

# Pattern of Locoregional Recurrence After Radical Surgery in Patients With Esophageal Squamous Cell Carcinoma and The Design of Target Volume of Postoperative Prophylactic Radiotherapy

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## Research

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# Abstract

**Objective** The study was undertaken to evaluate preferred sites for locoregional recurrence after radical surgery for patients with esophageal squamous cell carcinoma (ESCC) and to confirm the target volume of postoperative prophylactic radiotherapy.

**Methods** 139 patients with locoregional recurrent ESCC after radical esophagectomy without postoperative radiotherapy were registered in this study. The sites of locoregional recurrence for these patients were collected and influence factors of locoregional recurrence were analyzed.

**Results** The 1, 2, and 3-year progression-free survival rates were 48.2%, 18.0% and 8.6%, respectively. Mediastinum lymph node (LN) recurrence (74.2%) was the most frequent site of recurrence, following the anastomotic site (28.1%), supraclavicular LN (19.4%) and abdominal LN (15.1%) ( $P=0.000$ ). The upper mediastinum (72.7%) was one of the most common recurrence occurred in mediastinal LN. Compared with upper and middle segment of ESCC, lower segment had the highest recurrence rate of upper abdominal LN ( $P=0.001$ ). The predictive factors of anastomotic recurrence were the stage of pT3 or pT4, presence of nerve or vessel invasion, removed LN NO.  $\leq 17$ , presence of invasion or adhesion and without postoperative adjuvant chemotherapy. In addition, the risk factors of abdominal LN recurrence in patients with middle segment ESCC included the stage of pT3 or pT4, smoking history and without postoperative adjuvant chemotherapy.

**Conclusion** For thoracic ESCC, supraclavicular, upper mediastinum, subcarinal LNs and anastomosis should be incorporated within target volume of postoperative prophylactic radiotherapy. Regarding to lower segment ESCC, target volume should include upper abdominal LNs. And it need cautious evaluated about upper abdominal LNs when presence of clinicopathologic factor in middle segment ESCC.

## Introduction

Surgical resection is the primary therapy for thoracic esophageal cancers. However, the rich lymphatic capillary network in the esophageal mucosa and submucosa facilitate locoregional recurrences after surgery. It has been reported that 25.6–41.8% of patients develop locoregional recurrence [1, 2, 3]. The suppression of postoperative recurrences will ameliorate the survival of patients with ESCC after curative resection. Thus, it is of clinical important to understand the patterns and prognostic factors of recurrence after esophagectomy. Rates and patterns of postoperation locoregional recurrence have been described in previous systematic studies [2, 3, 4]. Nevertheless, to our knowledge, in the most of reports, the classification standard of mediastinal LN sites in lung cancer was common used in patients with ESCC [2, 5]. For esophageal cancer, it has extensive difference of the characteristics of the LN recurrence from lung cancer. In this study, we adopted the LN sites classification standard of ESCC according to the Japan Esophageal Society which showed more elaborate and highlighted LN metastatic features [6]. Several reports had demonstrated that postoperative prophylactic radiotherapy with chemotherapy could improve prognosis for patients with stage IIb-III ESCC after radical esophagectomy [7, 8]. Thus,

knowledge of locoregional recurrence sites provides useful information on the effectiveness of treatment and may allow better planning of therapeutic intervention in an effort to improve outcomes. In this study, we retrospectively analyzed the frequent position based on classification standard according to the handbook of the Japan Esophageal Society in patients with postoperative locoregional recurrence ESCC and tried to confirm the target volume of postoperative prophylactic radiotherapy.

## Methods

From January 2015 to January 2019, 139 patients with locoregional recurrent ESCC after radical esophagectomy without postoperative radiotherapy were registered in this study. Tumor stage classified according to the eighth edition of the TNM staging system of the American Joint Committee on Cancer for esophageal cancer [9]. The study protocol was approved by independent ethics committees in Jinling Hospital and each patient signed a written informed consent.

The classification standard of mediastinal LN sites were based the handbook of Japan Esophageal Society <sup>6</sup> and the radiographic anatomical delineation according to the detailed explain by Huang et al. [10]: No.105, upper thoracic paraesophageal lymph nodes; No.106rec, recurrent nerve lymph nodes (106recR/L); No.106, pre pretracheal lymph nodes (106pre); No.106tb, tracheobronchial lymph nodes (106tbR/L); No.107, subcarinal lymph nodes; No.108, middle thoracic paraesophageal lymph nodes; No.109, main bronchus lymph nodes (109R/L); No.110, lower thoracic paraesophageal lymph nodes; No.111, supradiaphragmatic lymph nodes; No.112ao, thoracic paraaortic lymph nodes (112ao); No.112pul, pulmonary ligament lymph nodes (112pulR/L); No.113, ligamentum arteriosum lymph nodes; No.114, anterior mediastinal lymph nodes; No. 101R, 101L, 105, 106recR, 106recL, 106pre, 106tbR, 106tbL, 113 and 114 constitute the upper mediastinum and No. 107 and 108 were located in the middle mediastinum while No.112 was located in the lower mediastinum.

