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A Nomogram to Predict Recurrence and Survival of High-Risk Patients Undergoing Sublobar Resection for Lung Cancer: An Analysis of a Multicenter Prospective Study (ACOSOG Z4032)

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Abstract

Background—Individualized prediction of outcomes may help with therapy decisions for patients with non-small cell lung cancer (NSCLC). We developed a nomogram by analyzing 17 clinical factors and outcomes from a randomized study of sublobar resection for NSCLC in high-risk operable patients. The study compared sublobar resection alone, to sublobar resection with brachytherapy. There were no differences in primary and secondary outcomes between the study arms, and were thus combined for this analysis.

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The Appendix can be viewed in the online version of this article [INSERT article doi] on http://www.annalsthoracicsurgery.org.

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Methods—The clinical factors of interest (considered as continuous variables) were assessed in a univariate Cox Proportional Hazards model for significance at the 0.10 level for their impact on overall survival (OS), local recurrence free survival (LRFS) and any recurrence free survival (RFS). The final multivariable model was developed using a stepwise model selection.

Results—173 of 212 patients had complete data on all 17 risk factors. Median (range) follow-up was 4.94 (0.04–6.22) years. The 5-year OS, LRFS and RFS were 58.4%, 53.2% and 47.4% respectively. Age, baseline DLCO % and maximum tumor diameter were significant predictors for OS, LRFS and RFS in the multivariable model. Nomograms were subsequently developed for predicting 5-year OS, LFRS and RFS.

Conclusions—Age, baseline DLCO% and maximum tumor diameter significantly predicted outcomes after sublobar resection. Such nomograms may be helpful for treatment planning in early stage NSCLC and to guide future studies.

Keywords

pulmonary function; lung cancer surgery; lung cancer clinical trials; lobectomy; segmentectomy; wedge resection; statistics (clinical trial)

Patients with early stage lung cancer and limited pulmonary reserve present significant challenges in management. The merits of surgical resection versus ablative techniques such as radiofrequency ablation (RFA) or stereotactic radiosurgery (SRS) are highly contentious[1,2,3,4,5]. For patients who undergo resection, the appropriateness of wedge resection versus segmentectomy is also an area of active debate[6,7,8]. In addition to the specifics of treatment, physicians caring for these patients must also recognize that the survival of these patients is determined to a large degree by the severity of their comorbidities. Consequently, the development of tools to predict the overall survival of these patients based on comorbidities and tumor characteristics could potentially allow for more individualized treatment decisions.

The present study was undertaken to develop a nomogram to predict survival of patients with early stage lung cancer who underwent sublobar resection, utilizing data from a prospective, randomized study (ACOSOG Z4032). The American College of Surgeons Surgical Oncology Group Z4032 trial was a multi-center, randomized study designed to compare outcomes following sublobar resection with brachytherapy to sublobar resection alone. Patients with clinical stage I non-small lung cancer were eligible for enrollment if they were considered high-risk for lobectomy. The study completed accrual in January of 2010 with enrollment of 224 patients.

The primary endpoint of the study was local recurrence, and results were published in 2014[9]. There was no statistically significant difference in the time to local recurrence, the overall local recurrence rates, patterns of recurrence (local, regional or distant), or overall survival between sublobar resection with or without brachytherapy. The overall 5-year survival rate was 61.4% in the sublobar group and 55.6% in the sublobar plus brachytherapy group (p=0.38). For the present study, therefore, data from both arms were combined.

MATERIAL AND METHODS

Data source

This was a secondary analysis of data from ACOSOG Z4032, which was a randomized study evaluating the role of intraoperative brachytherapy in patients who were considered high-risk for lobectomy. Eligible patients were required to have a biopsy-proven stage I lung cancer and were considered to be high-risk on the basis of one major criterion or two minor criteria (Table 1).

Data for the present study was obtained from review of the de-identified operative and pathology reports that were prospectively submitted to ACOSOG along with the required case-report forms[10]. Study sites were not queried for new information, and all information was available as part of the original data collection by ACOSOG (now part of the Alliance for Clinical Trials in Oncology). All patients provided written informed consent before trial enrollment in accordance with applicable guidelines. At each participating site, institutional review board approval was obtained in accord with an assurance filed with and approved by the US Department of Health and Human Services.

