Clinical outcomes of microscopic residual disease after bronchial sleeve resection for non–small cell lung cancer

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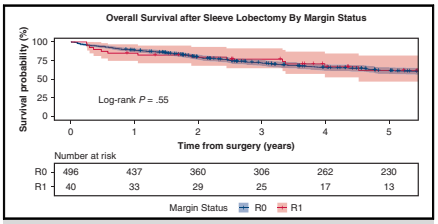
ABSTRACT

Objectives: To evaluate the significance of microscopic residual disease (MRD) at the bronchial resection margin after bronchial sleeve resection in non–small cell lung cancer.

Methods: We retrospectively reviewed 536 consecutive patients who underwent bronchial sleeve resection between 1995 and 2015. Clinical outcomes, including recurrence and long-term survival, were analyzed according to the bronchial resection margin status (R0 = complete resection and R1 = microscopic residual tumor).

Results: Forty patients (7.5%) were identified to have MRD. During a 52.4-month follow-up (range, 0.1-261.0 months), there was no significant difference in 5-year overall survival (61.8% vs 61.5%; $P = .550$) and 5-year recurrence-free survival (53.7% vs 59.0%; $P = .390$) between groups R1 and R0. Multivariable cox regression analysis demonstrated that the margin status (group R1) was not associated with significantly decreased overall survival and recurrence-free survival. In group R1, 3 patients (7.5%) showed locoregional recurrence, including 1 patient (2.5%) with anastomotic recurrence. There were no significant differences between both groups in anastomotic recurrence (2.5% vs 2.6%; $P = 1.000$), locoregional recurrence (7.5% vs 12.7%; $P = .476$), and distant recurrence (25.0% vs 23.2%; $P = .947$) rates. Subgroup analysis of group R1 revealed a significant trend toward an increasing recurrence rate as the pathological extent of MRD advanced toward invasive extramucosal carcinoma (P for trend = .015).

Conclusions: In our experience of bronchial sleeve resection, the oncologic outcome of MRD was not jeopardized. Furthermore, the pathological extent of MRD might be helpful for recurrence prediction and treatment planning. (J Thorac Cardiovasc Surg 2021;161:267-77)



No significant survival differences were found between R0 and R1 after sleeve resection.

THOR

CENTRAL MESSAGE

Long-term fate of bronchial sleeve resection was not severely hampered by microscopic residual disease alone, although its pathological extent could be considered for actual decision-making.

PERSPECTIVE

Considering the benefit of parenchymal-saving operation (sleeve resection), the oncologic hazard of microscopic residual disease (MRD) needs to be re-evaluated. The recurrence pattern and long-term survival outcome of R1 resection was comparable to those of its R0 counterpart. Furthermore, a subgroup at high recurrence risk can be identified based on the pathological extent of MRD.

See Commentaries on pages 278 and 279.

In curative-intent surgeries for non–small-cell lung cancer (NSCLC), it is imperative to achieve macroscopic and microscopic complete resections (R0). In the surgical management of central tumors, bronchial sleeve resection (BSR) is recommended to facilitate R0 resection.[1]

Scanning this QR code will take you to the article title page to access supplementary information.

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Abbreviations and Acronyms

BRM = bronchial resection margin
BSR = bronchial sleeve resection
CIS = carcinoma in situ
ESL = extended sleeve lobectomy
LN = lymph node
MRD = microscopic residual disease
NSCLC = non–small cell lung cancer
OS = overall survival
R0 = complete resection
R1 = microscopic residual tumor
RFS = recurrence-free survival

However, microscopic residual disease (MRD) (ie, microscopic residual tumor [R1]) at the bronchial resection margin (BRM) may be encountered even after BSR, resulting in a complicated situation. This situation can raise serious concerns that influence the decision regarding further resection, particularly if a patient has marginal pulmonary function or is not expected to tolerate pneumonectomy. Even if a patient can tolerate such a procedure, it remains debatable whether pneumonectomy-associated risk is justified in such circumstances. Moreover, no study has investigated whether adjuvant therapies; for example, chemotherapy and thoracic radiotherapy reduce the recurrence of MRD after BSR. It is unclear whether the pathological extent of MRD is related to recurrence risk after BSR.

Based on the rarity of R1 after BSR, the collection of clinical data with adequate cohort size is challenging. Although limited information could be inferred from the few available reports on general BSR,[2,3] to the best of our knowledge, no study has focused on the prognosis of this patient subset. We hypothesized that the prognosis of patients with R1 after BSR is not significantly compromised compared with that of patients with R0; further, the pathological extent of MRD is related to recurrence. We reviewed our 20-year institutional database to investigate the prognostic influence of BRM status on long-term clinical outcomes.

METHODS

Study Design and Population

This study was a retrospective review of prospectively collected data from a lung cancer database of a tertiary referral center. Clinical records of patients who underwent complete surgery for NSCLC between January 1995 and December 2015 at our institution were reviewed. The study was approved by the Samsung Medical Center Institutional Review Board (No. SMC 2019-04-064-001), and the need for patient consent was waived due to the retrospective nature of this study.

In total, 564 patients underwent BSR for NSCLC during this period. We excluded patients who underwent carinal sleeve pneumonectomy (n = 24) to eliminate the prognostic effects of pneumonectomy in advance. Patients with gross residual tumor [R2 disease] (n = 2) and R1 disease at the vascular resection margin (n = 2) were excluded because they are considered to have different prognostic characteristics. The final cohort included 536 eligible patients, who were divided into the following groups based on the BRM status: group R0 (R0 at the BRM) and group R1 (R1 at the BRM). The flow diagram of patient inclusion is presented in Figure 1; Figure 2 summarizes the study design.

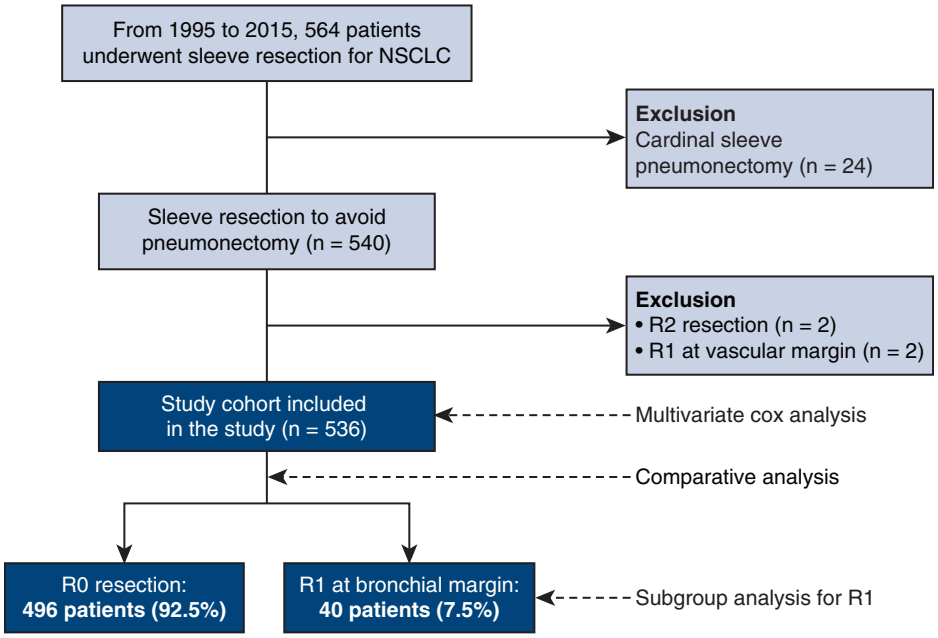


FIGURE 1. Flow diagram of patient inclusion in the study. *NSCLC*, Non–small cell lung cancer; *R0*, complete resection; *R1*, microscopic residual tumor; *R2*, gross residual disease.

