of 256 patients were diagnosed with node metastasis and qualified for the study, including 206 men and 50 women (age range 37-85 years, median 60). This included 205 upper thoracic cases and 51 of cervical lesion. The length of the primary tumors ranged from 1.0 cm to 9.0 cm, median 4.5 cm. The size of the enlarged lymph nodes ranged from 0.8 to 5.0 cm median 1.4 cm, mean 1.61 cm. The number of involved stations ranged from 1 to 7 median 2. The lymph node stations, with an involved probability of 10% or more, included the upper and middle neck, supraclavicular and lower neck, upper paraesophageal and upper paratracheal area for cervical lesions, and the supraclavicular and lower neck, upper paraesophageal, upper paratracheal, lower paratracheal, aortopulmonary and subcarinal areas for upper thoracic EC, respectively. The mid-upper neck nodes were more likely to be involved in cervical EC than thoracic EC (X^2 test, p=0.000). Fewer cervical EC involved the station 7 nodes than upper thoracic EC(X^2 test, p=0.006), and the supraclavicular nodes were more often involved in cervical lesions than upper thoracic lesions (X^2 test, p=0.029). However, the abdominal nodes showed a similar possibility of involvement (X^2 test, p=0.546). Our data suggest that the periesophageal and supraclavicular stations are the predominant involved areas for cervical and upper EC cases. The neck and upper mediastinal nodal station (above the arcus aortae level) should be electively irradiated for cervical EC and the supraclavicular, upper mediastinal and subcarinal area (station 7) should be included for upper thoracic EC. This study provides complementary data for the CTVn delineation, especially for advanced stage ESCC.

Key words: Esophageal squamous cell carcinoma, node metastasis, CT, radiation, clinical target volume

INTRODUCTION

Esophageal cancer (EC) is the eighth most common cancer worldwide and the sixth most common cause of cancer-related mortality (Kamangar et al., 2004). Squamous-cell carcinoma accounts for 95% of all esophageal carcinomas in China (Koshy et al., 2004). Cervical and upper thoracic lesions account for about 15% of all EC. The special and complicated anatomy limits the application of surgery and there
are relatively few data about the lymph node dissection in this part of EC (Koshy et al., 2004).

Definitive radiotherapy (RT) and/or chemo-radiotherapy (CRT) are options for advanced esophageal patients, especially in the case of the upper esophagus. For radiation, the gross tumor volume should include the primary tumor and the involved regional lymph nodes. When delineating the clinical target volume (CTV) for esophageal cancer, a radiation oncologist should make sure that the volume treated encompasses the tumor and lymph nodes at risk. It is generally accepted that the relative risk of nodal metastasis at a specific nodal location is dependent on the site of origin of the primary tumor (tumor location), but there is an overlap. In the precise irradiation area, the nodal CTV should be determined and outlined. To date there is no detailed report on the CTV delineation of lymph nodes in EC (Radiation Therapy Oncology Group, 2009; Minsky et al., 2002; ICRU 62, 1999).

The nodal spread of esophageal tumors may be extensive at initial clinical presentation. Several modalities, such as computed tomography (CT), ultrasonography, endoscopic ultrasonography (EUS) and positron emission tomography (PET) have been employed for the diagnosis of lymph node metastasis in esophageal cancer (Rausei et al., 2006; Keswani et al., 2009). CT is commonly used to guide subsequent treatment in China.

The present study observed the distribution of metastatic lymph nodes in CT images for newly diagnosed patients of cervical and upper thoracic EC in advanced stage. It aimed at providing a map of lymph node metastases, which may be helpful for determining the CTV of lymph node for radiation in upper EC.

**MATERIALS AND METHODS**

**Patients**

Between June 1, 2005 and April 1, 2011 CT imaging data in the CT center of the Shandong Tumor Hospi-

tal of China was reviewed for 3493 cases of esophageal lesions. For each case, the lesion was assessed and characterized by barium swallow, endoscopy, CT scan, and some of them by PET-CT and EUS. Barium swallow and endoscopy were performed to determine the presence, location and length of the esophageal lesions. Biopsy or brushing was performed to obtain the histological or cytological diagnosis of EC. CT was done to assess the extent of circumferential involvement and the local-regional lymph node status.

We enrolled those patients whose CT indicated node involvement, but who had never received prior treatment. Patients were also excluded if they had any other malignant tumor history. Patients suffering from active lung infections or with a lung tuberculous history were also excluded.

