ORIGINAL ARTICLE

Identification and Validation of Lymphovascular Invasion as a Prognostic and Staging Factor in Node-Negative Esophageal Squamous Cell Carcinoma

Qingyuan Huang, MD,[a,b,c] Kongjia Luo, MD, PhD,[a,c] Chun Chen, MD, PhD,[d] Geng Wang, MD,[e] Jietian Jin, MD,[a] Min Kong, MD,[f] Bifeng Li, MD,[d,g] Qianwen Liu, MD,[a,c] Jinhui Li, MB,[h] Tiehua Rong, MD, PhD,[a,c] Haiquan Chen, MD, PhD,[b] Lanjun Zhang, MD, PhD,[a,c] Yuping Chen, MD, PhD,[e] Chengchu Zhu, MD, PhD,[f] Bin Zheng, MD,[d] Jing Wen, MD, PhD,[a,c] Yuzhen Zheng, MD,[a,c] Zihui Tan, MD,[a,c] Xiuying Xie, BE,[a,c] Hong Yang, MD, PhD,[a,c] Jianhua Fu, MD, PhD[a,c,*]

[a]*Sun Yat-Sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, People's Republic of China*
[b]*Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, People's Republic of China*
[c]*Guangdong Esophageal Cancer Institute, Guangzhou, People's Republic of China*
[d]*Fujian Medical University Union Hospital, Fuzhou, People's Republic of China*
[e]*Cancer Hospital of Shantou University Medical College, Shantou, People's Republic of China*
[f]*Taizhou Hospital, Taizhou, People's Republic of China*
[g]*Xiamen Traditional Hospital, Xiamen, People's Republic of China*
[h]*School of Public Health, the University of Hong Kong, Hong Kong, People's Republic of China*

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ABSTRACT

Introduction: Lymphovascular invasion (LVI) is a histopathological feature that is associated with an increased risk for micrometastasis. The aim of this study was to determine the prognostic and staging value of LVI among patients with esophageal squamous cell carcinoma (ESCC) undergoing esophagectomy.

Methods: A prospective database of patients with ESCC was used to retrospectively analyze 666 cases to identify the relationship between LVI and survival, and to evaluate predictive accuracy of prognosis after combining LVI and the tumor, node, and metastasis (TNM) system. Pathological slides were reassessed by gastrointestinal pathologists according to the strict criteria; 1000-bootstrap resampling was used for internal validation, and 222 cases from an independent multicenter database were used for external validation.

Results: LVI was present in 33.8% of patients, and the proportion increased with advancing T and N classification. LVI was an independent predictor of unfavorable disease-specific survival (DSS) (hazard ratio = 1.59, 95% confidence interval: 1.30–1.94) and disease-free survival (DFS) (hazard ratio = 1.62, 95% confidence interval: 1.32–1.98) after T classification. Among node-negative patients, LVI and T classification were two independent predictors of DSS and DFS ($p < 0.001$). The risk score model combing LVI and T classification improved the predictive accuracy of the TNM system for DSS and DFS by 3.5% and 4.8%, respectively ($p < 0.001$). The external validation showed congruent results. The DSS of TxN0M0 disease with LVI was similar to the DSS of TxN1M0 (both $p > 0.05$). In contrast, LVI was not associated with DSS or DFS among node-positive patients.

Conclusions: The independent prognostic significance of LVI existed only in node-negative patients with ESCC, and the combination of LVI and the TNM system enhanced the predictive accuracy of prognosis. After confirmation,

*Corresponding author.

Drs. Huang, Luo, Chen, Wang, Jin, and Kong contributed equally.

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Address for correspondence: Jianhua Fu, MD, PhD, Sun Yat-Sen University Cancer Center, 651 Dong Feng Road East, Guangzhou 510060, People's Republic of China. E-mail: fu_jianhua@126.com

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node-negative patients with LVI might be considered for upstaging in pathological staging.

