# Prediction Models for Mediastinal Ultrasound-Guided Transbronchial Needle Aspiration in Potentially Operable Non-Small Cell Lung Cancer <br> A Prospective Study 

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background: Prediction models for mediastinal metastasis and its detection by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) have not been developed using a prospective cohort of potentially operable patients with non-small cell lung cancer (NSCLC).
research question: Can mediastinal metastasis and its detection by EBUS-TBNA be predicted with prediction models in NSCLC?
STUDY DESIGN AND METHODS: For the prospective development cohort, 589 potentially operable patients with NSCLC were evaluated (July 2016-June 2019) from five Korean teaching hospitals. Mediastinal staging was performed using EBUS-TBNA (with or without the transesophageal approach). Surgery was performed for patients without clinical $\mathrm{N}(\mathrm{cN})$ 2-3 disease by endoscopic staging. The prediction model for lung cancer staging-mediastinal metastasis (PLUS-M) and a model for mediastinal metastasis detection by EBUS-TBNA (PLUS-E) were developed using multivariable logistic regression analyses. Validation was performed using a retrospective cohort ( $\mathrm{n}=309$ ) from a different period (June 2019-August 2021).
RESULTS: The prevalence of mediastinal metastasis diagnosed by EBUS-TBNA or surgery and the sensitivity of EBUS-TBNA in the development cohort were $35.3 \%$ and $87.0 \%$, respectively. In PLUS-M, younger age ( $<60$ years and 60-70 years compared with $\geq 70$ years), nonsquamous histology (adenocarcinoma and others), central tumor location, tumor size ( $>3-5 \mathrm{~cm}$ ), cN 1 or $\mathrm{cN} 2-3$ stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were significant risk factors for $\mathrm{N} 2-3$ disease. Areas under the receiver operating characteristic curve (AUCs) for PLUS-M and PLUS-E were 0.876 ( $95 \%$ CI, $0.845-0.906$ ) and 0.889 ( $95 \% \mathrm{CI}, 0.859-0.918$ ), respectively. Model fit was good (PLUS-M: Hosmer-Lemeshow $P=.658$, Brier score $=0.129$; PLUS-E: Hosmer-Lemeshow $P=.569$, Brier score $=0.118$ ). In the validation cohort, PLUSM (AUC, 0.859 [ $95 \%$ CI, 0.817-0.902], Hosmer-Lemeshow $P=.609$, Brier score $=0.144$ ) and PLUS-E (AUC, 0.900 [ $95 \% \mathrm{CI}, 0.865-0.936]$ ], Hosmer-Lemeshow $P=.361$, Brier score $=$ 0.112 ) showed good discrimination ability and calibration.
interpretation: PLUS-M and PLUS-E can be used effectively for decision-making for invasive mediastinal staging in NSCLC.
TRIAL REGISTRY: ClinicalTrials.gov; No.: NCT02991924; URL: www.clinicaltrials.gov
CHEST 2023; 164(3):770-784
KEY WORDS: EBUS-TBNA; mediastinal staging; non-small cell lung cancer; prediction model

## Take-home Points

Study Question: Can mediastinal metastasis and its detection by endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) be predicted with prediction models in non-small cell lung cancer (NSCLC)?
Results: The prediction model for lung cancer staging-mediastinal metastasis (PLUS-M) and the prediction model for lung cancer staging-mediastinal metastasis detection by EBUS-TBNA (PLUSE) were developed using age, histologic type, tumor location, tumor size, clinical N stage by CT and clinical N stage by PET-CT. PLUS-M and PLUS-E showed good discrimination ability and calibration.
Interpretation: PLUS-M and PLUS-E can be used effectively for decision-making for invasive mediastinal staging in NSCLC.

Invasive mediastinal staging is an important step that guides treatment decision-making in non-small cell lung cancer (NSCLC). ${ }^{1-3}$ Currently, endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), which has high diagnostic values comparable with those of mediastinoscopy, ${ }^{4,5}$ is a primary method for invasive staging. ${ }^{1,2}$

Practice guidelines for mediastinal staging in NSCLC recommend invasive staging for specific risk groups for mediastinal metastasis. ${ }^{1,2,6-9}$ According to European Society of Thoracic Surgeons (ESTS) guidelines, preoperative staging is recommended in patients with clinical $\mathrm{N}(\mathrm{cN})$ 1-3 disease by CT or

PET, a central tumor or a tumor $>3 \mathrm{~cm}$ in size. ${ }^{2}$ CHEST guidelines recommend invasive staging for cN1-3 disease by CT, cN2-3 disease by PET and central tumors with grade 1 evidence and do not recommend invasive staging for peripheral tumors of $\leq 3 \mathrm{~cm}$ with cNO disease by CT and PET. ${ }^{1}$ National Institute for Health and Care Excellence guidelines have a narrow recommendation for invasive mediastinal staging: $\mathrm{cN1} 1-3$ disease by CT or PET-CT. ${ }^{8}$ Younger age ${ }^{10-15}$ and adenocarcinoma histology ${ }^{11-14,16-19}$ are reported to be risk factors for mediastinal metastasis, but are not reflected clearly in the staging guidelines. ${ }^{1,2,6-9}$ Factors related with mediastinal metastasis, such as radiologic lymph node (LN) abnormalities by CT or PET scan imaging, central tumor location, tumor size, age, and histologic type can be related with each other. However, current guidelines do not present estimations for the probability of N2-3 disease based on combinations of risk factors.

The decision to perform invasive staging is influenced by the staging method's diagnostic capability as well as the probability of mediastinal metastasis. A prediction model for the detection of N2-3 disease by EBUS-TBNA that takes into account multiple risk factors has been developed using the American College of Chest Physicians Quality Improvement Registry, Evaluation, and Education database: the A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer (HAL). ${ }^{13}$ The model focused on EBUS-TBNA results and did not include the surgical pathologic staging results, which are the gold standard for mediastinal staging.

ABBREVIATIONS: AUC = area under the receiver operating characteristic curve; $\mathrm{cN}=$ clinical $\mathrm{N} ; \mathrm{cT}=$ clinical T; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; ESTS = European Society of Thoracic Surgeons; EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine needle aspiration; $\mathrm{HAL}=$ A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer; $\mathrm{LN}=$ lymph node; NCC = National Cancer Center; NSCLC = non-small cell lung cancer; PLUS-E = prediction model for lung cancer staging-mediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-M = prediction model for lung cancer staging-mediastinal metastasis
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[^0]The aim of this study was to develop prediction models for mediastinal metastasis diagnosed by EBUS-TBNA or surgery and by EBUS-TBNA alone using a prospective
cohort of patients with potentially operable NSCLC, which will be useful for decision-making regarding invasive staging.