Statistical analysis

A total of 17 baseline clinical and patient related factors were included in this exploratory analysis. A complete case analysis including only patients with no missing data for any of the 17 factors was used. Local recurrence was defined as recurrence within the primary tumor lobe at the staple line (local progression), recurrence within the primary tumor lobe away from the staple line (involved lobe failure) or recurrence within hilar lymph nodes. Regional recurrence was defined as recurrence within another lobe on the same side as the resection, or within ipsilateral mediastinal of subcarinal lymph nodes. Distant recurrence was defined as recurrence within contralateral, mediastinal or hilar lymph nodes, or distant metastatic disease. Recurrence free survival was defined as the time from randomization to the earlier of any recurrence (local, regional or distant) or death from any cause.

Each factor was assessed in a univariable Cox proportional hazards model for overall survival (OS), local recurrence free survival (LRFS) and recurrence free survival (RFS) outcomes. Factors that were significant at the 0.10 level from the univariable models were then included in an initial multivariable model for each outcome. Race and histology were included in all of the initial multivariable models regardless of significance in the univariable models. The final multivariable model for developing the nomogram utilized a stepwise model selection approach ($p \leq 0.1$ for entering the model, and $p \leq 0.05$ for staying in the model).

Prior to developing a nomogram, the linearity assumption was tested using splines for all continuous factors in the final multivariable model for each outcome[11]. A nomogram based on the final multivariable model for each outcome was developed to predict for the 5-year OS, 5 year RFS and 5 year LRFS. Concordance index (optimism-corrected) and calibration plots were obtained for each model using internal bootstrapping to guard against over fitting. Statistical analyses were conducted by the Alliance Statistics and Data Center. SAS version 9.3 and R 3.0.3 were used for the analyses.

Nomogram Interpretation

A nomogram provides a graphical representation of a statistical predictive model, and allows for a numerical prediction of a clinical event (*e.g.* overall survival). The variable with the largest effect on the outcome will be assigned a maximum of 100 points. Other variables will be assigned a lower maximum value proportional to their effect size[12]. To predict the outcome, the total number of points is calculated, and a vertical line is drawn from the total points axis to the outcome axis.

The predictive ability of the nomogram is measured by the concordance-index (C-index), which ranges in value from 0.0 to 1.0. This index reflects the probability that when two random patients are selected, the patient with the higher predictive score will experience the measured outcome. The index ranges from 0.0 to 1.0 where 0.5 indicates a random prediction, 1.0 indicates a perfect prediction, and values <0.5 indicate prediction in the opposite direction.

RESULTS

Baseline Demographics

Data was frozen for this analysis on April 24, 2014. A total of 224 patients were registered. Two patients were excluded from all analyses: one patient from the SR arm had the intervention at a hospital that was not institutional review board approved; one patient on the SRB arm did not have surgery. An additional 10 registered patients (six in the SR arm and four in the SRB arm) were found to be ineligible. Furthermore, 39 patients were excluded due to incomplete data on one or more baseline factors. Thus, 173 randomized patients were included in this analysis (Figure 1). No imputation approaches for missing data were employed in this analysis.

Table 2 summarizes the 17 clinical variables for the 173 patients with complete data. Median age was 70 years, with a mean DLCO of 45% predicted. The majority of patients underwent a video-assisted thoracoscopic surgery (VATS) procedure (n=115, 66.5%) and a wedge resection was performed more often than a segmentectomy (74.6% vs. 25.4%). No lymph nodes were sampled in 61 (35.3%) patients. Squamous cell carcinoma (n=81, 46.8%) and adenocarcinoma (n=92, 53.2%) were equally common. Overall 58.4% of the 173 patients in this analysis were alive at 5 years.

Overall Survival

The results of the univariable and multivariable models for overall survival are provided in Table 3. Age, baseline DLCO%, margin-tumor ratio, maximum tumor diameter and histology were significant predictors of overall survival in the univariable analysis. Age, baseline DLCO% and maximum tumor diameter retained significance in the final multivariable model after stepwise selection. All continuous variables passed the formal test for linearity assumption.

