ISSN 1007-9327 (print)
ISSN 2219-2840 (online)

World Journal of *Gastroenterology*

World J Gastroenterol 2024 March 14; 30(10): 1261-1469

Published by Baishideng Publishing Group Inc

World Journal of Gastroenterology

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The *WJG* is now abstracted and indexed in Science Citation Index Expanded (SCIE), MEDLINE, PubMed, PubMed Central, Scopus, Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJG* as 4.3; Quartile category: Q2. The *WJG*'s CiteScore for 2021 is 8.3.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

LAUNCH DATE
October 1, 1995

FREQUENCY
Weekly

PUBLICATION DATE
March 14, 2024

PUBLISHING PARTNER
Shanghai Pancreatic Cancer Institute and Pancreatic Cancer Institute, Fudan University
Biliary Tract Disease Institute, Fudan University

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

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World J Gastroenterol 2024 March 14; 30(10): 1291-1294

DOI: 10.3748/wjg.v30.i10.1291

ISSN 1007-9327 (print) ISSN 2219-2840 (online)

EDITORIAL

Nomograms and prognosis for superficial esophageal squamous cell carcinoma

Hong Tao Lin, Ahmed Abdelbaki, Somashekar G Krishna

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Song T, China

Received: January 2, 2024
Peer-review started: January 2, 2024
First decision: January 19, 2024
Revised: January 28, 2024
Accepted: February 25, 2024
Article in press: February 25, 2024
Published online: March 14, 2024

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Abstract

In recent years, endoscopic resection, particularly endoscopic submucosal dissection, has become increasingly popular in treating non-metastatic superficial esophageal squamous cell carcinoma (ESCC). In this evolving paradigm, it is crucial to identify factors that predict higher rates of lymphatic invasion and poorer outcomes. Larger tumor size, deeper invasion, poorer differentiation, more infiltrative growth patterns (INF-c), higher-grade tumor budding, positive lymphovascular invasion, and certain biomarkers have been associated with lymph node metastasis and increased morbidity through retrospective reviews, leading to the construction of comprehensive nomograms for outcome prediction. If validated by future prospective studies, these nomograms would prove highly applicable in guiding the selection of treatment for superficial ESCC.

Key Words: Esophageal cancer; Esophageal squamous cell carcinoma; Esophageal resection; Endoscopic mucosal resection; Endoscopic submucosal dissection; Lymph node metastasis

Core Tip: As endoscopic resection becomes the standard of care for non-metastatic superficial esophageal squamous cell carcinoma (ESCC), it is imperative to identify cases with a high risk of lymphatic invasion. Current retrospective studies suggest an association between lymph node metastasis in superficial ESCC and factors such as larger tumor size, deeper invasion, poorer differentiation, more infiltrative growth patterns (INF-c), higher-grade tumor budding, positive lymphovascular invasion, and specific biomarkers. Future prospective studies are required to validate these findings, isolate other prognostic factors and confounders, and establish a more robust causal relationship.

Citation: Lin HT, Abdelbaki A, Krishna SG. Nomograms and prognosis for superficial esophageal squamous cell carcinoma. *World J Gastroenterol* 2024; 30(10): 1291-1294
URL: https://www.wjgnet.com/1007-9327/full/v30/i10/1291.htm
DOI: https://dx.doi.org/10.3748/wjg.v30.i10.1291

INTRODUCTION

Esophageal cancer ranks as the ninth most prevalent cancer and the sixth leading cause of cancer-related deaths worldwide[1]. Approximately 85% of primary esophageal cancer falls within the esophageal squamous cell carcinoma (ESCC) subtype, with the remainder primarily comprising esophageal adenocarcinoma (EAC)[2]. EAC typically affects the lower third of the esophagus due to gastric reflux, while ESCC predominantly originates from the squamous cells lining the upper and middle esophagus.

The incidence of ESCC is higher in specific regions, including Eastern Asia, Iran, Africa, and South America. It is conversely rare in North America and Europe. Factors such as smoking, alcohol consumption, low socioeconomic status, exposure to polycyclic aromatic hydrocarbons (*e.g.*, from smoked foods and air pollution), and certain dietary habits (*e.g.*, betel nut, hot liquids, pickled foods, and a diet low in fruits and vegetables) are associated with increased rates of ESCC development[3,4]. While the factors above are the most identified etiologies of ESCC, other causes include TP53 gene alterations, chromosomal alterations, genetic syndromes, slow NAT2 (n-acetyltransferase 2) acetylation, and certain variants of *Helicobacter pylori* infection[5].

In general, esophageal cancers are linked to significant mortality and morbidity. The mean 5-year survival rates (combining ESCC and EAC) have been estimated to be less than 20%, with worse outcomes in patients with histories of heavy alcohol and tobacco use. Intervention through surgical resection, with or without chemoradiotherapy, modestly improves mean 5-year survival rates to 35%-40%, depending on tumor characteristics[6].

TREATMENT AND PROGNOSIS

While esophageal cancer has historically been treated with surgical esophagectomy, the use of endoscopic resection (ER) for superficial ESCC has gained popularity in recent years as it is minimally invasive and well-tolerated, while also providing tissue samples for histological analysis. Current guidelines recommend ER for select patients due to its efficacy in removing lesions within the muscularis mucosa and some lesions in the submucosa depending on invasion depth[7,8]. However, ER alone is insufficient for tumors with deeper invasion or tumors with a high risk of lymph node metastasis (LNM) or lymphovascular invasion (LVI), necessitating surgical esophagectomy and neoadjuvant chemoradiotherapy (CRT).

