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Opinion

Locally Advanced Esophageal Squamous Cell Carcinoma Treated with Upfront Surgery: Nomogram-Based Survival Predictions and Treatment Recommendations

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Abstract

This study's objectives are to guide risk-dependent adjuvant therapy for Locally Advanced Esophageal Squamous Cell Carcinoma (LA-ESCC) after esophagectomy, measure survival benefit, and produce a predictive nomogram. An internal validation and independent external validation in a randomized controlled trial were performed as part of this single-center retrospective research of consecutive LA-ESCCs treated by curative-intent esophagectomy. Using the Cox proportional hazards model, a nomogram was created to estimate 5-year Overall Survival (OS) after factor selection by the least absolute shrinkage and selection operator regression. Its discriminative and predictive abilities were assessed using the calibration plot and Area Under the Curve (AUC), respectively. The quantification and plotting of the adjuvant therapy induced improvement in survival were done according to nomogram score. For model creation, internal validation, and external validation, respectively, a total of 1077, 718, and 118 patients were included. Gender, pathological T and N stages, differentiation, surgical margin, lymphovascular invasion, number of lymph nodes removed, and adjuvant therapy were the eight significant prognostic markers found by the nomogram. The nomogram demonstrated improved discriminative ability compared to TNM stage, with substantial differences in survival rates among various risk strata. The calibration plot showed a good level of agreement between the 5-year OS predicted by the nomogram and the actual OS. After external validation, consistent results were drawn. In nearly all patients (nomogram score 110 to 260) and patients mostly at high-intermediate risk (nomogram score 159 to 207), an adjuvant chemoradiotherapy or chemotherapy benefit of at least 10% on 5-year OS was anticipated. A highly accurate clinicopathological nomogram for predicting 5-year OS for LA-ESCC following esophagectomy has been devised. The suggested nomogram performed better than TNM stage and offered risk-based, personalized recommendations for adjuvant therapy.

Keywords: Esophageal squamous cell carcinoma • Esophagectomy

Introduction

Esophageal Carcinoma (EC) is a serious cancer that ranks sixth in death and seventh in incidence worldwide. EC is the third most prevalent cancer in China, with an estimated 477,900 new cases and 375,000 fatalities per year. The long-term survival of locally advanced EC is still far from satisfactory, despite the fact that neoadjuvant chemoradiotherapy followed by radical esophagectomy greatly increases survival and is advised as the standard therapy by the National Comprehensive Cancer Network (NCCN) recommendation. Actually, a significant portion of Chinese patients with locally advanced EC undergo surgery initially, and an alternate real-world multimodal treatment pattern in China is radical esophagectomy combined adjuvant chemoradiotherapy. It is still too early to declare the investigation into postoperative survival forecasts and adjuvant therapy options obsolete in the current neoadjuvant era.

After esophagectomy, there is high survival heterogeneity among patients with the same disease stage, making it challenging to make risk-adaptive postoperative therapy recommendations and obtain accurate survival forecasts based solely on TNM stage. In addition to disease stage, a large number of additional clinicopathological variables, including gender, tumor site, lymphovascular invasion, differentiation grade, and adjuvant therapy, are independently related with survival. In order to divide patients into different risk categories, provide personalized survival predictions, and direct risk-dependent adjuvant therapies, it is urgent to find a novel clinicopathological risk-stratification model that extends beyond the current TNM stage.

Both oncologists and patients can easily understand a statistical prediction model when presented in a nomogram's visual style. In line with this, when compared to traditional risk stratifications, the creation of nomograms to estimate risk in some cancers has enhanced predicted accuracy for clinical outcomes. On the basis of large-scale populations, some nomograms for predicting survival of locally progressed EC following esophagectomy have been established and have helped with survival prediction. However, in previously published nomograms, risk-dependent adjuvant medicines were infrequently suggested to individuals. Developing and validating a clinicopathological nomogram for Overall Survival (OS) in patients with Locally Advanced Esophageal Squamous Cell Carcinoma (LA-ESCC) following esophagectomy is the primary goal of this study. Based on nomogram score, risk-dependent and customized adjuvant therapies are then suggested.