Figure 2 shows the nomogram for predicting overall survival for patients undergoing sublobar resection for stage I lung cancer enrolled in ACOSOG Z4032. The C-index (optimism corrected) for 5-year OS is 0.622.

Figure 3 shows the calibration plot, demonstrating good agreement between the predicted and observed overall survival.

Recurrence-free survival

The results for the univariable and multivariable models for local recurrence-free and any recurrence-free survival are presented in Appendix Tables 1 and 2. Similar to overall survival outcome, age, baseline DLCO% and maximum tumor diameter were significant predictors in the final multivariable model for these outcomes. The C-index (optimism corrected) for 5-year LRFS and RFS were 0.606 and 0.591, respectively.

COMMENT

Nomograms are useful and accepted tools to predict the survival of cancer patients[13,14,15]. Nomograms provide a graphical display of the variables that are found to be statistically significant and their relative importance. Furthermore, the ability to incorporate multiple variables in a single model may allow nomograms to predict survival more accurately than standard TNM staging systems[16,17]. For lung cancer specifically, nomograms have been used to predict the response to tyrosine kinase inhibitors and the development of brain metastases following curative surgery[18,19].

To our knowledge only three studies, all published in 2015, have developed nomograms to predict survival following surgical resection of lung tumors. The first study investigated the predictors of survival following resection of synchronous lung cancer in multiple lobes[20]. This was a pooled analysis of six previously published datasets. In that study, adenocarcinoma histology, female gender, N0 status, tumor size less than 3 cm and age less than 70 years were predictive of improved survival. A similar study developed a nomogram to predict survival following resection of typical carcinoid tumors, using data from a multi-center European registry[21].

Most relevant to the present study was the publication by Liang *et al* of a nomogram to predict survival following surgical resection of stages I–IIIA lung cancer[22]. Data to construct the nomogram was pooled from over 5,000 patients from seven cardiothoracic centers in China. The nomogram was externally validated using a separate cohort of patients from the International Association for the Study of Lung Cancer dataset. The final nomogram demonstrated that gender, age, histology, number of sampled lymph nodes, and T and N stage were independent predictors for survival.

In the present analysis only three baseline factors (age, tumor size and DLCO%) were predictive of overall survival, local recurrence-free survival and any recurrence-free survival. It is important to note that only 173 patients with complete data for all 17 factors were included in this analysis, thus this is a relatively small study. No imputation approaches for missing data were employed.

To put these findings into the context of previous publications, it is important to emphasize the unique characteristics of patients enrolled in ACOSOG Z4032. First, it should be noted that only patients with clinical stage I disease were enrolled in the trial. In addition, only high-risk surgical patients on the basis of advanced age and cardiopulmonary function were eligible for this study. As a result of significant comorbidities, many of the deaths in this study were from causes other than cancer. Specifically, the overall 5-year survival was 61.4% in the sublobar resection group and 55.6% sublobar resection plus brachytherapy group. Among those who died, only 41% of deaths were from cancer. The remaining deaths were either from co-morbid disease (50%) or from unknown causes (8%).

The nomogram created in the present study should be considered exploratory and not necessarily applicable to standard-risk patients undergoing surgical resection (usually lobectomy) for lung cancer. The predictive model in our study is derived from data on high-risk surgical patients, who in most centers would be considered for sublobar resection and increasingly for alternative therapies such as stereotactic radiosurgery or radiofrequency ablation.

In the study from Liang *et al* discussed above, sampled lymph nodes, and T and N stage were found to be significant predictors of survival. However, in that study patients with stages I–IIIA were included, as opposed to ACOSOG Z4032, in which only patients with clinical stage I disease who were enrolled. The exclusion of advanced stage patients in the Z4032 trial likely explains why the degree of lymph node evaluation was not predictive of survival. In addition, we should note that results of pulmonary function testing were not even considered in the Liang study.

