Predicting Incomplete Resection in Non-Small Cell Lung Cancer Preoperatively: A Validated Nomogram

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Background. **Patients who are surgically treated for stage I to III non-small cell lung cancer (NSCLC) have dismal prognosis after incomplete (R1-R2) resection. Our study aimed to develop a prediction model to estimate the chance of incomplete resection based on preoperative patient-, tumor-, and treatment-related factors.**

Methods. **From a Dutch national cancer database, NSCLC patients who had surgical treatment without neoadjuvant therapy were selected. Thirteen possible predictors were analyzed. Multivariable logistic regression was used to create a prediction model. External validation was applied in the American National Cancer Database, whereupon the model was adjusted. Discriminatory ability and calibration of the model was determined after internal and external validation. The prediction model was presented as nomogram.**

Results. **Of 7156 patients, 511 had an incomplete resection (7.1%). Independent predictors were histology, cT stage, cN stage, extent of surgery, and open vs thoracoscopic approach. After internal validation, the corrected C statistic of the resulting nomogram was 0.72. Application of the nomogram to an external data set of 85,235 patients with incomplete resection in 2485 patients (2.9%) resulted in a C statistic of 0.71. Calibration revealed good overall fit of the nomogram in both cohorts.**

Conclusions. **An internationally validated nomogram is presented providing the ability to predict the individual chance of incomplete resection in patients with stage I to III NSCLC planned for resection. In case of a high predicted risk of incomplete resection, alternative treatment strategies could be considered, whereas a low risk further supports the use of surgical procedures.**

(Ann Thorac Surg 2021;111:1052-8)

Lung cancer is the most frequently diagnosed malignancy worldwide. In the Western world, non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancer cases and causes the highest number of cancer-related deaths.[1] Resection is standard of care for patients with stage I or II disease. The 5-year survival rates after surgical treatment are 52% to 89% for stage I disease and 33% to 52% for stage II disease. The rest of nonmetastatic patients have locally advanced (stage III) disease, representing a group with diverse primary tumor sizes and nodal extent.[2] Only a minority of stage III patients are considered resectable, and most receive concurrent or sequential chemoradiation associated with 5-year overall survival rates of approximately 20%.[3]

For patients who are fit for surgical treatment, the intention will be to perform a radical (R0) resection. Patients who have had an incomplete (R1-R2) resection have a worse prognosis than those with a complete resection.[4] Compared with an R0 resection, hazard ratios for death of 1.5 to 8.2 have been reported for R1-R2 resections when looking at overall survival after resection.[5] Being able to predict the chance of an

Accepted for publication May 27, 2020.

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The Supplemental Table can be viewed in the online version of this article [https://dx.doi.org/10.1016/j.athoracsur.2020.05.165] on https://www.annalsthoracicsurgery.org.

0003-4975
https://doi.org/10.1016/j.athoracsur.2020.05.165

incomplete resection before surgical treatment, using preoperative variables, would be of great value.

The purpose of this study was to create and internally and externally validate a prediction model with preoperative patient-, tumor-, and treatment-related factors that would enable prediction of a patient's individual probability of an incomplete resection by using 2 separate large national databases of stage I to III NSCLC patients.

Material and Methods

This observational study was approved by the University Medical Center Utrecht Institutional Review Board (project number 18-377/C). Use of the National Cancer Database (NCDB) data was exempt from Institutional Review Board evaluation because all patient information in the NCDB database was deidentified.

Study Population

We used a national database of the Netherlands Cancer Registry (managed by the Netherlands Comprehensive Cancer Organisation) of patients with NSCLC who were diagnosed between January 1, 2015, and December 31, 2018, and only included patients who had surgical treatment. The Netherlands Cancer Registry database contains in-depth patient, tumor, and treatment characteristics. All newly diagnosed cancer cases in the Netherlands are registered by trained independent data managers, based on information from electronic medical records, the Pathological Anatomical National Automated Archive (Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief), the national registry of hospital discharge diagnoses and diagnosis-treatment combinations (DTC). These data are translated to uniform and standardized data sets. Exclusion criteria were age younger than 18 years, cM1 stage, cTis, cT0, neoadjuvant chemotherapy or preoperative radiotherapy, or both, carcinoid histology, and time interval from diagnosis to resection exceeding 180 days. Reasons for excluding patients who underwent neoadjuvant therapy were to improve homogeneity of the population and the unavailability of data on restaging.