## Study Design and Methods <br> Study Population

This prospective cohort study was conducted at five teaching hospitals in Korea (National Cancer Center [NCC], Seoul National University Bundang Hospital, Asan Medical Center, Samsung Medical Center, and Seoul National University Hospital). Six hundred patients with potentially operable confirmed (or highly suspicious) NSCLC (age range, 18-80 years) were enrolled prospectively from July 2016 through June 2019 (development cohort) (enrollment criteria presented in e-Table 1). The sample size was calculated to be sufficient to generate a two-sided 95\% CI with a sample area under the receiver operating characteristic curve (AUC) of 0.8 with a width of 0.08 and an $\mathrm{N} 2-3$ disease prevalence of $35 \%$ (based on our previous studies ${ }^{20,21}$ ). We excluded tumors with subsolid nodules with solid parts of $\leq 1 \mathrm{~cm}$ in diameter and those with solid nodules that were cTlaN0 stage by CT and PETCT scan imaging. Contrast chest CT scans (axial slice thickness, $\leq$ 3 mm ) and PET-CT scans (without contrast) were requested within 30 days before EBUS-TBNA.

For model validation, we used a retrospective cohort from the NCC from a different period (June 2019-August 2021) with the same enrollment criteria and imaging requirements. This study was approved by the institutional review board of NCC (Identifiers: NCC-2016-0156 and 2021-0307) and other hospitals (Seoul National University Bundang Hospital Identifier: B-1608-360-301, Asan Medical Center Identifier: 2016-0713, Samsung Medical Center Identifier: 2016-07-125-003, and Seoul National University Hospital Identifier: 1608-006-784). Informed consent was obtained from all participants in the development cohort.

## EBUS-TBNA and Surgery

EBUS-TBNA in the development cohort was performed by six experienced bronchoscopists ( $\geq 500$ EBUS-TBNA procedures) under conscious sedation. We recommended LNs of $\geq 1 \mathrm{~cm}$ or mediastinal nodes showing positive PET scan findings be sampled when targets were accessible and smaller or that nodes with negative PET scan findings be sampled based on echo features, potential pathways for lymphatic metastasis, and impact of metastasis at the nodal station on treatment decision. We recommended that N3 nodes be sampled first, with at least two to three aspirations per target. ${ }^{22}$ N1 staging was not performed routinely. Final determination of procedural details was made by the attending bronchoscopists, taking into consideration patient tolerance. Aspirations using a transesophageal approach (endoscopic ultrasound with bronchoscope-guided fine needle aspiration [EUS-B-FNA]) were allowed when LNs were difficult to access by EBUS-TBNA, but were reachable by EUS-BFNA. ${ }^{20} \mathrm{cN}$ stage determined by EBUS-TBNA included EUS-B-FNA results. We recommended surgery with systematic LN dissection for patients without cN2-3 disease by EBUS-TBNA within 30 days after EBUS-TBNA.

## Data Collection

Data on age, sex, histologic findings, tumor location (central or peripheral), clinical T (cT) stage by size on axial chest CT scan and cN stage by CT, PET-CT, and EBUS-TBNA, as well as data on the EBUS-TBNA procedure, were collected. Age was converted into a categorical variable ( $<60$ years, $60-70$ years, and $\geq 70$ years). We
reviewed all nonsurgical and surgical lung cancer histologic results and classified them into three groups: squamous cell carcinoma, adenocarcinoma (including NSCLC with adenocarcinoma component), and others, based on final pathologic diagnosis including surgical results. A central tumor was defined as one located in the inner one-third of the hemithorax ${ }^{23}$ based on the innermost part of the tumor on CT scan. ${ }^{24,25}$ Lines dividing the hemithorax into thirds were drawn as concentric lines arising from the midline. ${ }^{24,25}$ The eighth edition of the International Association for the Study of Lung Cancer staging criteria was used for staging. ${ }^{26-28}$ For surgery cases, pathological N stage was reviewed. For patients with pathological Nx stage, at least 12 months of follow-up was performed to identify benign mediastinal LNs with a lack of radiologic disease progression. ${ }^{29}$

## Statistical Analysis

Development of Prediction Models: The characteristics of the development and validation cohorts were compared using the $\chi^{2}$ test, Fisher exact test, Wilcoxon rank-sum test, or Student $t$ test, as appropriate. The Prediction model for Lung cancer StagingMediastinal metastasis (PLUS-M) and the Prediction model for Lung cancer Staging-mediastinal metastasis detection by EBUSTBNA (PLUS-E) were developed. The primary outcome for the development of PLUS-M was the presence of N2 or N3 metastasis by EBUS-TBNA, surgery, or follow-up after surgery (for pathological Nx stage). We performed univariable logistic regression analysis for the following variables: age, sex, histologic findings, tumor location, cT stage by size, cN stage by CT, and cN stage by PET-CT. All variables with $P$ values of $<.2$ were included in the multivariable logistic regression analysis, and variables included in the final model were determined by the backward selection method with an elimination criterion of $P \geq$ .05. The primary outcome for development of PLUS-E was the presence of N 2 or N 3 metastasis by EBUS-TBNA. Univariable and multivariable logistic regression analyses were performed on the variables described above. Significant risk factors in PLUS-M were included in PLUS-E. The regression analysis results are presented as ORs with $95 \%$ CIs and $P$ values. Clinical nomograms were constructed for PLUS-M and PLUS-E based on multivariable logistic regression analyses.

Model Performance Assessment and Validation: For discrimination, AUCs for PLUS-M and PLUS-E were calculated in the development cohort. Internal validation was performed to calculate optimismadjusted AUCs using 1,000 bootstrap samples. Calibration was assessed for PLUS-M and PLUS-E using the Hosmer-Lemeshow test and the Brier score. Calibration plots (observed vs predicted) were created by dividing the predicted risk into deciles. Data from the validation cohort were applied to PLUS-M and PLUS-E and AUCs were calculated. Calibration was evaluated in the same way.

Application of the Models Using Probability Thresholds: To optimize the clinical application of the prediction models, probabilities of N2-3 disease predicted by PLUS-M and PLUS-E were calculated based on risk factors present. Using the ESTS, modified CHEST (cN1-3 disease by CT or PET-CT or central tumor), and National Institute for Health and Care Excellence guidelines as well as multiple probability thresholds for PLUS-M and PLUS-E ( $\geq 10 \%, 8 \%$, or $5 \%$ ) as criteria for selecting EBUS-TBNA candidates in the development and validation cohorts, we calculated
the sensitivity and negative predictive value of guidelines and models for N2-3 disease, expected detection rate of N2-3 disease by EBUSTBNA in confirmed N2-3 cases, unforeseen N2-3 disease rate after surgery, and EBUS-TBNA procedures prevented.