It may also be surprising that factors that surgeons traditionally associated with appropriate oncologic surgery, such as the degree of lymph node sampling, margin status, and the performance of a segmentectomy compared to a wedge resection were not significant predictors of survival in this dataset. However, this may be related to competing risk factors for mortality in these patients, as evidenced by 50% of deaths being unrelated to cancer in our series.

In our study diffusion capacity was the most important factor in predicting overall survival. Diffusion capacity was also found to be an important predictor of perioperative complications in an earlier analysis of data from Z4032[23]. Other authors have also identified pulmonary function as a strong predictor of long-term survival following surgical resection of lung cancer, independent of perioperative mortality[24,25]. Significant reduction in diffusion capacity is not only a marker of advanced emphysema; it is also associated with pulmonary hypertension and cardiac disease, both of which may have a significant impact on long-term survival.

There are important limitations to this study. First, the high-risk population of patients with operable stage I cancer used to develop the nomogram should be re-emphasized. In addition, a relatively small number of patients were utilized to develop the nomogram. It is possible that a larger dataset may have shown that other factors, such as margin status and degree of lymph node sampling do impact survival as shown previously[26]. We should also note that

the tumor histology in Z4032 did not incorporate the recent updates to adenocarcinoma classification[27]. It is likely that adenocarcinoma-*in-situ* or minimally invasive adenocarcinoma subtypes would be relevant in a survival nomogram, however this information was not available in our dataset. Similarly, PET scan data (specifically SUV_{max}) was not routinely collected in the case-report forms of Z4032, and was therefore not incorporated into the survival model.

Most importantly, the nomogram which we developed has not been validated using an external dataset. This is difficult given the unique characteristics of the patients enrolled in Z4032. A dataset of relatively healthy patients undergoing lobectomy for early-stage lung cancer (*e.g.* the IASCLC database) would not provide an appropriate comparison. However, we anticipate that a study comparing SRS to sublobar resection for high-risk patients (formerly ACOSOG Z4099, now the Stablemates study) will soon be open for accrual[28]. The study population in this upcoming study uses the same inclusion/exclusion criteria, and so a secondary objective of that study will be to externally validate these nomograms from Z4032.

The results of this analysis raise several questions when considering the optimal therapy for high-risk patients with NSCLC. Specifically, as traditional surgical quality measures do not appear to impact survival, is it reasonable to consider alternative approaches for these patients? In addition, are these nomograms valid for patients treated with non-operative therapy? Hopefully external validation of the nomograms developed in this study will address some of these questions.

