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EDITORIAL

Risk factors for lymph node metastasis in superficial esophageal squamous cell carcinoma

Yan-Bo Yu

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Abstract

In this editorial, we comment on the article by Wang *et al* published in the recent issue of the *World Journal of Gastroenterology* in 2023. We focused on identifying risk factors for lymph node metastasis (LNM) in superficial esophageal squamous cell carcinoma (SESCC) patients and how to construct a simple and reliable clinical prediction model to assess the risk of LNM in SESCC patients, thereby helping to guide the selection of an appropriate treatment plan. The current standard treatment for SESCC is radical esophagectomy with lymph node dissection. However, esophagectomy is associated with considerable morbidity and mortality. Endoscopic resection (ER) offers a safer and less invasive alternative to surgical resection and can enable the patient's quality of life to be maintained while providing a satisfactory outcome. However, since ER is a localized treatment that does not allow for lymph node dissection, the risk of LNM in SESCC limits the effectiveness of ER. Understanding LNM status can aid in determining whether patients with SESCC can be cured by ER without the need for additional esophagectomy. Previous studies have shown that tumor size, macroscopic type of tumor, degree of differentiation, depth of tumor invasion, and lymphovascular invasion are factors associated with LNM in patients with SESCC. In addition, tumor budding is commonly associated with LNM, recurrence, and distant metastasis, but this topic has been less covered in previous studies. By comprehensively evaluating the above risk factors for LNM, useful evidence can be obtained for doctors to select appropriate treatments for SESCC patients.

Key Words: Superficial esophageal squamous cell carcinoma; Endoscopic resection; Lymph node metastasis; Risk factors; Tumor budding; Predictive model

Core Tip: Endoscopic resection is a routine treatment for superficial esophageal squamous cell carcinoma, but the risk of lymph node metastasis (LNM) limits its application to some extent. Tumor size, invasion depth, tumor differentiation, tumor infiltrative growth pattern, tumor budding, and lymphovascular invasion were shown to be significantly correlated with LNM.

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INTRODUCTION

Esophageal cancer, the ninth most prevalent cancer and the sixth leading cause of cancer death worldwide, represents an important health concern that must be taken seriously. The overall 5-year survival rate is less than 15%. In 2020 alone, approximately 544000 deaths were attributed to esophageal cancer[1]. Esophageal squamous cell carcinoma (ESCC) is the most common subtype of esophageal cancer, accounting for 90% of esophageal cancers in Asia, Eastern Europe and Africa[2].

Malignant tumors localized to the mucosa or submucosa, with or without lymph node metastasis (LNM), are referred to as superficial esophageal squamous cell carcinoma (SESCC)[3,4]. The invasion of SESCC is limited to the mucosa and submucosa, causing no symptoms and posing challenges for early diagnosis of these patients. Currently, the use of new endoscopic techniques, such as magnifying endoscopy and narrow-band imaging endoscopy, and increased health awareness have significantly increased the detection rate of SESCC[5]. With detection at an early stage, timely and appropriate intervention usually results in a favorable prognosis.

The standard treatment for SESCC is radical esophagectomy with lymph node dissection. However, esophagectomy is not indicated for patients of advanced age or with multiple comorbidities due to the risk of complications and a significant reduction in quality of life postsurgery[6,7]. Endoscopic resection (ER) is a safer and less invasive alternative to surgical resection, which can maintain a patient's quality of life while achieving a satisfactory outcome. When the tumor is limited to the mucosa or submucosa, survival can reach 90% after endoscopic or surgical treatment[8]. The inability to perform lymph node dissection is the limitation associated with ER. Notably, prior research has demonstrated the importance of LNM in the unfavorable prognosis of SESCC[9,10] since a significantly lower 5-year survival rate has been observed in LNM-positive patients than in LNM-negative patients[11]. Even SESCC has the potential for LNM due to the abundance of the lymphocapillary plexus in the mucosa and submucosa of the lamina propria of the esophagus[12].

Because the probability of LNM increases proportionally with invasion depth, most current indications for ER in ESCC patients are formulated based on the depth of tumor invasion. The LNM rates were reported as follows: T1a-EP (epithelium) or T1a-LPM (lamina propria mucosa), 0.0%-3.3%; T1a-MM (muscularis mucosa) or T1b-SM1 (upper third of the submucosal layer), 0.0%-26.5%; and T1b-SM2, 22%-61%[13]. Generally, among ER, esophagectomy, and chemoradiotherapy, the treatment strategies for patients in the categories of T1a-MM and T1b-SM1 are regarded as borderline. According to the guidelines for esophageal cancer in Japan[14,15], clinical T1a-MM and T1b-SM1 SESCC are relative indications for ER, and additional treatment after ER is recommended for SESCC patients with lymphovascular invasion (LVI) or submucosal invasion. However, even if ER is performed, if the histopathological diagnosis is tumor depth [pT1a-MM, and LVI (+) or pT1b-SM], radical resection or additional treatment such as chemoradiotherapy is recommended due to considering the risk of LNM. The European Society of Gastrointestinal Endoscopy Guideline[16] suggests that endoscopic submucosal dissection might be considered for ESCC patients with noncircumferential clinical staging of T1a-MM/T1b-SM.

The predictors of LNM in SESCC patients can be assessed to determine whether they are likely to be cured by ER without additional esophagectomy or lymphadenectomy. Additionally, the clinicopathological risk factors associated with LNM in SESCC are still incompletely understood. Some imaging methods, such as endoscopic ultrasonography and CT, can be used to detect LNM in ESCC but have low accuracy, especially for T1 tumors[17,18]. In these cases, ER offers more precise staging in addition to therapeutic benefits[18].