All statistical analyses were performed using SAS version 9.4 software (SAS Institute, Inc.) and R version 4.1 .1 project software ( R Foundation for Statistical Computing). A $P$ value of $<.05$ was considered statistically significant

## Results

## Study Population, Procedure, and Outcome

Among 600 patients enrolled, 589 (NCC, $\mathrm{n}=459$; Seoul National University Bundang Hospital, $\mathrm{n}=52$; Asan Medical Center, $\mathrm{n}=42$; Samsung Medical Center, $\mathrm{n}=27$; and Seoul National University Hospital, $\mathrm{n}=9$ ) were included in the development cohort (e-Fig 1). Characteristics of the development cohort and the EBUS-TBNA procedure are presented in Table 1 and e-Table 2 (broken down by institution). In the development cohort, N2-3 disease prevalence was 35.3\% (208 of 589). EBUS-TBNA sensitivity was $87.0 \%$ (181 of 208). The sensitivity in patients with cN0-1 disease by PET-CT was $68.5 \%$ ( 37 of 54 ). The mean number of nodal stations per patient and number of aspirations per target for EBUS-TBNA (including EUS-B-FNA) were 3.1 and 3.2, respectively. At least two nodal stations were sampled in 565 patients (95.9\%). At least two aspirations per target were performed in 1,781 targets (98.2\%). EUS-B-FNA was performed in $7.8 \%$ of targets. Baseline characteristics of the validation cohort were similar with the development cohort, except for the number of targets and aspirations per target during EBUS-TBNA and the use of EUS-B-FNA (Table 1). The prevalence of N2-3 disease and the sensitivity of EBUS-TBNA in the validation cohort were $36.6 \%$ (113 of 309) and 81.4\% (92 of 113), respectively.

The final histologic findings of the development and validation cohorts and the source of data for histologic grouping used for the model development are presented in e-Tables 3 and 4, respectively. We used surgical results for histologic grouping in 122 patients ( $20.7 \%$ ) because nonsurgical methods were not used before surgery or because nonsurgical diagnosis was incomplete.

## Development of Prediction Models

Table 2 presents regression analysis results for PLUS-M. In the univariable analysis, younger age ( $<60$ years and 6070 years), male sex, other histologic group, central location, cT2 or cT3-4 stage, cN 1 or $\mathrm{cN} 2-3$ stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were statistically significant risk factors for N2-3 disease diagnosed by EBUS-TBNA or surgery. In the multivariable analysis,
younger age ( $<60$ years and 60-70 years), nonsquamous histology (adenocarcinoma and others), central location, cT2 stage, cN 1 or $\mathrm{cN} 2-3$ stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were statistically significant risk factors. PLUS-M was developed using age, histologic type, tumor location, cT stage by size, cN stage by CT , and cN stage by PET-CT as predictors. Sex was not included in the final prediction model because its effect was no longer significant when other risk factors were adjusted (male: OR, 1.08 [95\% CI, 0.63-1.87]; $P=.779$ ).

Table 3 presents regression analysis results for PLUS-E. In the univariable analysis, age $<60$ years, male sex, central location, cT2 or cT3-4 stage, cN1 or cN2-3 stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were statistically significant risk factors for N2-3 disease diagnosed by EBUS-TBNA. In the multivariable analysis, younger age ( $<60$ years and 60-70 years), nonsquamous histology (adenocarcinoma and others), cT2 stage, cN 1 or $\mathrm{cN} 2-3$ stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were statistically significant risk factors. Although tumor location ( $P=.262$ ) was not a significant predictor in the multivariable analysis, we included it in PLUS-E to maintain consistency with PLUS-M. Sex was not included in the prediction model because its effect was no longer significant when other risk factors were adjusted (male: OR, 1.02 [95\% CI, 0.57-1.82]; $P=.953$ ). We developed nomograms for PLUS-M and PLUS-E (Fig 1).

## Model Performance Assessment and Validation

AUCs (Fig 2, Table 4) and calibration plots (Fig 3) for the development and validation cohorts are presented. In the development cohort, the AUCs were 0.876 ( $95 \% \mathrm{CI}, 0.845-0.906$ ) and 0.889 ( $95 \% \mathrm{CI}, 0.859-0.918$ ) for PLUS-M and PLUS-E, respectively. The mean of optimism-adjusted AUCs for PLUS-M and PLUS-E were 0.866 and 0.879 , respectively (e-Fig 2). Model fit was good for PLUS-M (Hosmer-Lemeshow $P=.658$; Brier score $=0.129$ ) and PLUS-E (Hosmer-Lemeshow $P=.569$; Brier score $=0.118$ ) (Table 4). In the validation cohort, the AUCs for PLUS-M and PLUS-E were 0.859 ( $95 \% \mathrm{CI}, 0.817-0.902$ ) and 0.900 ( $95 \% \mathrm{CI}$, $0.865-0.936$ ), respectively. The validation cohort showed acceptable goodness of fit for PLUS-M (Hosmer-
table 1 ] Characteristics of Patients and the Applied EBUS-TBNA Procedure in the Development and Validation Cohorts

| Characteristics | Development Cohort ( $\mathrm{n}=589$ ) | Validation Cohort ( $\mathrm{n}=309$ ) | $P$ Value |
| :---: | :---: | :---: | :---: |
| Age, $\mathrm{y}^{\text {a }}$ | 66 (59-72) | 66 (61-72) | . 101 |
| $\geq 70$ | 212 (36.0) | 123 (39.8) |  |
| 60-70 | 221 (37.5) | 124 (40.1) |  |
| $<60$ | 156 (26.5) | 62 (20.1) |  |
| Sex, male | 372 (63.2) | 205 (66.3) | . 344 |
| Histologic type ${ }^{\text {b }}$ |  |  | . 764 |
| Squamous cell carcinoma ${ }^{\text {c }}$ | 162 (27.5) | 90 (29.1) |  |
| Adenocarcinoma ${ }^{\text {d }}$ | 397 (67.4) | 206 (66.7) |  |
| Others | 30 (5.1) | 13 (4.2) |  |
| Location ${ }^{\text {e }}$ |  |  | . 861 |
| Peripheral | 309 (52.5) | 164 (53.1) |  |
| Central | 280 (47.5) | 145 (46.9) |  |
| cT stage by size, $\mathrm{cm}^{\text {f }}$ |  |  | . 340 |
| cT1 ( $\leq 3$ ) | 294 (49.9) | 159 (51.5) |  |
| cT2 (> 3-5) | 210 (35.7) | 95 (30.7) |  |
| cT3 (>5-7) | 64 (10.9) | 39 (12.6) |  |
| cT4 (> 7) | 21 (3.6) | 16 (5.2) |  |
| cN stage by $\mathrm{CT}^{\text {g }}$ |  |  | . 711 |
| cNO | 320 (54.3) | 165 (53.4) |  |
| cN1 | 67 (11.4) | 40 (12.9) |  |
| cN2 | 170 (28.9) | 83 (26.9) |  |
| cN3 | 32 (5.4) | 21 (6.8) |  |
| cN stage by PET-CT ${ }^{\text {h }}$ |  |  | . 790 |
| cNO | 282 (47.9) | 141 (45.6) |  |
| cN1 | 66 (11.2) | 37 (12.0) |  |
| cN2 | 157 (26.7) | 80 (25.9) |  |
| cN3 | 84 (14.3) | 51 (16.5) |  |
| CN stage by EBUS-TBNA ${ }^{\text {i }}$ |  |  | . 394 |
| No cN2-3 | 408 (69.3) | 217 (70.2) |  |
| cN2 | 150 (25.5) | 70 (22.7) |  |
| cN3 | 31 (5.3) | 22 (7.1) |  |
| pN stage of patients without N2-3 by EBUS-TBNA | $\mathrm{n}=408$ | $\mathrm{n}=217$ | . 122 |
| $\mathrm{pNx}{ }^{\text {j }}$ | 9 (2.2) | 6 (2.8) |  |
| pNo | 321 (78.7) | 152 (70.0) |  |
| pN1 | 51 (12.5) | 38 (17.5) |  |
| pN2 | 27 (6.6) | 21 (9.7) |  |
| EBUS-TBNA ${ }^{\text {i }}$ procedure |  |  |  |
| No. of target LN stations per patient | $3.1 \pm 1.0$ | $2.7 \pm 1.0$ | $<.001$ |
| No. of aspirations per target | $3.2 \pm 1.1$ | $2.7 \pm 0.8$ | < . 001 |
| No. of positive LNs | 325 (17.9) | 171 (20.7) | . 096 |
| Use of EUS-B-FNA, targets | 142 (7.8) | 4 (0.5) | < . 001 |

