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Predicting Lymph Node Metastasis in Non-small Cell Lung Cancer

Prospective External and Temporal Validation of the HAL and HOMER Models

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e-Appendix 1.

Methods

All centers enrolled consecutive patients with NSCLC with clinical radiographic stage T1-3, N0-3, M0 disease based on PET-CT. Patients that did not have a PET scan were excluded (e-Table 1). The study was approved by the Institutional Review Board, Committee 4, Protocol PA16-0107 at the University of Texas MD Anderson on June 10, 2016 and was closed to enrollment on March 1, 2019. A waiver of informed consent was obtained because this was purely observational and all tests were part of the standard of care. Each site also obtained IRB approval for their local site. Sites did not all start at the same time, because IRB approval speed varied significantly between centers. To be included in the study, we specified a priori the start and end dates did not matter, so long as for a given center consecutive patients were enrolled.

Variable Definitions and Interaction Terms for HAL and HOMER

As previously published in the HAL and HOMER reports, the variable definitions used for both the HAL and HOMER models were developed a priori and provided to all sites before data abstraction.[1,2] The variables were chosen based on prior clinical research published in the literature or experience in clinical practice that suggested a possible relationship between the variable and the probability of nodal involvement.

All radiographic variables were determined by reviewing the radiology report and further image review by an interventional pulmonologist (or a supervised interventional pulmonary fellow). For computed tomography (CT) scans, abnormal lymph nodes were those measuring ≥ 1 cm in their short axis. If both contrast and non-contrast CT were available, the contrast-enhanced images were used to determine CT N stage. Positive emission tomography (PET) N stage was based on the radiologist's interpretation of mediastinal lymph node fluorodeoxyglucose (FDG) activity. In cases when standardized uptake values (SUV) measurements were recorded, a value ≥ 2.5 was considered as positive. For both CT and PET N stage, the highest abnormal N stage lymph node was recorded.

We specified a priori that we would use positron emission tomography and computed tomography (PET-CT) N stage using interactions between CT N stage and PET N stage, based on previous work that suggested that sensitivity of PET for mediastinal lymph node involvement is conditional on the size of the node on CT.[3] Because PET-CT images do not use contrast, we pre-specified that we would combine N0 and N1 disease for CT N stage but would keep them separate when determining PET N stage.

The location of the tumor (central vs. peripheral) was defined based on the location of the center of the tumor. Tumors defined as central 1/3rd location tumors were those that by CT were located within the inner 1/3rd of the hemi-thorax (with the hilum being the center) or

if the tumor was within the segmental airways. Tumors located in the outer 2/3rds of the hemithorax required that the tumor did not touch the segmental airways and that the tumor center was located outside the central 1/3rd of the lung (Figure E1).[4,5] The interpretation of tumor location was made by an interventional pulmonologist (or a supervised an interventional pulmonary fellow).

HAL and HOMER model development

As previously described,[1,2] it was pre-specified that HAL would be a binary logistic regression model that would estimate the probability of N2 or N3 (prN2|3) vs. the probability of N0 or N1 (prN0|1) disease and that HOMER would be an ordinal logistic regression model that would estimate the probability of N0 (prN0) vs. the probability of N1 (prN1) vs. the prN2|3. The HOMER model would be an ordinal logistic regression given that its outcomes have an intrinsic order (N0 < N1 < N2|3 as assessed by EBUS-TBNA).[1]

For both models, it was pre-specified that a univariate analysis of the variables would first be performed, and that variables that had a p-value ≤2.0 would be candidate variables for the multivariate ordinal logistic regression model. We specified a priori that we would use stepwise backward selection with an overall p-value ≤0.05 for variables to remain in the final models.[1,2]

For HOMER, it was specified a priori that because it was an ordinal logistic regression model, variables identified in univariate analysis would be checked for proportional odds assumption violations using the Score Test. For variables that violated the assumption, it was specified a priori that different slope parameters for each outcome would be allowed.[1]

Homer Model Predictions

When testing the proportional odds assumption for HOMER, it was observed that there were proportional odds assumption violation for the variable N stage by PET-CT.[1] As pre-specified, different slope parameters were allowed for this variable, making HOMER a partial proportional odds model[1,6] with two formulas, one to predict the probability of N1 disease or higher (prN1|2|3) vs N0 disease and another to predict the prN2|3 vs prN0|1.

The formula for predicting the prN1|2|3 disease is of the following form: prN1|2|3=exp(A)/(1+exp(A)), where A= -0.89-0.0292*(age of the patient)+0.4864*(location of the tumor=central 1/3rd of the lung)- 0.8217*(tumor histology= squamous cell carcinoma)+0.0635*(tumor histology=non-small cell lung carcinoma)-0.4097*(tumor histology=other primary lung cancer)+1.1738*(CT=N2|3, E7 PET=N0)+3.0832*(CT=N0|1, PET=N1)+2.9905*(CT= N2|3, PET=N1)+2.2595*(CT=N0|1, PET= N2|3)+3.7113*(CT=N2|3, PET=N2|3).

The formula for predicting the prN2|3 disease is the following: prN2|3=exp(C)/(1+exp(C)), where C=-1.1576-0.0292*(age of the patient)+ 0.4864*(location of the tumor=central 1/3rd of the lung)-0.8217*(tumor histology= squamous cell carcinoma)+0.0635*(tumor histology=non-small cell lung carcinoma)-0.4097*(tumor histology=other primary lung cancer)+0.9798*(CT=N2|3, PET=N0)+1.5937*(CT=N0|1, PET=N1)+0.9323*(CT= N2|3, PET=N1)+2.3599*(CT=N0|1, PET= N2|3)+3.7486*(CT=N2|3, PET=N2|3).

With the first formula we know the prN1|2|3 disease and the prN0 disease. With the second formula, we know the prN2|3 disease. Then, the prN1 disease can be obtained by subtracting the prN2|3 disease from the prN1|2|3 disease. Therefore, from these two formulas we know the prN0, prN1 and prN2|3.

Random Effects Model Exploratory Analysis

The primary analysis used a common fixed effects model for all centers since this is generalizable and could be applied everywhere. We then performed an exploratory analysis using random effects models to look test for the presence of center-level effects and to estimate how large these effects might be. We used the prospectively collected data from this study to create a random effects model with random intercept to capture center-level effects using the same variables that were used in HAL and HOMER. We label these random effects models r-HAL and r-Homer. Measures of discrimination for the random effects models are likely overly optimistic, since the models were derived from this dataset. The main purpose of assessing discrimination of r-HAL and r-HOMER is to serve as a conservative estimate of the upper limit of how well the variables used in HAL and HOMER could potentially perform if the model structure was changed to random effects. We compared the r-HAL and r-HOMER with the standard HAL and HOMER to see how much random effects modelling might improve performance.

Institution-Specific Calibrated Models Following the General Calibration Method

In the previously published HAL and HOMER reports, the discrimination of HAL and HOMER was good in all centers (ROC AUC 0.86 to 0.88), but calibration was off in two centers (HFH and JH).[1,2] A secondary analysis was performed in those studies to produce calibrated models specific to each participating institution, using the general calibration method proposed by Steyerberg, et al.[1,2,7] In this general calibration method, a logistic regression model is first fitted to the linear predictor (log odds) generated by the model as the only covariate.[7] The logistic regression model gives an intercept (a) and a slope (b). When the linear predictor is multiplied by b (slope) and a (intercept) is added, the raw predicted probabilities are adjusted and there is improvement in model fit with no change in model discrimination. In the HAL and HOMER reports, when performing the institution-specific calibrations the three outside institutions used for external validation (CCF, JH and HFH), the slope was set to unity for all centers (b=1) and only the institution-specific calibration intercepts (a) were estimated by doing the logistic regression models.[1,2]

For HAL, a binary logistic regression model, a single logistic regression was fitted with the linear predictor (i.e., the formula for predicting prN2|3 (vs. pN0|1) disease) as the only covariate; institution-specific calibration intercepts were estimated and added to the linear predictor of each center.[2] Model performance was then reassessed using the Brier Score, Hosmer-Lemeshow test, and ROC-AUC. The process of fitting a logistic regression to HAL's linear predictor (with slope set to 1), followed by the addition of the obtained institution-specific calibration intercepts (to their respective institutions) and assessment of model performance (Brier Score and Hosmer-Lemeshow test) was repeated until the institution-specific calibration intercepts with the lowest Brier Scores and highest Hosmer-Lemeshow p-values were found. As expected, the ROC-AUCs did not vary with the addition of calibration intercepts. The final intercepts that were used for institution-specific calibration for HAL are shown in e-Table 2.

Conversely, for HOMER, an ordinal logistic regression model with two linear predictors (i.e., one for the formula predicting pN1|2|3 (vs. pN0) disease and another for the formula predicting pN2|3 (vs. pN0|1) disease), two logistic regressions were fitted (one for each linear predictor as the only covariate); institution-specific intercepts were estimated obtained, and added to the two linear predictors of each center.[1] As done for HAL, model performance was then reassessed using the Brier Score, Hosmer-Lemeshow test, and ROC-AUC. The process of fitting a logistic regression to each of the two linear predictors for HOMER (with slope set to 1), followed by the addition of the obtained institution-specific calibration intercepts (to their respective linear predictors for each institution) and assessment of model performance (Brier Score and Hosmer-Lemeshow test) was repeated until the institution-specific calibration intercepts with the lowest Brier Scores and highest Hosmer-Lemeshow p-values were found. As expected, the ROC-AUCs did not vary with the addition of calibration intercepts. The final intercepts that were used for institution-specific calibration for HOMER are shown in e-Table 1.

Temporal Validation of Institution-Specific Calibrated Models

The institution-specific calibrated models obtained from the secondary analysis of the HAL and HOMER reports fitted that dataset well in those studies, but they have never been temporally validated.[1,2,7] Therefore, we performed an exploratory analysis using the previously published institution-specific calibrated models vs. the basic HAL and HOMER models at each of the three prior external validation sites (CCF, HFH, JH). We used the annotation c-HAL and c-HOMER to represent these institution-specific calibrated models with a suffix to represent the particular institution (e.g. c-HAL-HFH is the institution specific calibrated HAL models for HFH). We assessed performance of the institution-specific, calibrated models using the ROC-AUC for discrimination and Brier Score, Hosmer-Lemeshow test, and observed vs. forecast probabilities for calibration.

