[Original Research]

CHEST

Development and Validation of Web-Based Nomograms to Precisely Predict Conditional Risk of Site-Specific Recurrence for Patients With Completely Resected Non-small Cell Lung Cancer

A Multiinstitutional Study

Q10 Yang Zhang, MD; Difan Zheng, MD; Juntao Xie, MD; Yuan Li, MD; Yiyang Wang, MD; Chenguang Li, PhD;
Q1 Jiaqing Xiang, MD; Yawei Zhang, MD; Hong Hu, MD; Yihua Sun, MD; and Haiquan Chen, MD

BACKGROUND: There is currently no consensus regarding the optimal postoperative follow-up strategy for patients with completely resected non-small cell lung cancer (NSCLC). We aimed to develop web-based nomograms to precisely predict site-specific postoperative recurrence in patients with NSCLC and to guide individual surveillance strategies including when to follow up and what diagnostic tests to perform.

METHODS: We investigated the pattern of recurrence in a series of 2,017 patients with NSCLC (squamous cell carcinoma and nonlepidic invasive adenocarcinoma) who underwent complete surgical resection at Fudan University Shanghai Cancer Center (development cohort), and developed web-based clinicopathologic prediction models for conditional risk of site-specific recurrence based on Cox regression. The variables used in the analysis included sex, age, smoking history, tumor size, tumor histology, lymphovascular invasion, visceral pleural invasion, and pathologic TNM stage. A separate cohort of 3,308 patients with NSCLC from Shanghai Chest Hospital was used for external validation.

RESULTS: In the development cohort and the external validation cohort for the established nomograms to predict overall recurrence, thorax recurrence, abdomen recurrence, neck recurrence, brain recurrence, and bone recurrence, the C-statistics of Harrell et al were 0.743 and 0.748, 0.728 and 0.703, 0.760 and 0.749, 0.779 and 0.757, 0.787 and 0.784, and 0.777 and 0.739, respectively. The calibration plots showed optimal agreement between nomogram-predicted 3-year recurrence-free survival and actual 3-year recurrence-free survival.

CONCLUSIONS: These user-friendly nomograms can precisely predict site-specific recurrence in patients with completely resected NSCLC, based on clinicopathologic features. They may help physicians to make individual postoperative follow-up plans. CHEST 2018; ■(■):■-■

Q5 **KEY WORDS:** diagnostic imaging; lung cancer; surgery oncology; thoracic surgery

ABBREVIATIONS: HGADC = "high-grade" adenocarcinoma; LGADC = "low-grade" adenocarcinoma; LVI = lymphovascular invasion; NSCLC = non-small cell lung cancer; RFS = recurrence-free survival; SQCC = squamous cell carcinoma; VPI = visceral pleural invasion

AFFILIATIONS: From the Department of Thoracic Surgery (Drs Yang Zhang, Zheng, Xie, Xiang, Yawei Zhang, Hu, Sun, and Chen), Fudan University Shanghai Cancer Center, Shanghai, China; the Department of Oncology (Drs Yang Zhang, Zheng, Xie, Li, Xiang, Yawei Zhang, Hu, Sun, and Chen), Shanghai Medical College, Fudan University, Shanghai, China; the Department of Pathology (Dr Li), Fudan University Shanghai Cancer Center, Shanghai, China; the Department of Thoracic Surgery (Dr Wang), Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China; the Department of Lung Cancer (Dr Li), Tianjin Medical University Cancer Institute and Hospital, Tianjin, China; and the Institutes of Biomedical Sciences (Dr Chen), Fudan University, Shanghai, China.

FLA 5.5.0 DTD ■ CHEST1720_proof ■ 15 June 2018 ■ 4:25 am ■ EO: CHEST-17-2626

Lung cancer remains a major cause of cancer-related death worldwide despite advances in diagnosis and treatment.[1] Surgical resection offers the best opportunity of cure for patients with early-stage non-small cell lung cancer (NSCLC). However, even for patients with NSCLC who have undergone complete resection with curative intent, recurrence is still common and is a main obstacle for long-term survival of patients with this disease.[2,3] Appropriate surveillance after surgery is therefore necessary for the early detection of recurrent disease, which may result in timely therapies and potential improvement of patient survival. However, only a small number of studies have been published to address this issue,[4-6] with no consensus reached regarding the optimal postoperative follow-up strategy.