In summary, we found that age, diffusion capacity and the maximum tumor diameter were the three factors associated with survival in high-risk operable patients with early-stage lung cancer. These nomograms may be useful in selecting individualized treatment planning for these patients and will need to be validated in future studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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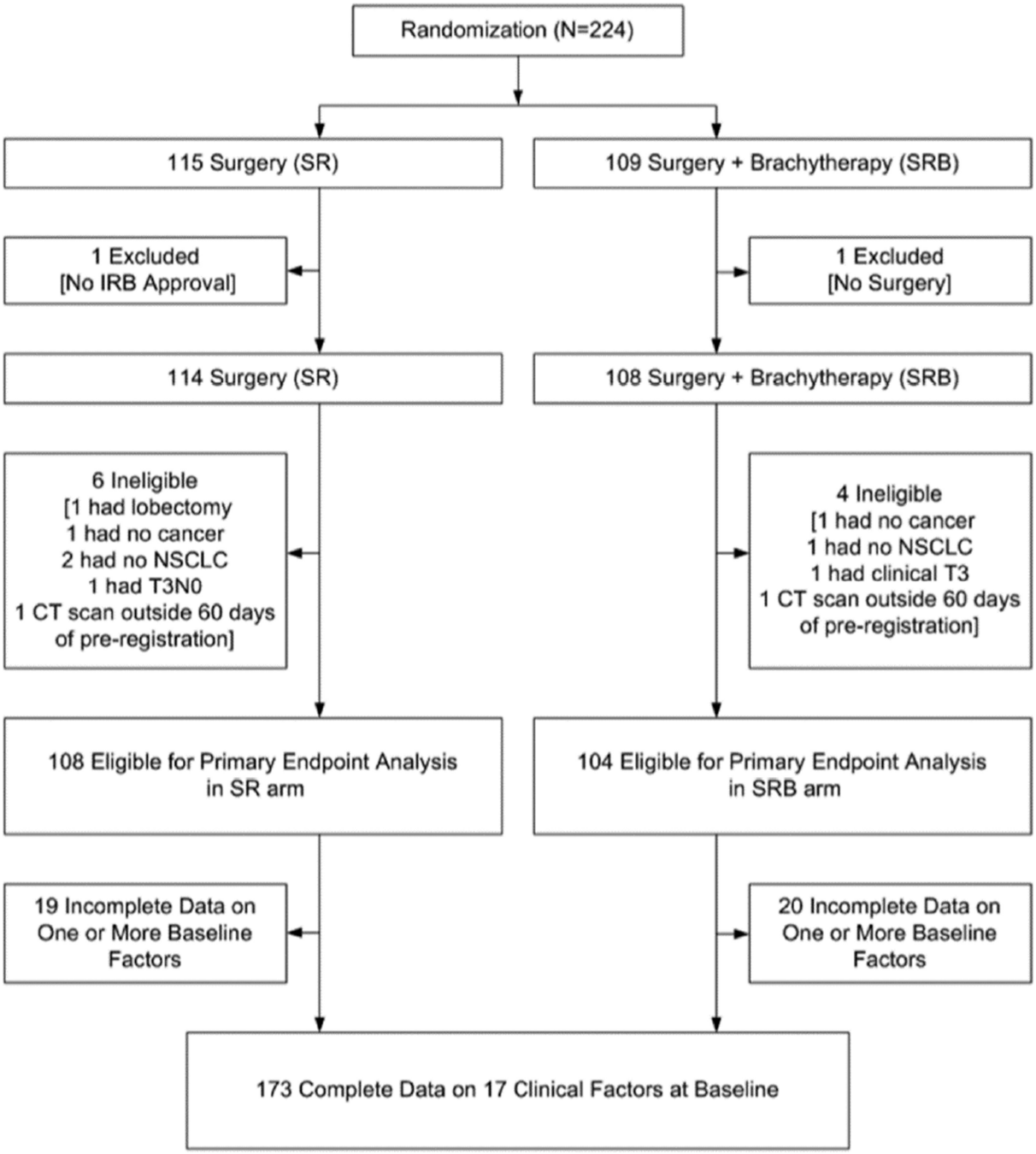