The location of locoregional recurrence includes the anastomotic site, tumor bed or LN drainage area (containing the supraclavicular, mediastinum, and upper abdominal LN) [11]. During examination periods, the first site recurrence was noted, and any additional recurrence found within 1 month was considered to have occurred simultaneously. The diagnosis of lymph node recurrence was based on PET-CT or CT. On the PET-CT images, a maximum standardized uptake value (SUVmax) of tumor tissue  $\geq 2.6$  was regarded as recurrence [12]. On the CT images, the positive LN was defined as the short axis  $\geq 1.0$  cm, with circular enhancement or the presence of necrosis [13]. The location of recurrent LN was based on the position of the central point on the CT images (confluent LNs were counted as one). Anastomotic recurrence was diagnosed by endoscopy or PET-CT.

Surgery complications include post-operative anastomotic leakage, active bleeding, chylothorax, atelectasis and pneumonia. Invaded or adhesion adjacent structures of primary tumor included the aorta, main bronchus or pleura mediastinal.

Disease-free survival (DFS) was defined as the time between the diagnosis of original cancer of esophagus and the diagnosis of locoregional recurrence. SPSS 24.0 statistical software was used for data analysis. A chisquare test was used for statistical data comparison. The Kaplan-Meier method was adopted to calculate the survival rate. *P*-values lower than 0.05 were considered statistically significant.

## Results

### Patient characteristics

The clinical characteristics of the enrolled patients are listed in Table 1. 139 presented with locoregional recurrence at 0.3-95.1 months after radical esophagectomy, with a median of 11.6 months. More than half (72/139, 51.8%) recurrences happened within 1 year after operation and within 2 years in 82% (114/139) patients. The number of patients with upper, middle, and lower segment ESCC was 20, 71, and 48, respectively. The diagnoses of the original esophageal cancer were all identified pathologically after radical esophagectomy; the number of patients with poorly, moderately and well differentiated was 52, 77, and 10, respectively. The median number of removed lymph nodes was 17 (range, 2-52) and the median number of positive nodes were 1(range, 0-16). The median length of original esophageal lesions was 3.6 cm (range 0.6-11.0 cm). 55.4% (77/139) of patients treated postoperative adjuvant chemotherapy (principally paclitaxel combine nadapltin) at least one cycle. 74(53.6%) cases were discovered the esophagus lesion had adhesions with surrounding tissues or organs during surgery, while without adhesions in 65(46.8%) cases. Surgery complications developed in 18% (25/139) of patients after radical esophagectomy, include 13 patients developed a post-operative anastomotic leakage, 5 atelectasis and pneumonia, 4 poor wound healing and 3 chylothorax.

### Sites of Locoregional Recurrence

The 1, 2, and 3-year DFS rates were 48.2%, 18.0% and 8.6%, respectively (Figure 1). The positions of locoregional recurrence after esophagectomy are showed in Table 2. Mediastinum lymph node (LN) recurrence (74.2%) was the most frequent site of recurrence, following the anastomotic site (28.1%), supraclavicular LN (19.4%) and abdominal LN (15.1%), which showed statistically difference ( $P=0.000$ ). The upper mediastinum (72.7%) was one of the most common recurrence occurred in mediastinal LN, followed by the middle (19.4%) and lower mediastinum (4.3%) ( $P=0.000$ ). The recurrent rates of No. 106pre, 106recR, 106recL and 106tbL in the upper mediastinum were exceptionally higher than the rest stations, which were 43.2%, 30.2%, 24.5%, 19.4% and 15.8%, respectively ( $P=0.000$ ). LNs recurrence of the middle mediastinum mainly occurred in No. 107 (15.8%) followed by No. 108 (3.6%) ( $P=0.001$ ). The recurrent LNs in the lower mediastinum discovered rarely and the recurrent rate of No.112 was 4.3%. The recurrence rates between the left and right supraclavicular LNs showed no statistically difference for ESCC ( $P=0.711$ ).