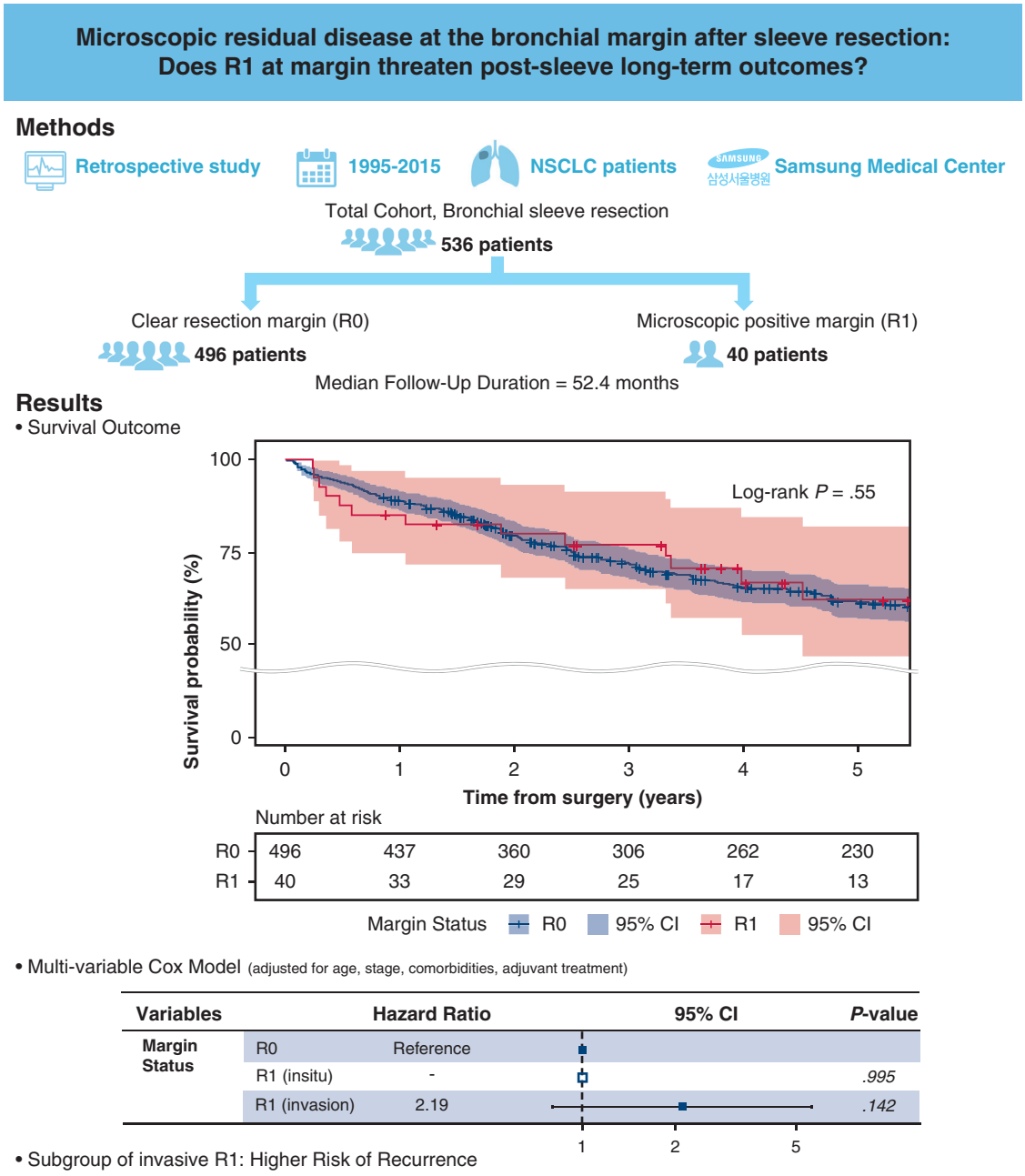
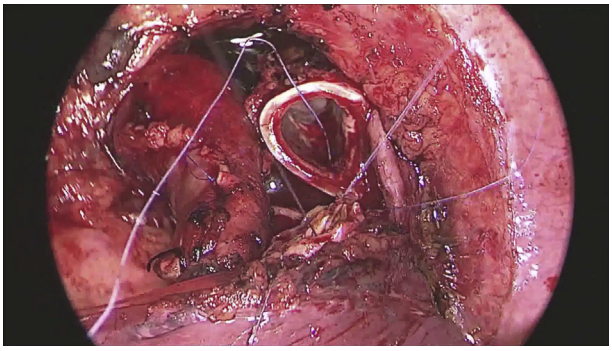


FIGURE 2. Graphical summary of the method, results, and implications of the study. *NSCLC*, Non–small cell lung cancer; *R0*, complete resection; *R1*, microscopic residual tumor; *R2*, gross residual disease; *CI*, confidence interval.

Epidemiologic, pathological, and prognostic characteristics, including age; sex; comorbidities; histological tumor type; clinical/pathological TNM stage; neoadjuvant/adjuvant treatment; and operative outcomes, were compared between the groups.

Preoperative Workup, Surgical Technique, and Treatment Protocol

Preoperative workup included chest roentgenography, bronchoscopy, chest computed tomography, spirometry, lung perfusion scan, and a thorough search



VIDEO 1. A double (vascular and bronchial) sleeve left upper lobectomy by thoracotomy. Video available at: https://www.jtcvs.org/article/S0022-5223(20)30518-3/fulltext.

for distant metastases (including positron-emission tomography scan). Mediastinoscopy or endobronchial ultrasound-guided transbronchial needle aspiration was performed to exclude N3 disease and assess the extent of N2 disease more accurately in patients who received neoadjuvant treatment.

We have described the details of the surgical technique for BSR previously.[4] After standard posterolateral thoracotomy at the fourth or fifth intercostal space, circumferential dissection of the bronchi and pulmonary artery was performed with careful examination of any extracapsular invasion or direct tumor involvement with vascular structures (Video 1). Proximal and distal resection margins were routinely controlled with intraoperative frozen section analysis whenever the result of frozen section analysis could affect surgical decision making. If MRD was confirmed intraoperatively, the decision to perform additional procedure (eg, pneumonectomy, extended sleeve resection [ESL], or no additional resection) was individually made by the operator. In case of suspected vascular invasion by the tumor and/or metastatic nodes, we aggressively resected and reconstructed the vessel (eg, double-sleeve operation). Mediastinal lymph node (LN) dissection included nodes at the stations 2R, 4R, 7, 8, 9, and 10R for right-sided tumors and 4L, 5, 6, 7, 8, 9, and 10L for left-sided tumors. Adjuvant radiotherapy and/or chemotherapy was optionally added for group R1 and pathological stage >II after multidisciplinary discussion.

Definitions and Follow-up

During 2011, the classification of positive margins of a resected bronchus was suggested in the International Association for the Study of Lung Cancer Staging Committee's review article.[5] For an intuitive understanding and ease of statistical comparison, we modified the suggested classification into a 4-tier system as follows (Figure 3, *A*): severe dysplasia/carcinoma in situ (CIS) confined to the mucosal epithelium, full-thickness CIS reaching the basement membrane, carcinoma presents in the peribronchial soft tissues without mucosal involvement, and invasive extramucosal carcinoma (peribronchial carcinoma observed by direct extension of mucosal carcinoma). Lung cancer pathological staging was based on the seventh edition of the American Joint Committee on Cancer staging manual. Follow-up data were obtained from the hospital case records, a questionnaire completed by the chest physician/general practitioner, or death certificates. The main outcome was overall survival (OS); that is, the time interval between the surgery date and death date/last follow-up date for censored patients. Recurrence-free survival (RFS) was defined as the time from surgery date to recurrence/death date. Locoregional recurrence was defined as recurrence within the surgical field such as those at the anastomotic site, pleural seeding, or regional and mediastinal LNs. Distant recurrence was defined as recurrence at all other sites of failure, including the contralateral lung or outside the hemithorax (eg, extrathoracic LNs and distant organs). Recurrence was categorized as no recurrence, anastomotic recurrence, locoregional recurrence, and distant recurrence.

Statistical Analysis

Categorical variables were compared using Pearson χ^2 test or Fisher exact test. For normally distributed continuous variables, mean $\pm$ standard deviation values are reported; these variables were compared using 2-sample Student *t* test, whereas median and interquartile range (IQR) values are reported for nonnormally distributed continuous variables; these variables were compared using the Mann-Whitney U test.

Survival curves were constructed using Kaplan-Meier method and compared univariately using log-rank test. Multivariable analysis for OS and RFS was performed using the Cox proportional hazards model. Model 1 was adjusted for variables with P value $< .2$ in the univariable analyses or clinically important variables. Model 2 was further adjusted for adjuvant treatment and an interaction term of BRM and the adjuvant treatment to study the role of adjuvant therapy. The significance of margin status was examined in the various definitions of MRD as follows: sensitivity analysis I, R0 versus R1-invasion; and sensitivity analysis II, R0 versus R1-insitu versus R1-invasion. In subgroup analysis of group R1, linear-by-linear association test was used to analyze the trend in recurrence rate among the ordered categories.

All reported P values were 2-sided. All statistical analyses were performed using SPSS version 25.0 (IBM-SPSS Inc, Armonk, NY).

RESULTS

Baseline Characteristics and Clinicopathological Data

Among the study patients, MRD at the BRM was confirmed in 40 patients (group R1, 7.5%), whereas complete resection was achieved in 496 patients (group R0, 92.5%). The baseline characteristics of both groups are described in Table 1. In groups R1 and R0, median age was 64.0 years (IQR, 55.0-69.0 years) and 63.0 years (IQR, 56.0-68.0 years), respectively ($P = .812$), and median tumor size was 3.0 cm (IQR, 2.2-4.1 cm) and 3.5 cm (IQR, 2.5-4.9 cm), respectively ($P = .057$). Results of preoperative pulmonary function tests were similar in both groups. The most common histology was squamous cell carcinoma in both groups (85% in group R1; 77% in group R0). There was no significant difference between the groups in the comorbidities, operative techniques, pathological stage, and dissected LN number (Table 1).

Median hospital stay was 12.5 days (IQR, 7.0-105.0 days) in group R1 and 14.0 days (IQR, 5.0-120.0 days) in group R0 ($P = .367$). There was no significant difference between the groups in perioperative morbidity and mortality. Expectedly, group R1 received more adjuvant treatment (Table 2).