**CT imaging**

All the patients received a dedicated chest/abdominal CT with IV and/or oral contrast, and, if necessary, a neck CT to assess the extent of circumferential involvement and the local-regional lymph node status for every case. Five mm-thick slices from the chest and abdomen and 3 mm in the neck area were used for lymph node staging.

**Diagnosis of EC and involved lymph nodes**

The cervical esophagus begins at the level of the lower margin of the cricoid cartilage and ends at the thoracic inlet. The thoracic esophagus extends from the thoracic inlet to the gastroesophageal junction and is divided into three regions. The upper thoracic portion extends from the thoracic inlet (at the level of the suprasternal notch) to the upper border of azygos vein. On CT scan images, the anatomic marks for different sections are those planes through the upper border of the suprasternal notch, azygos vein and left lower pulmonary vein, respectively. Endoscopy, barium swallow and CT were performed to determine the location and length. All of these parameters were considered to make a diagnosis.
The primary criterion for node metastasis is the size. However, the size and shape of normal lymph nodes vary according to their different locations in the body, and therefore different criteria are used to characterize a node as being abnormally enlarged. Other criteria, including the nodal enhancement pattern and the presence of extranodal tumor extension, are used to help assess the metastatic status. Lymph nodes were classified into the following groups according to a modified version of the lymph node mapping system for esophageal cancer proposed by RTOG (Radiation Therapy Oncology Group, 2009; Casson et al., 1994). We defined the group of 16 paraesophageal nodes, 17 left gastric artery nodes, 18 common hepatic artery nodes, 19 splenic artery nodes and 20 celiac nodes as the abdomen group (Group A) for statistical analysis.

Radiologists interpreted the CT images and recorded the presence, length and location of primary tumors. Cervical, mediastinal, and upper abdominal lymph nodes were considered to be positive for malignancy when they were larger than 8-12 mm (short-axis diameter). Only lesions localized above the azygos vein or no more than 25 cm from the incisors was viewed as upper EC and included in this study. For the long lesions involving both cervical and upper thoracic EC, the lesion center determined the location.

Statistical analysis

Statistical analysis was performed using the SPSS software system (version 13.0; SPSS Inc.) for MS Windows. The descriptive analysis was expressed in terms of frequency, mean and standard deviation. The $X^2$ test was performed to compare the frequency of different groups.

RESULTS

The length of the primary tumors ranged from 1.0 cm to 9.0 cm, median 4.5 cm. There were 97 cervical lesions and 371 upper thoracic lesions in this population. Among the 97 cervical EC cases, 10 lesions extended to the upper thoracic esophagus, 16 lesions involved the hypopharynx, 4 lesions involved both and 67 lesions were limited to the cervical esophagus. For the 371 upper thoracic EC cases, 17 of them extended to the cervical esophagus, 67 lesions extended to the mid-thoracic area and below the azygos vein level and 287 lesions were limited to the upper thoracic esophagus. A total of 256 (54.7%) patients had nodal involvement (including 35 cases with distant metastasis) at diagnosis and qualified for the study: this included 206 men and 50 women (age range 37-85 years, median 60). It included 51 cervical cases and 205 upper thoracic cases. The regional node metastatic rate was 52.58% and 55.26% for cervical and upper thoracic EC, respectively. The size of the enlarged lymph nodes ranged from 0.8 to 5.0 cm median 1.4 cm, mean 1.61 cm. The total number of involved stations was 107 for cervical EC and 491 for upper thoracic EC. The number of involved stations for each case ranged from 1 to 7, median 2. The detailed data are listed in Tables 1 and 2.

For upper EC, the paraesophageal and supraclavicular stations were the most common sites of involvement. Abdominal node metastasis is rare in our records. Only 2 out of 97 with cervical lesions and 12 out of 371 with upper thoracic EC showed enlarged abdominal nodes. Solitary metastatic nodal stations were as follows: 55 cases were paraesophageal, 21 supraclavicular, 5 upper paratracheal, 2 upper-middle neck, and 1 abdominal.

DISCUSSION

Currently, radiotherapy has a well-defined role in EC management. Together with surgery and chemotherapy, it represents the main treatment modality.
However, recent technological advances in radiation treatment (e.g. three dimensional conformal radiotherapy, intensity-modulated radiotherapy, image guided-radiotherapy, etc.) have progressively changed the practice in esophageal cancer. However, for the lymph node target volume of EC, there is no agreed and detailed guideline. It was said that the relative risk of nodal metastases at a specific nodal location depended on the site of the primary tumor. Some studies reported that the T stage, length of tumor and histological differentiation influence the pattern of lymph node metastases in thoracic ESCC (Huang et al., 2010). These factors should be considered comprehensively to design the CTV for RT of thoracic ESCC.