Keywords: Esophageal squamous cell carcinoma; Lymphovascular invasion; Prognosis; Tumor staging

Introduction

Multidisciplinary therapies have been demonstrated to improve the prognosis of some esophageal carcinoma subgroups,[1–5] and accurate prognostication and staging assessment are essential to tailoring an optimal multidisciplinary treatment. Although the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging system for esophageal carcinoma[6] has better performance in prognostication than the previous edition,[7,8] there is still space for improvement, especially for T2–3N0M0 disease.[9–12] Additional modifications still need to be proposed with improvement in the understanding of cancer biology.

Histopathological examination is the most practical and inexpensive method for the investigation of tumor behavior, particularly in comparison with molecular methods. Lymphovascular invasion (LVI) is a histopathological feature that is associated with biologically aggressive disease, and it can be easily and reliably evaluated using routine light microscopic examination. Indeed, LVI is an essential and important step in lymph node metastasis and systemic dissemination of cancer cells, and it is considered to increase the risk for micrometastases in localized carcinoma.[13] The unfavorable prognostic significance of LVI has been supported by studies involving solid tumors, such as breast carcinoma,[14,15] lung carcinoma,[16,17] and bladder carcinoma.[18] However, the role of LVI as a predictor of survival in esophageal squamous cell carcinoma (ESCC) has not been adequately investigated. Previous single-institutional studies have habitually been limited by small sample sizes as well as heterogeneity of tumor stages, histological subtypes, multidisciplinary treatment regimens, and adequacy of surgical resection, resulting in controversial conclusions.[19–26]

Herein, we conducted a cohort study to evaluate the impact of LVI on survival and to determine the role of LVI in ESCC staging, which were validated internally using 1000-bootstrap resamples and externally in four independent databases.

Methods

Study Population

An esophageal carcinoma database that was prospectively maintained by the Guangdong Esophageal Cancer Institute from January 1999 to December 2006 was retrospectively analyzed, and 1458 consecutive cases from Sun Yat-Sen University Cancer Center (Guangzhou, China) were enrolled. The database recorded information regarding sociodemographic data, disease extent, treatment administered, and follow-up status. The patients included in the current study fulfilled the following criteria: (1) histologically confirmed thoracic ESCC, (2) receipt of complete resection and regular follow-up, (3) no distant metastasis, (4) no previous malignant disease or second primary tumor, (5) no previous anticancer treatment or adjuvant treatment, (6) availability of qualified surgical specimens, and (7) age between 18 and 80 years. A total of 666 patients were eligible for our analysis according to the inclusion criteria (see Supplementary Fig. 1). The external validation cohort was composed of 795 patients from Sun Yat-Sen University Cancer Center (Guangzhou, Guangdong Province, People's Republic of China), Cancer Hospital of Shantou University Medical College (Shantou, Guangdong Province, People's Republic of China), Fujian Medical University Union Hospital (Fuzhou, Fujian Province, People's Republic of China), and Taizhou Hospital (Taizhou, Zhejiang Province, People's Republic of China) who were treated between January 2011 and December 2011. With the same criteria as just listed, 222 node-negative patients were included, and their samples were reevaluated by pathologist J. T. Jin. The pathological stage of every case was reevaluated according to the seventh edition of the AJCC staging system for esophageal carcinoma.[6] The institutional review board at each participating center approved the analysis of the anonymous data.

The preoperative workup was conducted as previously described[27] to confirm that patients were clinically fit for surgery. The surgical procedure included both right and left transthoracic esophagectomy. Only some tumors of the lower and middle sections of the thoracic esophagus received a left transthoracic esophagectomy with a longitudinal resection margin more than 5 cm from the tumor.[28] The tumor-bearing esophagus was resected en bloc together with the adjoining connective tissues. At least a two-field lymph node dissection, including standard, extended, or total dissection of the thoracic and abdominal lymph nodes, was performed in all patients.

Pathological Evaluation

All specimens were processed according to institutional protocols. In brief, the gross specimens and lymph nodes were collected in the specimen room by surgeons. Samples were fixed in 10% neutral buffered formalin immediately after collection and subsequently embedded in paraffin. Serial sections were stained with hematoxylin and eosin (HE). After careful selection, the