Sample size

Assumptions used for calculation of the sample size were based on the results obtained from a previous, slightly different version of the HAL model, where the ROC-AUC was 0.75,

with a 95% confidence interval (CI) lower limit of 0.73.[8] In this previous study, the prevalence of N2|3 disease was 27% with a 95% CI lower limit of 23%.[8]

For this study, we aimed to have a 95% CI lower limit above 0.70 (the lower limit ROC-AUC considered as acceptable) for the ROC-AUC. When calculating sample size, to be conservative, we used the previously obtained lower limits of the 95% CI of the ROC-AUC (0.73) and of the prevalence of N2|3 disease (23%) as our baseline estimates of the ROC-AUC and N2|3 prevalence, respectively. To obtain a ROC-AUC 95% CI with a lower limit of 0.70, the minimum sample size for the combined cohort was 1252 patients. We also explored a variety of other scenarios in sensitivity analysis, varying the prN2|3 disease and the ROC-AUC across the range of values deemed to be plausible, based on the 95% CI of published reports and this sample size was deemed conservative (e-Table 3). Therefore, we decided to enroll a minimum of 1300 patients across 13 institutions, where in an ideal scenario they would each enroll 100 consecutive patients, allowing assessment of discrimination and calibration to be determined for each institution. However, we observed that while some institutions rapidly enrolled patients, other smaller institutions enrolled patients more slowly. Therefore, we allowed larger institutions to continue enrolling past 100 patients while smaller institutions continued enrolling, provided they enrolled all consecutive patients, but the goal was to have as many institutions reach the 100-patient threshold as possible.

While model performance might be good for the entire cohort, prior data from AQuIRE suggested that there are between center differences in diagnostic yield, which made it important to determine whether the model performed well within each institution.[9] It would be possible for the model to perform well in the aggregated cohort but perform consistently poorly in particular institutions. For example, the model might perform well in 3 institutions while in 5 institutions the model could overestimate risk and be poorly calibrated and in 5 institutions the model might underestimate risk and be poorly calibrated but put together in a fixed effects model it might appear that the model had good performance. For the stratified analysis by institution, we pre-specified that for institutions enrolling ≥ 100 patients, discrimination and calibration performance would be assessed, since an n=100 would provide reasonably precise estimators of calibration and discrimination performance. If an institution enrolled less than 100 patients but ≥ 50 patients, only discrimination performance would be assessed, since observed vs. predicted plots would have too few patients in each decile and would therefore be unreliable. Finally, we had estimated that a sample size of 50 or more patients was necessary to obtain a stable ROC-AUC, so we pre-specified that if institutions enrolled less than 50 patients, they would be excluded from stratified analysis altogether, since estimates would be unreliable.

Reults

Random Effects Model

After performing the random effects models for HAL and HOMER using random intercepts, the r-HAL formula for predicting prN2|3 is:

$prN2|3 = \frac{\exp(A)}{1+\exp(A)}$ where $A = 0.2505 - 2.1946 - 0.0172 * (\text{age of patient}) + 0.2956 *$ I(location of the tumor = central third of the lung) $- 0.6324 *$ I(tumor histology = squamous cell carcinoma) $- 0.5634 *$ I(Nonsmall cell lung carcinoma) $- 0.8650 *$ I(other primary lung cancer) $+ 1.2905 *$ I(CT = N2|3, PET = N0) $+ 1.1786 *$ I(CT = N0|N1, PET = N1) $+$ $1.5064 *$ I(CT = N2|N3, PET = N1) $+ 3.0914 *$ I(CT = N0|1, PET = N2|3) $+ 4.1364 *$ I(CT = N2|3, PET = N2|3)

Note: I(X) is an indicator function and equals 1 if X is true, otherwise equals 0

The r-HOMER formula for predicting the prN1|2|3 disease is:

$prN1|2|3 = \frac{\exp(B)}{1+\exp(B)}$ where $B = 0.1246 - 1.815 - 0.0120 * (\text{age of the patient}) + 0.3421 *$ I(location of the tumor = central 1/3rd of the lung) $- 0.4426 *$ I(tumor histology = squamous cell carcinoma) $- 0.3345 *$ I(tumor histology = non − small cell lung carcinoma) $- 0.4194 *$ I(tumor histology = other primary lung cancer) $+ 0.5533 *$ I(CT = N2|3, PET = N0) $+ 2.5547 *$ I(CT = N0|1, PET = N1) $+ 3.0056 *$ I(CT = N2|3, PET = N1) $+ 2.4933 *$ I(CT = N0|1, PET = N2|3) $+ 3.6851 *$ I(CT = N2|3, PET = N2|3)

Note: I(X) is an indicator function and equals 1 if X is true, otherwise equals 0.

The r-HOMER formula for predicting the prN2|3 disease is:

$\text{prN2|3} = \frac{\exp(C)}{1+\exp(C)}$ where $C = -0.0150 - 2.6241 - 0.0120 * (\text{age of the patient}) + 0.3421 *$ I(location of the tumor = central 1/3rd of the lung) $- 0.4426 *$ I(tumor histology = squamous cell carcinoma) $- 0.3345 *$ I(tumor histology = nonsmall cell lung carcinoma) $- 0.4194 *$ I(tumor histology = other primary lung cancer) $+ 1.2151 *$ I(CT = N2|3, PET = N0) $+ 1.0058 *$ I(CT = N0|1, PET = N1) $+ 0.6209 *$ I(CT = N2|3, PET = N1) $+ 2.8754 *$ I(CT = N0|1, PET = N2|3) $+ 4.1919 *$ I(CT = N2|3, PET = N2|3)

Note: I(X) is an indicator function and equals 1 if X is true, otherwise equals 0.

It follows that using HOMER, the $\text{prN0} = 1 - \text{prN1|2|3}$ and $\text{prN1} = \text{prN1|2|3} - \text{prN2|3}$.

Temporal Validation of Institution-Specific Calibrated Models

Results of the exploratory analysis comparing baseline HAL vs. c-HAL and baseline HOMER vs. c-HOMER at CCF, JH, and HFH is shown in Tables E4 and E6, respectively. For all three centers, baseline HAL and baseline HOMER performed better than c-HAL and c-HOMER in all tests of calibration (Brier score, observed vs. forecast probabilities and Hosmer-Lemeshow p-value). This suggests that previously developed models using institution-specific calibration intercepts might be overfitted (i.e., modeling of the residual variation or noise). Overfitted models provide results that are overly optimistic when first developed, however the models are not a true representation of reality and therefore are not reproducible in different data sets and perform poorly when applied to new data sets.[10] In this exploratory analysis, this pattern is observed for the institution-specific calibrated models, suggesting that calibration resulted in overfitting of the models. Conversely, the baseline HAL and HOMER models continued to perform well across multiple institutions.

Estimation of the post-test probability of N2 or N3 disease by EBUS using HAL

After estimating the probability of N2|3 disease by EBUS using HAL, the predictions can be used to estimate the post-test probability of N2 or N3 disease following a negative EBUS result. In order to calculate the post-test probability of N2|3 disease following a negative EBUS, the following assumptions are made: the sensitivity of EBUS is 0.89 as reported by the ACCP guidelines, specificity of EBUS is 1.0 and therefore the likelihood ratio for negative EBUS = (1-sensitivity)/specificity = 0.11.[11-15]

The calculations are as follows:

- Pre-test probability of N2|3 disease= prN2|3/sensitivity of EBUS when PET-CT N stage is N2
- Then convert the pre-test probability of N2|3 disease to pre-test odds= pre-test probability of N2|3 disease/ (1-0.pre-test probability of N2|3 disease)
- Following Bayes Theorem, post-test disease odds= pre-test odds x likelihood ratio for negative EBUS= pre-test odds of N2|3 disease x 0.11
- Convert the post-test disease odds to post-test probability following a negative EBUS of N2|3 as follows: post-test probability of disease =post-test odds of N2|3 disease/ (1+post-test odds of N2|3 disease).

Discussion

HAL and HOMER are two clinical prediction rules that estimate malignant nodal involvement as determined by EBUS-TBNA. Previous studies predicted N2|3 disease as determined by mediastinoscopy or thoracotomy in order to guide surgical decisions.[16-22] However, current guidelines have now replaced mediastinoscopy with EBUS-TBNA as the first sampling technique of the mediastinum in patients with NSCLC[11], so clinical prediction rules for malignant nodal involvement as determined by EBUS-TBNA are useful.

Previous studies from the AQuIRE registry have suggested that significant institution-specific differences can occur in terms of bronchoscopic diagnostic yield, with EBUS-TBNA yield varying from 37%-54% which might impact model performance.[9,23] Consistent with AQuIRE, in the random effects model we found evidence of center-level effects. However, accounting for these center-level effects did not improve model performance significantly. In addition, random effects models, even if more accurate, are less generalizable and therefore not practical for clinicians, since they require data from each institution to make predictions. We also tested HAL and HOMER vs. our previously published institution-specific calibrated models that used the general calibration method. Both HAL and HOMER outperformed their institution-specific counterparts, suggesting that the base HAL and HOMER models are robust and stable over time.

Given that mediastinoscopy cannot sample N1 nodes[24], the true gold standard for mediastinal and hilar staging is thoracotomy. So, one could argue that it would be best to predict N0, N1 and N2|3 disease as determined by thoracotomy. However, that would be necessary if we were trying to determine the sensitivity and specificity of EBUS-TBNA or to predict the pretest probability of nodal disease. But this study is not determining sensitivity and specificity of EBUS-TBNA, so use of a surgical gold-standard is not applicable. This study is also not predicting a pretest probability; it is predicting diagnostic yield of EBUS-TBNA for N0, N1, or N2|3 disease. The positive predictive value (PPV) of EBUS-TBNA is close to 100%, so we assert that predicting the diagnostic yield of EBUS-TBNA nodal involvement is clinically useful. Below some threshold diagnostic yield, EBUS-TBNA will not be cost-effective. We should note that the prediction of diagnostic yield for a test is different than predicting the results of the gold standard (thoracotomy in this case). A rule which accurately predicts the pretest probability of nodal disease by thoracotomy does not necessarily imply whether a given test is warranted or not.

For instance, consider a case where conventional TBNA vs. EBUS-TBNA are being evaluated for a patient. A rule that accurately predicts the probability of nodal disease by thoracotomy does not inform us whether conventional TBNA is warranted. What we want to know is the probability the test (conventional TBNA) will be positive and the probability that the alternative test (EBUS-TBNA) will be positive. A prediction rule based on thoracotomy results would be good for estimating the pretest probability of disease but could not tell us which test is better or if either test is necessary.

To guide the decision on whether a given test needs to be done requires information on the diagnostic yield of that specific test in a patient, which is different than the probability that there is disease present as assessed by the gold standard (i.e., pretest probability). If the sensitivity of conventional TBNA or EBUS-TBNA was fixed across all groups, then diagnostic yield would be equal to the pretest probability multiplied by sensitivity, since TBNA specificity is essentially 100%. But if sensitivity varies significantly across strata such an analytic approach would not work, and a recent meta-analysis reported that the sensitivity of EBUS-TBNA does vary depending on the PET-CT status of the mediastinal lymph nodes.[25] For instance, studies demonstrated that sensitivity of EBUS ranged from 13.6% to 94.1%[26,27] in patients with PET-CT N0 disease, from 67% to 82%[27,28] in patients with PET-CT N1 disease, and from 72.7% to 94.2%[13,29-32] in patients with PET-CT N2|3 disease. Therefore, it is not appropriate to use a single pooled estimate of sensitivity for all patients.

