

RESEARCH ARTICLE

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Characteristics of Lymph Node Metastasis in Esophageal Squamous-Cell Carcinoma Undergoing Upfront Minimally Invasive Esophagectomy: A Prospective Surgical Cohort Study

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Abstract

Introduction: This study aims to evaluate the characteristics of lymph node metastasis (LNM) in patients with early esophageal squamous cell carcinoma (ESCC) undergoing upfront minimally invasive esophagectomy and extended two-field lymph node dissection. **Patients and methods:** This prospective study was conducted from October 2022 to May 2024. All patients with early esophageal squamous cell carcinoma (ESCC) who underwent minimally invasive esophagectomy and extended two-field lymph node dissection were selected for this study. Postoperative lymph nodes were divided into the upper thoracic, middle thoracic, lower thoracic, and abdominal lymph node groups. Univariate and multivariable logistic regression analyses were performed to identify risk factors associated with lymph node metastasis (LNM). Disease-free survival (DFS) was assessed using the Kaplan–Meier method. **Results:** The overall rate of LNM was 30%, with increasing incidence by pathological T stage: 14.3% in pT1a, 32.1% in pT1b, and 50% in pT2. LNM was most frequently observed in upper thoracic and abdominal lymph node groups. Univariate analysis identified poor differentiation, lymphovascular/perineural invasion (LVI/PNI), tumor size >2 cm, and increased esophageal wall thickness on endoscopic ultrasound as significant risk factors. However, in multivariable analysis, only tumor size >2 cm remained independently associated with LNM (OR 5.47; 95% CI: 1.05–32.65; $p = 0.04$). Patients without LNM had significantly longer DFS compared to those with LNM (22.4 vs. 14.5 months; $p = 0.003$). **Conclusion:** Lymph node metastasis can occur even in early-stage esophageal squamous cell carcinoma. Poor differentiation, lymphovascular/perineural invasion, tumor size >2 cm, and esophageal wall thickness on endoscopic ultrasound were identified as independent prognostic factors for lymph node metastasis.

Keywords: Esophageal squamous cell carcinoma- Lymph node metastasis- Minimally invasive esophagectomy

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Introduction

Esophageal cancer is one of the diseases with a poor prognosis among gastrointestinal cancers with a high propensity for lymph node metastasis and a 5-year survival time of less than 20% [1]. Lymph node metastasis plays a critical role in disease staging, prognosis determination, and treatment decision-making. Current esophageal cancer treatment involves a multi-modality approach, in which esophagectomy and lymph node dissection are radical treatment methods.

According to current treatment guidelines, upfront surgery is recommended for patients with cT1b tumors or cT1a tumors with surgical indications, provided there is no clinical or radiological evidence of lymph node metastasis [2]. In contrast, if lymph node metastasis is suspected preoperatively, patients are generally referred for neoadjuvant therapy. Nevertheless, a considerable proportion of esophageal cancer patients who undergo upfront surgery are still found to have lymph node

metastasis at the time of resection, with reported rates ranging from 14.8% [3] to 21.8% [4]. This discrepancy underscores the need for a thorough evaluation of preoperative lymph node metastasis in these patients.

Given these concerns, it is necessary to investigate the incidence and associated factors of lymph node metastasis in patients with early-stage esophageal squamous cell carcinoma (ESCC) who undergo upfront minimally invasive esophagectomy (MIE). By conducting this study, we aim to provide valuable insights into the patterns and influencing factors of lymph node metastasis in these patients.

Materials and Methods

Data collection

This is a prospective study involving 50 selected patients, all diagnosed with early-stage thoracic ESCC who underwent upfront surgery with the National Comprehensive Cancer Network (NCCN) guidelines

[2]. All patients underwent 3D thoraco-laparoscopic esophagectomy and extended two-field lymph node dissection (including upper thoracic lymph nodes according to Matsuda’s classification [5]). This study was conducted at the Vietnam National Cancer Hospital from October 2022 to May 2024.