As demonstrated in Table 3, for different segments of ESCC, the sites of No.106pre, 106recR, 106recL and 106tbL lymph nodes all showed the relatively higher recurrence rates. Compared with lower and middle segments ESCC, upper segment represents the highest recurrent rate in the site of No.106tbR ( $P=0.029$ ). The recurrent rates of upper abdominal LNs for upper, middle, and lower segments ESCC were 0%, 9.9%, and 29.2%, respectively, with statistically significant differences ( $P= 0.001$ ). However, the recurrent rates of the supraclavicular LNs, mediastinal LNs and anastomosis site demonstrated no significantly difference in three segments of thoracic ESCC, respectively. ( $P= 0.964$ ,  $P= 0.766$  and  $P=0.676$ ).

## Relations between clinicopathologic factors and locoregional recurrence

The relations between clinicopathologic factors and anastomotic recurrence were displayed in Table 4. The predictive factors of anastomotic recurrence were patients with the stage of pT3 or pT4 of original neoplasms during surgery, presence of nerve or vessel invasion, removed LN NO.  $\leq 17$ , presence of invasion or adhesion or without postoperative adjuvant chemotherapy after radical surgery. The collections between clinicopathologic factors and supraclavicular LNs recurrence were showed in Table 5. The results revealed that there was no relationship between each clinicopathologic factor and supraclavicular LNs recurrence. For patients with middle segment ESCC, the high risk factors of upper abdominal LN recurrence included the stage of pT3 or pT4 of original neoplasms during surgery, smoking history and without postoperative adjuvant chemotherapy (Table 6).

## Discussion

Locoregional recurrences may occur along the entire "esophageal bed" from the cervical lymph node, anastomotic site, and the mediastinum to intra-abdominal lymph nodes with different frequencies according to the primary localization of tumor [14]. The results of this study showed that the recurrent rates of upper mediastinal LNs and subcarinal LNs, especially in site No. 106pre (43.2%), 106recR (30.2%), 106recL (24.5%) and 106tbL (19.4%), were high. Similar results were reported by Cai et al. and Li et al. Cai et al. [2] enrolled 140 patients with postoperative recurrent or metastatic ESCC. The supraclavicular and station 1–5 and 7 LNs had highest recurrent rates among other positions of postoperative locoregional recurrence. Furthermore, Li et al. [5] reported that in the 126 patients with locoregional LNs recurrence of ESCC, the mediastinal LN recurrent rate was significantly higher compared with the rate of supraclavicular and upper abdominal LNs, and the upper (73.8%) mediastinum LNs had the significantly recurrent tendency, which was consistent with the results in our study. The potential reason was that there were intricate anatomical structures and large blood vessels and nerves were plenty and may increase the difficulty of completely lymphadenectomy in the upper mediastinum. Second, the esophagus has a well known complex submucosal lymphatic drainage system which may facilitate spread of tumor cells via sub-mucosal lymphatics.

In our study, there was no statistically difference in the rates of supraclavicular, mediastinal and anastomosis recurrence among upper, middle and lower ESCC, which was corresponding with the results notified in other report [5]. Furthermore, the recurrent positions of lower ESCC were also gathered at the supraclavicular and upper mediastinal lymph nodes, especially at stations No. 106pre(47.9%), 106recR(35.4%), 106recL(33.3%), 106tbL(22.9%), 104L (16.7%) and 101R(16.7%), similar results were demonstrated in other reports[5, 15]. Therefore, supraclavicular, upper mediastinum LNs and subcarinal LNs should be included in the target volume of postoperative prophylactic radiotherapy of all segments thoracic ESCC.

Anastomosis recurrence was common in our sample (28.1%), which was consistent with other previous study. Mandard et al.[16] found residual tumors at autopsy in the esophageal stumps of 27% of patients after surgery for carcinoma of esophagus. Yu et al.[17] in a retrospective study indicated that anastomosis recurrence rates were 29% in post-operative esophageal cancer patients received adjuvant combined modality therapy consisting of four cycles of fluorouracil-based chemotherapy and loco-regional radiotherapy without coverage of the anastomotic site. The recurrent mass usually arises from an esophagogastrostomy site, and leads to luminal narrowing. However, in reported cases recurrence at the anastomotic site is not common pattern [3]. Wang et al. [18] found that the recurrence rate of anastomotic site was 9.8% for esophageal squamous cell carcinoma, and they recommend that anastomotic site should be excluded from the target volumes of post-operative radiotherapy. The possible reason was that more than half original neoplasma of esophagus locates at the upper and middle mediastinum in this study and increase the surgical operation inconvenient. The predictive factors of anastomosis recurrence were patients with the stage of pT3 or pT4 of original neoplams during surgery, presence of nerve or vessel invasion, removed LN NO.≤ 17, presence of invasion or adhesion or without postoperative adjuvant chemotherapy after radical surgery. Based on the results of our study, anastomosis site should be covered in the target volume of postoperative prophylactic radiotherapy of all segments thoracic ESCC.