A more empiric approach is to directly measure and predict diagnostic yield for EBUS-TBNA, which our prediction rules does. Although our study has the weakness of sacrificing knowledge of the true disease prevalence because we could not do thoracotomy in all patients with negative EBUS-TBNA results, the ability to predict diagnostic yield is practical and clinically relevant.

Another consideration regarding the use of thoracotomy as the basis for prediction rules regarding nodal disease is the potential for selection bias and generalizability of results across various patient populations. Prediction rules that estimate the probability of nodal involvement based on thoracotomy would not necessarily be generalizable to patients being considered for SABR because of inability to tolerate surgical resection. Indeed, a study that developed a prediction rule for malignant lymph node involvement as determined by surgical staging would risk selection bias, because non-surgical candidates considered for therapy with SABR would be excluded. Such a prediction rule still might work in non-surgical candidates, but it would require additional validation and would be informative in regard to pretest probability but not whether a EBUS-TBNA should be done – for that we need a prediction of diagnostic yield. HOMER provides that prediction of diagnostic yield.

Our study has strengths and weaknesses that are worth mentioning. One of the strengths is that both HAL and HOMER were independently validated in 13 hospitals. While there was evidence of center-level effects, both models performed well across multiple institutions in terms of their ability to predict malignant lymph node involvement. Also, HAL and HOMER demonstrated stability through a 10-year time-period in four institutions. So, even though both models have the weakness that the Hosmer-Lemeshow test showed some statistically significant calibration error beyond random variation, the magnitude of the calibration error is relatively modest such that the models remain informative. Another strength that our study has is that HOMER can inform the decision on whether EBUS-TBNA should be done in patients who are being considered for SABR. Mediastinoscopy cannot sample N1 nodes,[24] so prediction rules that estimate the probability of nodal involvement as assessed by mediastinoscopy would not be sufficient for this problem.

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e-Table 1. Exclusion Criteria for Patients of the Combined Validation Data

Reason of exclusion	Number of patients meeting exclusion criteria
PET[a] was not performed prior to treatment	130
Clinical-radiographic suspicion of a synchronous primary malignancy	2
Pathology report for the biopsy of the lung tumor demonstrated benign histology	69
Clinical-radiographic M stage was M1	94
Evidence of T4 invasion by CT[b]	31
Systematic EBUS-sampling was not performed	12
Pathology report for the biopsy of the lung tumor demonstrated small cell lung cancer	49
Primary site of malignancy was different than the lung (e.g., primary site of cancer was breast with lung metastasis)	3
Total	390

Definitions of abbreviations: PET: Positron Emission Tomography; CT: Computed Tomography Note: All patients had at least one reason of exclusion recorded and some patients had more than one reason of exclusion recorded (e.g., a patient both had evidence of T4 invasion by CT and PET was not performed prior to treatment).

e-Table 2. Institution-Specific Calibration Intercepts for the HAL and HOMER Models

Linear predictor	Cleveland Clinic Foundation	Henry Ford Hospital	Johns Hopkins
HAL model Calibration intercept[a] for the linear predictor for prN2|3 (vs. N0|1) disease	+0.26	+0.92	0.89
HOMER model Calibration intercept[b] for the linear predictor for prN1|2|3 (vs. N0) disease	+0.18	+1.06	+1.10
Calibration intercept[b] for the linear predictor for prN2|3 (vs. N0|1) disease	+0.26	+0.90	+0.90

Definition of abbreviations: prN2|3: probability of N2 or N3 disease; N0|1: N0 or N1; prN1|2|3: probability of N1 disease or higher

Note: The institution-specific calibration intercepts were calculated following the general calibration method proposed by Steyerberg et. al. in the HAL[a] and HOMER[b] reports.[1,2,7]

e-Table 3. Sample Size Calculation of the Entire Cohort Based on a Previous Version of HAL

Confidence Level[a]	Total Subjects N[b]	% of N2|3[c]	N stage N2|3[d]	N stage N0|1[e]	Sample AUC[f]	Distance from AUC to Limit[g]	Lower 95% Conf. Limit[h]
0.950	1322	23	304	1018	0.700	0.030	0.670
0.950	1279	24	307	972	0.700	0.030	0.670
0.950	1236	25	309	927	0.700	0.030	0.670
0.950	1200	26	312	888	0.700	0.030	0.670
0.950	1167	27	315	852	0.700	0.030	0.670
0.950	1132	28	317	815	0.700	0.030	0.670
0.950	1103	29	320	783	0.700	0.030	0.670
0.950	1077	30	323	754	0.700	0.030	0.670
0.950	**1252**	**23**	**288**	**964**	**0.730**	**0.030**	**0.700**
0.950	1213	24	291	922	0.730	0.030	0.700
0.950	1172	25	293	879	0.730	0.030	0.700
0.950	1135	26	295	840	0.730	0.030	0.700
0.950	1100	27	297	803	0.730	0.030	0.700
0.950	1071	28	300	771	0.730	0.030	0.700
0.950	1041	29	302	739	0.730	0.030	0.700
0.950	1017	30	305	712	0.730	0.030	0.700
0.950	1200	23	276	924	0.750	0.030	0.720
0.950	1158	24	278	880	0.750	0.030	0.720
0.950	1120	25	280	840	0.750	0.030	0.720
0.950	1085	26	282	803	0.750	0.030	0.720
0.950	1052	27	284	768	0.750	0.030	0.720
0.950	1021	28	286	735	0.750	0.030	0.720

0.950	993	29	288	705	0.750	0.030	0.720
0.950	970	30	291	679	0.750	0.030	0.720
0.950	1139	23	262	877	0.770	0.030	0.740
0.950	1100	24	264	836	0.770	0.030	0.740
0.950	1064	25	266	798	0.770	0.030	0.740
0.950	1027	26	267	760	0.770	0.030	0.740
0.950	996	27	269	727	0.770	0.030	0.740
0.950	968	28	271	697	0.770	0.030	0.740
0.950	941	29	273	668	0.770	0.030	0.740
0.950	917	30	275	642	0.770	0.030	0.740
0.950	1074	23	247	827	0.790	0.030	0.760
0.950	1033	24	248	785	0.790	0.030	0.760
0.950	1000	25	250	750	0.790	0.030	0.760
0.950	965	26	251	714	0.790	0.030	0.760
0.950	937	27	253	684	0.790	0.030	0.760
0.950	911	28	255	656	0.790	0.030	0.760
0.950	883	29	256	627	0.790	0.030	0.760
0.950	860	30	258	602	0.790	0.030	0.760
0.950	478	23	110	368	0.700	0.050	0.650
0.950	463	24	111	352	0.700	0.050	0.650

[a]Confidence Level=the proportion of confidence intervals (constructed with this same confidence level, sample size, etc.) that would contain the true coefficient alpha; [b]N= the total number of subjects sampled; [c]Percentage of patients with N2 or N3 disease where this percentage= 100 x N2|3 / N; [d]N2|3: number of subjects with N2 or N3 disease; [e]N0|1: number of subjects with N0 or N1 disease; [f]Sample AUC: the anticipated value of the sample area under the receiver operating characteristic curve; [g]Distance from AUC to Limit: the distance from the lower limit to the AUC; [h]Lower Confidence Limit is the actual limit that would result from a dataset with these statistics.

Note: shown in bold is the minimum target sample size for the combined cohort, where AUC=0.73, lower limit 95% CI=0.70, and prevalence of N2|3 disease=23%.

e-Table 4: Clinical Characteristics by N Stage (N0|1 vs. N2|3) as Determined by EBUS-TBNA for All Included Patients (n=1799).

Variable	N	N0|1 (n=1370)	N2|3 (n=429)	P-value
Age, M (SD)	1799	70.0 (9.5)	67.6 (9.7)	<0.001
Gender, n (%)	1799			0.170
Female		587 (76.1)	184 (23.9)	
Male		783 (76.2)	245 (23.8)	
Race, n (%)	1785			0.222
Asian		59 (83.1)	12 (16.9)	
Black		192 (77.1)	57 (22.9)	
Other		39 (66.1)	20 (33.9)	
White or Caucasian		1066 (76.1)	334 (23.9)	
ASA, n (%)	1779			0.012
0		5 (100.0)	0 (0.0)	
1		18 (58.1)	13 (41.9)	
2		179 (70.7)	74 (29.3)	
3		1094 (77.5)	317 (22.5)	
4		74 (74.8)	25 (25.3)	
Tobacco history, n (%)	1779			0.330
Current		391 (74.4)	133 (25.4)	
Never used		159 (79.9)	40 (20.1)	
Prior use		820 (76.2)	256 (23.8)	
Tumor size, M (SD)	1779	4.49 (2.22)	3.94 (2.34)	<0.001
Tumor.size , n (%)	1779			<0.001
<=3 cm		740 (81.1)	173 (19.0)	
>3 cm but <=5 cm		366 (70.8)	151 (29.2)	
>5cm		264 (71.5)	105 (28.5)	
Lobar Location, n (%)	1799			<0.001
Left lower lobe		202 (80.5)	49 (19.5)	
Left upper or lingula		400 (82.0)	88 (18.0)	
Right lower or middle lobe		313 (73.1)	115 (26.9)	
Right upper lobe		455 (72.0)	177 (28.0)	
Tumor location, n (%)	1799			<0.001
Central 1/3rd		324 (67.6)	155 (32.4)	
Outer 2/3rd		1046 (79.2)	274 (20.8)	
Histology, n (%)	1799			0.153
Adenocarcinoma		722 (74.4)	249 (25.6)	
Other		57 (83.8)	11 (16.8)	
Squamous		454 (77.3)	133 (22.7)	
Poorly-differentiated NSCLC		137 (79.2)	36 (20.8)	

Nodule in the same lobe, n (%) No Yes	1799	 1190 (77.1) 180 (70.6)	 354 (22.9) 75 (29.4)	0.024
Nodule in the same lung, n (%) No Yes	1799	 1279 (77.2) 91 (63.6)	 377 (22.8) 52 (36.4)	<0.001
N stage CT, n (%) 0 1 2 3	1799	 817 (94.0) 181 (85.8) 261 (53.9) 111 (47.2)	 52 (6.0) 30 (14.2) 223 (46.1) 124 (52.8)	<0.001
N stage PET, n (%) 0 1 2 3	1799	 822 (96.7) 238 (91.5) 174 (40.6) 136 (52.3)	 28 (3.2) 22 (8.5) 255 (59.4) 124 (48.7)	<0.001
N stage by PET-CT, n (%) CT=N0 or N1, PET=N0 CT=N0 or N1, PET=N1 CT=N0 or N1, PET=N2|3 CT=N2 or N3, PET=N0 CT=N2 or N3, PET=N1 CT=N2 or N3, PET=N2|3	1799	 708 (97.5) 199 (91.7) 91 (66.4) 114 (91.9) 39 (90.7) 219 (36.7)	 18 (2.4) 18 (8.3) 46 (33.6) 10 (8.1) 4 (9.3) 333 (60.3)	<0.001
M stage, n (%) M0 Mx	1799	 1283 (76.5) 87 (71.9)	 395 (23.5) 34 (28.1)	0.256