For the purpose of external validation, we used an American national cohort of lung cancer patients from the NCDB who underwent operations between January 1, 2011, and December 31, 2014. The NCDB database consists of deidentified information of patient demographics, tumor characteristics, and patient survival for approximately 70% of the United States population. The NCDB is a project of the American Cancer Society and the Commission on Cancer of the American College of Surgeons.[6] Exclusion criteria were the same.

Variables

Variables analyzed included age, sex, history of malignancy (except nonmelanoma skin cancer), World Health Organization performance status, lateralization (left or right sided), tumor location (upper lobe, lower lobe and other [middle lobe, main bronchus or overlapping locations]), histology,[7,8] differentiation grade, clinical T stage and N stage according to the American Joint Committee on Cancer, 8th Edition, extent of surgery (categorized as sublobar [wedge or segmental resection], lobar/bilobar, sleeve lobectomy or pneumonectomy), surgical approach (open vs video-assisted), and hospital volume (1-29, 30-59 and $\geq$60 yearly surgical lung cancer procedures per hospital).

For incidence years in which data regarding cT stage were only available according to the 7th Edition, the variable was converted to cT stage according to the 8th Edition when possible. This was not possible for 512 patients diagnosed in 2015-2016 with cT3 tumors (7.2% of the total study population); consequently, the variable was counted as missing and handled accordingly.

In the development set, incomplete resection was exclusively defined as microscopic incomplete resection (R1) or as macroscopic incomplete resection (R2), without supplementary criteria. In the external validation data set, incomplete resection was defined as gross or microscopic residual tumor in resection margins or as residual tumor not otherwise specified.

Statistics

Continuous variables are depicted as mean $\pm$ SD or medians with interquartile ranges, depending on the normality of the data distribution. Differences in continuous variables between patients with R1 to R2 resection and patients with R0 resection were assessed with the unpaired t test or Mann-Whitney U test, respectively. Differences in nominal and ordinal categorical variables were respectively assessed with the χ^2 test and the Mann-Whitney U test.

Model Development

All steps in the statistical analyses and reporting adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement.[9] Logistic regression was performed for the clinical variables. No restrictions were placed on these variables, because the number of incomplete resections was sufficient to allow for approximately 50 variables following the 1 variable per 10 events rule of thumb.[10] Odds ratios (ORs) with 95% confidence intervals (CIs) were obtained. Multicollinearity was assessed with Spearman correlations before modeling and the variance inflation factor (VIF) in the first step of the modeling process. A correlation coefficient of more than 0.7 or a VIF of more than 5, or both, were considered to indicate multicollinearity. In case of multicollinearity, the clinically most relevant variables were kept in the model. Potential interactions of histology with overall stage, surgical approach with overall stage, and surgical approach with cN stage and cT stage were assessed, because we hypothesized that the chance of incomplete resection could be different for histologic types and surgical approach depending on tumor stage and nodal status.

Missing data were considered to be missing at random. Multiple imputation by chained equations was used to impute missing data, creating 20 new data sets. All of the