According to our study, the recurrence rates of upper abdominal lymph node vary greatly based on location of ESCC and lower segment ESCC showed more frequently recurrent rates of lymph node, consistent with other previous study [19]. For patients with middle segment ESCC, the high risk factors of upper abdominal LN recurrence included the stage of pT3 or pT4 of original neoplasm during surgery, smoking history and without postoperative adjuvant chemotherapy. Thus, the target volume of postoperative prophylactic radiotherapy of lower segment ESCC should included upper abdominal LN region. Whether upper abdominal LN region was incorporated within the target volume of postoperative prophylactic radiotherapy of middle segment ESCC should be combination with high risk factors and need further investigation in the further.

There was no relationship between clinicopathologic factors and supraclvicular LNs recurrence. In our study, tumor bed recurrence was rarely discovered, probably by reason of tumor bed adjacent to thoracic vertebra and may be confused with middle (No. 108, 3.6%) and lower mediastinum LNs (No.112, 4.3%). Therefore, tumor bed should be exclude the target volume of postoperative prophylactic radiotherapy.

## Conclusion

For thoracic ESCC, supraclavicular, upper mediastinum, subcarinal LNs and anastomosis should be incorporated within target volume of postoperative prophylactic radiotherapy. Regarding to lower segment ESCC, target volume should include upper abdominal LNs. And it need cautious evaluated about upper abdominal LNs when presence of clinicopathologic factor in middle segment ESCC.

## Abbreviations

ESCC: Esophageal squamous cell carcinoma;

LN: Lymph node

DFS: Disease-free survival

## Declarations

## Acknowledgements

Not applicable

## Disclaimers

None. It is never been presented/ published before in any form.

## Authors' contributions

Zhen Wang and Yuanhu Yao are the corresponding author of the article. Xiangnan Qiu is the first author, contributed to the data analysis and manuscript editing. Yuanhu Yao designed the research, interpreted the data. Zhen Wang revised the paper. Shenghua Jing, Changchen Jiang, Xixu Zhu, Aomei Li and Zetian Shen performed the data extraction. All authors read and approved the final manuscript.

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## Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

# Ethics approval and consent to participate

All patients in our research signed a written informed consent before the assessment. All procedures in this research were performed in accordance with the principles of the Research Ethics Committee of Jinling Hospital Hospital and with the 1964 Helsinki Declaration and its amendments.

## Consent for publication

Not applicable

## Competing interests

The authors declare that they have no competing interests.

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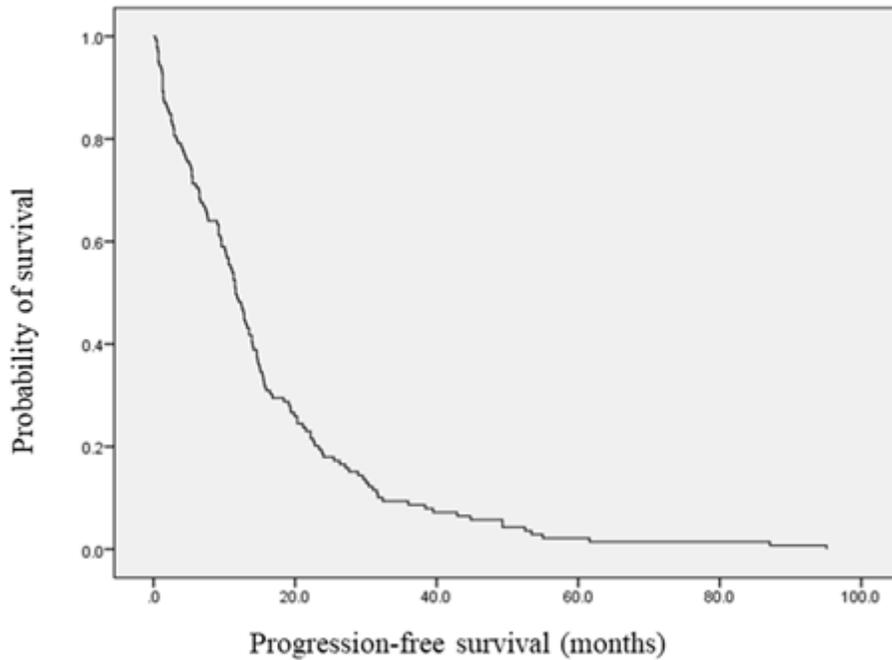
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## Tables

Due to technical limitations, tables are only available as a download in the Supplemental Files section.

## Figures



**Figure 1**

Kaplan-Meier estimating the probability of progression free survival among 139 patients with disease of locoregional recurrence after esophagectomy.

## Supplementary Files

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