Computed tomography (CT) is the primary modality for imaging malignancy in the chest. It is used in staging the disease, planning treatment, evaluating response and estimating prognosis. In our hospital, CT is recommended for initial imaging following confirmation of malignancy at pathology analysis, primarily to rule out unresectable or distant metastatic disease.

### Table 1. Patient data

<table>
<thead>
<tr>
<th></th>
<th>Cervical</th>
<th>Upper thoracic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases</td>
<td>97</td>
<td>371</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>81</td>
<td>282</td>
</tr>
<tr>
<td>Female</td>
<td>16</td>
<td>89</td>
</tr>
<tr>
<td>Age (medium) years</td>
<td>58 (37-85)</td>
<td>60 (37-85)</td>
</tr>
<tr>
<td>Length cm</td>
<td>4 (2-5.5)</td>
<td>5 (1-9)</td>
</tr>
<tr>
<td>N0M0</td>
<td>46</td>
<td>166</td>
</tr>
<tr>
<td>N+, M0</td>
<td>47</td>
<td>174</td>
</tr>
<tr>
<td>N+, M1</td>
<td>4</td>
<td>31</td>
</tr>
</tbody>
</table>

### Table 2. Distribution of involved Station of lymph node

<table>
<thead>
<tr>
<th>Node group</th>
<th>Node station</th>
<th>Limits of short-axis (mm)</th>
<th>Cervical EC (n; %)</th>
<th>Upper thoracic EC (n; %)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper and middle neck</td>
<td>CX</td>
<td>8</td>
<td>15 (15.46%)</td>
<td>8 (2.16%)</td>
<td>0.000</td>
</tr>
<tr>
<td>Supraclavicular and lower neck</td>
<td>1</td>
<td>8</td>
<td>30 (30.93%)</td>
<td>76 (20.49%)</td>
<td>0.029</td>
</tr>
<tr>
<td>Upper paraesophageal</td>
<td>8</td>
<td>23 (23.71%)</td>
<td>145 (39.08%)</td>
<td>0.005</td>
<td></td>
</tr>
<tr>
<td>Upper paratracheal</td>
<td>2R/L</td>
<td>10</td>
<td>11 (11.34%)</td>
<td>51 (13.75%)</td>
<td>0.534</td>
</tr>
<tr>
<td>Lower paratracheal</td>
<td>4R/L</td>
<td>10</td>
<td>8 (8.25%)</td>
<td>45 (12.13%)</td>
<td>0.283</td>
</tr>
<tr>
<td>Aortopulmonary</td>
<td>5</td>
<td>10</td>
<td>8 (8.25%)</td>
<td>65 (17.52%)</td>
<td>0.025</td>
</tr>
<tr>
<td>Anterior mediastinal</td>
<td>6</td>
<td>10</td>
<td>7 (7.22%)</td>
<td>21 (5.66%)</td>
<td>0.565</td>
</tr>
<tr>
<td>Subcarinal</td>
<td>7</td>
<td>12</td>
<td>3 (3.09%)</td>
<td>48 (12.94%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Middle-lower paraesophageal</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>10 (2.69%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary ligament nodes</td>
<td>9</td>
<td>10</td>
<td>0</td>
<td>2 (0.54%)</td>
<td></td>
</tr>
<tr>
<td>Tracheobronchial</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>8 (2.16%)</td>
<td></td>
</tr>
<tr>
<td>Diaphragmatic</td>
<td>15</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>16,17,18,19,20</td>
<td>10</td>
<td>2 (2.06%)</td>
<td>12 (3.23%)</td>
<td>0.546</td>
</tr>
</tbody>
</table>
The majority of CT studies record the short-axis diameter of a lymph node, as this is the most reproducible measurement (Huang et al., 2010). In our CT center, for esophageal cancer images, cervical and thoracic lymph nodes with a diameter greater than 10mm in the short axis are generally considered abnormal. On the abdominal CT scan, a 10 mm cut-off of short axis nodal diameter is indicative of abdominal, paracardiac and gastrohepatic ligament areas.