Long-Term Survival Outcomes and the Significance of BRM Status Main Analysis (R0 vs R1)

The median follow-up duration was 44.9 months (IQR, 21.5-69.5 months) in group R1 and 54.8 months (IQR, 22.9-99.3 months) in group R0. The 5-year OS rate in

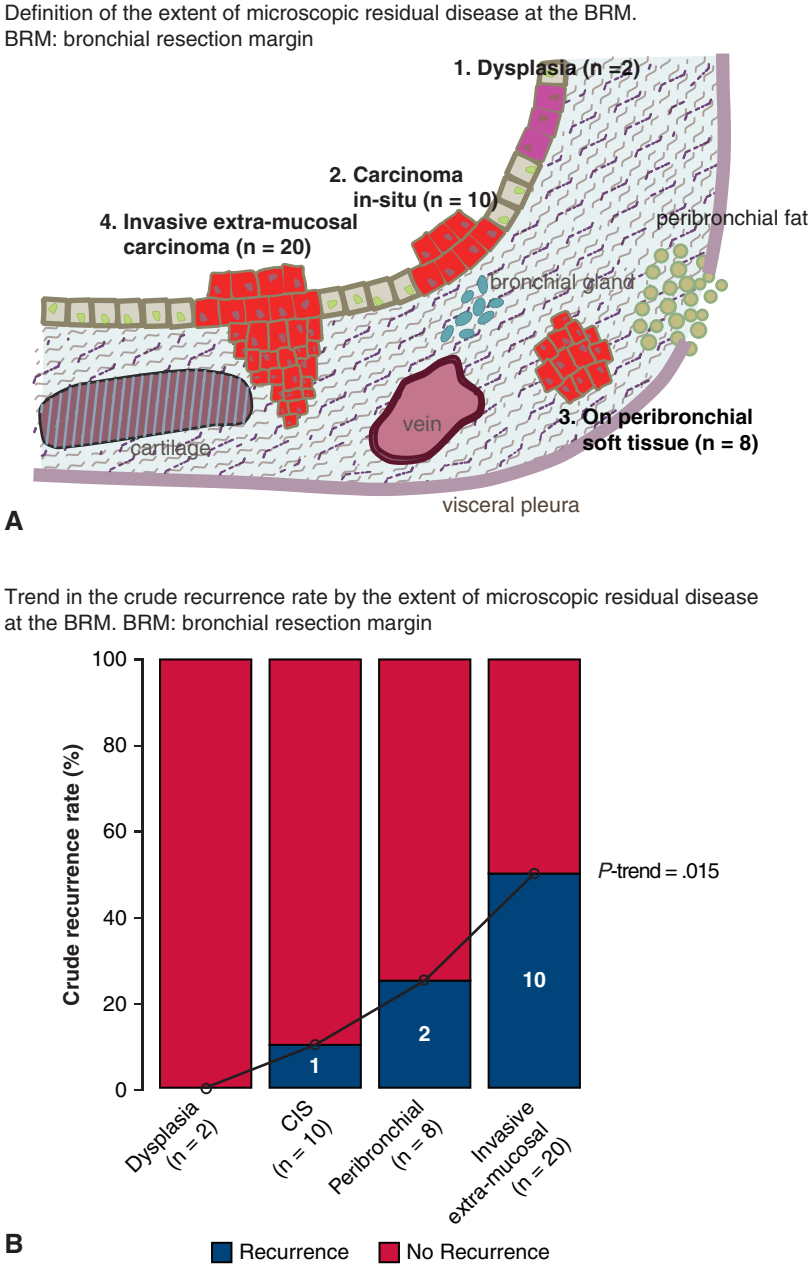


FIGURE 3. A, Definition of the extent of microscopic residual disease at the BRM bronchial resection margin. B, Trend in the crude recurrence rate by the extent of microscopic residual disease at the BRM. *CIS*, Carcinoma in situ.

groups R1 and R0 was 61.8% and 61.5%, respectively (log-rank $P = .550$) (Figure 4, *A*). The 5-year RFS rate was comparable in both groups (53.7% in group R1 and 59.0% in group R0; log-rank $P = .390$) (Figure 4, *B*). In the multivariable model, the BRM status (group R1) was not associated with decreased OS (adjusted hazard ratio [aHR], 1.04; 95% confidence interval [CI], 0.64-1.70; $P = .871$) (Table 3 and Figure E1) and RFS (aHR, 0.84; 95% CI, 0.47-1.49; $P = .548$) (Table 4) in model 1. The interaction term between BRM and adjuvant treatment was revealed not statistically significant for OS (P for interaction = .571) and RFS (P for interaction = .480) in model 2.

Sensitivity Analyses

In the sensitivity analysis I (R0 vs R1-invasion [n = 28]), the intergroup difference was not univariately significant for OS and RFS (Figure E2). Multivariable cox model also

TABLE 1. Clinicopathologic characteristics

Variables (clinical)	R1 group (n = 40)	R0 group (n = 496)	*P* value
Age, y	64.0 (55.0-69.0)	63.0 (56.0-68.0)	.812
Male sex	39 (97.5%)	445 (89.7%)	.161
Tumor size, cm	3.0 (2.2-4.1)	3.5 (2.5-4.9)	.057
Tumor location (% of right tumor)	47.5%	40.7%	.402
Preoperative PFT values			
FEV1, L	2.5 (2.2-2.9)	2.5 (2.1-2.8)	.493
DLco, mL/mmHg/min	18.2 (15.8-18.5)	18.0 (15.9-18.3)	.948
Clinical TNM stage*			.196
IA	3 (7.5%)	31 (6.3%)	
IB	9 (22.5%)	172 (34.7%)	
IIA	4 (10.0%)	86 (17.3%)	
IIB	11 (27.5%)	104 (21.0%)	
IIIA	13 (32.5%)	96 (19.4%)	
IIIB	0 (0.0%)	7 (1.4%)	
Neoadjuvant CCRT	7 (17.5%)	45 (9.1%)	.094
Comorbidities			
Hypertension	16 (40.0%)	141 (28.4%)	.172
Diabetes Mellitus	11 (27.5%)	88 (17.7%)	.187
COPD	4 (10.0%)	34 (6.9%)	.671
Heart Failure	1 (2.5%)	27 (5.4%)	.663
CKD	1 (2.5%)	1 (0.2%)	.344
Stroke	1 (2.5%)	22 (4.4%)	.861
Variables (operative/ pathologic)			
Operative techniques			
Extended sleeve	4 (10.0%)	58 (11.7%)	1.000
Double sleeve	8 (20.0%)	77 (15.5%)	.456
Histological type			.348
Squamous	34 (85.0%)	382 (77.0%)	
Adenocarcinoma	4 (10.0%)	50 (10.1%)	
Others	2 (5.0%)	64 (12.9%)	
Pathological TNM stage*			.118
ypCR	0 (0.0%)	8 (1.6%)	
IA	1 (2.5%)	49 (9.9%)	
IB	9 (22.5%)	124 (25.0%)	
IIA	8 (20.0%)	129 (26.0%)	
IIB	4 (10.0%)	66 (13.3%)	
IIIA	17 (42.5%)	107 (21.6%)	
IIIB	1 (2.5%)	4 (0.8%)	
IV	0 (0.0%)	9 (1.8%)	
The number of LN dissected	22 (14-28)	21 (16-30)	.634

Values are presented as n (%) or median (interquartile range). *PFT*, pulmonary function test; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl mono-oxide; *TNM*, tumor, node and metastasis; *CCRT*, concurrent chemoradiation therapy; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *ypCR*, pathological complete response; LN, lymph node. *The IASLC 7th edition of TNM classification was used.

TABLE 2. Postoperative outcomes and adjuvant treatment profiles

Variables	R1 group (n = 40)	R0 group (n = 496)	*P* value
Hospital stay, d	12.5 (10-16)	14.0 (10-19)	.367
Hospital mortality	0 (0.0%)	13 (2.6%)	.613
Complications			
BPF	1 (2.5%)	14 (2.8%)	1.000
Pneumonia	3 (7.5%)	23 (4.6%)	.432
ARDS	1 (2.5%)	13 (2.6%)	1.000
Prolonged air leak	5 (12.5%)	37 (7.5%)	.228
Supraventricular arrhythmia	4 (10.0%)	57 (11.5%)	1.000
Wound dehiscence/infection	0 (0.0%)	10 (2.0%)	1.000
Adjuvant Treatment			
None	7 (17.5%)	251 (50.6%)	<.001
Chemotherapy	7 (17.5%)	136 (27.4%)	
Radiotherapy	15 (37.5%)	69 (13.9%)	
Both	11 (27.5%)	40 (8.1%)	

Values are presented as n (%) or median (interquartile range). *BPF*, bronchopleural fistula; *ARDS*, acute respiratory distress syndrome.

supported the insignificant influence of BRM status for OS and RFS (Tables E1-E4).

In the sensitivity analysis II (R0 vs R1-insitu [n = 12] vs R1-invasion [n = 28]), we found no significant difference among the 3 groups in univariable analyses (Figure E3). The subgroup of R1-invasion seemed to be associated with decreased OS (aHR, 2.16; 95% CI, 0.76-6.16; $P = .149$) (Figure E4) and decreased RFS (aHR, 1.71; 95% CI, 0.41-7.10; $P = .461$) in multivariable model 2, although the results did not reach statistical significance.

