Original Article

Selection for adjuvant chemotherapy in completely resected stage I non-small cell lung cancer: external validation of a Chinese prognostic risk model

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Background: The ability to sub-stratify survival within stage I is an important consideration as it is assumed that survival is heterogeneous within this sub-group. Liang *et al.* recently published a nomogram to predict post-operative survival in patients undergoing lung cancer surgery. The aim of our study is external validation of their published nomogram in a British cohort focusing on stages IA and IB to determine applicability in selection of adjuvant chemotherapy within stage I.

Methods: Patient variables were extracted and the score individually calculated. Receiver operative characteristics curve (ROC) was calculated and compared with the original derivation cohort and the discriminatory ability was further quantified using survival plots by splitting our (external) validation cohort into three tertiles and Kaplan Meier plots were constructed and individual curves tested using Cox regression analysis on Stata 13 and R 3.1.2 respectively.

Results: A total of 1,238 patients were included for analysis. For all patients from stage IA to IIB the mean (SD) score was 9.95 (4.2). The ROC score comparing patients who died versus those that remained alive was 0.62 (95% CI: 0.58 to 0.67). When divided into prognostic score tertiles, survival discrimination remained evident for the entire cohort, as well as those for stage IA and IB alone. The P value comparing survival between the middle and highest score with baseline (low score) was P=0.031 and P=0.034 respectively.

Conclusions: Our results of external validation suggested lower survival discrimination than reported by the original group; however discrimination between survival remained evident for stage I.

Keywords: Lung cancer; external validation; nomogram

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Introduction

Surgical resection is the most common treatment for patients with localized non-small cell lung cancer (NSCLC) (1). Currently guidelines recommend adjuvant chemotherapy for patients with completely resected pathologic stage II NSCLC (2). No guidelines currently recommend additional chemotherapy for patients with completely resected pathologic stage I disease. However, the cancer specific survival in this best prognostic group is 60% to 80% with an expected 5 years recurrence rate of 30% to 55% (3-5).

The ability to sub-stratify survival within stage I is

Table 1 Modified prognostic score

Variable	Score
Age (years)	
<60	0
60–70	1.5
>70	4
Histology	
Bronchioloalveolar Ca	0
Squamous Ca	1.1
Adenocarcinoma	2.3
Large cell Ca	3.2
Adenosquamous Ca	4.8
Other	5.8
Number of LN stations sampled	
>7	0
≤7	2.3
Sex	
Male	1.4
Female	0
T Stage	
T1a	0
T1b	1.6
T2a	3.3
T2b	6.4
T3	8.4
N Stage	
N0	0
N1	5.6

LN, lymph node.

therefore important consideration as survival can be heterogeneous within this sub-group, and the ability to accurately predict sub-sets with poor outcomes despite stage I disease could be used to help select appropriate patients for adjuvant chemotherapy.

Recently, Liang *et al.* published a Chinese multi-institutional logistic regression derived model to predict post-operative survival in over 5,000 patients undergoing lung cancer surgery for all stages (6). The aim of our study is external validation of their published nomogram in a British cohort focusing on stages IA and IB to determine applicability in selection of adjuvant chemotherapy within stage I.

Materials and methods

Between 30 April, 2007 and 11 February, 2015, 1,442 consecutive patients who underwent resection for primary NSCLC at our institutions (Departments of Thoracic Surgery, Royal Brompton and Harefield NHS Trust Hospitals) were retrospectively analyzed from a prospectively collected database.

Patients' data were collected including the following variables: sex, age, histologic subtype, type of operation, type of resection, number of lymph node stations sampled and pathologic tumor stage. Pathologic staging was characterized according to the seventh edition of the American Joint Committee on Cancer TNM staging system. Only patients diagnosed with NSCLC who underwent radical resection and pathologically stage I to II were included in this study. Neither neoadjuvant and/or adjuvant chemotherapy nor radiation therapy was performed for the patients during that period of time. We excluded 118 patients with carcinoid tumors (not in the original Chinese development set) and 86 patients without complete data on lymph node assessment leaving 1,238 patients for validation (validation cohort). Patients were followed up using the NHS tracing service through to February 2015.

Statistical analysis

Receiver operative characteristics curve (ROC) was calculated and compared with the original derivation cohort and the discriminatory ability was further quantified using survival plots by splitting our (external) validation cohort into three tertiles and Kaplan Meier plots were constructed and individual curves tested using Cox regression analysis on Stata 13 and R 3.1.2, respectively. The model performance for predicting outcome was evaluated by calculating the concordance index (C-index).

Prognostic scores were calculated using assigned variable values of the published Chinese coefficients (*Table 1*). The number of lymph node variable however had to be modified, as our center does not count individual nodes. Therefore, we substituted the number of lymph node stations rather than the number of actual nodes for the purposes of this work.

