Determination of the Irradiation Field for Clinical T1-T3N0M0 Thoracic/Abdominal Esophageal Cancer Based on the Postoperative Pathological Results

Tatsuya Nakamura, Syunzo Hatooka, Takeshi Kodaira, Hiroyuki Tachibana, Natsuo Tomita, Rie Nakahara, Haruo Inokuchi, Nobutaka Mizoguchi, Akinori Takada, Masayuki Shinoda and Nobukazu Fuwa

Department of Radiation Oncology, Southern Tohoku Proton Therapy Center, Fukushima, Japan

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Objective: In patients with thoracic/abdominal esophageal cancer with no clinical evidence of lymph node metastasis, there is no consensus about whether the irradiation field should include regional lymph nodes. In this study, the extent of the irradiation field for clinical stage T1-3N0M0 esophageal cancer was determined based on the postoperative pathological results.

Methods: From July 1989 to June 2008, 103 patients diagnosed with clinical stage T1-3N0M0 thoracic/abdominal esophageal cancer underwent standard esophagectomy and regional lymph node dissection at the Aichi Cancer Center Hospital. Of these 103 patients, the pathological results of the resected specimens could be confirmed in 95 (92%) patients. The pathological lymphatic spread was reviewed retrospectively, and the extent of the irradiation field was determined based on the postoperative pathological results.

Results: Of 95 patients with clinical stage T1-3N0M0 esophageal cancer, 40 (42.1%) had pathological lymph node metastases, and the frequency of nodal metastases was studied by tumor location. The rates of lymph node metastases for the upper, middle, lower and abdominal esophagus were 37.5%, 32.5%, 46% and 70%, respectively.

Conclusions: Pathological lymph nodes metastases are often seen after operation in clinical stage T1-3N0M0 esophageal cancer. In the present study, the optimal lymph nodes to be included in the irradiation field were determined according to the primary site in the esophagus.

Key words: radiation therapy — surgery — pathology

INTRODUCTION

Esophageal cancer is an increasingly common malignancy. This neoplasm is devastating because of its aggressive clinical course and high mortality rate. The long-term survival rate is not high due to the high incidence of advanced and/or metastatic disease at the time of diagnosis. Over two decades, several treatment modalities have been developed to improve the survival of patients with esophageal cancer. Among these, surgical resection remains the preferred choice. It currently provides the best palliation for dysphagia and local control, as well as the best chance for cure when compared with other therapeutic options. However, as definitive chemoradiation has been gradually improving, the boundaries of treatment strategies have become blurred in patients with resectable locoregional esophageal cancer (1).

Compared with other digestive cancers, widespread lymph metastases occur easily in esophageal cancer. While lymph nodes metastases are not seen clinically, pathological lymph nodes metastases are often seen after operation (2,3). The treatment of thoracic esophageal cancer is endoscopic mucosal resection for mucosal cancer, while in cases with invasion beyond the submucosa, surgery is standard treatment, because the rate of lymph nodes metastases is high (2,4,5). Some articles have reported the treatment results of chemoradiation for esophageal cancer (6–8). However, in radiotherapy, there is no clear consensus about the clinical target volume (CTV), in particular, about whether regional...
lymph nodes should be included in cases in which no lymph nodes metastases of thoracic/abdominal esophageal cancer are evident clinically. Since three-field lymph nodes dissection is generally performed during surgery, there is reason to believe that, in radiotherapy, the three-field lymph nodes area should be included in the CTV as a prophylactic irradiation field for patients with no clinical evidence of lymph nodes metastases. However, the irradiation field based on the three-field lymph nodes area is too large, since it causes severe late toxicities, such as heart failure, pericardial effusion, pleural effusion and radiation pneumonitis (9).

In the present study, pathological lymphatic spread was reviewed retrospectively after surgery in cases with clinical stage T1-3N0M0 thoracic/abdominal esophageal cancer, and the irradiation field for such cases was considered.

PATIENTS AND METHODS

From July 1989 to June 2008, 103 patients diagnosed as having thoracic or abdominal esophageal cancer with clinical stage T1-3N0M0 referring to the 1997 UICC-TNM staging system underwent standard esophagectomy and regional lymph nodes dissection at the Aichi Cancer Center Hospital. Of these 103 patients, the pathological results of the resected specimen could be confirmed in 95 (92%) patients. The ages of the 73 males and 22 females ranged from 36 to 81 years, with a median of 64 years. The patients’ characteristics are shown in Table 1.