Figure 1.
Patient CONSORT Diagram

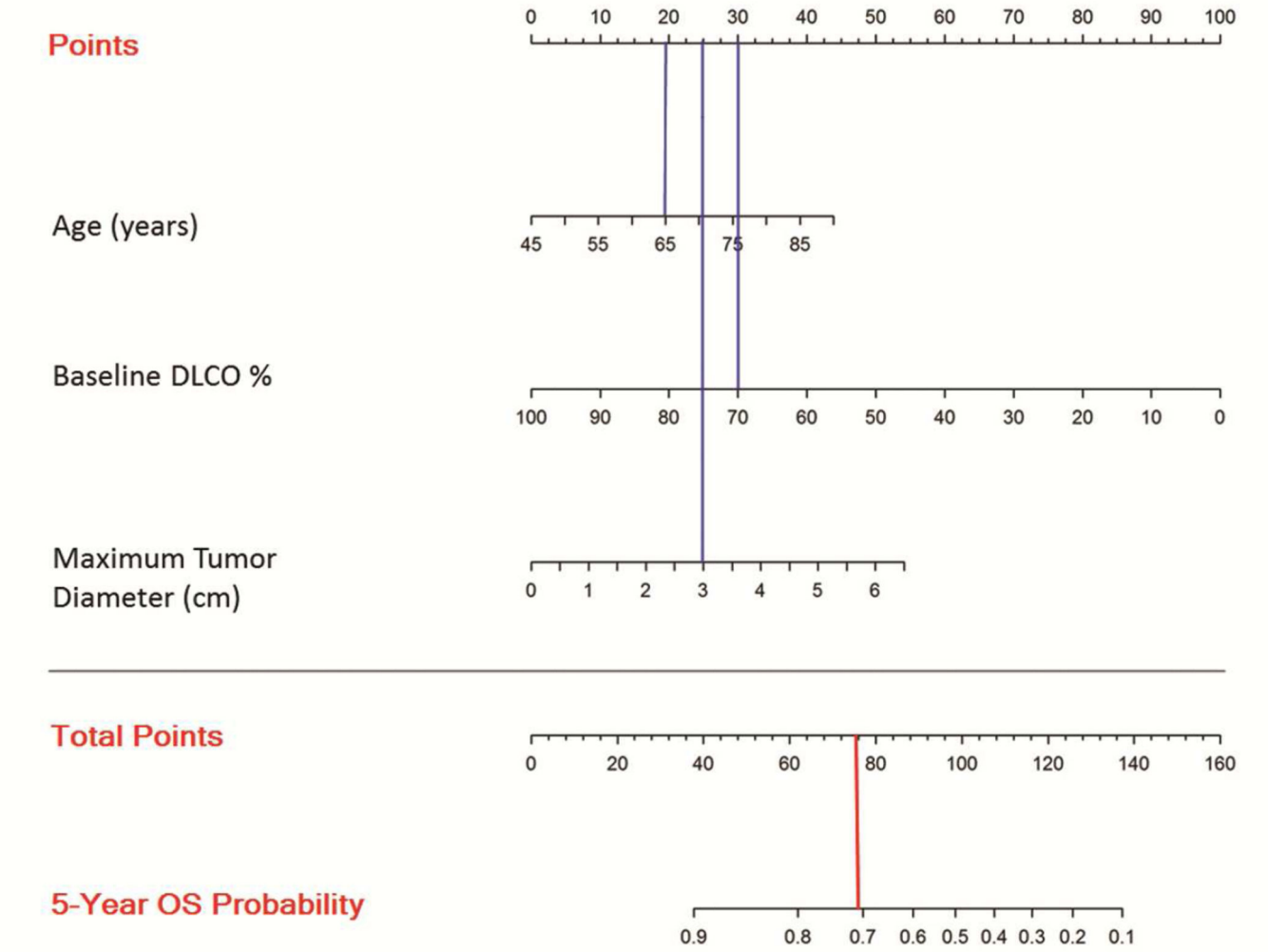

Figure 2.
Nomogram for predicting 5-year overall survival

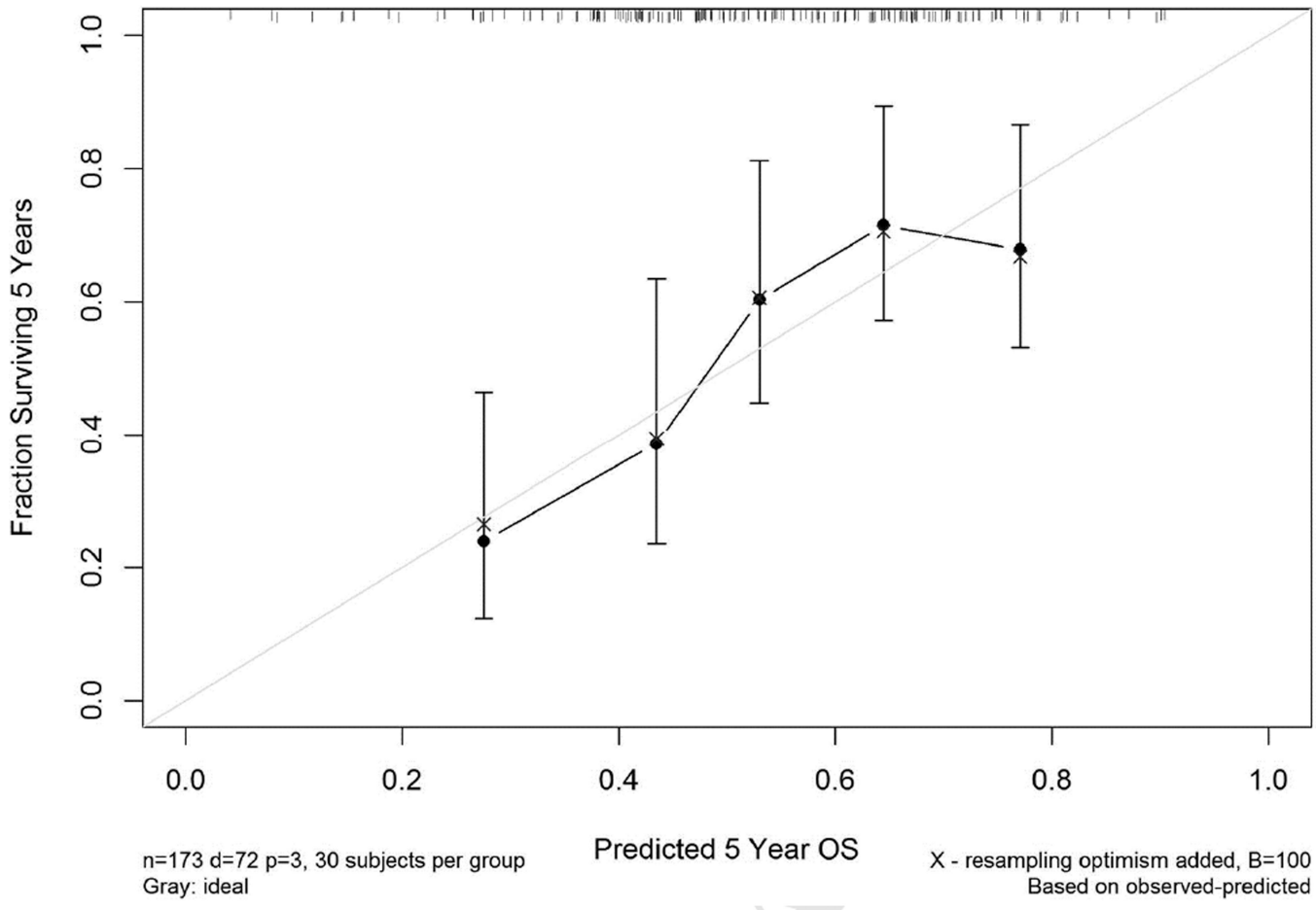

Figure 3.
Calibration plot for the 5-year overall survival nomogram

Table 1

Entry criteria for enrollment in ACOSOG Z4032. Patients must have either one major or two minor criteria.

Major Criteria	**SR** ** **(N=114)**	**SRB** ** **(N=108)**
1. FEV1 ≤ 50% predicted	67 (58.8%)	49 (45.4%)
2. DLCO ≤ 50% predicted	72 (63.2%)	74 (68.5%)
Minor Criteria		
1. Age ≥75	43 (37.7%)	42 (38.9%)
2. FEV1 51–60% predicted	18 (15.8%)	25 (23.1%)
3. DLCO 51–60% predicted	19 (16.7%)	19 (17.6%)
4. Pulmonary hypertension (defined as a pulmonary artery systolic pressure greater than 40mmHg) as estimated by echocardiography or right heart catheterization	4 (3.5%)	1 (0.9%)
5. Poor left ventricular function (defined as an ejection fraction of 40% or less)	9 (7.9%)	3 (2.8%)
6. Resting or Exercise Arterial pO2 ≤ 55 mm Hg or SpO2 ≤ 88%	5 (4.4%)	6 (5.6%)
7. pCO2 > 45 mm Hg	3 (2.6%)	3 (2.8%)
8. Modified Medical Research Council (MMRC) Dyspnea Scale ≥ 3.	31 (27.2%)	17 (15.7%)