Pattern of Recurrence

There was no significant difference between the groups in recurrence rate during the follow-up (32.5% in group R1 vs 35.9% in group R0). Furthermore, we found no differences in the locoregional recurrence rate and its pattern (Table 5). In group R0, locoregional recurrence was confirmed in 63 patients (12.7%), including recurrence at the anastomotic site (n = 13), mediastinal LNs (n = 21), and ipsilateral hemithorax (n = 29). Distant recurrence was detected in 115 patients (19.6%), including lung-to-lung metastasis (n = 38), extrathoracic LN (n = 7), and other distant metastasis (n = 70).

In group R1, locoregional recurrence was confirmed in 3 patients (7.5%), including recurrence at the anastomotic site (n = 1), mediastinal LN (n = 1), and ipsilateral hemithorax (n = 1). Distant recurrence was found in 10 patients

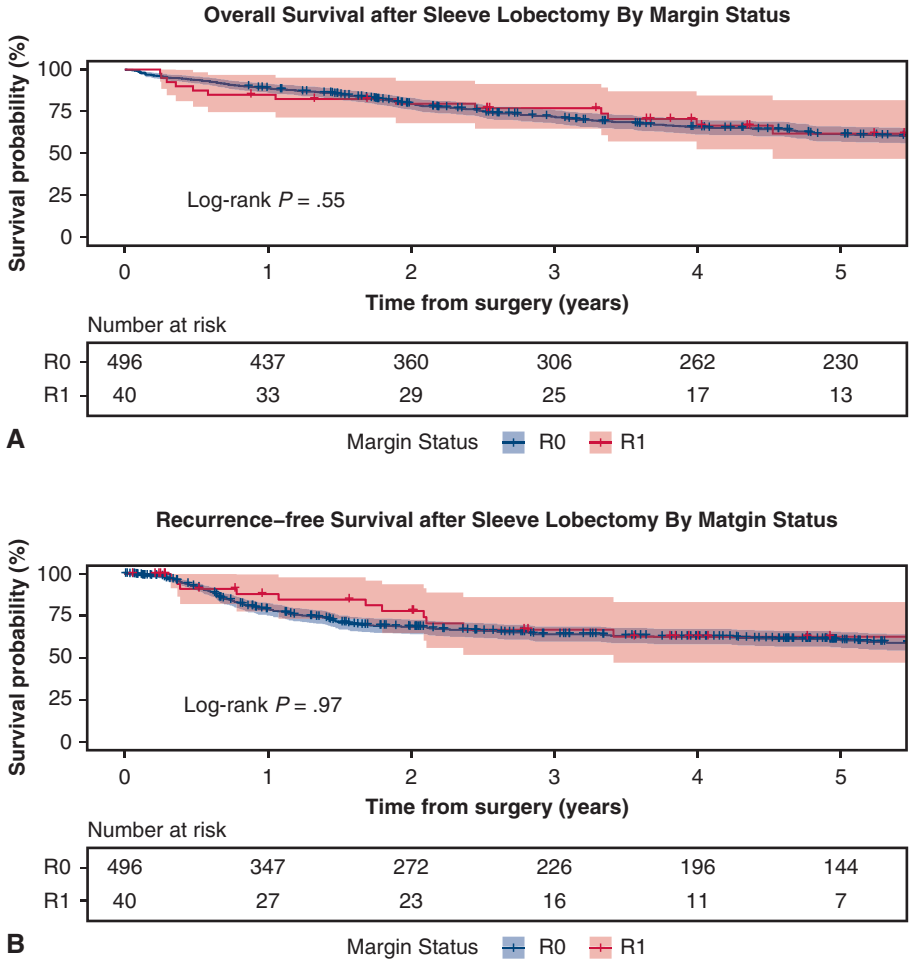


FIGURE 4. A, Overall survival. B, Recurrence-free survival according to the margin status. *R0*, Complete resection; *R1*, microscopic residual tumor.

(25.0%), including lung-to-lung metastasis (n = 7), extrathoracic LN (n = 1), and other distant metastasis (n = 2). The pattern of distant recurrence was not significantly different between both groups ($P = .327$) (Table 5).

Subgroup Analysis in Group R1: Influence of the Pathological Extent of MRD

The pathological extent in group R1 was classified according to the predefined subgroups (Figure 3, *A*). Twelve patients were found to have minimal extent including subgroup 1 (n = 2) and subgroup 2 (n = 10). Patients with invasive pathological extent above CIS included subgroup 3 (n = 8) and subgroup 4 (n = 20).

Recurrence outcomes were further analyzed according to the pathological extent of MRD. Dysplasia/CIS showed minimal recurrence events (0 out of 2 and 2 out of 8, respectively). On the contrary, as the location of residual carcinoma changed from the endobronchial side (subgroup 1) to the outer bronchial wall (subgroup 4), the number of any recurrences increased (P for trend = .015), with a crude recurrence rate of 50% (10 out of 20) in subgroup 4 (Figure 3, *B*). Distant recurrence showed an increasing trend as the extent advanced toward invasive extramucosal carcinoma (P for trend = .039), whereas locoregional recurrence did not significantly differ among subgroups (P for trend = .340) (Figure E5).

DISCUSSION

Macroscopic and microscopic radical resections are the most important goal of surgery in the management of NSCLC. However, R1 resection after pulmonary resection is not so rare, with a reported prevalence of 4% to 5% (IQR, 1.2%-17%).[6] BSR can be a good solution for positive margins after conventional lobectomy for central tumors. Since its introduction in 1959,[7] BSR has prevailed throughout the thoracic surgery community[8] and is currently a recommended procedure to avoid pneumonectomy when anatomically, functionally, and technically feasible.[1]

TABLE 3. Cox-proportional hazard model for overall survival after bronchial sleeve resection

Outcome	Variables	Crude model		Multivariable model 1		Multivariable model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
		Overall survival					
	Age						
	(continuous)	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001
	Sex						
	Female	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	Male	1.36 (0.86-2.14)	.192	1.11 (0.69-1.77)	.672	1.09 (0.68-1.75)	.724
	Comorbidities						
	HTN	1.18 (0.90-1.56)	.225	0.91 (0.67-1.23)	.536	0.92 (0.68-1.24)	.581
	DM	1.34 (0.99-1.81)	.056	1.10 (0.79-1.52)	.578	1.11 (0.79-1.54)	.551
	COPD	1.43 (0.86-2.39)	.165	1.55 (0.91-2.64)	.109	1.56 (0.91-2.66)	.105
	Heart failure	1.74 (1.06-2.86)	.027	1.41 (0.85-2.35)	.186	1.45 (0.87-2.41)	.156
	CKD	2.56 (0.36-18.34)	.348	1.46 (0.18-11.77)	.722	1.38 (0.17-11.25)	.762
	CVA	1.88 (1.13-3.13)	.015	1.46 (0.85-2.51)	.167	1.47 (0.86-2.51)	.164
	Pathologic Stage						
	I	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	II	1.32 (0.97-1.80)	.077	1.52 (1.08-2.13)	.015	1.50 (1.07-2.11)	.019
	III	2.16 (1.57-2.97)	<.001	2.33 (1.61-3.37)	<.001	2.36 (1.63-3.42)	<.001
	IV	3.22 (1.40-7.45)	.006	3.94 (1.68-9.24)	.002	3.95 (1.69-9.28)	.002
	Margin						
	R0	**1 (Reference)**	-	**1 (Reference)**	-	**1 (Reference)**	-
	R1	**1.16 (0.72-1.88)**	**.546**	**0.97 (0.59-1.60)**	**.902**	**1.29 (0.46-3.58)**	**.629**
	Adjuvant Treatment						
	None	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	CTx	0.93 (0.67-1.28)	.652	0.76 (0.53-1.08)	.124	0.80 (0.56-1.15)	.228
	RTx	1.37 (0.99-1.91)	.060	1.24 (0.87-1.79)	.238	1.23 (0.84-1.80)	.294
	Both	1.32 (0.85-2.05)	.220	0.97 (0.58-1.61)	.910	0.93 (0.54-1.59)	.790

However, MRD can be encountered at BRM even after BSR. In such challenging situations, the following questions could be raised. After BSR, is it reasonable to perform pneumonectomy for all patients with R1 resection? Given the risk of pneumonectomy, can adjuvant treatment be performed instead of further resection? If the pathological extent of MRD is minimal, are only close follow-ups sufficient? The decision should be made considering the elusive balance between oncologic hazard (recurrence risk) of MRD and benefits of parenchymal sparing surgery. However, there is no evidence regarding what information should be used to make decisions. Therefore, the prevalence, recurrence patterns, and long-term outcomes of R1 after BSR might be valuable information for decision making in such clinical situations.

Pneumonectomy is a disease in itself and an independent prognostic factor for long-term survival outcomes after lung cancer surgery.[9] According to the recent studies, pneumonectomy seems to be associated with inferior long-term outcomes compared with BSR.[10,11] Thus, it is difficult to justify the routine application of pneumonectomy when intraoperative frozen sections reveal MRD after BSR (Table E5). We previously described ESL as part of the effort for further resection of bronchus while partially preserving the lung parenchyma.[4] However, ESL may not always feasible anatomically and technically and might not guarantee R0. Therefore, the decision for further resection should be made very carefully considering that the next step could be pneumonectomy.