Definition of abbreviations: NSCLC: non-small cell lung cancer; N0|1: N0 or N1 disease; N2|3: N2 or N3 disease

e-Table 5. Comparison of HAL with Institution Specific Calibrated HAL Model at Three Institutions

Performance Measure	Cleveland Clinic Foundation	Henry Ford Hospital	Johns Hopkins
Brier Score			
HAL	0.092	0.136	0.141
Institution specific c-HAL[a]	0.095	0.160	0.167
Hosmer-Lemeshow p-value			
HAL	0.70	0.29	0.28
Institution specific c-HAL[a]	0.29	<0.001	<0.001
Observed vs. Forecast			
Observed prN2|3	0.181	0.269	0.285
HAL forecast prN2|3	0.216	0.290	0.303
Institution specific c-HAL[a] forecast prN2|3	0.247	0.416	0.422
ROC-AUC[b]			
HAL	0.913 (0.879-0.945)	0.848 (0.771-0.924)	0.838 (0.776-0.899)
Institution specific c-HAL[a]	0.913 (0.879-0.945)	0.848 (0.771-0.924)	0.838 (0.776-0.899)

Definition of abbreviations: prN2|3: probability of N2 or N3 disease; ROC-AUC: Area Under the Receiver Operating Characteristic Curve.

[a]c-HAL: calibrated HAL model, generated by using the general calibration method applied to a specific institution's prior data set.

[b]Note that the ROC AUC is the same for HAL and the c-HAL models. The general calibration method used to generate the c-HAL models does not impact model discrimination, it only changes calibration. When measuring calibration, lower Brier scores are better; higher Hosmer-Lemeshow p-values are better; forecast probabilities closer to the observed probabilities are better. The base HAL model outperforms the c-HAL model in every institution, as measured by Brier score, Hosmer-Lemeshow test, and observed vs. predicted plots.

e-Table 6: Clinical Characteristics by N Stage (N0 vs. N1 vs. N2|3) as Determined by EBUS-TBNA for All Non-MD Anderson Included Patients (n=1244).

Variable	N	N0 (n=800)	N1 (n=122)	N2|3 (n=322)	P-value
Age, M (SD)	1244	70.2 (9.5)	69.4 (9.9)	67.5 (9.6)	<0.001
Gender, n (%) Female Male	1244	 338 (64.8) 462 (64.)	 45 (8.6) 77 (10.7)	 139 (26.6) 183 (23.4)	0.470
Race, n (%) Asian Black Other White or Caucasian	1234	 31 (83.8) 147 (68.4) 26 (50.0) 591 (63.6)	 2 (5.4) 18 (8.4) 7 (13.5) 94 (10.1)	 4 (10.8) 50 (23.3) 19 (36.6) 245 (26.3)	0.049
ASA, n (%) 0 1 2 3 4	1244	 4 (80.0) 16 (53.3) 143 (60.3) 572 (65.3) 65 (67.1)	 1 (20.0) 1 (3.3) 23 (9.7) 89 (10.2) 8 (8.3)	 0 (0.0) 13 (43.3) 71 (30.0) 215 (24.5) 23 (24.0)	0.209
Tobacco history, n (%) Current Never used Prior use	1244	 264 (63.2) 83 (67.5) 449 (64.4)	 39 (9.2) 16 (13.0) 67 (9.6)	 117 (27.6) 24 (19.5) 181 (26.0)	0.385
Tumor size, M (SD)	1244	3.47 (2.23)	4.11 (2.46)	3.99 (2.45)	<0.001
Tumor.size , n (%) <=3 cm >3 cm but <=5 cm >5cm	1244	 436 (70.7) 222 (60.2) 142 (55.0)	 50 (8.1) 36 (9.8) 36 (14.0)	 131 (19.0) 111 (30.1) 80 (31.50)	<0.001
Lobar Location, n (%) Left lower lobe Left upper or lingula Right lower or middle lobe Right upper lobe	1244	 107 (60.1) 223 (69.9) 172 (59.5) 298 (65.1)	 30 (16.9) 31 (9.8) 32 (11.1) 29 (6.13)	 41 (23.0) 65 (20.4) 85 (29.4) 131 (28.6)	0.001
Tumor location, n (%) Central 1/3rd Outer 2/3rd	1244	 171 (52.3) 629 (68.6)	 43 (13.2) 79 (8.6)	 113 (34.6) 209 (22.8)	<0.001

Histology, n (%) Adenocarcinoma Other Squamous Poorly-differentiated NSCLC	1244	 404 (62.9) 38 (74.5) 273 (64.4) 85 (66.9)	 58 (9.0) 6 (11.8) 42 (9.9) 16 (12.6)	 180 (28.0) 7 (13.7) 109 (25.7) 26 (20.5)	0.220
Nodule in the same lobe, n (%) No Yes	1244	 693 (66.2) 107 (54.3)	 99 (9.5) 23 (11.7)	 255 (24.4) 67 (34.0)	0.005
Nodule in the same lung, n (%) No Yes	1244	 751 (65.5) 49 (50.5)	 114 (9.9) 8 (8.3)	 282 (24.6) 40 (41.2)	0.002
N stage CT, n (%) 0 1 2 3	1244	 526 (88.1) 64 (46.4) 146 (42.9) 64 (37.9)	 29 (4.9) 55 (39.9) 29 (8.5) 9 (5.3)	 42 (7.0) 19 (13.8) 163 (48.5) 96 (56.8)	<0.001
N stage PET, n (%) 0 1 2 3	1244	 512 (93.8) 101 (54.6) 94 (29.3) 93 (48.4)	 15 (2.8) 71 (38.4) 28 (8.7) 8 (4.2)	 19 (3.5) 13 (7.0) 199 (62.0) 91 (47.4)	<0.001
N stage by PET-CT, n (%) CT=N0 or N1, PET=N0 CT=N0 or N1, PET=N1 CT=N0 or N1, PET=N2|3 CT=N2 or N3, PET=N0 CT=N2 or N3, PET=N1 CT=N2 or N3, PET=N2|3	1244	 431 (94.3) 88 (55.4) 71 (59.7) 81 (91.0) 13 (50.0) 116 (29.4)	 14 (3.1) 59 (37.1) 11 (9.2) 1 (1.1) 12 (46.2) 25 (6.4)	 12 (2.6) 12 (7.5) 37(31.1) 7(7.9) 1 (3.8) 253 (64.2)	<0.001
M stage, n (%) M0 Mx	1244	 728 (64.7) 72 (61.0)	 110 (9.8) 12 (10.2)	 288 (25.6) 34 (28.8)	0.716

Definition of abbreviations: NSCLC: non-small cell lung cancer; N2|3: N2 or N3

e-Table 7. Comparison of HOMER with Institution Specific Calibrated HOMER Model at Three Institutions

Performance Measure	Cleveland Clinic Foundation	Henry Ford Hospital	Johns Hopkins
Brier Score			
HOMER	0.286	0.392	0.376
Institution specific c-HOMER[a]	0.290	0.414	0.437
Hosmer-Lemeshow p-value			
HOMER	0.02	0.01	0.02
Institution specific c-HOMER[a]	0.01	0.001	<0.0001
Observed vs. Forecast prN1|2|3 (vs. N0)			
Observed prN1|2|3	0.263	0.389	0.363
HOMER forecast prN1|2|3	0.290	0.361	0.380
Institution specific c-HOMER[a] forecast prN1|2|3	0.315	0.515	0.524
Observed vs. Predicted prN2|3 (vs. N0|1)			
Observed prN2|3	0.182	0.269	0.285
HOMER forecast prN2|3	0.218	0.289	0.302
Institution specific c-HOMER[a] forecast prN2|3	0.249	0.412	0.421
ROC-AUC[b] for predicting prN1|2|3 (vs. N0) disease			
HOMER		0.81 (0.73-0.90)	0.80 (0.74-0.87)
Institution specific c-HOMER[a]	0.85(0.80-0.91)	0.81 (0.73-0.90)	0.80 (0.74-0.87)
	0.85 (0.80-0.91)		
ROC-AUC[b] for predicting prN2|3 (vs. N0|1) disease			
HOMER			0.84 (0.78-0.90)
Institution specific c-HOMER[a]	0.91 (0.88-0.95)	0.85(0.77-0.92)	0.84(0.78-0.90)
	0.91 (0.88-0.95)	0.85(0.77-0.92)	

Definitions of abbreviations: probability of N1|2|3: N1 disease or higher; prN2|3: probability of N2 or N3 disease; ROC-AUC: Area Under the Receiver Operating Characteristic Curve; N0|1: N0 or N1

[a]c-HOMER: calibrated HOMER model, generated by using the general calibration method applied to a specific institution.