(Continued)
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| Characteristics | Development Cohort $(\mathrm{n}=589)$ | Validation Cohort $(\mathrm{n}=309)$ | $P$ Value |
| :--- | :---: | :---: | :---: |
| Distribution of target LN stations | $\mathrm{n}=1,813$ | $\mathrm{n}=828$ | .094 |
| 2 R | $236(13.0)$ | $86(10.4)$ |  |
| 4 R | $535(29.5)$ | $237(28.6)$ |  |
| 4 L | $317(17.5)$ | $141(17.0)$ |  |
| 7 | $554(30.6)$ | $289(34.9)$ |  |
| Other N2/N3 locations | $61(3.4)$ | $19(2.3)$ |  |
| Hilar/interlobar or peripheral locations | $110(6.1)$ | $56(6.8)$ |  |

Data are presented as No. (\%), median (interquartile range), or mean $\pm \mathrm{SD}$. $\mathrm{cN}=$ clinical N ; $\mathrm{cT}=$ clinical $T$; EBUS-TBNA $=$ endobronchial ultrasoundguided transbronchial needle aspiration; EUS-B-FNA = endoscopic ultrasound with bronchoscope-guided fine needle aspiration; LN = lymph node; $\mathrm{pN}=$ pathological N .
${ }^{a}$ At the date EBUS-TBNA was performed; age $\geq 18$ years and $<80$ years.
${ }^{\mathrm{b}}$ Based on the final pathologic diagnosis including surgical results.
${ }^{\text {che }}$ Pure squamous cell carcinoma.
${ }^{\text {d }}$ Non-small cell carcinoma with adenocarcinoma component ( $>10 \%$ ) and multiple primary cancers that included adenocarcinoma (solid part $>1 \mathrm{~cm}$ ) were classified as adenocarcinomas.
${ }^{e}$ Ambiguous cases were determined by the agreement of two pulmonologists.
${ }^{\mathrm{f}}$ Tumor size of solid component was measured on axial CT scans.
${ }^{9}$ Node positivity by CT scan was determined by size criteria: short diameter on axial CT scan of $\geq 1 \mathrm{~cm}$.
${ }^{h}$ Node positivity by PET-CT scan was determined by visual comparison with mediastinal blood pool: higher fluorodeoxyglucose F18 uptake than mediastinal blood pool.
'Including EUS-B-FNA.
${ }^{\mathrm{j}}$ All patients with pNx who underwent sublobar resection were classified as having no mediastinal metastasis (no disease progression for 12 months).

Lemeshow $P=.609$; Brier score $=0.144$ ) and PLUS-E (Hosmer-Lemeshow $P=.361$; Brier score $=0.112$ ) (Table 4).

## Application of the Models Using Probability Thresholds

In e-Table 5, we present predicted probabilities of N2-3 disease calculated by PLUS-M and PLUS-E for 486 risk groups. The probability ranges are wide, varying based on the combination of risk factors present in each group (PLUS-M, 0.5\%-95.6\%; PLUS-E, $0.4 \%-94.2 \%$ ). Expected diagnostic results after applying guideline recommendations or varying probability thresholds for PLUS-M or PLUS-E as criteria for selecting EBUSTBNA candidates in the development (Table 5) ${ }^{1,2,8}$ and validation (e-Table 6) cohorts are presented. When the ESTS criteria were applied in the development cohort, the sensitivity for capturing N2-3 disease, EBUS-TBNA N2-3 disease detection rate, and unforeseen N2-3 disease rate were $96.6 \%, 84.6 \%$, and $7.7 \%$, respectively. When a $10 \%$ PLUS-M probability threshold was applied, they were $93.3 \%, 83.2 \%$ and $8.4 \%$, respectively. This prevented 73 more EBUS-TBNA procedures than using the ESTS criteria. Use of a $10 \%$ PLUS-E probability threshold resulted in a higher unforeseen $\mathrm{N} 2-3$ rate (9.1\%) than use of a $10 \%$ PLUS-M probability threshold and prevented more EBUS-TBNA procedures. In the validation cohort, unforeseen N2-3 rates were slightly
higher than in the development cohort ( $10 \%$ PLUS-M threshold, 10.5\%) (e-Table 6).

## Discussion

We developed prediction models for mediastinal metastasis (PLUS-M) and its detection by EBUSTBNA (PLUS-E) in potentially operable NSCLC. To our knowledge, our prediction models are the first to use EBUS-TBNA and surgical staging results from a prospective cohort to predict mediastinal metastasis and its detection by EBUS-TBNA. EBUS-TBNA was performed in all patients, and surgical stage was obtained in patients without mediastinal metastasis by EBUS-TBNA. Contrast chest CT scan imaging and integrated PET-CT scan imaging were performed within 30 days before EBUS-TBNA, which enhances the quality of radiologic N staging, especially cN 1 staging by CT scan imaging. Younger age $(<60$ years and 60-70 years), adenocarcinoma, other nonsquamous histology, central location, tumor size ( $>3-5 \mathrm{~cm}$ ), cN1 or cN2-3 stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were risk factors for N2-3 disease diagnosed by EBUS-TBNA or surgery. High AUCs were observed with PLUS-M (0.876) and PLUS-E ( 0.889 ) in the development cohort. Models were validated internally using bootstrapping. AUCs for PLUS-M (0.859) and PLUS-E (0.900) also were