Microscopic disease in normal sized nodes and lymph node enlargement caused by benign conditions limit the CT accuracy of nodal involvement in esophageal carcinoma to 39% to 85% (Glazer et al., 1985). According to a meta-analysis, the sensitivity and specificity of CT for regional lymph node metastases were 0.50 (95% CI 0.41-0.60) and 0.83 (95% CI 0.77-0.89) in thoracic tumor, respectively (van Vliet et al., 2008). But most of these data came from resectable esophageal cancer (with a relatively early stage or occult metastasis). Most false-negative CT scans have involved lymph nodes with only microscopic involvement. De Langen and colleagues reported that the prevalence of metastasis strongly increases above the 15 mm short-axis threshold rather than 10 mm at CT scanning for mediastinal lymph nodes (de Langen et al., 2006). In our present study, the size of the enlarged lymph nodes ranged from 0.8 to 5.0 cm median 1.4 cm, mean 1.61 cm, and the number of involved stations ranged from 1 to 7 median 2. For those advanced cases, enlarged lymph nodes are present at multiple stations and/or grouped in one station. It is reasonable that enlarged nodes represent metastasis in this kind of environment. In other words, the CT accuracy should be higher in this present study.

In our study, for upper thoracic EC, the periesophageal nodes were the most involved stations and the periesophageal stations was the only involved site in 55 cases. The involved rate was higher than in the cervical area (39.08% vs 23.71%). This is different from those reported resectable cases in which the cervical area has more possibility of being involved. Chen et al. (2009) reported that for the upper esophageal 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%) nodes. In Li’s (Li et al., 2007) study, the proportions of lymph node metastases were 41.6%, 19.44%, and 8.3% in neck, thoracic mediastinum and abdominal cavity, respectively, for patients with upper thoracic esophageal carcinomas. There are some interpretations for our results. The anatomical studies of the esophagus showed that the lymphatic routes to periesophageal nodes originate from the muscle layer (Motoyama et al., 2009; Tachimori et al., 2011; Kuge et al., 2003). In our cases, most of them suffered a more than mucosal infiltration with advanced T stage, and the afferents from the esophagus to the regional node (periesophageal) usually seemed to be more responsible because of their intermuscular origins. The second possibility may be the size criteria of 8 mm as the involved node for the supraclavicular area. In some institutions, supraclavicular lymph nodes with a short axis greater than 5 mm are considered to be pathological (Fultz et al., 2002).

The supraclavicular station is the most common site for cervical EC and the second most involved area for upper thoracic EC. Most supraclavicular involvements are accompanied by the involvement of mediastinal nodes but there are still a few cases of solitary metastasis in supraclavicular area. Esophageal cancer is notorious for its ability to spread intramurally to locations distant from the primary tumor. As mentioned above, there are different lymphatic draining routes according to lesion depth. Due to the extended longitudinal but restricted transverse territory of the direct drainage system without a nodal relay, when superficial esophageal carcinoma is found, the cervical nodes may suffer from a greater possibility of metastasis than the periesophageal nodes.

The lower mediastinal area is less likely to be involved in the population of upper EC. Based on CT diagnosis, there were few abdominal node metastases in cervical and upper thoracic EC, even in the advanced stage. These data are similar to those resectable cases in our cancer center, where the rates of lymph node metastases in patients with upper
Thoracic tumors was 5.6% (3/54) for the abdominal area (de Langen et al., 2006).

The node spread of upper thoracic EC showed a relatively upstream pattern in the advanced stage. Based on our study, the selective station should include supraclavicular, paraesophageal, paratracheal and aortopulmonary nodes, and subcarinal areas. Our data suggest that in the supraclavicular station, the upper mediastinal and subcarinal levels are the predominant areas involved in upper thoracic EC.

If a lymph node station has a probability of 10% or more of being involved, it should be included in the CTV. Based on our observations, the specific regional nodes include the supraclavicular, upper and lower cervical and periesophageal nodes for the cervical EC. Our data show a bidirectional pattern including cervical and upper thoracic lymph node stations, but few in the subcarinal area and lower mediastinal stations. All of this information suggests that the selective node station should include the cervical and upper mediastinal nodes (above arcus aortae level) for cervical EC.

In conclusion, our data suggest that the periesophageal station of upper mediastinal is the predominant area involved in cervical and upper EC cases. The neck and upper mediastinal nodal stations (above arcus aortae level) should be electively irradiated for cervical EC and the supraclavicular, upper mediastinal (except anterior mediastinal nodes, station 6) and subcarinal area (station 7) should be included as clinical nodal target volume for upper thoracic EC. This study provides complementary data for the CTV delineation of node irradiation, especially for advanced stage ESCC.

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