[b]Note that the ROC AUC is the same for HOMER and the c-HOMER models. The general calibration method used to generate the c-HOMER models does not impact model discrimination, it only changes calibration.

e-Table 8. Association between Tumor Size and N2 or N3 Malignant Nodal Involvement by EBUS when PET-CT N stage is N0

Tumor size	N0|1 by EBUS (n=565)	N2|3 by EBUS (n=12)	Proportion of patients with N2|3 disease by EBUS, (95% CI)	Total	P-value[a]
Patients with tumors measuring ≤3cm	369	10	0.026 (0.013-0.048)	379	P=0.235
Patients with tumors measuring >3cm	196	2	0.010(0.001-0.036)	198	

Definition of abbreviations: N0|1: N0 or N1; N2|3: N2 or N3; CI: credible interval

[a]p-value for Fisher's exact test.

e-Table 9. Predicted Probabilities N2|3 Disease for a Given Change in the Explanatory Variables in the Development Cohort Using HAL

CT PET N stage	Age	Histology	Location	Predicted prN2|3
CT=N0 or N1, PET=N0	40	Adeno	Central 1/3rd	0.152
CT=N0 or N1, PET=N0	40	Adeno	Outer 2/3rd	0.090
CT=N0 or N1, PET=N0	40	Squamous	Central 1/3rd	0.073
CT=N0 or N1, PET=N0	40	Squamous	Outer 2/3rd	0.042
CT=N0 or N1, PET=N0	40	NSCLC	Central 1/3rd	0.171
CT=N0 or N1, PET=N0	40	NSCLC	Outer 2/3rd	0.103
CT=N0 or N1, PET=N0	40	Other	Central 1/3rd	0.097
CT=N0 or N1, PET=N0	40	Other	Outer 2/3rd	0.056
CT=N0 or N1, PET=N0	50	Adeno	Central 1/3rd	0.116
CT=N0 or N1, PET=N0	50	Adeno	Outer 2/3rd	0.068
CT=N0 or N1, PET=N0	50	Squamous	Central 1/3rd	0.054
CT=N0 or N1, PET=N0	50	Squamous	Outer 2/3rd	0.031
CT=N0 or N1, PET=N0	50	NSCLC	Central 1/3rd	0.131
CT=N0 or N1, PET=N0	50	NSCLC	Outer 2/3rd	0.077
CT=N0 or N1, PET=N0	50	Other	Central 1/3rd	0.073
CT=N0 or N1, PET=N0	50	Other	Outer 2/3rd	0.042
CT=N0 or N1, PET=N0	60	Adeno	Central 1/3rd	0.088
CT=N0 or N1, PET=N0	60	Adeno	Outer 2/3rd	0.051
CT=N0 or N1, PET=N0	60	Squamous	Central 1/3rd	0.040
CT=N0 or N1, PET=N0	60	Squamous	Outer 2/3rd	0.023
CT=N0 or N1, PET=N0	60	NSCLC	Central 1/3rd	0.100
CT=N0 or N1, PET=N0	60	NSCLC	Outer 2/3rd	0.058
CT=N0 or N1, PET=N0	60	Other	Central 1/3rd	0.055
CT=N0 or N1, PET=N0	60	Other	Outer 2/3rd	0.031
CT=N0 or N1, PET=N0	70	Adeno	Central 1/3rd	0.066
CT=N0 or N1, PET=N0	70	Adeno	Outer 2/3rd	0.038
CT=N0 or N1, PET=N0	70	Squamous	Central 1/3rd	0.030

CT=N0 or N1, PET=N0	70	Squamous	Outer 2/3rd	0.017
CT=N0 or N1, PET=N0	70	NSCLC	Central 1/3rd	0.075
CT=N0 or N1, PET=N0	70	NSCLC	Outer 2/3rd	0.043
CT=N0 or N1, PET=N0	70	Other	Central 1/3rd	0.041
CT=N0 or N1, PET=N0	70	Other	Outer 2/3rd	0.023
CT=N0 or N1, PET=N0	80	Adeno	Central 1/3rd	0.049
CT=N0 or N1, PET=N0	80	Adeno	Outer 2/3rd	0.028
CT=N0 or N1, PET=N0	80	Squamous	Central 1/3rd	0.022
CT=N0 or N1, PET=N0	80	Squamous	Outer 2/3rd	0.012
CT=N0 or N1, PET=N0	80	NSCLC	Central 1/3rd	0.056
CT=N0 or N1, PET=N0	80	NSCLC	Outer 2/3rd	0.032
CT=N0 or N1, PET=N0	80	Other	Central 1/3rd	0.030
CT=N0 or N1, PET=N0	80	Other	Outer 2/3rd	0.017
CT=N0 or N1, PET=N1	40	Adeno	Central 1/3rd	0.464
CT=N0 or N1, PET=N1	40	Adeno	Outer 2/3rd	0.324
CT=N0 or N1, PET=N1	40	Squamous	Central 1/3rd	0.275
CT=N0 or N1, PET=N1	40	Squamous	Outer 2/3rd	0.174
CT=N0 or N1, PET=N1	40	NSCLC	Central 1/3rd	0.499
CT=N0 or N1, PET=N1	40	NSCLC	Outer 2/3rd	0.356
CT=N0 or N1, PET=N1	40	Other	Central 1/3rd	0.342
CT=N0 or N1, PET=N1	40	Other	Outer 2/3rd	0.224
CT=N0 or N1, PET=N1	50	Adeno	Central 1/3rd	0.388
CT=N0 or N1, PET=N1	50	Adeno	Outer 2/3rd	0.260
CT=N0 or N1, PET=N1	50	Squamous	Central 1/3rd	0.218
CT=N0 or N1, PET=N1	50	Squamous	Outer 2/3rd	0.134
CT=N0 or N1, PET=N1	50	NSCLC	Central 1/3rd	0.422
CT=N0 or N1, PET=N1	50	NSCLC	Outer 2/3rd	0.289
CT=N0 or N1, PET=N1	50	Other	Central 1/3rd	0.276
CT=N0 or N1, PET=N1	50	Other	Outer 2/3rd	0.175
CT=N0 or N1, PET=N1	60	Adeno	Central 1/3rd	0.317
CT=N0 or N1, PET=N1	60	Adeno	Outer 2/3rd	0.205
CT=N0 or N1, PET=N1	60	Squamous	Central 1/3rd	0.169

CT=N0 or N1, PET=N1	60	Squamous	Outer 2/3rd	0.102
CT=N0 or N1, PET=N1	60	NSCLC	Central 1/3rd	0.349
CT=N0 or N1, PET=N1	60	NSCLC	Outer 2/3rd	0.229
CT=N0 or N1, PET=N1	60	Other	Central 1/3rd	0.218
CT=N0 or N1, PET=N1	60	Other	Outer 2/3rd	0.134
CT=N0 or N1, PET=N1	70	Adeno	Central 1/3rd	0.254
CT=N0 or N1, PET=N1	70	Adeno	Outer 2/3rd	0.159
CT=N0 or N1, PET=N1	70	Squamous	Central 1/3rd	0.130
CT=N0 or N1, PET=N1	70	Squamous	Outer 2/3rd	0.077
CT=N0 or N1, PET=N1	70	NSCLC	Central 1/3rd	0.282
CT=N0 or N1, PET=N1	70	NSCLC	Outer 2/3rd	0.179
CT=N0 or N1, PET=N1	70	Other	Central 1/3rd	0.170
CT=N0 or N1, PET=N1	70	Other	Outer 2/3rd	0.102
CT=N0 or N1, PET=N1	80	Adeno	Central 1/3rd	0.199
CT=N0 or N1, PET=N1	80	Adeno	Outer 2/3rd	0.122
CT=N0 or N1, PET=N1	80	Squamous	Central 1/3rd	0.099
CT=N0 or N1, PET=N1	80	Squamous	Outer 2/3rd	0.057
CT=N0 or N1, PET=N1	80	NSCLC	Central 1/3rd	0.223
CT=N0 or N1, PET=N1	80	NSCLC	Outer 2/3rd	0.138
CT=N0 or N1, PET=N1	80	Other	Central 1/3rd	0.130
CT=N0 or N1, PET=N1	80	Other	Outer 2/3rd	0.077
CT=N0 or N1, PET=N2 or N3	40	Adeno	Central 1/3rd	0.657
CT=N0 or N1, PET=N2 or N3	40	Adeno	Outer 2/3rd	0.516
CT=N0 or N1, PET=N2 or N3	40	Squamous	Central 1/3rd	0.457
CT=N0 or N1, PET=N2 or N3	40	Squamous	Outer 2/3rd	0.318
CT=N0 or N1, PET=N2 or N3	40	NSCLC	Central 1/3rd	0.688
CT=N0 or N1, PET=N2 or N3	40	NSCLC	Outer 2/3rd	0.551
CT=N0 or N1, PET=N2 or N3	40	Other	Central 1/3rd	0.536
CT=N0 or N1, PET=N2 or N3	40	Other	Outer 2/3rd	0.390
CT=N0 or N1, PET=N2 or N3	50	Adeno	Central 1/3rd	0.584
CT=N0 or N1, PET=N2 or N3	50	Adeno	Outer 2/3rd	0.438
CT=N0 or N1, PET=N2 or N3	50	Squamous	Central 1/3rd	0.381

CT=N0 or N1, PET=N2 or N3	50	Squamous	Outer 2/3rd	0.255
CT=N0 or N1, PET=N2 or N3	50	NSCLC	Central 1/3rd	0.618
CT=N0 or N1, PET=N2 or N3	50	NSCLC	Outer 2/3rd	0.473
CT=N0 or N1, PET=N2 or N3	50	Other	Central 1/3rd	0.458
CT=N0 or N1, PET=N2 or N3	50	Other	Outer 2/3rd	0.319
CT=N0 or N1, PET=N2 or N3	60	Adeno	Central 1/3rd	0.507
CT=N0 or N1, PET=N2 or N3	60	Adeno	Outer 2/3rd	0.364
CT=N0 or N1, PET=N2 or N3	60	Squamous	Central 1/3rd	0.311
CT=N0 or N1, PET=N2 or N3	60	Squamous	Outer 2/3rd	0.200
CT=N0 or N1, PET=N2 or N3	60	NSCLC	Central 1/3rd	0.543
CT=N0 or N1, PET=N2 or N3	60	NSCLC	Outer 2/3rd	0.397
CT=N0 or N1, PET=N2 or N3	60	Other	Central 1/3rd	0.382
CT=N0 or N1, PET=N2 or N3	60	Other	Outer 2/3rd	0.256
CT=N0 or N1, PET=N2 or N3	70	Adeno	Central 1/3rd	0.430
CT=N0 or N1, PET=N2 or N3	70	Adeno	Outer 2/3rd	0.295
CT=N0 or N1, PET=N2 or N3	70	Squamous	Central 1/3rd	0.249
CT=N0 or N1, PET=N2 or N3	70	Squamous	Outer 2/3rd	0.155
CT=N0 or N1, PET=N2 or N3	70	NSCLC	Central 1/3rd	0.465
CT=N0 or N1, PET=N2 or N3	70	NSCLC	Outer 2/3rd	0.326
CT=N0 or N1, PET=N2 or N3	70	Other	Central 1/3rd	0.312
CT=N0 or N1, PET=N2 or N3	70	Other	Outer 2/3rd	0.201
CT=N0 or N1, PET=N2 or N3	80	Adeno	Central 1/3rd	0.356
CT=N0 or N1, PET=N2 or N3	80	Adeno	Outer 2/3rd	0.235
CT=N0 or N1, PET=N2 or N3	80	Squamous	Central 1/3rd	0.195
CT=N0 or N1, PET=N2 or N3	80	Squamous	Outer 2/3rd	0.119
CT=N0 or N1, PET=N2 or N3	80	NSCLC	Central 1/3rd	0.389
CT=N0 or N1, PET=N2 or N3	80	NSCLC	Outer 2/3rd	0.261
CT=N0 or N1, PET=N2 or N3	80	Other	Central 1/3rd	0.249
CT=N0 or N1, PET=N2 or N3	80	Other	Outer 2/3rd	0.156
CT=N2 or N3, PET=N0	40	Adeno	Central 1/3rd	0.320
CT=N2 or N3, PET=N0	40	Adeno	Outer 2/3rd	0.207
CT=N2 or N3, PET=N0	40	Squamous	Central 1/3rd	0.171