Precise estimation of site-specific recurrence risk is crucial to guide surveillance strategies, including when to follow up and what diagnostic tests to perform. Ideally, effective screening should be performed in patients with high risk of recurrence at specific sites, while unnecessary diagnostic tests in regions of lower risk of recurrence should be avoided. We therefore undertook this study to comprehensively investigate the pattern of postoperative recurrence in a large series of patients with completely resected NSCLC. User-friendly web-based clinicopathologic prediction models to estimate conditional risk of site-specific recurrence were developed and externally validated to guide individual postoperative follow-up plans.

Methods

Patients

This was a retrospective study. The development cohort included a series of patients who underwent surgical resection with curative intention at the Department of Thoracic Surgery, Fudan University Shanghai Cancer Hospital from April 2008 to February 2015. The following clinicopathologic data were prospectively collected: sex, age, smoking history, tumor size, tumor histology, lymphovascular invasion (LVI), visceral pleural invasion (VPI), pathologic TNM stage, sites of first recurrence, and recurrence-free survival (RFS). Inclusion criteria for this study included pathologically confirmed stage I-III NSCLC with complete resection. Exclusion criteria included history of malignancy, neoadjuvant therapy, compromised resection, positive surgical margins, and death due to surgical complications.

Chest CT scans, ultrasonography of abdominal and cervical/supraclavicular regions, and brain MRI or CT scans were performed every 4 months for the first 3 years after surgery, every 6 months for 3 to 5 years, and annually after 5 years. Bone scanning was performed annually. We also performed telephone follow-up, and suggested to those patients who reported clinical symptoms that they undergo imaging tests. Sites of first recurrence were classified as "thorax," "abdomen," "neck," "brain," and "bone" according to the follow-up diagnostic tests. For suspected metastatic lymph nodes in the cervical/supraclavicular regions diagnosed by ultrasound, we usually performed needle aspiration biopsy. For suspected organ metastasis in the abdominal region diagnosed by ultrasound, other imaging tests (MRI, CT, or PET/CT scan) were usually performed, and needle aspiration biopsy was conducted when necessary. RFS was defined as the time from surgical resection to disease recurrence. Patients without evidence of recurrence were censored at the time of last negative follow-up. Deaths without recurrence were treated as censored. Patients who never came to follow-up and could not be reached by telephone were deemed as "lost to follow-up."

This study was conducted in line with the Helsinki Declaration, and was approved by the Institutional Review Board of Fudan University Shanghai Cancer Center (IRB#090977-1). Informed consent was waived by the institutional review board because this was a retrospective study.

Statistical Analysis

The association of clinicopathologic variables with RFS was estimated using Cox proportional hazards models. Variables with a P value less than .05 in univariate analysis were entered into multivariate survival analysis. The multivariate Cox regression models (backward selection, using the Akaike information criterion as the stopping rule) were used to identify independent predictors, which were included in the nomograms. The proportional hazards assumption of Cox regression was tested with the "cox.zph" function of the "survival" package in R.[7]

Prediction models were then complemented with a tool to predict conditional survival probabilities.[8] The concordance index (C-index, or C-statistic) of Harrell et al was used to measure the discriminative ability of prognostic models.[9] Calibration (concordance between predicted and observed) of prediction models was evaluated by visual inspection of calibration plots. Model calibration was also measured by the Brier score.[10] For internal validation of the predictive accuracy of the nomograms, 1,000 bootstrap resamples were applied to calculate the bias-corrected C-index and the extent of "overfitting."[11] In addition, the nomograms were externally validated using a separate cohort of 3,308 patients with stage I-III NSCLC from Shanghai Chest Hospital to assess their general applicability. Patients in the external validation cohort also met the inclusion and exclusion criteria.

Statistical analysis was performed in Stata (version SE/11.1; StataCorp) and R (version 3.3.1; R Foundation for Statistical Computing). Web-based nomograms were developed using R and JavaScript. All tests were two-sided, and statistical significance was set at $P < .05$.

Detailed information about materials and methods is presented in e-Appendix 1.

FUNDING/SUPPORT: This work was supported by the National Natural Science Foundation of China [Grants 81330056, 81372525, 81422029, 81401886, 81572253, 81572264] and by the Health and Family Planning Commission of Shanghai Municipality [Grant No. 2013ZYJB0301].

Drs Zhang, Zheng, and Xie contributed equally to this work.

CORRESPONDENCE TO: Haiquan Chen, MD, Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, 270 Dong-An Rd, Shanghai 200032, China; e-mail: hqchen1@yahoo.com; Yihua Sun, MD, Department of Thoracic Surgery, Fudan University Shanghai Cancer Center, 270 Dong-An Rd, Shanghai 200032, China; e-mail: sun_yihua76@hotmail.com

DOI: https://doi.org/10.1016/j.chest.2018.04.040