## tAble 2 ] Univariable and Multivariable Logistic Regression Analyses for PLUS-M

| Variable | N2-3 Disease by EBUS-TBNA or surgery |  | Univariable Analysis |  | Multivariable Analysis |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Negative Results ( $\mathrm{n}=381$ ) | Positive Results ( $\mathrm{n}=208$ ) | OR (95\% CI) | $P$ Value | OR (95\% CI) | $P$ Value |
| Age, y |  |  |  |  |  |  |
| $\geq 70$ | 153 (40.2) | 59 (28.4) | 1 | (.016) | 1 | ( $<.001$ ) |
| 60-70 | 136 (35.7) | 85 (40.9) | 1.62 (1.08-2.43) | . 019 | 2.43 (1.43-4.13) | . 001 |
| < 60 | 92 (24.1) | 64 (30.8) | 1.80 (1.16-2.80) | . 008 | 4.02 (2.16-7.49) | <. 001 |
| Sex |  |  |  |  |  |  |
| Female | 153 (40.2) | 64 (30.8) | 1 |  | $\ldots$ |  |
| Male | 228 (59.8) | 144 (69.2) | 1.51 (1.06-2.16) | . 024 | $\ldots$ | $\ldots$ |
| Histology type |  |  |  |  |  |  |
| Squamous cell carcinoma | 103 (27.0) | 59 (28.4) | 1 | (.040) | 1 | ( $<.001$ ) |
| Adenocarcinoma | 265 (69.6) | 132 (63.5) | 0.87 (0.59-1.27) | . 474 | 4.03 (2.27-7.18) | <. 001 |
| Others | 13 (3.4) | 17 (8.2) | 2.28 (1.04-5.03) | . 041 | 3.85 (1.39-10.66) | . 009 |
| Location |  |  |  |  |  |  |
| Peripheral | 232 (60.9) | 77 (37.0) | 1 |  | 1 |  |
| Central | 149 (39.1) | 131 (63.0) | 2.65 (1.87-3.75) | $<.001$ | 1.68 (1.02-2.76) | . 042 |
| CT stage by size |  |  |  |  |  |  |
| cT1 | 227 (59.6) | 67 (32.2) | 1 | ( $<.001$ ) | 1 | (.009) |
| cT2 | 113 (29.7) | 97 (46.6) | 2.91 (1.98-4.27) | $<.001$ | 2.27 (1.34-3.83) | . 002 |
| cT3-4 | 41 (10.8) | 44 (21.2) | 3.64 (2.19-6.03) | <. 001 | 1.59 (0.78-3.26) | . 204 |
| cN stage by CT |  |  |  |  |  |  |
| cNO | 276 (72.4) | 44 (21.2) | 1 | ( $<.001$ ) | 1 | ( $<.001$ ) |
| cN1 | 37 (9.7) | 30 (14.4) | 5.09 (2.86-9.06) | $<.001$ | 3.40 (1.63-7.11) | . 001 |
| cN2-3 | 68 (17.9) | 134 (64.4) | 12.36 (8.03-19.03) | $<.001$ | 5.75 (3.15-10.48) | $<.001$ |
| cN stage by PET-CT |  |  |  |  |  |  |
| cNO | 253 (66.4) | 29 (13.9) | 1 | ( $<.001$ ) | 1 | ( $<.001$ ) |
| cN1 | 41 (10.8) | 25 (12.0) | 5.32 (2.84-9.97) | $<.001$ | 5.27 (2.43-11.46) | <. 001 |
| cN2-3 | 87 (22.8) | 154 (74.0) | 15.44 (9.69-24.60) | <. 001 | 11.24 (6.14-20.58) | <. 001 |

 transbronchial needle aspiration; PLUS-M = prediction model for lung cancer staging-mediastinal metastasis.

TABLE 3 ] Univariable and Multivariable Logistic Regression Analyses for PLUS-E

| Variable | N2-3 Disease by EBUS-TBNA |  | Univariable Analysis |  | Multivariable Analysis |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Negative Results ( $\mathrm{n}=408$ ) | Positive Results ( $\mathrm{n}=181$ ) | OR (95\% CI) | $P$ Value | OR (95\% CI) | $P$ Value |
| Age, y |  |  |  |  |  |  |
| $\geq 70$ | 159 (39.0) | 53 (29.3) | 1 | (.063) | 1 | (<.001) |
| 60-70 | 149 (36.5) | 72 (39.8) | 1.45 (0.95-2.20) | . 083 | 1.85 (1.07-3.19) | . 027 |
| < 60 | 100 (24.5) | 56 (30.9) | 1.68 (1.07-2.64) | . 024 | 3.50 (1.84-6.69) | $<.001$ |
| Sex |  |  |  |  |  |  |
| Female | 162 (39.7) | 55 (30.4) | 1 |  | $\ldots$ |  |
| Male | 246 (60.3) | 126 (69.6) | 1.51 (1.04-2.19) | . 031 | $\ldots$ | $\ldots$ |
| Histologic type |  |  |  |  |  |  |
| Squamous cell carcinoma | 109 (26.7) | 53 (29.3) | 1 | (.105) | 1 | ( $<.001$ ) |
| Adenocarcinoma | 283 (69.4) | 114 (63.0) | 0.83 (0.56-1.23) | . 349 | 3.79 (2.11-6.82) | $<.001$ |
| Others | 16 (3.9) | 14 (7.7) | 1.80 (0.82-3.96) | . 144 | 2.77 (1.01-7.60) | . 048 |
| Location |  |  |  |  |  |  |
| Peripheral | 241 (59.1) | 68 (37.6) | 1 |  | 1 |  |
| Central | 167 (40.9) | 113 (62.4) | 2.40 (1.67-3.44) | $<.001$ | 1.35 (0.80-2.28) | . 262 |
| cT stage by size |  |  |  |  |  |  |
| cT1 | 237 (58.1) | 57 (31.5) | 1 | ( $<.001$ ) | 1 | (.025) |
| cT2 | 125 (30.6) | 85 (47.0) | 2.83 (1.90-4.22) | $<.001$ | 2.16 (1.23-3.76) | . 007 |
| cT3-4 | 46 (11.3) | 39 (21.5) | 3.53 (2.11-5.90) | <. 001 | 1.52 (0.73-3.17) | . 269 |
| cN stage by CT |  |  |  |  |  |  |
| cNO | 290 (71.1) | 30 (16.6) | 1 | ( $<.001$ ) | 1 | ( $<.001$ ) |
| cN1 | 43 (10.5) | 24 (13.3) | 5.40 (2.89-10.08) | < 001 | 3.49 (1.60-7.61) | . 002 |
| cN2-3 | 75 (18.4) | 127 (70.2) | 16.37 (10.21-26.24) | <. 001 | 7.54 (4.01-14.18) | $<.001$ |
| cN stage by PET-CT |  |  |  |  |  |  |
| cNO | 264 (64.7) | 18 (9.9) | 1 | ( $<.001$ ) | 1 | ( $<.001$ ) |
| cN1 | 47 (11.5) | 19 (10.5) | 5.93 (2.90-12.13) | $<.001$ | 5.74 (2.43-13.56) | < . 001 |
| cN2-3 | 97 (23.8) | 144 (79.6) | 21.77 (12.66-37.45) | <. 001 | 13.46 (6.95-26.04) | <. 001 |

Data are presented as No. (\%), unless otherwise indicated. Pvalues in parenthesis are from the Type III test for overall group differences. $\mathrm{cN}=\mathrm{clinical} \mathrm{N} ; \mathrm{cT}=\mathrm{clinical} \mathrm{T}$; EBUS-TBNA $=$ endobronchial ultrasound guided transbronchial needle aspiration; PLUS-E = prediction model for lung cancer staging-mediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration.