CT=N2 or N3, PET=N0	40	Squamous	Outer 2/3rd	0.103
CT=N2 or N3, PET=N0	40	NSCLC	Central 1/3rd	0.352
CT=N2 or N3, PET=N0	40	NSCLC	Outer 2/3rd	0.232
CT=N2 or N3, PET=N0	40	Other	Central 1/3rd	0.221
CT=N2 or N3, PET=N0	40	Other	Outer 2/3rd	0.136
CT=N2 or N3, PET=N0	50	Adeno	Central 1/3rd	0.257
CT=N2 or N3, PET=N0	50	Adeno	Outer 2/3rd	0.161
CT=N2 or N3, PET=N0	50	Squamous	Central 1/3rd	0.132
CT=N2 or N3, PET=N0	50	Squamous	Outer 2/3rd	0.078
CT=N2 or N3, PET=N0	50	NSCLC	Central 1/3rd	0.285
CT=N2 or N3, PET=N0	50	NSCLC	Outer 2/3rd	0.181
CT=N2 or N3, PET=N0	50	Other	Central 1/3rd	0.172
CT=N2 or N3, PET=N0	50	Other	Outer 2/3rd	0.103
CT=N2 or N3, PET=N0	60	Adeno	Central 1/3rd	0.202
CT=N2 or N3, PET=N0	60	Adeno	Outer 2/3rd	0.123
CT=N2 or N3, PET=N0	60	Squamous	Central 1/3rd	0.100
CT=N2 or N3, PET=N0	60	Squamous	Outer 2/3rd	0.058
CT=N2 or N3, PET=N0	60	NSCLC	Central 1/3rd	0.226
CT=N2 or N3, PET=N0	60	NSCLC	Outer 2/3rd	0.139
CT=N2 or N3, PET=N0	60	Other	Central 1/3rd	0.132
CT=N2 or N3, PET=N0	60	Other	Outer 2/3rd	0.078
CT=N2 or N3, PET=N0	70	Adeno	Central 1/3rd	0.156
CT=N2 or N3, PET=N0	70	Adeno	Outer 2/3rd	0.093
CT=N2 or N3, PET=N0	70	Squamous	Central 1/3rd	0.075
CT=N2 or N3, PET=N0	70	Squamous	Outer 2/3rd	0.043
CT=N2 or N3, PET=N0	70	NSCLC	Central 1/3rd	0.176
CT=N2 or N3, PET=N0	70	NSCLC	Outer 2/3rd	0.106
CT=N2 or N3, PET=N0	70	Other	Central 1/3rd	0.100
CT=N2 or N3, PET=N0	70	Other	Outer 2/3rd	0.058
CT=N2 or N3, PET=N0	80	Adeno	Central 1/3rd	0.120
CT=N2 or N3, PET=N0	80	Adeno	Outer 2/3rd	0.070
CT=N2 or N3, PET=N0	80	Squamous	Central 1/3rd	0.056

CT=N2 or N3, PET=N0	80	Squamous	Outer 2/3rd	0.032
CT=N2 or N3, PET=N0	80	NSCLC	Central 1/3rd	0.135
CT=N2 or N3, PET=N0	80	NSCLC	Outer 2/3rd	0.080
CT=N2 or N3, PET=N0	80	Other	Central 1/3rd	0.076
CT=N2 or N3, PET=N0	80	Other	Outer 2/3rd	0.043
CT=N2 or N3, PET=N1	40	Adeno	Central 1/3rd	0.305
CT=N2 or N3, PET=N1	40	Adeno	Outer 2/3rd	0.196
CT=N2 or N3, PET=N1	40	Squamous	Central 1/3rd	0.162
CT=N2 or N3, PET=N1	40	Squamous	Outer 2/3rd	0.097
CT=N2 or N3, PET=N1	40	NSCLC	Central 1/3rd	0.336
CT=N2 or N3, PET=N1	40	NSCLC	Outer 2/3rd	0.220
CT=N2 or N3, PET=N1	40	Other	Central 1/3rd	0.209
CT=N2 or N3, PET=N1	40	Other	Outer 2/3rd	0.128
CT=N2 or N3, PET=N1	50	Adeno	Central 1/3rd	0.244
CT=N2 or N3, PET=N1	50	Adeno	Outer 2/3rd	0.152
CT=N2 or N3, PET=N1	50	Squamous	Central 1/3rd	0.124
CT=N2 or N3, PET=N1	50	Squamous	Outer 2/3rd	0.073
CT=N2 or N3, PET=N1	50	NSCLC	Central 1/3rd	0.271
CT=N2 or N3, PET=N1	50	NSCLC	Outer 2/3rd	0.171
CT=N2 or N3, PET=N1	50	Other	Central 1/3rd	0.162
CT=N2 or N3, PET=N1	50	Other	Outer 2/3rd	0.097
CT=N2 or N3, PET=N1	60	Adeno	Central 1/3rd	0.191
CT=N2 or N3, PET=N1	60	Adeno	Outer 2/3rd	0.116
CT=N2 or N3, PET=N1	60	Squamous	Central 1/3rd	0.094
CT=N2 or N3, PET=N1	60	Squamous	Outer 2/3rd	0.054
CT=N2 or N3, PET=N1	60	NSCLC	Central 1/3rd	0.214
CT=N2 or N3, PET=N1	60	NSCLC	Outer 2/3rd	0.131
CT=N2 or N3, PET=N1	60	Other	Central 1/3rd	0.124
CT=N2 or N3, PET=N1	60	Other	Outer 2/3rd	0.073
CT=N2 or N3, PET=N1	70	Adeno	Central 1/3rd	0.148
CT=N2 or N3, PET=N1	70	Adeno	Outer 2/3rd	0.088
CT=N2 or N3, PET=N1	70	Squamous	Central 1/3rd	0.071

CT=N2 or N3, PET=N1	70	Squamous	Outer 2/3rd	0.040
CT=N2 or N3, PET=N1	70	NSCLC	Central 1/3rd	0.166
CT=N2 or N3, PET=N1	70	NSCLC	Outer 2/3rd	0.100
CT=N2 or N3, PET=N1	70	Other	Central 1/3rd	0.094
CT=N2 or N3, PET=N1	70	Other	Outer 2/3rd	0.055
CT=N2 or N3, PET=N1	80	Adeno	Central 1/3rd	0.113
CT=N2 or N3, PET=N1	80	Adeno	Outer 2/3rd	0.066
CT=N2 or N3, PET=N1	80	Squamous	Central 1/3rd	0.053
CT=N2 or N3, PET=N1	80	Squamous	Outer 2/3rd	0.030
CT=N2 or N3, PET=N1	80	NSCLC	Central 1/3rd	0.128
CT=N2 or N3, PET=N1	80	NSCLC	Outer 2/3rd	0.075
CT=N2 or N3, PET=N1	80	Other	Central 1/3rd	0.071
CT=N2 or N3, PET=N1	80	Other	Outer 2/3rd	0.041
CT=N2 or N3, PET=N2 or N3	40	Adeno	Central 1/3rd	0.884
CT=N2 or N3, PET=N2 or N3	40	Adeno	Outer 2/3rd	0.809
CT=N2 or N3, PET=N2 or N3	40	Squamous	Central 1/3rd	0.770
CT=N2 or N3, PET=N2 or N3	40	Squamous	Outer 2/3rd	0.650
CT=N2 or N3, PET=N2 or N3	40	NSCLC	Central 1/3rd	0.898
CT=N2 or N3, PET=N2 or N3	40	NSCLC	Outer 2/3rd	0.830
CT=N2 or N3, PET=N2 or N3	40	Other	Central 1/3rd	0.821
CT=N2 or N3, PET=N2 or N3	40	Other	Outer 2/3rd	0.718
CT=N2 or N3, PET=N2 or N3	50	Adeno	Central 1/3rd	0.848
CT=N2 or N3, PET=N2 or N3	50	Adeno	Outer 2/3rd	0.756
CT=N2 or N3, PET=N2 or N3	50	Squamous	Central 1/3rd	0.710
CT=N2 or N3, PET=N2 or N3	50	Squamous	Outer 2/3rd	0.576
CT=N2 or N3, PET=N2 or N3	50	NSCLC	Central 1/3rd	0.866
CT=N2 or N3, PET=N2 or N3	50	NSCLC	Outer 2/3rd	0.781
CT=N2 or N3, PET=N2 or N3	50	Other	Central 1/3rd	0.771
CT=N2 or N3, PET=N2 or N3	50	Other	Outer 2/3rd	0.651
CT=N2 or N3, PET=N2 or N3	60	Adeno	Central 1/3rd	0.804
CT=N2 or N3, PET=N2 or N3	60	Adeno	Outer 2/3rd	0.694
CT=N2 or N3, PET=N2 or N3	60	Squamous	Central 1/3rd	0.642

CT=N2 or N3, PET=N2 or N3	60	Squamous	Outer 2/3rd	0.499
CT=N2 or N3, PET=N2 or N3	60	NSCLC	Central 1/3rd	0.825
CT=N2 or N3, PET=N2 or N3	60	NSCLC	Outer 2/3rd	0.724
CT=N2 or N3, PET=N2 or N3	60	Other	Central 1/3rd	0.711
CT=N2 or N3, PET=N2 or N3	60	Other	Outer 2/3rd	0.578
CT=N2 or N3, PET=N2 or N3	70	Adeno	Central 1/3rd	0.750
CT=N2 or N3, PET=N2 or N3	70	Adeno	Outer 2/3rd	0.625
CT=N2 or N3, PET=N2 or N3	70	Squamous	Central 1/3rd	0.568
CT=N2 or N3, PET=N2 or N3	70	Squamous	Outer 2/3rd	0.422
CT=N2 or N3, PET=N2 or N3	70	NSCLC	Central 1/3rd	0.776
CT=N2 or N3, PET=N2 or N3	70	NSCLC	Outer 2/3rd	0.657
CT=N2 or N3, PET=N2 or N3	70	Other	Central 1/3rd	0.643
CT=N2 or N3, PET=N2 or N3	70	Other	Outer 2/3rd	0.500
CT=N2 or N3, PET=N2 or N3	80	Adeno	Central 1/3rd	0.687
CT=N2 or N3, PET=N2 or N3	80	Adeno	Outer 2/3rd	0.550
CT=N2 or N3, PET=N2 or N3	80	Squamous	Central 1/3rd	0.491
CT=N2 or N3, PET=N2 or N3	80	Squamous	Outer 2/3rd	0.349
CT=N2 or N3, PET=N2 or N3	80	NSCLC	Central 1/3rd	0.717
CT=N2 or N3, PET=N2 or N3	80	NSCLC	Outer 2/3rd	0.584
CT=N2 or N3, PET=N2 or N3	80	Other	Central 1/3rd	0.569
CT=N2 or N3, PET=N2 or N3	80	Other	Outer 2/3rd	0.423