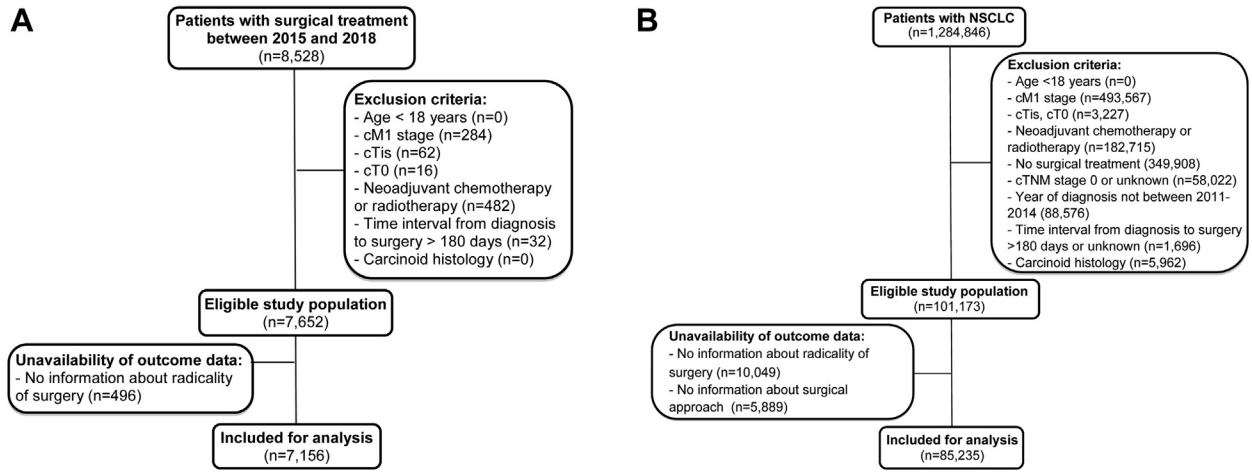

Figure 1. Flowchart of patient inclusion for (A) the development cohort and (B) the validation cohort. (NSCLC, non-small cell lung cancer.)

listed predictors, including significant interaction terms and the outcome, were included in the imputation procedure.[11] All modeling steps were pooled over these data sets. The first modeling step included all variables, after which variables were excluded using stepwise backward selection based on Akaike information criterion.[12]

Model Performance and Validation

Discriminative ability of the model was assessed with the C statistic. Internal validation was performed by 2000 bootstrap resamples of each of the 20 imputed data sets in which all modeling steps were repeated by backward elimination of redundant variables. With this, the optimism and shrinkage factors were calculated, enabling correction of the final model's intercept, β-coefficients, and C statistic. The corrected intercept and β-coefficients were used in further analyses. Model calibration was assessed by plotting octiles of predicted vs observed probabilities.

External validation was performed in the NCDB cohort with the corrected model from the development set. Calibration performance was assessed with calibration plots, after which the intercept of the logistic regression model was updated based on the difference in incidence in incomplete resections between the 2 cohorts.

Nomogram and Risk Score

A nomogram was created for the final model in both the development set after correction for optimism as well as for the intercept-updated model derived from external validation. All analyses were performed with "mice" and "rms" packages in R 3.6.3 software (The R Foundation for Statistical Computing, Vienna, Austria).

Results

After exclusion, 7156 patients in the validation cohort were eligible for the analysis (Figure 1A). Of these patients, 6645 underwent a complete resection, 511 had a R1 or R2 resection (7.1%), consisting of 460 (6.4%) microscopic residual tumors (R1) and 51 (0.7%) macroscopic residual tumors (R2). The mean age was 66.4 ± 8.7 years, and 3866 patients were men (54.0%). Information of baseline patient- and treatment-related characteristics is reported in Supplemental Table 1.

The external validation data set included 85,235 patients (Figure 1B); of these, 82,750 patients underwent a complete resection, and 2,485 had an incomplete resection (2.9%). The mean age was 68.1 ± 9.5 years, and 40,210 patients were men (47.2%).

Table 1. Final Multivariable Logistic Regression Model (After Internal Validation) for the Prediction of Incomplete Resection

Variable	Corrected OR (95% CI)	*P* Value
Histology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	0.69 (0.57-0.84)	<.001
Other	0.79 (0.57-1.10)	.16
Clinical T stage		
cT1	Reference	
cT2	1.98 (1.51-2.60)	<.001
cT3	2.90 (2.15-3.91)	<.001
cT4	4.50 (3.19-6.35)	<.001
Extent of resection		
Sublobar	Reference	
Lobar/bilobar	0.45 (0.32-0.63)	<.001
Sleeve lobectomy	0.86 (0.51-1.44)	.56
Pneumonectomy	0.69 (0.46-1.06)	.09
Surgical approach		
Endoscopic	Reference	
Open	1.42 (1.10-1.84)	.008
Clinical N stage		
cN0	Reference	
cN1	1.96 (1.56-2.46)	<.001
cN2/3	1.73 (1.22-2.46)	.002

Corrected intercept: −2.54.