Figure $1-A, B$, Nomograms for PLUS-M (A) and PLUS-E (B) for predicting mediastinal metastasis based on risk predictors. $c N=c l i n i c a l ~ N ; ~ c T=$ clinical T; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-E = prediction model for lung cancer stagingmediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-M = prediction model for lung cancer staging-mediastinal metastasis.


Figure $2-A, B, A U C s$ of the development and validation cohorts for PLUS-M (A) and PLUS-E (B). Applied factors related to mediastinal metastasis for PLUS-M and PLUS-E are age, histologic type, tumor location, clinical T stage by size, clinical $N$ stage by CT, and clinical $N$ stage by PET-CT. $A U C=$ area under the receiver operating characteristic curve; $P L U S-E=$ prediction model for lung cancer staging-mediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-M $=$ prediction model for lung cancer staging-mediastinal metastasis.
high in the validation cohort. Calibration results showed acceptable goodness of fit for PLUS-M and PLUS-E in the development and validation cohorts.

Other prediction models for mediastinal metastasis have been published. The HAL model was developed using a registry cohort ( $n=633$ ) and validated with a prospective cohort. ${ }^{13,30}$ The model was developed using EBUS-TBNA results without surgery data. Younger age, adenocarcinoma, central location, and higher N stage by PET-CT were associated with a higher probability of detecting $\mathrm{cN} 2-3$ disease by EBUS-TBNA (AUC, 0.85 ). ${ }^{13}$ Verdial et al ${ }^{31}$ developed a prediction model to diagnose nodal metastasis using a prospective cohort ( $\mathrm{n}=123$, EBUS-TBNA, $\mathrm{n}=20$ ). Model parameters were tumor size and location, LN abnormalities by CT or PET scan imaging, and tumor maximum standardized uptake value (AUC, 0.82 ). The study was relatively small and did not focus on EBUS-TBNA. A model by Shafazand and Gould ${ }^{11}$ used mediastinoscopy and surgery results for staging ( $\mathrm{n}=566$ ). cN stages by CT and PET were not included in the model (AUC, 0.70). Guinde et al ${ }^{25}$ developed the Quebec prediction model to predict mediastinal metastasis in NSCLC with radiologically normal mediastinum ( $\mathrm{N}=502$ ) using four variables:
tumor location, the largest mediastinal LN size, presence of cN 1 disease, and tumor maximum standardized uptake value (AUC, 0.84 ). Other prediction models usually have evaluated the probability of unforeseen mediastinal metastasis in retrospective surgical cohorts. ${ }^{10,12,14,15,32}$ Recently, prediction models using radiomics or machine learning algorithms have been published. ${ }^{33-35}$ These methodologies need more research.

Current guidelines recommend invasive staging for specific risk groups of patients with NSCLC. ${ }^{1,2,6,8,9}$ In PLUS-M, cN1 (OR, 3.40) or cN2-3 stage (OR, 5.75) by CT and cN 1 (OR, 5.27) or $\mathrm{cN} 2-3$ stage (OR, 11.24) by PET-CT were significant risk factors for mediastinal metastasis, which agrees with guidelines. ${ }^{1,2,6,8} \mathrm{cN}$ stage by PET-CT showed a higher association than cN stage by CT. The risk from central tumor location was not so high (OR, 1.68) compared with other risk factors. We defined tumor location using concentric lines arising from the midline. ${ }^{24}$ Assessment using other definitions of tumor location may be needed. ${ }^{13,24}$ Tumor size of $>3$ and $\leq 5 \mathrm{~cm}$ was a significant risk factor for N2-3 disease (OR, 2.27). But the risk by size of $>5 \mathrm{~cm}(O R, 1.59)$ was not significant in multivariable analysis, which could be


Figure $3-A-D$, Calibration plots of observed frequencies vs predicted probabilities by PLUS-M ( $A, C$ ) and PLUS-E ( $B$, $D$ ) in the development and validation cohorts. PLUS-E $=$ prediction model for lung cancer staging-mediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-M = prediction model for lung cancer staging-mediastinal metastasis.
due to its association with other risk factors, our enrollment criteria of potential operability, and sample size. Beyond the guideline recommendations, younger age ( $<60$ years: OR, 4.02; 60-70 years: OR, 2.43 ) was a risk factor for mediastinal metastasis. Other prediction models also found younger age as a risk factor of N2-3 disease, ${ }^{10-15}$ which could be related to tumor characteristics and the late detection of cancer at a younger age. ${ }^{36}$ We used 60 years and 70 years as the cutoffs for age to optimize clinical use. Other studies have used other cutoffs or age as a continuous variable for the evaluation of age as a predictor of N2-3 disease. ${ }^{10-15}$

In PLUS-M, adenocarcinoma (OR, 4.03) and other nonsquamous histology (OR, 3.85) were risk factors compared with pure squamous cell carcinoma in multivariable analysis. Adenocarcinoma with mixed histologic findings, such as adenosquamous cell carcinoma, was included in adenocarcinoma. ${ }^{12}$
Adenocarcinoma as a risk factor for $\mathrm{N} 2-3$ disease has
been reported. ${ }^{11-14,16-19}$ Subsolid tumors with a solid component of $\leq 1 \mathrm{~cm}$ were excluded in this study because adenocarcinoma presenting as ground-glass opacity nodules are related to a low risk for LN metastasis. ${ }^{19,37}$ The other nonsquamous histology showed an increased risk for N2-3 disease, which was observed in previous studies. ${ }^{11,13,16}$ However, interpretation is limited because of the heterogeneity of this group. More studies may be needed to investigate less prevalent histologic types. Although we found histologic type to be a predictor of N2-3 disease, its practical use can be difficult. Histologic type may not be confirmed before EBUS-TBNA. Our models use final histologic type, including surgical results, because nonsurgical diagnostic methods and yields can vary among institutions. Surgical diagnosis can be more precise than nonsurgical. Moreover, in some patients, histologic diagnosis can be made only through surgery, as we observed in our cohort, because of the technical difficulty of preoperative diagnosis or preference for upfront surgery in strongly suspected NSCLC.
table 4 ] Model Performance Assessment and Validation Tests for PLUS-M and PLUS-E

| Cohort | Characteristic |  | PLUS-M |  |  | PLUS-E |  |  |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
|  | Prevalence of N2-3 Disease | Sensitivity of EBUS-TBNA | AUC (95\% CI) | HosmerLemeshow $P$ Value | Brier Score | AUC (95\% CI) | HosmerLemeshow $P$ Value | Brier Score |
| Development $(\mathrm{n}=589)$ | 35.3 (208/589) | 87.0 (181/208) | 0.876 (0.845-0.906) | . 658 | 0.129 | 0.889 (0.859-0.918) | . 569 | 0.118 |
| Validation $(n=309)$ | 36.6 (113/309) | 81.4 (92/113) | 0.859 (0.817-0.902) | . 609 | 0.144 | 0.900 (0.865-0.936) | . 361 | 0.112 |


 mediastinal metastasis.