Data extraction, evaluation, and follow-up

Age and sex of the patient, Karnofsky Performance Status (KPS), pathological characteristics (location, length, stage for the tumor and lymph node, differentiation, surgical margin, lymphovascular invasion, nerve invasion, and number of lymph nodes resection), adjuvant chemotherapy or chemoradiotherapy, and follow-up information were all included in this data set (follow-up duration and survival). Continuous variables were compared as both continuous and categorical variables and were categorized using clinical reasoning or statistical techniques. Age was divided into groups of 64 years, 65 years-74 years, or 75 years. The classification of tumor length was 5 cm. The KPS score ranges from 70 to 80 or 90 to 100. Lymph node resection counts were categorized as 15 or>15. The illness site was divided into three categories: top (18 cm-23 cm from incisors), middle (24 cm-32 cm from incisors), and bottom (from tracheal bifurcation midway to gastroesophageal junction) (from midway between tracheal bifurcation and gastroesophageal junction to gastroesophageal junction, including abdominal esophagus; 32 cm-40 cm from incisors). No malignancy was found at the resection margin, hence the surgical margin was classified as negative. Additionally, the histologic distinction was rated as moderate or poor. Medical records and pathology reports were used to gather clinicopathological data.

Following treatment, routine clinical and laboratory tests were performed. Computed Tomography (CT) was the most common imaging technique. Positron Emission Tomography-Computed Tomography (PET-CT) was strongly advised for patients whose CT scan revealed a recurrence or

progression in order to provide a conclusive diagnosis. Every three months for the first two years, every six months for the following three years, and then annually were used as the intervals for follow-up assessments. The Response Evaluation Criteria in Solid Tumors were used to evaluate treatment response. Clinical records, phone calls to the deceased's families, or the Chinese Bureau of Population Statistics' central registry were used to determine the dates of their deaths.

Nomogram construction

The primary cohort was used to create the prognostic nomogram. In the invariable Cox regression analysis, clinically significant covariates with a p-value of less than 0.05 were selected. Additionally, factors that had been previously identified as being strongly related with long-term survival were taken into account. Demographics (age and gender), KPS, pathologic features (location, length, T stage, N stage, differentiation, surgical margin, lymphovascular invasion, nerve invasion, and number of lymph node resection), and adjuvant therapy were the variables that were screened. The Least Absolute Shrinkage and Selection Operator (LASSO) regression algorithm was used with the chosen variables. The appropriate tuning parameter lambda for LASSO logistic regression was confirmed using cross-validation. The 5-year OS rate was then predicted using a multivariate Cox proportional hazard analysis using the most significant variables determined by LASSO.

Discussion

To create a predictive nomogram for LA-ESCC following esophagectomy and direct risk-dependent adjuvant medications, this study involved a sizable number of Chinese patients. Based on eight key clinicopathological parameters and with a median follow-up of more than 5 years, a predictive nomogram with satisfactory discrimination and calibration was created, with thorough internal and external validations. The nomogram significantly increased predicted accuracy by 4%-8% as compared to the 8th AJCC TNM stage. Adjuvant chemoradiotherapy/chemotherapy survival advantages were quantified according to nomogram scores, and patients were given risk-dependent, customized treatment recommendations. These findings offered fresh proof in favor of using nomograms to predict survival and direct precise adjuvant therapy in patients with LA-ESCC following esophagectomy. According to earlier research, the nomogram's most significant prognostic factor was pathological T stage, which was followed by pathological N stage and adjuvant chemoradiotherapy. This shows the significance of adjuvant chemoradiotherapy in improving survival. The nomogram scores of patients with pT3N0M0 plus adjuvant chemoradiotherapy, for instance, were even lower than those with pT2N0M0 plus observation when other clinicopathological factors were the same, indicating that locally advanced disease with effective postoperative chemoradiotherapy has a greater potential to show a non-inferior survival than early disease. Adjuvant radiation could dramatically improve local control rates and reduce local recurrences in patients with LA-ESCC, which led to a prolonged OS. In the prospective RCT, the inclusion of postoperative concurrent chemoradiotherapy and radiation in LA-ESCCs significantly increased the 3-year OS rate by 18.5% and 12.8%, respectively, when compared to surgery alone. Chemotherapy and radiation therapy each contributed to improvements in the 3-year OS of 12.8% and 5.7%, indicating that adjuvant radiotherapy has a more significant effect than chemotherapy. The inclusion of adjuvant radiation to chemotherapy generally resulted in an increase of 10%-20% in the 5-year OS rate, according to this real-world retrospective analysis. In contrast, adjuvant chemotherapy by itself could only enhance the 5-year OS rate in a small percentage of patients by up to 10%.