Here, we tried to refute the prejudice that patients with MRD after BSR should be related to markedly compromised outcomes. Multivariable survival analysis showed that the result of MRD was consistently not significant after adjusting covariates. Notwithstanding, it is hard to say that R1 after BSR will yield similar oncologic outcome compared with R0 because our cohort was small-

TABLE 4. Cox-proportional hazard model for recurrence-free survival after bronchial sleeve resection

Outcome	Variables	Crude model		Multivariable model 1		Multivariable model 2	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Recurrence-free survival							
	Age						
	(continuous)	1.02 (1.01-1.04)	.005	1.02 (1.00-1.04)	.012	1.02 (1.00-1.04)	.014
	Sex						
	Female	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	Male	0.95 (0.60-1.51)	.834	0.94 (0.58-1.52)	.801	0.92 (0.57-1.49)	.728
	Comorbidities						
	HTN	1.11 (0.81-1.52)	.501	0.97 (0.69-1.36)	.866	0.97 (0.69-1.37)	.872
	DM	1.42 (1.01-2.01)	.046	1.32 (0.91-1.90)	.144	1.36 (0.94-1.98)	.102
	COPD	0.60 (0.28-1.27)	.181	0.64 (0.30-1.37)	.247	0.66 (0.31-1.43)	.294
	Heart failure	1.25 (0.68-2.30)	.468	1.03 (0.55-1.93)	.929	1.08 (0.57-2.03)	.819
	CKD	0.00 (0.00-infinite)	.993	0.00 (0.00-infinite)	.994	0.00 (0.00-infinite)	.994
	CVA	1.47 (0.78-2.77)	.239	1.39 (0.72-2.67)	.327	1.38 (0.72-2.66)	.329
	Pathologic Stage						
	I	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	II	1.22 (0.85-1.77)	.281	1.36 (0.91-2.03)	.139	1.36 (0.91-2.04)	.137
	III	2.61 (1.82-3.73)	<.001	3.08 (2.03-4.67)	<.001	3.17 (2.09-4.81)	<.001
	IV	4.50 (1.79-11.32)	.001	5.41 (2.10-13.92)	<.001	5.49 (2.13-14.12)	<.001
	Margin						
	R0	**1 (Reference)**	**-**	**1 (Reference)**	**-**	**1 (Reference)**	**-**
	R1	**0.99 (0.56-1.74)**	**.969**	**0.87 (0.48-1.55)**	**.628**	**0.97 (0.24-4.02)**	**.972**
	Adjuvant Treatment						
	None	1 (Reference)	-	1 (Reference)	-	1 (Reference)	-
	CTx	0.96 (0.68-1.37)	.836	0.72 (0.49-1.06)	.098	0.76 (0.51-1.13)	.171
	RTx	1.23 (0.82-1.83)	.319	0.92 (0.59-1.41)	.690	0.87 (0.55-1.37)	.542
	Both	1.37 (0.85-2.18)	.193	0.68 (0.39-1.16)	.154	0.63 (0.35-1.12)	.113

Model 1 : adjusted for age, sex, comorbidities, pathologic stage, adjuvant treatment. Model 2 : further adjusted for an interaction term of margin:adjuvant treatment. (margin:-adjuvant were not significant, *P* for interaction = .480). *HR*, hazard ratio; *HTN*, hypertension; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; CKD, chronic kidney disease; CVA, cerebrovascular accident; CTx, chemotherapy; RTx, radiotherapy.

numbered and not matched for several prognostic factors. Rather, it is possible to assume that R1 after sleeve lobectomy is at least not inferior to pneumonectomy in terms of oncologic outcomes. Coherent data from representative studies[2,8,9,12] indicates that sleeve lobectomy has a greater long-term benefit than pneumonectomy. Based on our previous publication,[11] the 5-year OS after pneumonectomy was 32.1%, much lower than that of group R1 in the current study. Admittedly, the baseline characteristics of the pneumonectomy cohort might not be comparable with those of our study cohort. However, this difference is not negligible, and a potential reason could include the advantage of parenchymal-saving surgery.

Regarding the pattern of recurrence, we found that locoregional recurrence is not a dominant mechanism of failure in group R1 as well as group R0 after BSR. No significant difference of locoregional recurrence was observed in the intergroup comparison (R0 vs R1) and subgroup analysis of R1. In recent publications after curative surgery for operable lung cancer (pT1 4N0-2; stage I-IIIA),[13-17] the locoregional recurrence rate was reported from 8% to 25%. Despite the difficulty of direct comparison to previous studies with different designs, it should be noted that the R1 after sleeve lobectomy might have noninferior locoregional failure risk compared to historical cohorts of standard lobectomy. Collectively, it can be reasonably assumed that the patients with R1 after BSR benefited from the prognostic advantages of parenchymal-saving surgery along with tolerable locoregional recurrence risk.

As for the subgroup analysis of the pathological extent of R1, invasive extramucosal carcinoma showed

TABLE 5. Pattern of recurrence

Variables	R1 group (n = 40)	R0 group (n = 496)	*P* value
Follow-up duration, m	44.9 (21.5-69.5)	54.8 (22.9-99.3)	.172
Total recurrence	13 (32.5%)	178 (35.9%)	.796
Locoregional recurrence	3 (7.5%)	63 (12.7%)	.476
Anastomotic recurrence	1 (2.5%)	13 (2.6%)	1.000
Distant recurrence	10 (25.0%)	115 (23.2%)	.947
Sites of regional recurrence			.572
Mediastinal LNs	1 (2.5%)	21 (4.2%)	
Other ipsilateral hemi-thorax	1 (2.5%)	29 (5.9%)	
Sites of distant recurrence (initial)			.327
Lung-to-lung	7 (17.5%)	38 (7.7%)	
Extrathoracic LNs	1 (2.5%)	7 (1.4%)	
Bone	2 (5.0%)	27 (5.4%)	
Brain	0 (0.0%)	20 (4.0%)	
Liver	0 (0.0%)	12 (2.4%)	
Multiple organs*	0 (0.0%)	11 (2.2%)	
Time to recurrence, m	21.6 (9.4-28.4)	10.6 (6.7-18.8)	.120

Values are presented as n (%) or median (interquartile range). *LN*, lymph node. *Multiple distant organs include adrenal gland, heart, kidney, pancreas, small bowel and skin.

a significantly increased recurrence. Consistent with previous findings,[18,19] prognostic heterogeneity was observed according to the pathological extent of MRD. Previous report[20] described that even CIS should be subclassified according to different prognostic groups. In our study, subgroup 1 was included because of the suggested definition of MRD at BRM[5] and the difficulty of distinguishing severe dysplasia from CIS. We found that subgroups 1 and 2 collectively seemed to have negligible influence on the recurrence and long-term survival. Conversely, a significant proportion of patients in subgroup 4 experienced recurrence. It is noteworthy that multivariable Cox model from sensitivity analysis II demonstrated the similar result. Though not statistically significant, R1-invasion seemed to be associated with decreased OS and RFS after BSR. Consequently, our results might indicate the role of the pathological extent of MRD in the identification of patients with higher recurrence risk.

To simultaneously analyze the effects of adjuvant therapy and pathological extent, multivariable analysis for group R1 is mandatory; however, the size of group R1 was too small to generate an effective model. Instead, we developed a multivariable model of the entire cohort to address this issue with inclusion of an interaction term of BRM and adjuvant treatment. The interaction was not statistically significant throughout entire analyses and cannot demonstrate significant survival benefit of adjuvant treatment for R1.

Based on the abovementioned data, it is cautiously suggested that ending the surgery with R1 can be a viable option in the following highly selected populations: compromised group: high-risk group for pneumonectomy, regardless of the pathological extent of R1 (benefit of parenchymal sparing is expected to be high) and intentional group: average-to-low-risk group for pneumonectomy with minimal burden of MRD, including CIS or less lesion (oncologic hazard of R1 is expected to be low).

There are several limitations to this study. First, the conclusion from our data is neither decisive nor evident, owing to the very small number of patients with invasive R1. To be specific, the wide confidence intervals of survival estimates and hazard ratios strongly suggest the potential influence of type II error, which precludes reasonable inferences from our data. Second, we performed pooled analysis for the group R1 that included clinically heterogeneous patients in terms of the disease burden and pathological extent of residual carcinoma. Although clinical heterogeneity was partially overcome using multivariable model, large-scale studies with propensity-matching or prospective design are needed. Third, because the prognostic results of CIS after general lung resection are previously reported as benign,[18,21] many surgeons/institutions may already be applying the same principle to BSR. However, there has been no validation for applicability and our real-world data may be helpful for establishing solid evidence. Lastly, pathological extent was analyzed according to the results of the permanent pathologic report. To use this information in surgical decision making, pathological extent of MRD should be available intraoperatively. However, in actual practice, determination of the exact microscopic extent by frozen section is often limited. There may be a discrepancy between the results of frozen and permanent reports. Further efforts, including close cooperation with pathologists, are required to enable real-time assessment of microscopic extents to aid in surgical decision making.