Surgery procedure

Thoracic Phase: We used two positions: semiprone or a hybrid of semiprone and left lateral. Five trocars were placed in both positions. Lymph node dissection was performed according to the recommendations of the Japanese Esophageal Society [6]. The middle and lower thoracic lymph node were dissected first. The right recurrent laryngeal nerve (RLN) lymph nodes were dissected later, by opening the superior mediastinal pleura along the vagus nerve and finding the root of the RLN. Subsequently, the left RLN lymph nodes were removed. The trachea was retracted to the right, and the fat layer containing the lymph nodes was removed from the starting position under the aortic arch to the cervical paraesophageal lymph nodes. Dissection of this lymph node group was performed in the semiprone or left lateral position.

Abdominal Phase: The abdominal phase was also performed laparoscopically, including lymph node dissection of the group around the celiac artery, lesser curvature, and bilateral diaphragmatic crus. Reconstruction was performed by using a gastric tube. Anastomosis was completed at the neck using either a circular stapler or the hand-sewn technique.

Postoperatively, the patient was immediately extubated and placed in the intensive care unit. Postoperative complications were monitored, diagnosed, and classified according to the Japan Clinical Oncology Group postoperative complication criteria, based on the extended Clavien-Dindo classification [7].

The postoperative lymph node groups were divided as follows: upper thoracic (105, 106RecR, 106RecL, 106tbL), middle thoracic (107, 108, 109 bilaterally), lower thoracic (110, 111, 112Pul, 112Ao), and abdominal (1, 2, 3a, 7, 8, 9, 11p, 19, 20). Postoperative pathology was reported by a single experienced doctor from the Pathology and Molecular Biology Center at the Vietnam National Cancer Hospital.

Statistical analysis

Data collection and statistical analysis were performed using SPSS software (version 20; SPSS Inc., Chicago, IL, USA). Risk factors for lymph node metastasis

were analyzed using the Chi-square test or Fisher’s exact test, as appropriate. Univariate and multivariate logistic regression analyses were conducted to identify independent predictors of lymph node metastasis. Disease free survival was estimated using the Kaplan–Meier method and assessed using the log-rank test. A p-value < 0.05 with a 95% confidence interval was considered statistically significant.

This prospective, cross-sectional study has been reported in line with the Strengthening the Reporting of Cohort, Cross-sectional and case-control studies in Surgery (STROCSS) guideline [8].

Results

Among the 50 patients who underwent upfront minimally invasive esophagectomy and extended two-field lymph node dissection, the overall rate of lymph node metastasis was 30%. Stratified by pathological T stage, the rate of lymph node metastasis was 14.3% in pT1a, 32.1% in pT1b, and 50% in pT2 patients. By region, lymph node metastases were observed in the upper thoracic and abdominal regions across all T stages, with the highest rates seen in T2 tumors (Table 1).

Patients with positive lymph nodes had significantly greater preoperative wall thickness on endoscopic ultrasound (5.1 ± 1.4 mm vs. 3.8 ± 1.5 mm, $p = 0.01$), and higher proportions of poor differentiation ($p = 0.04$), lymphovascular/perineural invasion (LVI/PNI) ($p = 0.05$), and tumor length >2 cm ($p = 0.02$) (Table 2).

Univariate logistic regression (Table 3) confirmed that poor differentiation (OR 6.22, $p = 0.02$), LVI/PNI (OR 5.17, $p = 0.03$), tumor length >2 cm (OR 4.57, $p = 0.02$), and wall thickness (OR 1.69, $p = 0.03$) were significantly associated with lymph node metastasis. In the multivariable model, only tumor length >2 cm remained statistically significant (OR 5.47; 95% CI: 1.05–32.65; $p = 0.04$).

Regarding disease-free survival (DFS), patients without lymph node metastasis had a significantly higher mean DFS (22.4 vs. 14.5 months, respectively). The Kaplan–Meier survival analysis (Figure 1) and log-rank test confirmed a significant difference between the two groups ($\chi^2 = 8.77$, $p = 0.003$).