Incompleteness of histologic information reduces generalizability of the models. To increase the usefulness of the models in patients without histologic information, we placed the histologic findings at the right-most position in e-Table 5, which presents the predicted probabilities according to risk factors. This allows the N2-3 disease probability ranges for combinations of the other risk factors to be seen when no histologic information is presented.

Predictors used in PLUS-M were included in PLUS-E because the models are paired. Central tumor location was not a statistically significant risk factor for PLUS-E, which may be related to sample size. PLUS-E predicts the probability of detecting N2-3 disease with EBUSTBNA based on data from experienced bronchoscopists (sensitivity, 87.0\%). The sensitivity of EBUS-TBNA differs by practitioner, procedure protocol, and institution. Therefore, we think that PLUS-E should be viewed as a reference. PLUS-E is similar with the HAL model. ${ }^{13}$ The advantage of PLUS-E, compared with the HAL model, is that it predicts the performance of EBUSTBNA in different risk groups, because it is paired with PLUS-M.

Prediction models should assist decision-making for invasive staging. We provided nomograms and probabilities predicted by PLUS-M and PLUS-E based on risk factors present (Fig 1, e-Table 5) which can be used for EBUS-TBNA candidate selection or help to guide decision making during the performance of EBUSTBNA. However, determining the probability threshold for omitting EBUS-TBNA in mediastinal staging is difficult. A rate of unforeseen N2 disease at the time of surgery of $10 \%$ generally is acceptable. ${ }^{2,25}$ When a $10 \%$ PLUS-M probability threshold was applied as criteria for selecting EBUS-TBNA candidates in the development cohort, the expected unforeseen N2-3 rate after surgery was $8.4 \%$. This was slightly higher than that seen when applying ESTS criteria (7.7\%), but applying the threshold prevented 73 EBUS-TBNA procedures compared with applying ESTS criteria. Because EBUSTBNA generally is a safe procedure, ${ }^{38,39}$ lower PLUS-M thresholds may be chosen to diagnose more N2-3 disease using EBUS-TBNA. PLUS-E thresholds can be used to prevent more EBUS-TBNA procedures, but less N2-3 disease would be diagnosed by EBUS-TBNA, compared to PLUS-M thresholds of the same level. The quality and sensitivity of EBUS-TBNA at a center should be considered when applying the models to expect unforeseen N2-3 rates. The validation cohort, in which EBUS-TBNA sensitivity was $81.4 \%$, showed slightly
tABLE 5 ] Expected Results After Applying Guideline Recommendations ${ }^{\text {a }}$ or PLUS-M or PLUS-E Probability Thresholds as Criteria for Selecting EBUS-TNBA Candidates in the Development Cohort

| EBUS-TBNA Staging Groups | Sensitivity of Guidelines and Models for N2-3 Disease | Negative Predictive Value of Guidelines and Models for N23 Disease | Detection of N2-3 Disease by EBUSTBNA | Unforeseen N2-3 Disease ${ }^{\text {b }}$ | Prevented EBUSTBNA, \% of Development Cohort |
| :---: | :---: | :---: | :---: | :---: | :---: |
| Development cohort ( $\mathrm{n}=589$ ) | $\ldots$ | $\ldots$ | $\begin{gathered} 87.0(181 / 208) \\ (81.7-91.3) \end{gathered}$ | $\begin{gathered} 6.6(27 / 408) \\ (4.4-9.5) \end{gathered}$ | 0 (0/589) |
| ESTS guidelines ${ }^{2}(\mathrm{n}=456)^{\text {c }}$ | $\begin{gathered} 96.6(201 / 208) \\ (93.2-98.6) \end{gathered}$ | $\begin{gathered} 94.7(126 / 133) \\ (89.5-97.9) \end{gathered}$ | $\begin{gathered} 84.6(176 / 208) \\ (79.0-89.2) \end{gathered}$ | $\begin{gathered} 7.7(32 / 413) \\ (5.4-10.8) \end{gathered}$ | $\begin{gathered} 22.6(133 / 589) \\ (19.3-26.2) \end{gathered}$ |
| Modified CHEST guidelines ${ }^{1}(\mathrm{n}=425)^{\text {d }}$ | $\begin{gathered} 95.2(198 / 208) \\ (91.3-97.7) \end{gathered}$ | $\begin{gathered} 93.9(154 / 164) \\ (89.1-97.0) \end{gathered}$ | $84.1(175 / 208)$ (78.4-88.8) | $\begin{gathered} 8.0(33 / 414) \\ (5.6-11.0) \end{gathered}$ | $\begin{gathered} 27.8(164 / 589) \\ (24.3-31.7) \end{gathered}$ |
| NICE guidelines ${ }^{8}(\mathrm{n}=350)^{\mathrm{e}}$ | $\begin{gathered} 88.9(185 / 208) \\ (83.9-92.9) \end{gathered}$ | $\begin{gathered} 90.4(216 / 239) \\ (85.9-93.8) \end{gathered}$ | $\begin{gathered} 80.8(168 / 208) \\ (74.7-85.9) \end{gathered}$ | $\begin{gathered} 9.5(40 / 421) \\ (6.9-12.7) \end{gathered}$ | $\begin{gathered} 40.6(239 / 589) \\ (36.6-44.7) \end{gathered}$ |
| PLUS-M probability $\geq 10 \%(\mathrm{n}=383)$ | $\begin{gathered} 93.3(194 / 208) \\ (89.0-96.3) \end{gathered}$ | $\begin{gathered} 93.2(192 / 206) \\ (88.9-96.2) \end{gathered}$ | $\begin{gathered} 83.2(173 / 208) \\ (77.4-88.0) \end{gathered}$ | $\begin{gathered} 8.4(35 / 416) \\ (5.9-11.5) \end{gathered}$ | $\begin{gathered} 35.0(206 / 589) \\ (31.1-39.0) \end{gathered}$ |
| PLUS-M probability $\geq 8 \%(\mathrm{n}=451)$ | $\begin{gathered} 95.7(199 / 208) \\ (91.9-98.0) \end{gathered}$ | $\begin{gathered} 93.5(129 / 138) \\ (88.0-97.0) \end{gathered}$ | $84.1(175 / 208)$ (78.4-88.8) | $\begin{gathered} 8.0(33 / 414) \\ (5.6-11.0) \end{gathered}$ | $\begin{gathered} 23.4(138 / 589) \\ (20.1-27.1) \end{gathered}$ |
| PLUS-M probability $\geq 5 \%(n=517)$ | $\begin{gathered} 98.6(205 / 208) \\ (95.8-99.7) \end{gathered}$ | $\begin{aligned} & 95.8(69 / 72) \\ & (88.3-99.1) \end{aligned}$ | $\begin{gathered} 86.1(179 / 208) \\ (80.6-90.5) \end{gathered}$ | $\begin{gathered} 7.1(29 / 410) \\ (4.8-10.0) \end{gathered}$ | $\begin{gathered} 12.2(72 / 589) \\ (9.7-15.1) \end{gathered}$ |
| PLUS-E probability $\geq 10 \%(\mathrm{n}=342)$ | $\begin{gathered} 91.3(190 / 208) \\ (86.7-94.8) \end{gathered}$ | $\begin{gathered} 92.7(229 / 247) \\ (88.7-95.6) \end{gathered}$ | $\begin{gathered} 81.7(170 / 208) \\ (75.8-86.7) \end{gathered}$ | $\begin{gathered} 9.1(38 / 419) \\ (6.5-12.2) \end{gathered}$ | $\begin{gathered} 41.9(247 / 589) \\ (37.9-46.0) \end{gathered}$ |
| PLUS-E probability $\geq 8 \%(\mathrm{n}=351)$ | $\begin{gathered} 91.3(190 / 208) \\ (86.7-94.8) \end{gathered}$ | $\begin{gathered} 92.4(220 / 238) \\ (88.3-95.5) \end{gathered}$ | $\begin{gathered} 81.7(170 / 208) \\ (75.8-86.7) \end{gathered}$ | $\begin{gathered} 9.1(38 / 419) \\ (6.5-12.2) \end{gathered}$ | $\begin{gathered} 40.4(238 / 589) \\ (36.4-44.5) \end{gathered}$ |
| PLUS-E probability $\geq 5 \%(n=447)$ | $\begin{gathered} 94.7(197 / 208) \\ (90.7-97.3) \end{gathered}$ | $\begin{gathered} 92.3(131 / 142) \\ (86.6-96.1) \end{gathered}$ | $84.1(175 / 208)$ (78.4-88.8) | $\begin{gathered} 8.0(33 / 414) \\ (5.6-11.0) \end{gathered}$ | $\begin{gathered} 24.1(142 / 589) \\ (20.7-27.8) \end{gathered}$ |
| PLUS-M probability $\geq 10 \%$ and PLUS-E probability $\geq 5 \%(n=383)$ | $\begin{gathered} 93.3(194 / 208) \\ (89.0-96.3) \end{gathered}$ | $\begin{gathered} 93.2(192 / 206) \\ (88.9-96.2) \end{gathered}$ | $\begin{gathered} 83.2(173 / 208) \\ (77.4-88.0) \end{gathered}$ | $\begin{gathered} 8.4(35 / 416) \\ (5.9-11.5) \end{gathered}$ | $\begin{gathered} 35.0(206 / 589) \\ (31.1-39.0) \end{gathered}$ |