CONCLUSIONS

R1 after BSR generally showed long-term outcomes that are not significantly jeopardized in terms of oncologic outcomes. It remains unclear whether adjuvant treatment is beneficial for R1 after BSR. Care should be taken in cases of invasive extramucosal carcinoma owing to its high risk of recurrence. It is important to make careful individual decisions with multifactorial assessment of age, performance status, comorbidity, pulmonary function, feasibility of alternative surgical procedures (eg, ESL), and pathological extent of MRD, if available. Because the conclusion largely comes from the speculation on the data without sufficient statistical power, it should be interpreted carefully. Further

studies with prospective designs are needed to verify our findings.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: lung cancer, sleeve lobectomy, microscopic residual disease, survival

THOR

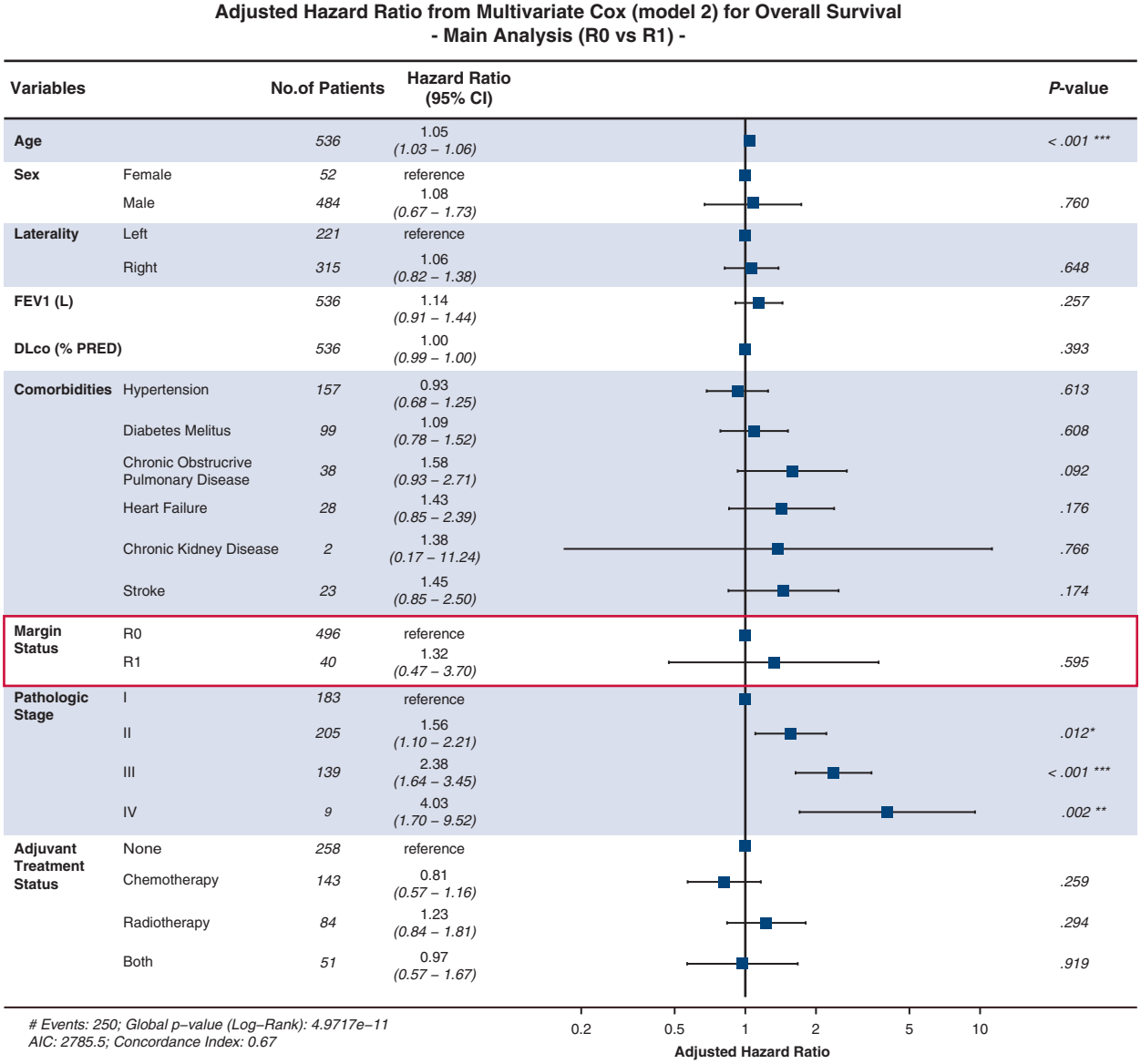


FIGURE E1. Forest plot of multivariable model 2 for overall survival: Main analysis. *R0*, Complete resection; *R1*, microscopic residual tumor; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl monoxide; *PRED*, predicted.

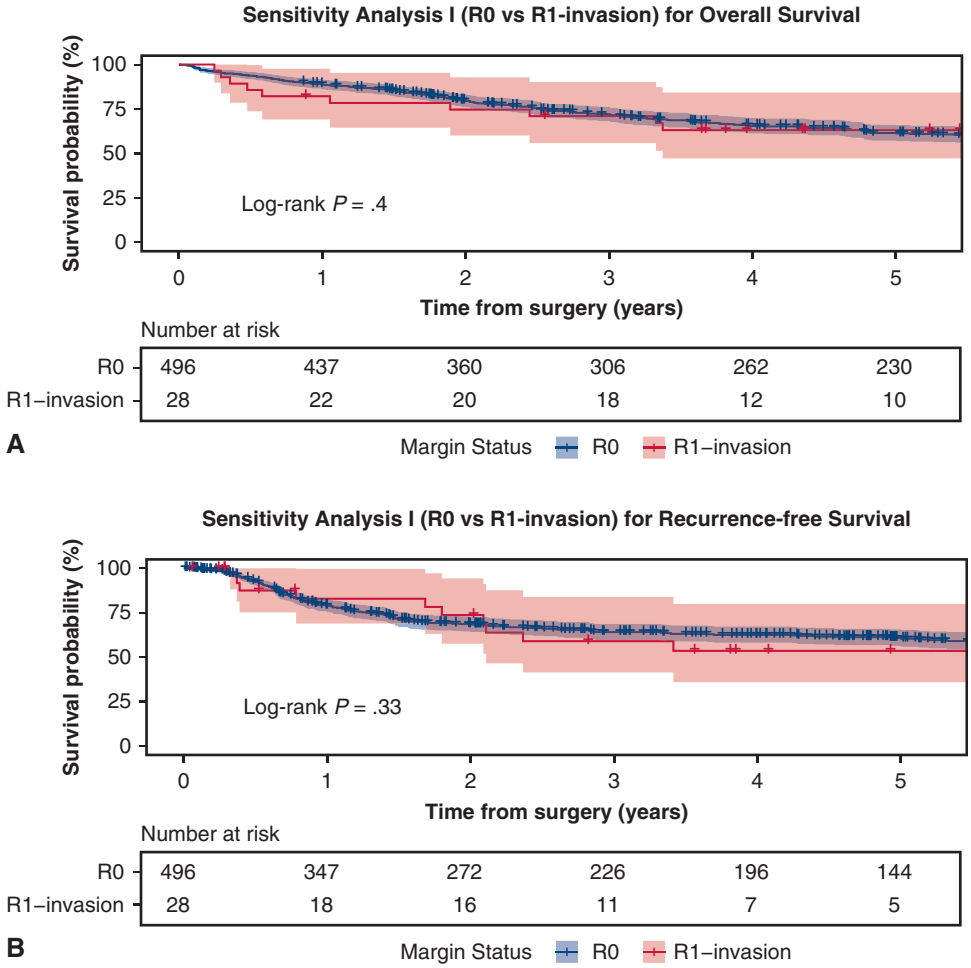


FIGURE E2. Sensitivity analysis I. A, Overall survival. B, Recurrence-free survival. *R0*, Complete resection; *R1*, microscopic residual tumor.