Definition of variables: NSCLC: non-small cell lung cancer; prN2|3: probability of N2 or N3 disease

To find the scenario you are interested in, recognize that the scenarios are organized basted 1st on the CT N stage, then by the PET N stage, then by age, cancer type, and finally by tumor location. Probabilities are based on the development cohort.

e-Table 10. Predicted Probabilities of N0, N1 and N2|3 Disease for a Given Change in the Explanatory Variables in the Development Cohort Using HOMER

PET-CT	Histology	Location	Age	Predicted probability of N0	Predicted Probability of N1	Predicted Probability of N2|3
CT=N0 or N1, PET=N0	Adenocarcinoma	Central 1/3rd	60	0.896	0.022	0.081
CT=N0 or N1, PET=N0	Adenocarcinoma	Outer 2/3rd	60	0.934	0.015	0.052
CT=N0 or N1, PET=N0	Squamous cell	Central 1/3rd	60	0.952	0.011	0.037
CT=N0 or N1, PET=N0	Squamous cell	Outer 2/3rd	60	0.970	0.007	0.023
CT=N0 or N1, PET=N0	Non-small cell	Central 1/3rd	60	0.890	0.024	0.086
CT=N0 or N1, PET=N0	Non-small cell	Outer 2/3rd	60	0.930	0.016	0.055
CT=N0 or N1, PET=N0	Other lung primary	Central 1/3rd	60	0.929	0.016	0.055
CT=N0 or N1, PET=N0	Other lung primary	Outer 2/3rd	60	0.955	0.010	0.035
CT=N0 or N1, PET=N0	Adenocarcinoma	Central 1/3rd	70	0.921	0.017	0.062
CT=N0 or N1, PET=N0	Adenocarcinoma	Outer 2/3rd	70	0.950	0.011	0.039
CT=N0 or N1, PET=N0	Squamous cell	Central 1/3rd	70	0.963	0.008	0.028
CT=N0 or N1, PET=N0	Squamous cell	Outer 2/3rd	70	0.977	0.005	0.018
CT=N0 or N1, PET=N0	Non-small cell	Central 1/3rd	70	0.916	0.018	0.066
CT=N0 or N1, PET=N0	Non-small cell	Outer 2/3rd	70	0.947	0.012	0.041
CT=N0 or N1, PET=N0	Other lung primary	Central 1/3rd	70	0.946	0.012	0.042
CT=N0 or N1, PET=N0	Other lung primary	Outer 2/3rd	70	0.966	0.008	0.026
CT=N0 or N1, PET=N0	Adenocarcinoma	Central 1/3rd	80	0.940	0.014	0.047

CT=N0 or N1, PET=N0	Adenocarcinoma	Outer 2/3rd	80	0.962	0.009	0.029
CT=N0 or N1, PET=N0	Squamous cell	Central 1/3rd	80	0.972	0.006	0.021
CT=N0 or N1, PET=N0	Squamous cell	Outer 2/3rd	80	0.983	0.004	0.013
CT=N0 or N1, PET=N0	Non-small cell	Central 1/3rd	80	0.936	0.014	0.050
CT=N0 or N1, PET=N0	Non-small cell	Outer 2/3rd	80	0.960	0.009	0.031
CT=N0 or N1, PET=N0	Other lung primary	Central 1/3rd	80	0.959	0.009	0.032
CT=N0 or N1, PET=N0	Other lung primary	Outer 2/3rd	80	0.974	0.006	0.020
CT=N0 or N1, PET=N1	Adenocarcinoma	Central 1/3rd	60	0.284	0.413	0.303
CT=N0 or N1, PET=N1	Adenocarcinoma	Outer 2/3rd	60	0.392	0.397	0.211
CT=N0 or N1, PET=N1	Squamous cell	Central 1/3rd	60	0.474	0.365	0.161
CT=N0 or N1, PET=N1	Squamous cell	Outer 2/3rd	60	0.595	0.300	0.105
CT=N0 or N1, PET=N1	Non-small cell	Central 1/3rd	60	0.271	0.412	0.317
CT=N0 or N1, PET=N1	Non-small cell	Outer 2/3rd	60	0.377	0.401	0.222
CT=N0 or N1, PET=N1	Other lung primary	Central 1/3rd	60	0.374	0.402	0.224
CT=N0 or N1, PET=N1	Other lung primary	Outer 2/3rd	60	0.493	0.356	0.151
CT=N0 or N1, PET=N1	Adenocarcinoma	Central 1/3rd	70	0.347	0.408	0.245
CT=N0 or N1, PET=N1	Adenocarcinoma	Outer 2/3rd	70	0.464	0.370	0.166
CT=N0 or N1, PET=N1	Squamous cell	Central 1/3rd	70	0.547	0.328	0.125
CT=N0 or N1, PET=N1	Squamous cell	Outer 2/3rd	70	0.663	0.257	0.081
CT=N0 or N1, PET=N1	Non-small cell	Central 1/3rd	70	0.333	0.410	0.257
CT=N0 or N1, PET=N1	Non-small cell	Outer 2/3rd	70	0.448	0.377	0.175
CT=N0 or N1, PET=N1	Other lung primary	Central 1/3rd	70	0.445	0.378	0.177

CT=N0 or N1, PET=N1	Other lung primary	Outer 2/3rd	70	0.566	0.317	0.117
CT=N0 or N1, PET=N1	Adenocarcinoma	Central 1/3rd	80	0.416	0.389	0.195
CT=N0 or N1, PET=N1	Adenocarcinoma	Outer 2/3rd	80	0.537	0.334	0.130
CT=N0 or N1, PET=N1	Squamous cell	Central 1/3rd	80	0.618	0.286	0.096
CT=N0 or N1, PET=N1	Squamous cell	Outer 2/3rd	80	0.725	0.214	0.062
CT=N0 or N1, PET=N1	Non-small cell	Central 1/3rd	80	0.401	0.394	0.205
CT=N0 or N1, PET=N1	Non-small cell	Outer 2/3rd	80	0.521	0.342	0.137
CT=N0 or N1, PET=N1	Other lung primary	Central 1/3rd	80	0.517	0.344	0.139
CT=N0 or N1, PET=N1	Other lung primary	Outer 2/3rd	80	0.636	0.274	0.090
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	60	0.475	0.042	0.483
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	60	0.595	0.040	0.365
CT=N0 or N1, PET=N2 or N3	Squamous cell	Central 1/3rd	60	0.673	0.036	0.292
CT=N0 or N1, PET=N2 or N3	Squamous cell	Outer 2/3rd	60	0.770	0.028	0.202
CT=N0 or N1, PET=N2 or N3	Non-small cell	Central 1/3rd	60	0.459	0.042	0.499
CT=N0 or N1, PET=N2 or N3	Non-small cell	Outer 2/3rd	60	0.580	0.040	0.380
CT=N0 or N1, PET=N2 or N3	Other lung primary	Central 1/3rd	60	0.577	0.040	0.383
CT=N0 or N1, PET=N2 or N3	Other lung primary	Outer 2/3rd	60	0.689	0.035	0.276
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	70	0.548	0.041	0.411
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	70	0.663	0.036	0.301
CT=N0 or N1, PET=N2 or N3	Squamous cell	Central 1/3rd	70	0.734	0.031	0.235
CT=N0 or N1, PET=N2 or N3	Squamous cell	Outer 2/3rd	70	0.817	0.024	0.159
CT=N0 or N1, PET=N2 or N3	Non-small cell	Central 1/3rd	70	0.532	0.041	0.427

CT=N0 or N1, PET=N2 or N3	Non-small cell	Outer 2/3rd	70	0.649	0.037	0.314
CT=N0 or N1, PET=N2 or N3	Other lung primary	Central 1/3rd	70	0.646	0.037	0.317
CT=N0 or N1, PET=N2 or N3	Other lung primary	Outer 2/3rd	70	0.748	0.030	0.222
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	80	0.619	0.039	0.343
CT=N0 or N1, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	80	0.725	0.032	0.243
CT=N0 or N1, PET=N2 or N3	Squamous cell	Central 1/3rd	80	0.787	0.027	0.187
CT=N0 or N1, PET=N2 or N3	Squamous cell	Outer 2/3rd	80	0.857	0.019	0.124
CT=N0 or N1, PET=N2 or N3	Non-small cell	Central 1/3rd	80	0.604	0.039	0.357
CT=N0 or N1, PET=N2 or N3	Non-small cell	Outer 2/3rd	80	0.712	0.033	0.255
CT=N0 or N1, PET=N2 or N3	Other lung primary	Central 1/3rd	80	0.710	0.033	0.257
CT=N0 or N1, PET=N2 or N3	Other lung primary	Outer 2/3rd	80	0.799	0.026	0.176
CT=N2 or N3, PET=N0	Adenocarcinoma	Central 1/3rd	60	0.728	0.081	0.191
CT=N2 or N3, PET=N0	Adenocarcinoma	Outer 2/3rd	60	0.813	0.060	0.126
CT=N2 or N3, PET=N0	Squamous cell	Central 1/3rd	60	0.859	0.047	0.094
CT=N2 or N3, PET=N0	Squamous cell	Outer 2/3rd	60	0.908	0.032	0.060
CT=N2 or N3, PET=N0	Non-small cell	Central 1/3rd	60	0.715	0.084	0.201
CT=N2 or N3, PET=N0	Non-small cell	Outer 2/3rd	60	0.803	0.063	0.134
CT=N2 or N3, PET=N0	Other lung primary	Central 1/3rd	60	0.801	0.064	0.135
CT=N2 or N3, PET=N0	Other lung primary	Outer 2/3rd	60	0.868	0.045	0.088
CT=N2 or N3, PET=N0	Adenocarcinoma	Central 1/3rd	70	0.782	0.069	0.149
CT=N2 or N3, PET=N0	Adenocarcinoma	Outer 2/3rd	70	0.854	0.049	0.098
CT=N2 or N3, PET=N0	Squamous cell	Central 1/3rd	70	0.891	0.037	0.072