CI, confidence interval; OR, odds ratio.

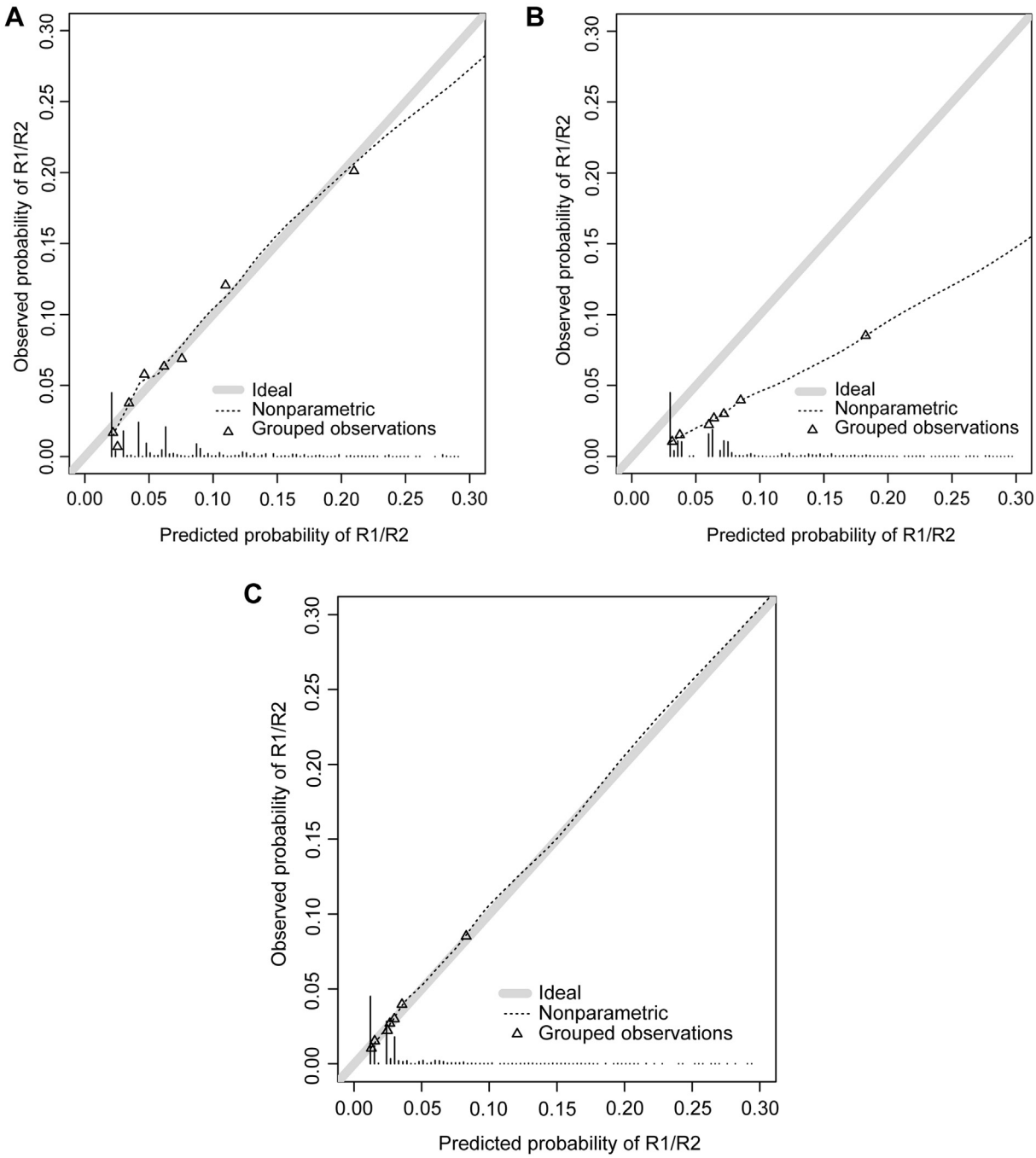

Figure 2. Calibration plot with predicted probability (deciles) vs observed probability, respectively for (A) internal validation, (B) external validation without updated intercept, and (C) external validation with updated intercept.

After backwards stepwise selection, the final model consisted of histology, cT stage, cN stage, extent of surgery, and surgical approach (Table 1).

The apparent C statistic was 0.74 and the corrected C statistic (after internal validation) was 0.72, indicating good discriminative ability of the final model. The intercept and β-coefficients were corrected for 6% optimism. Overall calibration of the model was good over the range of observed probabilities (Figure 2A).

The final model is presented as a nomogram (Figure 3). For the development cohort, low-, intermediate-, and high-risk score subgroups were created for scores 0 to 2, more than 2 to 4, and more than 4, respectively, for which predicted probabilities of R1 to R2 resection were 