** One patient may have multiple criteria; all randomized non-excluded patients

Table 2

Baseline Characteristics

Factors	N (%) (*n*=173)
Arm	
Sublobar resection (SR)	89 (51.4%)
SR+Brachytherapy	84 (48.6%)
Age in years (median, range)	70.0 (49.0 – 87.0)
BMI (median, range)	27.3 (15.6 – 75.7)
Baseline Performance Status	
0	37 (21.4%)
1	96 (55.5%)
2	40 (23.1%)
Race	
White	162 (93.6%)
Black or African American	10 (5.8%)
Unknown	1 (0.6%)
Method of payment	
Uninsured/Medicaid	20 (11.6%)
Private and/or Medicare	146 (84.4%)
Military and/or Veterans Sponsored	3 (1.7%)
Other Means of Payment	4 (2.3%)
ASA class on surgery day	
I/II	20 (11.6%)
III/IV	153 (88.4%)
Baseline DLCO% (median, range)	45.0 (8.0 – 97.0)
Baseline FEV1% (median, range)	5.0 (22.0 – 110.0)
Surgery Approach	
Thoracotomy	58 (33.5%)
VATS	115 (66.5%)
Type of Resection	
Segmentectomy	44 (25.4%)
Wedge Resection	129 (74.6%)
Lymph Node Evaluation	
None	61 (35.3%)
MLND/Sampling	112 (64.7%)
Histology Type	
Adenocarcinoma	92 (53.2%)
Squamous Cell Carcinoma	81 (46.8%)
Clinical Nodule Size	
≤2 cm	107 (61.8%)
>2 cm	66 (38.2%)

Factors	N (%) (*n*=173)
Actual Margin Size (cm) (median, range)	1.0 (0.0 – 3.6)
Maximum Tumor Diameter (cm) (median, range)	1.8 (0.4 – 6.5)
Margin Tumor Ratio (median, range)	0.5 (0.0 – 4.0)

Table 3

Univariable and Multivariable Cox Proportional Hazards Model Results for Overall Survival (n=173, events=72).

Factors	Univariable Model		Initial Multivariable Model	
	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Arm: SRB vs. SR	1.17 (0.73, 1.86)	0.51	-	-
Age	1.03 (1.00, 1.06)	0.06	1.03 (1.01, 1.06)	0.04
BMI	1.00 (0.97, 1.03)	0.87	-	-
Baseline Performance Status		0.59	-	-
Baseline Performance Status : 2 vs. 0	1.02 (0.53, 1.96)	0.96	-	-
Baseline Performance Status: 1 vs. 0	0.79 (0.45, 1.40)	0.42	-	-
Race: White vs. Others[1, 3]	2.09 (0.66, 6.64)	0.21	1.51 (0.46, 4.94)	0.50
Method of payment: Uninsured/Medicaid vs. Others	1.05 (0.50, 2.18)	0.91	-	-
ASA class: III/IV vs. I/II	1.51 (0.69, 3.28)	0.30	-	-
Baseline DLCO%	0.97 (0.96, 0.99)	<0.01	0.97 (0.95, 0.99)	<0.01
Baseline FEV1%	1.00 (0.99, 1.02)	0.61	-	-
Surgery Approach: VATS vs. Thoracotomy	1.16 (0.70, 1.90)	0.56	-	-
Type of Resection: Wedge Resection vs. Segmentectomy	0.72 (0.44, 1.20)	0.21	-	-
Clinical Nodule Size: >2 cm vs. ≤2 cm	1.33 (0.83, 2.12)	0.24	-	-
Actual Margin Size (cm)	0.81 (0.61, 1.08)	0.15	-	-
Maximum Tumor Diameter (cm)	1.37 (1.06, 1.78)	0.02	1.29 (1.00, 1.68)	0.05
Margin Tumor Ratio [2,3]	0.66 (0.44, 0.98)	0.04	-	-
Lymph Node Evaluation: MLND/Sampling vs. None	0.93 (0.57, 1.49)	0.75	-	-
Histology Type: Squamous cell carcinoma vs. Adenocarcinoma[1,3]	1.63 (1.02, 2.60)	0.04	1.24 (0.76, 2.02)	0.39

[1]Race and histology were included in the initial multivariable model regardless of significance in the univariable model, due to clinical consideration and a noticeable trend across outcomes.

[2]Factors with p-value < 0.1 were included in the initial multivariable model. A stepwise model selection was utilized to get the final multivariate model.

[3]The stepwise selection eliminated this factor from the final multivariable model used for developing the nomogram.