CT=N2 or N3, PET=N0	Squamous cell	Outer 2/3rd	70	0.930	0.025	0.045
CT=N2 or N3, PET=N0	Non-small cell	Central 1/3rd	70	0.771	0.071	0.158
CT=N2 or N3, PET=N0	Non-small cell	Outer 2/3rd	70	0.846	0.051	0.103
CT=N2 or N3, PET=N0	Other lung primary	Central 1/3rd	70	0.844	0.052	0.104
CT=N2 or N3, PET=N0	Other lung primary	Outer 2/3rd	70	0.898	0.035	0.067
CT=N2 or N3, PET=N0	Adenocarcinoma	Central 1/3rd	80	0.828	0.056	0.116
CT=N2 or N3, PET=N0	Adenocarcinoma	Outer 2/3rd	80	0.887	0.039	0.075
CT=N2 or N3, PET=N0	Squamous cell	Central 1/3rd	80	0.916	0.029	0.055
CT=N2 or N3, PET=N0	Squamous cell	Outer 2/3rd	80	0.947	0.019	0.034
CT=N2 or N3, PET=N0	Non-small cell	Central 1/3rd	80	0.818	0.059	0.123
CT=N2 or N3, PET=N0	Non-small cell	Outer 2/3rd	80	0.880	0.041	0.079
CT=N2 or N3, PET=N0	Other lung primary	Central 1/3rd	80	0.879	0.041	0.080
CT=N2 or N3, PET=N0	Other lung primary	Outer 2/3rd	80	0.922	0.027	0.051
CT=N2 or N3, PET=N1	Adenocarcinoma	Central 1/3rd	60	0.303	0.513	0.183
CT=N2 or N3, PET=N1	Adenocarcinoma	Outer 2/3rd	60	0.414	0.464	0.121
CT=N2 or N3, PET=N1	Squamous cell	Central 1/3rd	60	0.497	0.413	0.090
CT=N2 or N3, PET=N1	Squamous cell	Outer 2/3rd	60	0.617	0.326	0.057
CT=N2 or N3, PET=N1	Non-small cell	Central 1/3rd	60	0.290	0.517	0.193
CT=N2 or N3, PET=N1	Non-small cell	Outer 2/3rd	60	0.399	0.473	0.128
CT=N2 or N3, PET=N1	Other lung primary	Central 1/3rd	60	0.396	0.474	0.130
CT=N2 or N3, PET=N1	Other lung primary	Outer 2/3rd	60	0.516	0.400	0.084
CT=N2 or N3, PET=N1	Adenocarcinoma	Central 1/3rd	70	0.368	0.488	0.144

CT=N2 or N3, PET=N1	Adenocarcinoma	Outer 2/3rd	70	0.487	0.420	0.093
CT=N2 or N3, PET=N1	Squamous cell	Central 1/3rd	70	0.570	0.361	0.069
CT=N2 or N3, PET=N1	Squamous cell	Outer 2/3rd	70	0.683	0.273	0.043
CT=N2 or N3, PET=N1	Non-small cell	Central 1/3rd	70	0.354	0.495	0.152
CT=N2 or N3, PET=N1	Non-small cell	Outer 2/3rd	70	0.471	0.430	0.099
CT=N2 or N3, PET=N1	Other lung primary	Central 1/3rd	70	0.468	0.432	0.100
CT=N2 or N3, PET=N1	Other lung primary	Outer 2/3rd	70	0.588	0.348	0.064
CT=N2 or N3, PET=N1	Adenocarcinoma	Central 1/3rd	80	0.439	0.450	0.111
CT=N2 or N3, PET=N1	Adenocarcinoma	Outer 2/3rd	80	0.560	0.369	0.071
CT=N2 or N3, PET=N1	Squamous cell	Central 1/3rd	80	0.640	0.308	0.052
CT=N2 or N3, PET=N1	Squamous cell	Outer 2/3rd	80	0.743	0.224	0.033
CT=N2 or N3, PET=N1	Non-small cell	Central 1/3rd	80	0.423	0.459	0.118
CT=N2 or N3, PET=N1	Non-small cell	Outer 2/3rd	80	0.544	0.380	0.076
CT=N2 or N3, PET=N1	Other lung primary	Central 1/3rd	80	0.541	0.383	0.077
CT=N2 or N3, PET=N1	Other lung primary	Outer 2/3rd	80	0.657	0.295	0.049
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	60	0.175	0.036	0.790
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	60	0.256	0.046	0.698
CT=N2 or N3, PET=N2 or N3	Squamous cell	Central 1/3rd	60	0.325	0.052	0.623
CT=N2 or N3, PET=N2 or N3	Squamous cell	Outer 2/3rd	60	0.439	0.057	0.504
CT=N2 or N3, PET=N2 or N3	Non-small cell	Central 1/3rd	60	0.166	0.034	0.800
CT=N2 or N3, PET=N2 or N3	Non-small cell	Outer 2/3rd	60	0.244	0.045	0.711
CT=N2 or N3, PET=N2 or N3	Other lung primary	Central 1/3rd	60	0.242	0.045	0.714

CT=N2 or N3, PET=N2 or N3	Other lung primary	Outer 2/3rd	60	0.341	0.054	0.605
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	70	0.221	0.042	0.737
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	70	0.316	0.052	0.633
CT=N2 or N3, PET=N2 or N3	Squamous cell	Central 1/3rd	70	0.392	0.056	0.552
CT=N2 or N3, PET=N2 or N3	Squamous cell	Outer 2/3rd	70	0.512	0.057	0.431
CT=N2 or N3, PET=N2 or N3	Non-small cell	Central 1/3rd	70	0.210	0.041	0.749
CT=N2 or N3, PET=N2 or N3	Non-small cell	Outer 2/3rd	70	0.302	0.051	0.647
CT=N2 or N3, PET=N2 or N3	Other lung primary	Central 1/3rd	70	0.299	0.050	0.650
CT=N2 or N3, PET=N2 or N3	Other lung primary	Outer 2/3rd	70	0.410	0.057	0.533
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Central 1/3rd	80	0.275	0.048	0.676
CT=N2 or N3, PET=N2 or N3	Adenocarcinoma	Outer 2/3rd	80	0.382	0.056	0.563
CT=N2 or N3, PET=N2 or N3	Squamous cell	Central 1/3rd	80	0.463	0.058	0.479
CT=N2 or N3, PET=N2 or N3	Squamous cell	Outer 2/3rd	80	0.584	0.055	0.361
CT=N2 or N3, PET=N2 or N3	Non-small cell	Central 1/3rd	80	0.263	0.047	0.690
CT=N2 or N3, PET=N2 or N3	Non-small cell	Outer 2/3rd	80	0.367	0.055	0.578
CT=N2 or N3, PET=N2 or N3	Other lung primary	Central 1/3rd	80	0.364	0.055	0.581
CT=N2 or N3, PET=N2 or N3	Other lung primary	Outer 2/3rd	80	0.482	0.057	0.460

CT= computed tomography; PET= positron emission tomography; N2|3= N2 or N3 disease

To find the scenario you are interested in, recognize that the scenarios are organized basted 1st on the CT N stage, then by the PET N stage, then by age, cancer type, and finally by tumor location. Probabilities are based on the development cohort.

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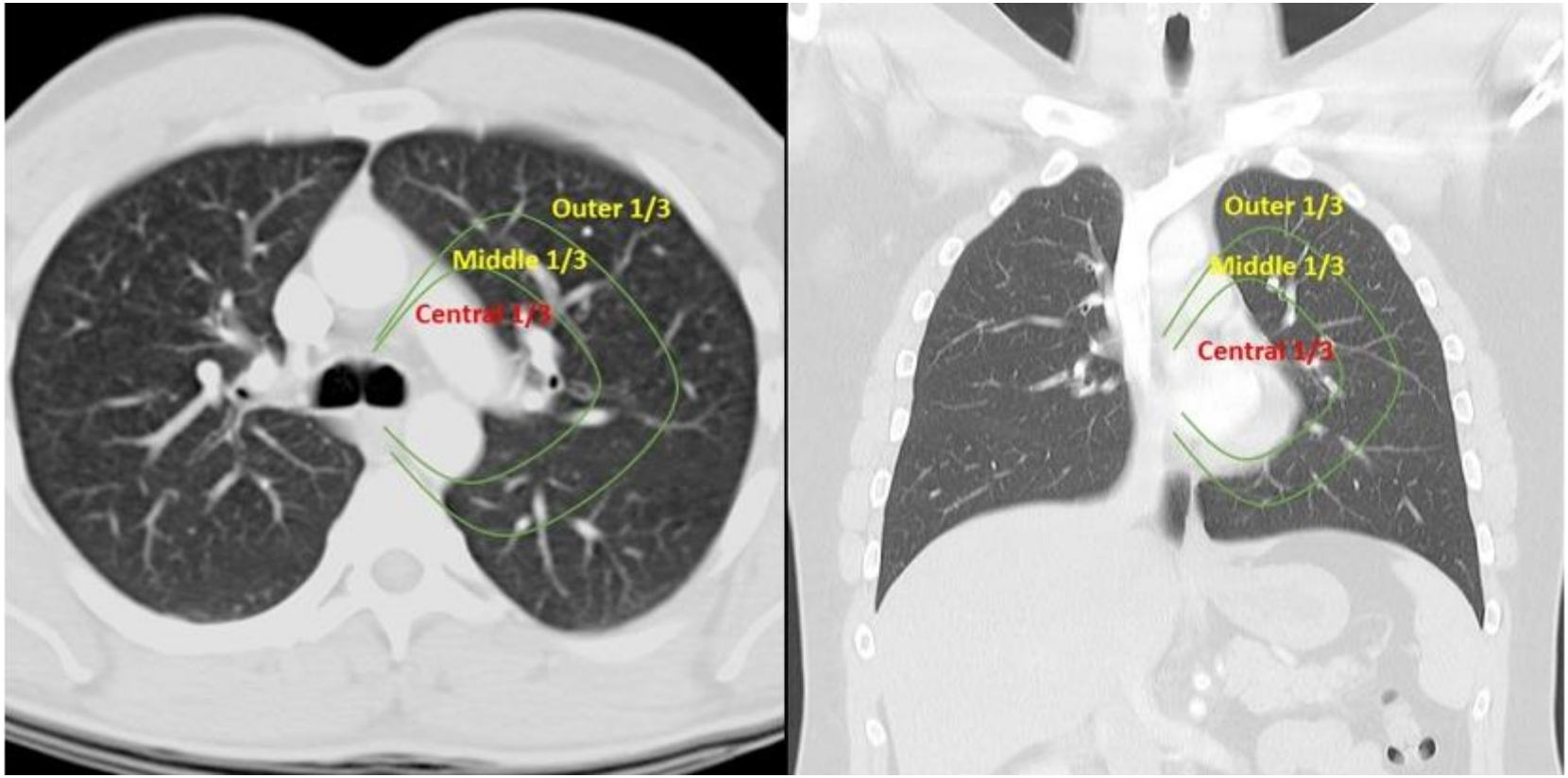
e-Figure 1. Central tumors were defined as tumors located within the inner one-third of the hemi-thorax or if any part of the tumor is within the segmental airways on CT (shown in red). Peripheral tumors were defined as tumors located in the outer two-thirds of the hemi-thorax, with the tumor not touching the segmental airways and located outside the central one-third of the hemi-thorax on CT (shown in yellow). [5]



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