While both endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR) fall under the ER umbrella, ESD is superior to EMR, particularly for larger tumor sizes. A retrospective study by Kawashima *et al*[9] found that for tumors > 15 mm, ESD has a higher *en-bloc* resection rate (100% *vs* 64.3%, $P < 0.001$) and a lower 5-year cumulative local recurrence rate (0% *vs* 8.3%, $P < 0.01$). Despite EMR and ESD, some high-risk patients may require further treatment for complete tumor eradication.

The retrospective study titled "Risk Factors and a Predictive Nomogram for LNM in Superficial Esophageal Squamous Cell Carcinoma", by Wang *et al*[10], aims to assess prognostic factors for LNM in patients specifically diagnosed with the ESCC subtype of esophageal cancer. Investigators enrolled patients with superficial ESCC undergoing esophagectomy and lymph node dissection. They collected detailed pathological information to comprehensively analyze and identify LNM risk factors. Findings indicated that patients with positive LNM were more likely to have larger tumors, deeper invasion, poorer differentiation, more infiltrative growth patterns (INF-c), higher-grade tumor budding, and positive LVI. Multivariate regression analysis confirmed these factors as independent risk factors for LNM.

Based on these findings, a predictive nomogram incorporating tumor size, invasion depth, tumor differentiation, tumor budding, tumor infiltrative growth pattern, and LVI was developed. The nomogram exhibited good predictive performance (AUC 0.789 and 0.827 on the receiver operating characteristics curve for the training and validation sets, respectively), facilitating the assessment of LNM risk and guiding post-ESD treatment decisions.

Despite the paper's advancements, it is crucial to acknowledge the study's limitations. As this is a retrospective study, there is an increased potential for biases in case selection and the inability to collect other relevant measures (*e.g.*, LNM rates after EMR and ESD, changes in outcome with neoadjuvant CRT, *etc.*). Despite multivariate regression analysis, there is still an increased risk for confounders with retrospection as the impact of factors such as age, tumor proximity to blood

and lymphatic vessels, smoking, and alcohol use cannot be ascertained. Additionally, this study excludes cases where fewer than 12 lymph nodes were dissected. Confounders (*e.g.*, from anatomical variation or grossly visible lymphadenopathy due to metastasis) may result in a greater or fewer number of lymph nodes dissected during surgery, and these may influence which cases are selected downstream.

The aims of this study in predicting the outcome of ESCC are not unprecedented. A 2021 retrospective study on 407 ESCC patients demonstrated that a low-performance status [≥ 2 Eastern Cooperative Oncology Group Performance Status (ECOG-PS)] was significantly associated with increased early mortality. Additionally, higher rates of late mortality were associated with male sex, positive smoking history, high ECOG-PS score, high Charlson Comorbidity Index score, low psoas muscle mass index, and low prognostic nutritional index[11]. Moreover, other previous studies have developed similar nomograms for ESCC LNM[12] and evaluated factors like tumor budding and infiltrative growth patterns[13,14]. However, this investigation provides additional data from 474 ESCC patients to determine independent LNM risk factors through multivariate regression analysis, with greater statistical power and significance.

CONCLUSION

The emergent popularity of ESD and EMR provides effective tools in the management of superficial early-stage ESCC. These minimally invasive and cost-effective interventions reduce complications and recovery time compared to traditional esophagectomy. However, esophagectomy, along with lymph node dissection and CRT, may be necessary if there is deeper tissue invasion or a high likelihood of LNM or LVI. Therefore, there is significant clinical and financial value in being able to accurately predict cases where esophagectomy and the addition of CRT may be necessary. Due to the limitations associated with current retrospective studies on predicting LNM and LVI with superficial ESCC, future prospective multicenter studies are required to validate the nomogram's reliability. Prospective study designs would reduce selection bias, permit evaluation of other risk factors and confounders, and present stronger arguments for causation. It would also allow for further exploration of LNM rates with ESD as opposed to EMR, which may influence the selection of specific endoscopic techniques in certain patients and circumstances. A prospective avenue of research could explore molecular biomarkers, given their association with specific outcomes. For instance, the lack of phosphatase and tensin homolog (PTEN), a tumor suppressor, correlates with an elevated rate of locoregional LNM in ESCC at 60.5%, compared to cases with PTEN presence at 36.1%. In contrast, heightened expression of STMN1 (stathmin 1), a cytoskeleton regulator, is linked to a higher 3-year post-surgery LNM rate of 52%, as opposed to cases with low STMN1 expression at 33.8%[15]. Recent studies show potential in predicting locoregional metastasis and poorer outcomes in patients with superficial ESCC. Upon validation in future research, these findings could lead to the development of enhanced guidelines that facilitate improved identification of patients likely to benefit from ESD and EMR procedures.

FOOTNOTES

Author contributions: Lin HT, Abdelbaki A, and Krishna SG wrote the paper; all authors have read and approved the final manuscript.

Conflict-of-interest statement: None of the authors have any relevant conflicts to disclose.

Country/Territory of origin: United States

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S-Editor: Lin C
L-Editor: A
P-Editor: Zhao YQ

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