Discussion

In this study, the overall rate of lymph node metastasis (LNM) in patients with early-stage esophageal squamous cell carcinoma (ESCC) who underwent upfront minimally

Table 1. Rate of Lymph Node Metastasis Divided by T stage and Lymph Node Group

Group	Postoperative pathology stage			Total
	pT1a	pT1b	pT2	
Upper thoracic	7.10%	14.30%	25%	14%
Middle thoracic	0	14.30%	25%	12%
Lower thoracic	0	7.20%	12.50%	6%
Abdominal	7.10%	10.70%	25%	12%
Total	14.30%	32.10%	50%	30%

Table 2. Analyze the Relationship between Related Factors and Lymph Node Metastasis Characteristics

Factors	LN-positive (n=15)	LN-negative (n=35)	p value (Chi-square test / Fisher's exact test)
Age (year) Mean \pm SD	55.6 \pm 6.1	58.1 \pm 5.6	0.17
Comorbidities			0.08
Yes	6 (50%)	6 (50%)	
No	9 (23.7%)	29 (76.3%)	
Smoking			0.56
Yes	9 (27.3%)	24 (72.7%)	
No	6 (35.3%)	11 (64.7%)	
Tumor location			0.42
Middle thoracic	5 (23.8%)	16 (76.2%)	
Lower thoracic	10 (34.5%)	19 (65.5%)	
T stage			0.22
T1	11 (26.2%)	31 (73.8%)	
T2	4 (50%)	4 (50%)	
Preoperative wall thickness on endoscopic ultrasound (mm)	5.1 \pm 1.4	3.8 \pm 1.5	0.01
Differentiation			0.04
Moderate	9 (24.3%)	28 (75.7%)	
Poor	6 (66.7%)	3 (33.3%)	
Lymphovascular/ Perineural invasion			0.05
Yes	6 (60%)	4 (40%)	
No	9 (22.5%)	31 (77.5%)	
Tumor length(cm)			0.02
\leq 2cm	7 (20.0%)	28 (80%)	
$>$ 2cm	8 (53.3%)	7 (46.7%)	

Table 3. Univariate Analysis and Multivariable Logistic Model for Occult Lymph Node Metastasis

Factor	Univariate logistic model		Multivariable logistic model	
	OR (95% CI)	P value	OR (95% CI)	P value
T stage (T1 vs T2)	2.82 (0.60 – 13.24)	0.19	2.5 (0.20 – 30.77)	0.46
Differentiation (Moderate vs poor)	6.22 (1.29 – 30.10)	0.02	5.1(0.65 – 40.32)	0.12
Lymphovascular/ Perineural invasion	5.17 (1.19 – 22.40)	0.03	6.33 (0.65 – 61.81)	0.11
Tumor length (\leq 2cm vs $>$ 2cm)	4.57 (1.23 – 16.94)	0.02	5.47 (1.05 – 32.65)	0.04
Preoperative endoscopic ultrasound wall thickness (mm)	1.69 (1.07 – 2.67)	0.03	1.46 (0.77 – 2.77)	0.24

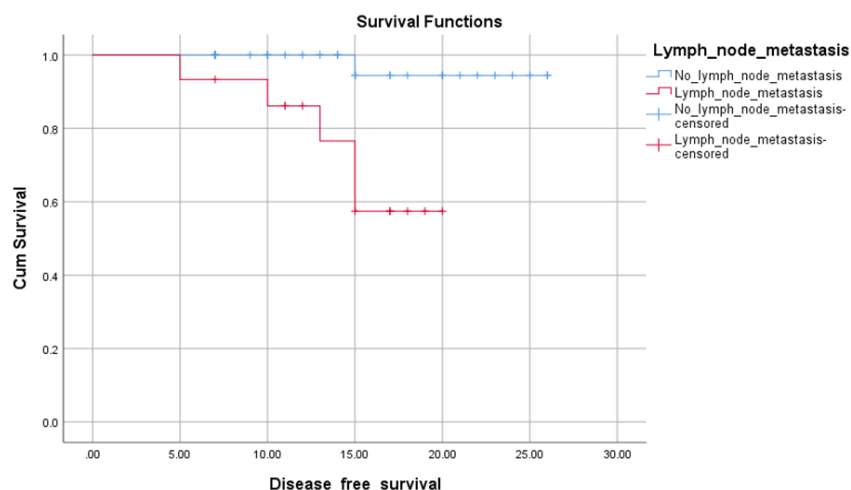


Figure 1. Kaplan–Meier Curves for Disease-Free Survival in Patients with Lymph Node Metastasis. (Kaplan–Meier curves comparing disease-free survival between lymph node positive and lymph node negative patients. Log-rank test was used to compare survival distributions)