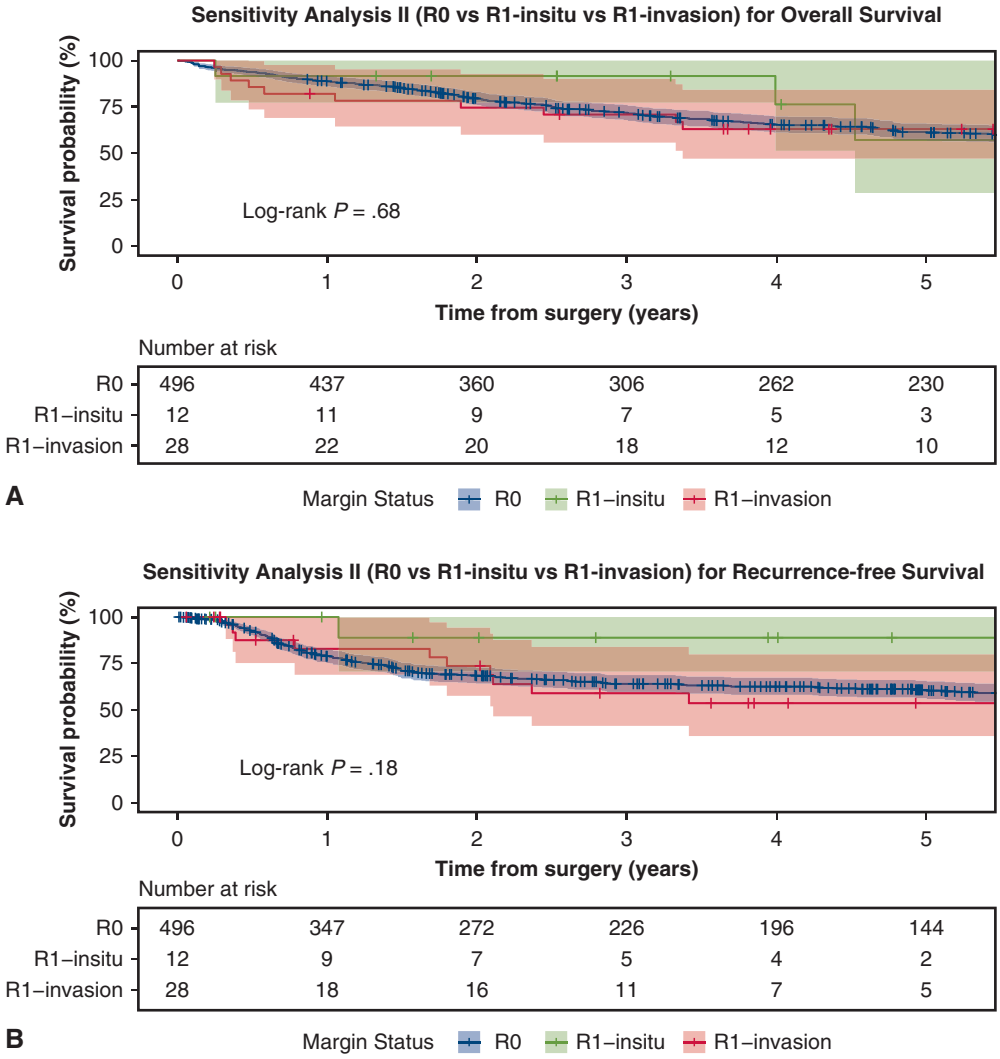


FIGURE E3. Sensitivity analysis II. A, Overall survival and B, Recurrence-free survival. *R0*, Complete resection; *R1*, microscopic residual tumor.

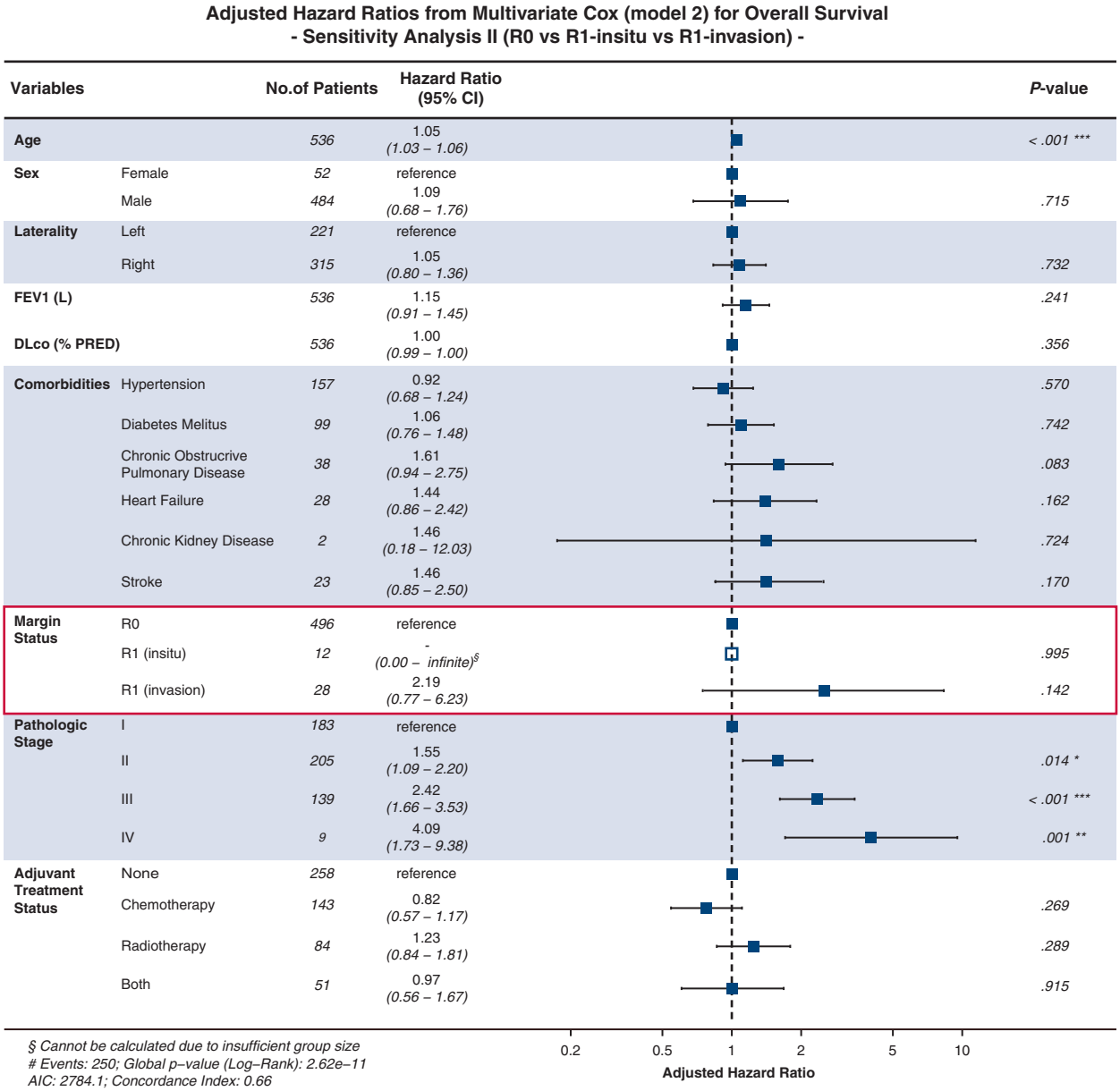
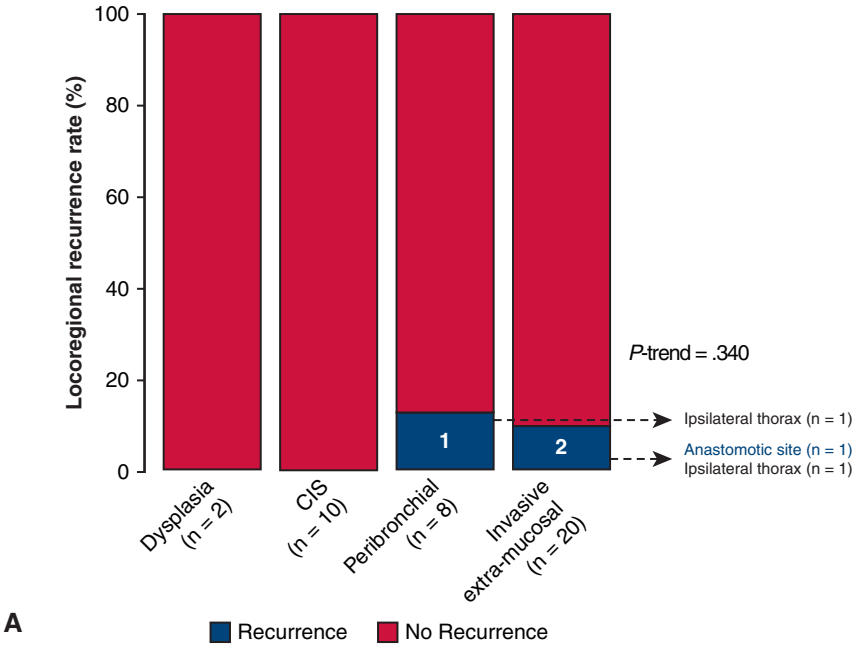


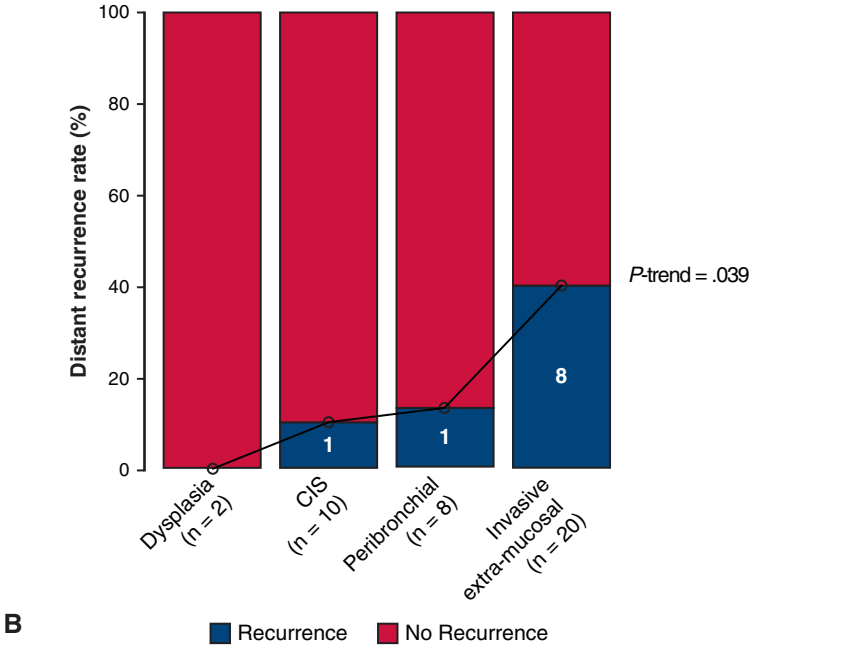
FIGURE E4. Forest plot of multivariable model 2 for overall survival: Sensitivity analysis II. *R0*, Complete resection; *R1*, microscopic residual tumor; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl monoxide; *PRED*, predicted.