Results

Of the 1,238 patients included, 657 (53.1%) were male and

Table 2 Patient demographic and clinicopathologic characteristics

Characteristics	N, (%)
Sex	
Male	581 (46.9)
Female	657 (53.1)
Age	
<60	228 (18.4)
60–70	513 (41.4)
>70	497 (40.2)
Histologic subtype	
Bronchioloalveolar Ca	12 (1.0)
Adenocarcinoma	679 (54.9)
Squamous Ca	324 (26.2)
Adenosquamous Ca	16 (1.3)
Large cell Ca	23 (1.8)
Other	184 (14.8)
Type of operation	
VATS	272 (22.0)
Open	966 (78.0)
Type of resection	
Lobectomy	1,014 (81.9)
Segmentectomy	62 (5.0)
Pneumonectomy	37 (2.9)
Wedge resection	85 (6.9)
Sleeve resection	40 (3.3)
Pathologic T category	
T1a	334 (27.0)
T1b	283 (22.8)
T2a	356 (28.7)
T2b	105 (8.5)
T3	160 (13.0)
Pathologic N category	
N0	1,064 (86.0)
N1	174 (14.0)
Pathologic TNM stage	
IA	537 (43.4)
IB	299 (24.1)
IIA	208 (16.8)
IIB	194 (15.7)
Number of LN stations sampled	
≤7	886 (71.5)
>7	352 (28.5)

VATS, video-assisted thoracic surgery; TNM, tumor node metastasis; LN, lymph node.

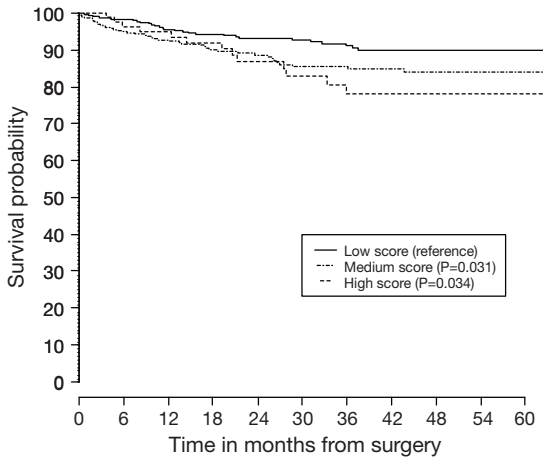

Figure 1 Survival discrimination within stage I.

581 (46.9%) were female. The median age at admission was 66 years (range, 13 to 89). The clinicopathologic characteristics of patients are summarized in *Table 2*.

The mean prognostic score for all patients from stage IA to IIB was a mean (SD) of 9.95 (4.2). The ROC score comparing patients who died versus those that remained alive was 0.62 (95% CI: 0.58 to 0.67). When divided into prognostic score tertiles, survival discrimination remained evident for the entire validation cohort, as well as those for stage IA and IB alone. The P value comparing survival between the middle and highest score with baseline (low score) was P=0.031 and P=0.034 respectively (*Figure 1*). The C-index for overall survival was 0.61 [standard error (SE) of 0.02] and the C-index for stage I survival was 0.57 (SE of 0.03).

Discussion

After complete surgical resection, the prognoses expressed in terms of 5-year survival rates, are commonly accepted to be 60% to 80% for stage I and 30% to 50% for stage II, which are remarkably heterogeneous, leading to a number of investigators seeking to refine the prognostic ability with defined TNM categories (4). The most pertinent clinical application is the potential to sub select patients within stage I for consideration of adjuvant chemotherapy. We validated the risk model proposed by Liang *et al.* using a British cohort focusing on stages IA and IB and found reasonable discrimination within stage I (6).

We expected differences in clinicopathologic characteristics between the Chinese and British cohorts. The majority of patients in the Chinese cohort were male, compared with the almost balanced distribution

in our cohort and the Chinese cohort (in general) was younger. We also noticed differences in the distribution of bronchioloalveolar and 'other' histologic subtypes (5.1% *vs.* 1% and 1.3% *vs.* 14.8%, respectively). Finally, the percentage of patients with stage I in the Chinese and validation cohorts were 47.0% and 67.5%, respectively. Despite these discrepancies between the two cohorts, the Chinese nomogram performed reasonably well.

On the application of the model the number of lymph nodes harvested was included as a variable in the risk model. This was a difficult measure, as the number of lymph nodes also varies greatly from one station to another and between laboratories and pathologists (7-11). Extraction modality of the nodal tissue sometimes leads to over or underestimation of accurate number of lymph nodes (12,13). We analyzed the number of sampled stations instead of the number of harvested lymph nodes. But more disconcerting is that the variable itself is a deterministic feature. What this means is that surgeons potentially have the "ability" to influence prognosis by the number of lymph nodes harvested. Most risk models are based on factors that cannot be "influenced".

A significant number of patients with NSCLC undergoing curative resection ultimately die of systemic recurrence (14,15). The evidence supporting the use of adjuvant chemotherapy in stage II and III is broad and it has become the standard treatment for patients following complete resection within these stages (2,16,17). Despite conflicting researches, most studies demonstrate no benefits of adjuvant chemotherapy for stage IA NSCLC and currently it is not indicated for patients following complete resection (2,18-22). However, current trials that focus specifically on earlier stage indicate no clear consensus regarding the benefit of adjuvant chemotherapy for patients with stage IB. Both CALGB 9633 study and JABR 10 trial showed similar results and supported consideration of adjuvant chemotherapy only for large IB tumors. Nevertheless, this favor did not remain consistent in late follow-up reanalysis and the debate whether adjuvant chemotherapy is an effective application for stage IB NSCLC remains controversial (2,23-25). In scope of these debates, we aimed to validate the Chinese nomogram by focusing on stages IA and IB to determine applicability in selection of adjuvant chemotherapy within stage I.

In conclusion, our results of external validation suggested lower survival discrimination than reported by the original group; however discrimination between survival remained evident for stage I. The Chinese model could be useful for better estimation of survival of individual patients after surgery and for identifying subgroups of patients, especially in stage I, who may benefit from an adjuvant treatment strategy.

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None

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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