Therapeutic guidelines now manage and advise adjuvant therapies mostly based on pathological TNM stage. Although additional prognostic indicators are frequently taken into account whenmaking decisions, it is not always evident what the quantitative relationship is between these prognostic factors and long-term survival. The survival improvement attributed to each prognostic factor may be simply measured and quantified following the successful establishment of a nomogram. Most crucially, we developed an intuitive and visual survival improvement curve matching to each nomogram score after receiving adjuvant therapy, taking into account that adjuvant therapy was the only component selected by oncologists. Oncologists receive direct and unambiguous clinical evidence to help them make an informed decision regarding a patient's tailored care. Additionally, patients now have easier access to health information because to the data visualization of risk-dependent survival improvement, which lowers the communication gap between patients and oncologists.

This study's merits included a large sample size, thorough validation, and a prescription for adjuvant therapy based on risk. First, more than 2000 LA-ESCC patients were enrolled, with a median follow-up of more than 5 years. It was thought that the prognostic nomogram based on this sizable cohort would offer accurate and useful survival prediction for Chinese patients. Second, thorough internal and external validations were carried out. After external validation in a separate population with entirely distinct features, it was shown that the nomogram's accuracy and reliability were nearly similar, indicating a good degree of generalizability for various patients.

Third, quantitative survival advantages following adjuvant therapy may be easily computed, and patients might receive risk-dependent, tailored adjuvant treatment recommendations based on their nomogram scores. Fourth, this nomogram derived from real-world data offered substantial and useful utility for clinical decision-making. Its implementation was made easier by the simple accessibility of these prognostic indicators from medical records. This study has some shortcomings that should be taken into account. First of all, this study was retrospective and included certain biases or confounders. Although multivariable analysis was used in this investigation, biases were still present and were challenging for statistical optimization to completely eliminate. When evaluating these findings, it is important to keep in mind that this study was retrospective. Second, as the data used for this study came from a single Chinese institute, external validation was crucial to enhancing the reliability of the findings. The external cohort's validation was less robust due to the small sample size. Third, the post-operative KPS score was not taken into account independently in this investigation, despite pre-operative KPS being balanced between groups and having a negligible impact on prognosis. At our hospital, the multidisciplinary team's judgement typically guided adjuvant treatment decisions. Lack of post-operative KPS should be considered one of many potential biases. Patients' post-operative general health may also have an impact on the prognosis. Fourth, as the main pathogenic kind, treatment regimen, and image method in follow-up differ from those in this study, care should be taken when using this nomogram on patients from Western nations. In China, CT is the most used imaging technique, but PET-CT is now often employed for follow-up in Western countries. Fifth, because there were no clinicopathological characteristics at the molecular or genetic level in this study, further investigation into the gene mutation profile, tumor microenvironment, and signaling pathways is advised.

Conclusion

In conclusion, we have developed and validated a nomogram that can predict 5-year OS for LA-ESCC after esophagectomy with a high degree of accuracy based on a large-scale cohort in China. The proposed nomogram shows better performance than the current TNM stage and provides risk-dependent and individualized adjuvant treatment options for Chinese patients.

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