Data are presented as \% (No./Total No.) (95\% CI), unless otherwise indicated. EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; ESTS = European Society of Thoracic Surgeons; NICE = National Institute for Health and Care Excellence; PLUS-E = prediction model for lung cancer staging-mediastinal metastasis detection by endobronchial ultrasound-guided transbronchial needle aspiration; PLUS-M = prediction model for lung cancer staging-mediastinal metastasis
${ }^{\text {a }}$ The PLUS-M and PLUS-E definition of central tumor was used when calculating results for the guidelines.
${ }^{\text {b }}$ The expected rate of N2-3 disease diagnosed by lymph node dissection when surgery is performed in patients with cNO-1 disease by EBUS-TBNA or noncandidates for EBUS-TBNA according to guidelines and models.
${ }^{c}$ cN1-3 disease by CT or PET-CT, central tumor, or tumor $>3 \mathrm{~cm}$.
${ }^{d}$ cN1-3 disease by CT or PET-CT or central tumor: modified from the original CHEST recommendations.
${ }^{e}$ CN1-3 disease by CT or PET-CT.
higher unforeseen N2-3 rates than the development cohort (e-Table 6). More research that takes into consideration clinical factors such as availability of histology and cost-effectiveness are needed for model adoption.

Our study had several limitations. As we discussed, our prediction models can be difficult to use in some clinical settings, such as when histology, contrastenhanced CT scan imaging for N1 staging, or PET-CT scan imaging are not available. We did not provide modified models accounting for such clinical scenarios. Another limitation is that the main institution was the major contributor to the cohorts ( $77.9 \%$ of the development cohort and $100 \%$ of the validation cohort). The characteristics of the retrospective validation cohort generally were similar to those of the development cohort, except for the slightly lower sensitivity of EBUS-TBNA, which may be related with the lower number of targets and aspirations during EBUS-TBNA and underuse of EUS-B-FNA. The models showed good discrimination ability in the validation cohort, but prospective external validation from other hospitals that were not included in the study is needed to explore the usefulness of the models. Another limitation is that tumor maximum standardized uptake value on PET-

CT scan imaging, which was used in other prediction models, ${ }^{25,31,32}$ was not evaluated in our study because we accepted PET-CT scans obtained using different protocols and scanners. We did not include patients older than 80 years. Tumor size was measured on axial chest CT scan imaging only.

## Interpretation

We developed prediction models for mediastinal metastasis (PLUS-M) and its detection by EBUS-TBNA (PLUS-E) in potentially operable NSCLC. Younger age, adenocarcinoma, other nonsquamous histology, central tumor location, tumor size ( $>3-5 \mathrm{~cm}$ ), cN 1 or $\mathrm{cN} 2-3$ stage by CT, and cN 1 or $\mathrm{cN} 2-3$ stage by PET-CT were risk factors for mediastinal metastasis in PLUS-M. The high AUCs and good calibration of PLUS-M and PLUS-E suggest that these models can be used effectively for decision-making for invasive mediastinal staging in NSCLC.

## Funding/Support

This work was supported by the National Cancer Center Grants 1610240, 1910220, and 2210500.

## Financial/Nonfinancial Disclosures

None declared.

## Acknowledgments

Author contributions: B. H. is the guarantor of the content of the manuscript, including the data and analysis. H. S. C and H. I. Y. equally contributed to data analysis and interpretation and the writing of the manuscript. B. H., H. I. Y., C.-M. C., K. L., and Y. S. P. contributed to the design of this study and performed bronchoscopy for patients in the development cohort. E. Y. P. and S. P. contributed to statistical analysis. E. Y. P. contributed to writing of the manuscript. G. K. L. contributed to interpretation of cytopathologic results of endoscopic staging and surgery. All authors contributed substantially to the acquisition and interpretation of data for the work and drafting the work or revising it critically for important intellectual content. All authors approved the final manuscript.

Role of sponsors: The funders had no role in the study design, collection, analysis, or interpretation of data; writing of the report; or in the decision to submit the article for publication.

Other contributions: The authors thank all patients, clinical trial nurses, and staff of the bronchoscopy unit at the National Cancer Center, Seoul National University Bundang

Hospital, Asan Medical Center, Samsung
Medical Center, and Seoul National University Hospital, Korea.
Additional information: The e-Figures and e -Tables are available online under
"Supplementary Data."

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    DOI: https://doi.org/10.1016/j.chest.2023.03.041