3.5%, 8.4%, and 19.8%, respectively. These probabilities were concordant with the observed probabilities of 3.3%, 8.4%, and 19.8%, respectively. For the validation cohort, low-, intermediate-, and high-risk score subgroups were

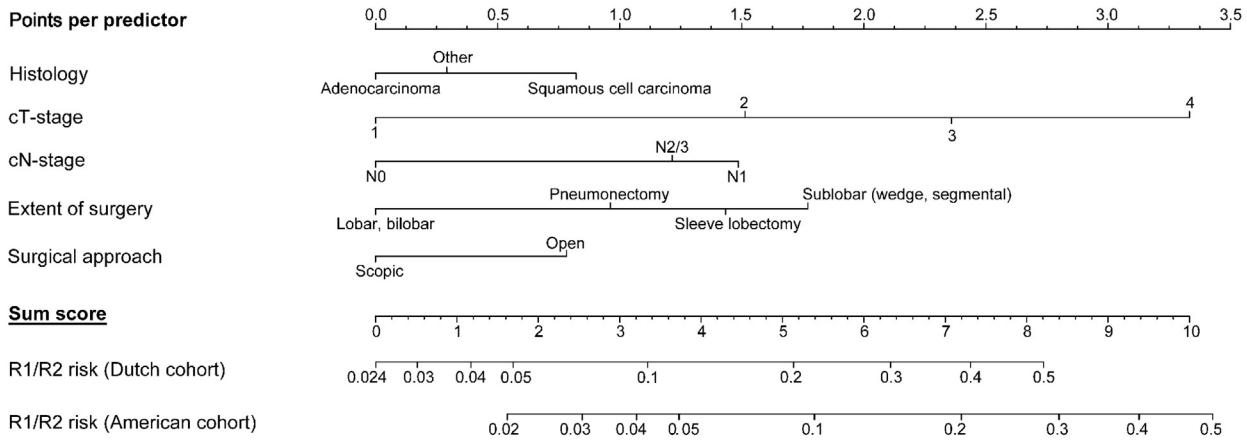

Figure 3. Nomogram for preoperative prediction of incomplete resection risk in stage I to III non-small cell lung cancer. The numbers listed at the upper line of the figure indicate the points to be assigned per predictor. By summing up all points, the predicted risk of incomplete resection can be read out by drawing a vertical line from the "Sum score" line to the 2 bottom lines of the figure.

created for scores 0 to 4, more than 4 to 6, and more than 6, respectively, for which predicted probabilities of R1 to R2 resection were 2.2%, 7.4%, and 16.7%, respectively. These probabilities also were concordant with the observed probabilities of 2.2%, 7.5%, and 17.1%, respectively. The linearity assumption with the logit of the outcome was not violated, indicating appropriate goodness of fit.