RISK FACTORS FOR LNM IN SESCC

Previous studies have shown that tumor size, macroscopic type of tumor, degree of differentiation, depth of tumor invasion, and LVI are factors associated with LNM in patients with SESCC[8]. In the recent issue of the *World Journal of Gastroenterology*, Wang *et al*[19] published an interesting paper titled "Risk factors and a predictive nomogram for LNM in superficial esophageal squamous cell carcinoma." This study developed a useful nomogram model to predict LNM risk in superficial ESCC patients. In this retrospective study, 474 SESCC patients who underwent esophagectomy at West China Hospital of Sichuan University from January 1, 2009 to January 31, 2016, were enrolled in the final analysis. Of those, 90 of the 474 (16.48%) patients had LNM, and the LNM rate was 3.29% (5/152) for T1a tumors and 26.40% (85/322) for T1b tumors. Variables such as tumor size, invasion depth, tumor differentiation, tumor infiltrative growth (INF)

pattern, tumor budding (TB), and LVI were significantly associated with LNM according to univariate analysis. Multivariate logistic regression analysis also showed that tumor size, invasion depth, tumor differentiation, the INF (tumor infiltrative growth) pattern, TB, and LVI were independent risk factors for LNM. The ROC curve showed that this nomogram had good predictive performance in both the training set and the validation set, with AUCs of 0.789 [95% confidence interval (95%CI): 0.737-0.841] and 0.827 (95%CI: 0.755-0.899), respectively.

In several studies, scholars have proposed predictive models for LNM in patients with superficial ESCC, but these models have several limitations[20,21]. As the invasion depth increases, the probability of LNM in SESCC increases proportionally. A limitation of some studies is that no further stratification of the submucosa was performed. The nomogram established by Wang *et al*[19] involved tumor categorization into 3 grades by depth of infiltration: MM, SM1, and SM2 and above. An invasion depth deeper than SM1 [odd ratio (OR): 15.517, 95%CI: 4.707-51.158] was an independent risk factor for LNM.

Wang *et al*[19] also incorporated TB into a prediction model, which has rarely been addressed in previous studies. TB is a morphological phenomenon of diffuse mucous infiltrative growth, characterized by the presence of isolated cells or clusters of tumor cells (up to 5 cells) scattered in the stroma at a variable distance from the invasive front of the tumor [22]. These cells detach from the tumor mass and migrate into the adjacent stroma, representing the first step toward invasive growth followed by metastasis. The presence of TB is commonly associated with a more aggressive cancer phenotype and is correlated with LNM, recurrence, and distant metastasis and thus poor survival. One hypothesis suggests that TB mimics epithelialmesenchymal transition, a process in which cells change from an epithelial phenotype expressing E-calmodulin and cytokeratin to a mesenchymal phenotype expressing vimentin and N-cadherin[23]. When cancer cells acquire a mesenchymal phenotype, cell polarity and intercellular adhesion are lost, leading to invasion and metastasis[24]. However, there are also hypotheses that the mechanism of TB is not related to epithelialmesenchymal transition[25,26]. Although underlying the mechanism is unclear, TB can be identified as a histopathological predictor of LNM or poor prognosis in gastrointestinal carcinoma including esophageal adenocarcinoma, ESCC, lung squamous cell carcinoma, and cervical cancer[27]. However, only a few studies have focused on TB and its importance in the prognosis of ESCC. There is no gold standard for determining the threshold value of TB in patients with SESCC.

In the study by Mitobe *et al*[28], univariate analysis showed that TB in SESCC was significantly associated with LNM. However, this study failed to show that TB was an independent risk factor for LNM. Min *et al*[20] reported that the presence of TB had borderline importance for LNM prediction. Fuchinoue *et al*[29] showed that the cutoff values for high-grade TB evaluated using hematoxylin-eosin (HE) staining or immunohistochemistry (IHC) were 2 and 11, respectively. High-grade TB, as evaluated using HE staining (P = 0.007) and IHC ($P \leq 0.001$), was significantly correlated with LNM. For tumors with pT1a-MM to pT1b-SM1, high-grade TB evaluated using IHC was correlated with LNM (P = 0.050). Li *et al*[30] found that TB according to a three-tiered grading system (low-TB, 0-4; middle-TB, 5-15; high-TB, ≥ 16) was an excellent prognostic indicator for LNM and survival based on IHC staining using a 20 × objective lens. Wang *et al*[19] categorized TB into three types based on HE staining: No budding, low-grade TB (1 to 4 budding foci at a 20 × objective lens), and high-grade TB (≥ 5 budding foci at a 20 × objective lens). The study showed that high-grade TB (OR: 3.905, 95%CI: 1.387-10.995) was positively correlated with LNM risk in SESCC patients. Furthermore, unlike previous studies, multifactorial regression analysis in this study showed that TB was an independent risk factor for LNM, helping to promote the use of tumor outgrowth in SESCC pathology diagnosis and advance its inclusion in routine pathology reporting.

CONCLUSION

In summary, ER is known to be a routine treatment for SESCC, and considering the impact of LNM on patient prognosis, it is crucial to explore the predictors of LNM before ER in patients with SESCC. In addition, in patients with ER-treated SESCC, medical practitioners must assess the risk of LNM and thus the need for further esophagectomy based on post-ER pathological diagnosis. As a result, a practical decision-making tool built on multifactor analysis for assessing LNM risk is essential.

FOOTNOTES

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