The Japanese Society for Esophageal Disease divides the esophagus into five segments (Fig. 1). The cervical esophagus is defined as extending from the lower border of the cricoid cartilage to the thoracic inlet (the suprasternal notch), which is approximately 18 cm from the upper incisor teeth. The intrathoracic esophagus is divided into three regions: upper thoracic (Ut), middle thoracic (Mt) and lower thoracic (Lt). The Ut portion extends from the thoracic inlet to the level of the tracheal bifurcation, which is approximately 24 cm from the upper incisor teeth. The Mt portion is the proximal half of the portion of esophagus between the tracheal bifurcation and the esophagogastric junction. Its inferior margin is approximately 32 cm from the upper incisor teeth. The distal half of the portion of the esophagus between the tracheal bifurcation and the esophagogastric junction. Its inferior margin is approximately 32 cm from the upper incisor teeth. The distal half of the portion of the esophagus between the tracheal bifurcation and the esophagogastric junction is further divided into two parts: the proximal part, which is in the thorax and is called Lt, and the distal part from the esophageal hiatus to the esophagogastric junction, which is called the abdominal esophagus (Ae).

If the primary tumor extends over two portions of the esophagus, the site is determined by the location of the main lesion.

Overall, 8 patients had Ut lesions, 40 had Mt lesions, 37 had Lt lesions and 10 had Ae lesions. Forty-three (45%) had clinical T1 tumors, 14 (15%) had clinical T2 tumors and 38 (40%) had clinical T3 tumors. On pathology, 40 patients (42%) had lymph nodes metastases despite have been staged as clinical N0.

All patients underwent preoperative evaluation involving barium swallow examination, endoscopy with biopsy and computed tomography (CT) scans from the neck to the abdomen. Evidence of clinical lymph nodes metastases was checked on 10-mm-thick enhanced CT scans from the level of the carotid bifurcation to the bottom of the liver. Contrast enhancement was applied by drip infusion of 100–120 ml of nonionic iodinated contrast material, taking 90 s. Images were obtained with a window width of 300–400 Hounsfield Units (HU) and with a center level of 50–95 HU for favorable soft tissue contrast in the neck and mediastinum. From 2004, positron emission tomography (PET) is also performed to check metastases.

The locations of the lymph nodes were classified according to the guidelines for clinical and pathologic studies on carcinoma of the esophagus formulated by the Japanese Esophageal Society (2007, 10th Edition) (Fig. 2).

The criterion for positive clinical lymph node metastasis was the presence of a nodule recognized as a lymph node on CT, regardless of its size.
The definitions of the lymph nodes sites are presented in Fig. 2. The lymph nodes at Sites 101 and 104 are located in the neck, those at Sites 105, 106, 107, 108, 109, 110 and 111 are located in the mediastinum, and those at Sites 1, 2, 3, 7 and 9 are located in the abdomen. The clinical stage was diagnosed at a conference involving thoracic surgeons, gastroenterologists, medical oncologists, diagnostic radiologists and radiation oncologists. None of the patients had evidence of lymph node or distant organ metastases on preoperative evaluation. Postoperative staging according to the 1997 UICC-TNM classification was based on pathological examination of the resected specimens, including the dissected lymph nodes.

RESULTS

The results of the pathological examination and the locations of lymph nodes metastases are shown in Table 2. Of the 95 patients, 40 (42.1%) had pathological lymph nodes metastases. The frequency of nodal metastases was 3 patients (37.5%) in 8 cases of Ut lesions, 13 (32.5%) patients in 40 cases of Mt lesions, 17 (46%) patients in cases of 37 Lt lesions and 7 (70%) patients in cases of 10 Ae lesions. On histology, 81 (85%) had squamous cell carcinoma, 8 (9%) had adenocarcinoma, 3 (3%) had carcinosarcoma, 2 (2%) had small cell carcinoma and 1 (1%) had adenosquamous carcinoma (Table 1).

In Ut lesions, Site 101, 105 and 109 lymph nodes were seen 22%, Site 104 lymph node metastasis was seen 11% pathologically. In Mt lesions, Site 101, 106 rec, 107 and 3 lymph nodes metastases were seen over 10%, Site 108, 109, 110, and 2 lymph nodes metastases were seen over 6% pathologically. In Lt lesions, Site 1, 2 and 7 lymph nodes metastases were seen over 12%, Site 110 and 9 lymph nodes metastases were seen over 9% pathologically. In Ae lesions, Site 1, 2 and 3 lymph nodes metastases were seen over 27% pathologically.

DISCUSSION

Esophageal carcinoma is not a single entity, and the disease does not have a uniformly poor prognosis. As with any other malignancy, the stage of esophageal carcinoma has both prognostic and therapeutic importance (10–12). The anatomic extent of the tumor is the most accurate predictor of survival (12). This can be assessed using the TNM classification system by evaluation of the degree of tumor invasion (T), the status of regional lymph nodes (N) and the presence of distant metastatic sites (M). In particular, lymph node staging is an important independent prognostic indicator (13). In addition to the lymph node classification, which indicates only whether the patient does (N1) or does not (N0) have regional lymph node involvement, the number and location of involved lymph nodes also affect the prognosis (14).