In external validation, the predicted probability of complete resection resulting from the developed model was lower than the observed probability, which was consistent across the whole risk range (ie, not specific for low- or high-risk groups). The intercept of the model was updated based on the incidence difference of complete resection between the cohorts. The model was recalibrated, with predicted probabilities corresponding to observed probabilities (Figures 2B, 2C). The C statistic resulting from application of the final model to the external validation set was 0.71. In Figure 4, use of the nomogram is illustrated by a case description.

Comment

An internationally validated nomogram that enables individual pretreatment prediction of the probability of complete resection in patients with newly diagnosed stage I to III NSCLC is presented. The chance of complete resection is high in well-selected patients. An increased risk of incomplete resection is predicted by non-adenocarcinoma histology, higher cT stage, clinical lymph node metastases, the extent of surgery, and an open surgical approach.

The positive impact of a complete resection on survival has been clearly established.[4,5,13,14] Adenocarcinoma histology influenced completeness of resection positively, but regarding the predictive power of histology for completeness of resection, no relevant references were identified. A possible explanation could be the previously reported fact that squamous cell carcinomas more often are located centrally.[15] Indeed, more squamous cell tumors were located in the main bronchus in the current data sets, but no information on central vs peripheral localization was available in the national database. Because the terminology central vs

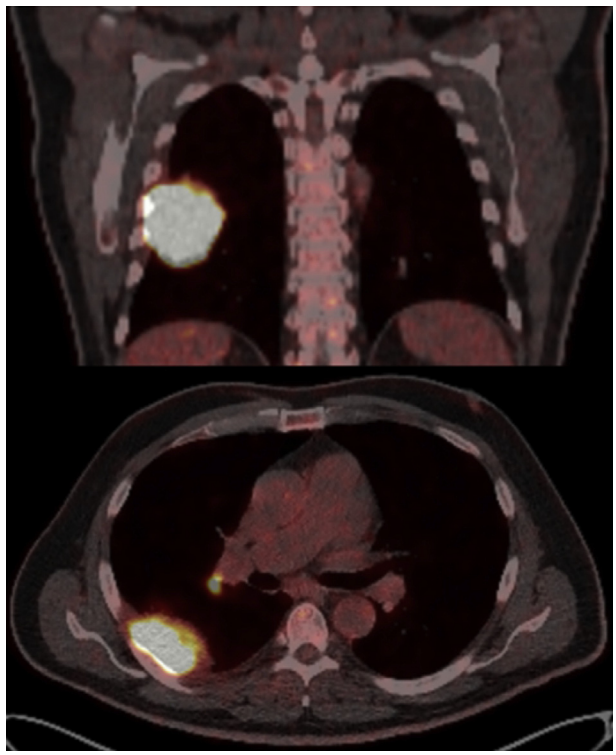

Figure 4. Example of the nomogram being used. Coronal and axial positron emission tomographic-computed tomographic images of a Dutch male patient with a cT4 N1 M0 squamous cell carcinoma of the right lower lobe. An open lobectomy was performed. The nomogram sum score is 6.3 points, which translates into an individual risk of 30% for incomplete resection. Pathology after lobectomy with thoracic wall resection revealed R1 resection.

peripheral tumors is not used systematically in patient medical records, the only way to determine this variable is by interpreting imaging, which cannot be performed by registry data managers. Such a location variable was therefore not part of the current analyses.

For tumor staging, a higher pT, pN, or overall stage correlated with worse outcome in several previous studies.[13,16-19] In accordance with the findings of the current study, lower T and N stages were associated with complete resection in 2 previous large studies,[4,14] as did anatomic resection vs wedge resections[4] and lobectomy vs pneumonectomy.[14] Sublobar resection has been identified as predictor of recurrence.[20,21] Stage I NSCLC patients after pneumonectomy or lobectomy had a higher 5-year survival compared with limited resections in a retrospective cohort of 3315 patients.[18] Younger age has been associated with better cancer-related outcomes in many studies,[13,16-19] but this variable appeared redundant in the prediction of complete resection in our model.