invasive esophagectomy was 30%, with a clear increasing trend by pathological T stage: 14.3% in T1a, 32.1% in T1b, and 50% in T2. This finding confirms that LNM can occur even in the early stages of disease, particularly in tumors invading the submucosa (T1b) or muscularis propria (T2), which is important for treatment selection and recurrence risk assessment. Our results are similar with previous reports, including the landmark study by Akiyama, which analyzed 717 patients who underwent esophagectomy with three-field lymph node dissection. That study reported markedly higher LNM rates: 28.6% in T1a, 54.1% in T1b, and 69.7% in T2 [9]. More recent studies have reported LNM rates in T1a ESCC ranging from 5–16%, and in T1b ranging from 16–38.2%, which are comparable to our findings [10, 11].

Regarding the risk factors associated with lymph node metastasis, univariate analysis in our study revealed that poor differentiation, lymphovascular/perineural invasion, tumor size >2 cm, and esophageal wall thickness on endoscopic ultrasound were all statistically significant. However, in the multivariate regression model, only tumor size >2 cm was identified as an independent prognostic factor, suggesting that this criterion should be carefully considered when selecting a treatment strategy. Agreeing with our findings, the study by Dong Tian et al. also identified risk factors associated with lymph node metastasis, including tumor differentiation and submucosal invasion [10]. In addition, hematological parameters such as high-density lipoprotein cholesterol (HDL-C) and the alanine aminotransferase/aspartate aminotransferase (ALT/AST) ratio were also found to be significantly associated with lymph node metastasis. In our study, the preoperative staging was mainly based on endoscopic ultrasound and contrast-enhanced CT. However, these imaging methods have limitations in detecting small lymph node metastases. These limitations may lead to under or over staging before surgery.

In addition, the disease-free survival (DFS) in patients without lymph node metastasis was 22.4 months, significantly longer than that in patients with (14.5 months, $p = 0.003$). This finding enhances that lymph node metastasis remains a key prognostic factor after surgery, even in cases where radical resection and lymphadenectomy have been performed. These results suggest the need for close postoperative surveillance and consideration of adjuvant therapy in high-risk patients.

This study is limited by small sample size, which may reduce the statistical power and limit the generalizability of our findings. Therefore, the multivariate analysis should be interpreted with caution. Future studies with larger sample sizes and multi-center cohorts are needed to validate the predictive factors identified in this study.

Conclusion, our study confirms that lymph node metastasis can occur even in early-stage esophageal squamous cell carcinoma. Poor differentiation, lymphovascular/perineural invasion, tumor size >2 cm, and esophageal wall thickness on endoscopic ultrasound were identified as independent prognostic factors for lymph node metastasis. The significant impact of lymph node metastasis on disease-free survival highlights the necessity of comprehensive preoperative staging and

vigilant postoperative monitoring. Moreover, adjuvant therapy should be considered in patients classified as high risk.

Author Contribution Statement

BVP: Surgeon, study design, data collection, data statistics, data interpretation, preparation of manuscript, literature analysis/search, resources, supervision; DDN: Surgeon, study design, data collection, data statistics, data interpretation, preparation of manuscript, literature analysis/search, resources, supervision; ADT: Surgeon, study design, data collection, data statistics, data interpretation, preparation of manuscript, literature analysis/search, resources. All authors read and approved the final manuscript.

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Scientific body approval / Thesis statement

This study is part of an approved institutional research project and is not part of a student thesis.

Conflicts of interest: The authors declare that they have no financial conflict of interest with regard to the content of this report.

Ethical approval

The study was approved on April 4, 2023 by the Ethics Committee of Hanoi Medical University (Approval No.: 875/GCN-HĐĐĐNCYSH-ĐHYHN). All procedures were performed in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

Availability of data

The datasets used and analyzed are available from the corresponding author.

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