Staging of lymph nodes with CT imaging is very important in treatment planning for patients with esophageal cancer, and it has a great effect on the surgery and/or radiotherapy. CT can be used to assess not only primary esophageal tumors but also all regional lymph nodes sites. The CT findings have a major role in radiotherapy treatment planning.
for esophageal cancer (15, 16). In radiotherapy treatment planning, it is most important to include the primary tumor and all metastatic lymph nodes within the radiation fields of the definitive dose, and the CT findings can be readily translated into irradiation fields.

There have been several studies using CT and/or MR imaging for the detection of mediastinal lymph nodes metastases from esophageal cancer (15, 17–21). In most of these studies, the size criterion of a diameter of 10 mm was used to identify malignant lymph nodes; this is the most common diagnostic criterion in patients with bronchogenic carcinoma (22, 23). However, it is unclear whether this widely used size criterion for malignant lymph nodes is appropriate for patients with esophageal cancer. In recent years, the role and potential value of PET scanning in certain tumors have widely been investigated (24–28). Markedly increased 18-F-fluorodeoxyglucose (FDG) uptake in esophageal cancer has been documented in several studies (29–32), and they have reported that PET using FDG shows greater sensitivity in the diagnosis of involved regional lymph nodes than CT. This suggests that PET may have a role in evaluating esophageal cancer stage (29–31). Most of these studies assessed the degree of accuracy with which PET detected metastases in lymph nodes as a measure of lymph node staging. Neither CT nor PET can specifically define enlarged nodes that harbor cancer. Therefore, in the present study, any lymph node detected on CT and/or PET was considered positive for metastasis. From 2004, multi-detector row CT was begun to be used in our hospital. At the same time, we use PET together with 10 mm slice CT, and if necessary we reconstructed thin slices focusing mediastinum to check in detail. This may be a stricter criterion than in previous reports (15, 17–19, 21, 33, 34). Compared with other digestive cancers, lymph nodes metastases in esophageal cancer often show skip metastases. There has been controversy regarding how much of the lymph area to include in the irradiation field in cases of esophageal cancer. It would be better to include all of the lymph area in the irradiation field, but this makes the field so large that it may also increase the toxicity.

The results of the present study show the correlation between adjacent regional lymph nodes involvement and tumor location. However, the involvement of distal regional nodes, regardless of tumor location, was unpredictable. In the present study, the lymph nodes that should be included in the irradiation area for different tumor locations were examined. The recommendations for which lymph nodes to include in the irradiation field of clinical stage T1-3N0M0 esophageal cancer are shown in Table 3. Over 9% frequency of lymph nodes metastases are pointed out. When the primary lesion is located in the upper esophagus, at least the 101 and 104 lymph nodes should be included as the superior border of the field, and the 109 lymph nodes should also be included as the inferior border of the field. When the primary lesion is located in the middle esophagus, at least the 101 and 106 rec lymph nodes should be included as the superior border of the field, and the 3 lymph nodes should be included as the inferior border of the field. When the primary lesion is located in the lower esophagus, at least the 110 lymph nodes should be included as the superior border...
of the field, and the 3 lymph nodes should be included as the inferior border of the field. When the primary lesion is located in the Ae, at least the 2 lymph nodes should be included as the superior border of the field and the 3 lymph nodes should be included as the inferior border of the field. Other lymph nodes may be included in the irradiation field automatically because they are located between the superior and inferior borders indicated, but it is necessary to check that they are included in the field (Fig. 2).

For Mt tumors, the irradiation field is too large; it is attributable to increased toxicities, for example, radiation pneumonitis. So, it is necessary to combine chemotherapy and radiation. If chemotherapy is combined with radiation, these fields could be used in prophylactic irradiation only. These fields are considered if over 90% probability of pathological lymph nodes metastases could be covered. But it is also important to make adjustment for irradiation fields flexibly in the treatment of elderly patients or patients with respiratory problems.

It has been found that approximately half of the surgical specimens from patients with submucosal cancer are positive for lymph node metastasis (35–37). Irradiation around the primary lesions may have been effective in eradicating subclinical lymph node metastasis, or the cancer cells observed in the surgical specimens may not have had the proliferative capacity to produce macroscopic metastasis. However, the most frequent sites of metastasis were the lymph nodes outside the irradiation fields (7).

Therefore, the usefulness of comparing extensive field radiotherapy and involved field radiotherapy with local irradiation to the primary lesion only for clinical T1-3N0M0 thoracic/abdominal esophageal cancer needs to be investigated in clinical trials (7,38).

**CONCLUSION**

Pathological lymph nodes metastases are often seen after operation in cases of esophageal cancer diagnosed as clinical stage T1-3N0M0. In the present study, the lymph nodes that should be included in the irradiation field were determined according to the primary site in the esophagus.

### Conflict of interest statement

None declared.

### References