The incidence rates of 7.1% incomplete resections in the Dutch development population and of 2.9% in the American external validation cohort are comparable to previously reported incidences (range, 2%-17%).[4,13,16] Nevertheless, this difference is larger than expected at first sight. The higher incidence of complete resections in the external validation cohort could be attributed to more prevalent low cT stages in the American cohort. This could be the consequence of partial implemented lung cancer screening in the United States (although only 3.3%-3.9% of eligible smokers were screened),[22] which is not yet implemented in the Netherlands. Another explanation is the number of computed tomographic examinations per 1000 inhabitants per year in the Netherlands in 2015 to 2018. This was almost 70% lower than in the United States, which might have resulted in later diagnoses of NSCLC.[23]

More sublobar resections were observed in the external validation cohort, which was probably a consequence of the lower clinical tumor stages. Also, adenocarcinoma histology and well-differentiated tumors were more prevalent. These favorable factors could partially explain the higher numbers of complete resection. Additionally, tumor localization in the main bronchus or overlapping parts of the lung was twice as low; these localizations are more prone to incomplete resections. When updating the intercept of the original corrected model from the development set, the predictions for the external cohort were in line with the observed probabilities. In other terms, the adjusted model can be used in the American population. The results of the external validation indicate that the validated nomogram predictors are likely to result in similar good discriminatory ability for other countries. However, for more precise individualized risk prediction in those countries, the model may require recalibration based on national registries.

The presented prediction model may serve as a useful tool for making surgery-related decisions in patients with NSCLC. This should ideally be tested prospectively. Because complete resection is associated with better survival,[5] an alternative treatment approach might be preferred in case of a substantial pretreatment probability of an incomplete resection. Examples of alternative strategies include different surgical techniques, neoadjuvant chemoradiotherapy (trimodality treatment), definitive chemoradiotherapy with the omission of surgical resection, or stereotactic radiotherapy.[24-26] One could, for example, consider a risk of incomplete resection of 10% or more to be substantial, given the dismal consequences of R1-R2 resections.

Study Limitations

When a prediction model is being created, the direction of associations in a multivariable model can differ for independent variables and causal relationship between individual factors, and outcome is not necessarily present. The nomogram should be interpreted and used only with careful appreciation of its limitations. Most importantly, for this predictive study, no causality between predictors and the outcome can be inferred.

Secondly, although the development data set was extensive in nature, there may be other useful non-registered predictors. In that regard, clinical imaging information was lacking in the databases, whereas some studies demonstrated the predictive value of imaging for tumor invasion and resectability.[27-29] In high-risk patients, performing additional positron emission tomographic/magnetic resonance imaging might help in risk assessment for incomplete resection.[28]

The study results were strengthened by internal and external validation, the multitude of different variables, and the large population-based NSCLC data sets reflecting real-world (and not trial-related) outcomes with a low risk of selection bias. These large databases give the opportunity to answer questions for less frequent oncologic scenarios, including incomplete resection margins, with sufficient statistical power.

Conclusions

To better predict incompleteness of resection in NSCLC patients, a nomogram was developed and validated based on variables histology, cT stage, cN stage, extent of surgery, and surgical approach. The nomogram enables pretreatment calculation of the individual probability of a complete resection in stage I to III NSCLC patients fit for surgical treatment. The corrected C statistics were 0.72 and 0.71 after internal and external validation, respectively, indicating good discriminative ability of the final model. Overall in these patients, a high percentage of complete resections was observed. In case of a substantial predicted risk of incomplete resection, a larger extent of surgery or alternative treatment strategies should be considered, such as induction chemotherapy or definitive chemoradiotherapy with the omission of surgical treatment. A low predicted risk further supports the use of primary resection.

This work was supported by the Netherlands Comprehensive Cancer Organisation and the National Cancer Database with the supply of data. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-

profit sectors, and the authors have no conflicts of interest relevant to this work.

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