Trend in the ***locoregional*** recurrence rate by the extent of microscopic residual disease at the BRM. BRM: bronchial resection margin



A

Trend in the ***distant*** recurrence rate by the extent of microscopic residual disease at the BRM. BRM: bronchial resection margin



B

FIGURE E5. A, Trend in the locoregional recurrence rate. B, Trend in the distant recurrence rate by the extent of microscopic residual disease at the bronchial resection margin (*BRM*). *CIS*, Carcinoma in situ.

TABLE E1. Cox-proportional hazard model for overall survival after bronchial sleeve resection: Sensitivity analysis I (invasive microscopic residual tumor [R1] only)

Outcome	Variable		Crude model		Multivariable model 1		Multivariable model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall survival								
	Age	(continuous)	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001
	Sex	Female	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Male	1.34 (0.85-2.11)	.212	1.03 (0.64-1.65)	.894	1.08 (0.67-1.74)	.739
	Tumor location	Left	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Right	1.13 (0.87-1.46)	.346	1.12 (0.86-1.45)	.417	1.07 (0.82-1.39)	.647
	FEV1 (L)	(continuous)	1.12 (0.91-1.40)	.288	1.16 (0.92-1.47)	.213	1.16 (0.92-1.47)	.210
	DLco (%)	(continuous)	1.00 (0.99-1.00)	.455	1.00 (0.99-1.00)	.307	1.00 (0.99-1.00)	.322
	Comorbidities	HTN	1.17 (0.89-1.55)	.261	0.91 (0.67-1.22)	.515	0.91 (0.67-1.24)	.552
		DM	1.38 (1.02-1.87)	.038	1.11 (0.80-1.55)	.537	1.07 (0.76-1.50)	.704
		COPD	1.42 (0.84-2.40)	.188	1.52 (0.88-2.64)	.134	1.54 (0.88-2.67)	.129
		Heart failure	1.74 (1.06-2.85)	.029	1.36 (0.82-2.28)	.235	1.44 (0.86-2.42)	.164
		CKD	2.53 (0.35-18.10)	.355	1.43 (0.18-11.55)	.738	1.49 (0.18-12.32)	.710
		CVA	1.88 (1.13-3.12)	.015	1.46 (0.85-2.50)	.169	1.47 (0.85-2.52)	.166
	Pathologic stage	I	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		II	1.33 (0.97-1.81)	.074	1.45 (1.05-2.00)	.025	1.55 (1.09-2.21)	.014
		III	2.19 (1.59-3.03)	<.001	2.36 (1.68-3.30)	<.001	2.43 (1.66-3.55)	<.001
		IV	3.22 (1.39-7.44)	.006	4.04 (1.71-9.57)	.001	4.03 (1.70-9.54)	.002
	Margin	**R0**	**1 (Reference)**	**–**	**1 (Reference)**	**–**	**1 (Reference)**	**–**
		R1-invasion	**1.26 (0.73-2.16)**	**.406**	**1.10 (0.63-1.92)**	**.729**	**2.16 (0.76-6.16)**	**.149**
	Adjuvant treatment	None	1 (Reference)	–			1 (Reference)	–
		CTx	0.93 (0.67-1.28)	.645			0.82 (0.57-1.17)	.265
		RTx	1.38 (0.99-1.93)	.058			1.22 (0.83-1.80)	.313
		Both	1.28 (0.82-2.00)	.283			0.96 (0.56-1.66)	.896

Model 1 was adjusted for age, sex, tumor location, preoperative pulmonary function tests (FEV1 and DLco), comorbidities, and pathologic stage. Model 2 was further adjusted for adjuvant treatment and an interaction term of margin:adjuvant treatment. (margin:adjuvant were not significant, *P* for interaction = .703 by Wald test). *HR*, Hazard ratio; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl mono-oxide; *HTN*, hypertension; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *CVA*, cerebrovascular accident; *R0*, complete resection; *CTx*, chemotherapy; *RTx*, radiotherapy.

TABLE E2. Cox-proportional hazard model for recurrence-free survival after bronchial sleeve resection: Sensitivity analysis I (invasive microscopic residual tumor [R1] only)

Outcome	Variable		Crude model		Multivariable model 1		Multivariable model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Recurrence-free survival								
	Age	(continuous)	1.02 (1.01-1.04)	.004	1.02 (1.01-1.04)	.004	1.02 (1.01-1.04)	.009
	Sex	Female	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Male	0.95 (0.59-1.50)	.814	0.84 (0.51-1.36)	.472	0.89 (0.54-1.45)	.637
	Tumor location	Left	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Right	1.01 (0.75-1.34)	.962	1.00 (0.74-1.35)	.990	0.97 (0.72-1.32)	.857
	FEV1 (L)	(continuous)	1.00 (0.78-1.28)	.990	0.95 (0.73-1.24)	.711	0.95 (0.73-1.23)	.693
	DLco (%)	(continuous)	1.00 (0.99-1.00)	.526	1.00 (0.99-1.00)	.424	1.00 (0.99-1.00)	.506
	Comorbidities	HTN	1.11 (0.81-1.52)	.522	0.95 (0.68-1.34)	.785	0.97 (0.69-1.37)	.884
		DM	1.52 (1.08-2.15)	.018	1.38 (0.95-2.00)	.091	1.40 (0.96-2.03)	.082
		COPD	0.63 (0.30-1.35)	.238	0.73 (0.34-1.58)	.422	0.70 (0.32-1.51)	.359
		Heart failure	1.23 (0.67-2.26)	.503	1.02 (0.54-1.91)	.960	1.05 (0.56-1.99)	.874
		CKD	0.00 (0.00-∞)	.993	0.00 (0.00-∞)	.994	0.00 (0.00-∞)	.994
		CVA	1.44 (0.76-2.73)	.261	1.31 (0.68-2.52)	.419	1.36 (0.71-2.62)	.358
	Pathologic stage	I	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		II	1.20 (0.83-1.73)	.338	1.15 (0.79-1.68)	.462	1.30 (0.86-1.96)	.211
		III	2.58 (1.80-3.70)	<.001	2.50 (1.73-3.62)	<.001	3.01 (1.97-4.61)	<.001
		IV	4.36 (1.73-10.96)	.002	4.96 (1.93-12.73)	<.001	5.55 (2.14-14.36)	<.001
	Margin	**R0**	**1 (Reference)**	**–**	**1 (Reference)**	**–**	**1 (Reference)**	**–**
		R1-invasion	**1.34 (0.74-2.40)**	**.331**	**1.16 (0.63-2.11)**	**.634**	**1.71 (0.41-7.10)**	**.461**
	Adjuvant treatment	None	1 (Reference)	–			1 (Reference)	–
		CTx	0.98 (0.69-1.40)	.927			0.79 (0.53-1.16)	.229
		RTx	1.29 (0.86-1.92)	.217			0.88 (0.56-1.41)	.604
		Both	1.34 (0.83-2.16)	.228			0.66 (0.37-1.17)	.154

Model 1 was adjusted for age, sex, tumor location, preoperative pulmonary function tests (ie, FEV1 and DLco), comorbidities, and pathologic stage. Model 2 was further adjusted for adjuvant treatment and an interaction term of margin:adjuvant treatment. (margin:adjuvant were not significant, *P* for interaction = .726 by Wald test). *HR*, Hazard ratio; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl mono-oxide; *HTN*, hypertension; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *R0*, complete resection; *CVA*, cerebrovascular accident; *CTx*, chemotherapy; *RTx*, radiotherapy.

TABLE E3. Cox-proportional hazard model for overall survival after bronchial sleeve resection: Sensitivity analysis II (margin variable with 3 levels)

Outcome	Variable		Crude model		Multivariable model 1		Multivariable model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Overall survival								
	Age	(continuous)	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001	1.05 (1.03-1.06)	<.001
	Sex	Female	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Male	1.36 (0.86-2.14)	.192	1.05 (0.65-1.68)	.846	1.09 (0.68-1.76)	.715
	Tumor location	Left	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Right	1.12 (0.87-1.45)	.373	1.11 (0.86-1.44)	.431	1.05 (0.80-1.36)	.732
	FEV1 (L)	(continuous)	1.11 (0.89-1.37)	.349	1.14 (0.90-1.43)	.276	1.15 (0.91-1.45)	.241
	DLco (%)	(continuous)	1.00 (0.99-1.00)	.487	1.00 (0.99-1.00)	.326	1.00 (0.99-1.00)	.356
	Comorbidities	HTN	1.18 (0.90-1.56)	.225	0.93 (0.69-1.24)	.609	0.92 (0.68-1.24)	.570
		DM	1.34 (0.99-1.81)	.056	1.08 (0.78-1.50)	.633	1.06 (0.76-1.48)	.742
		COPD	1.43 (0.86-2.39)	.165	1.54 (0.91-2.62)	.111	1.61 (0.94-2.75)	.083
		Heart failure	1.74 (1.06-2.86)	.027	1.37 (0.82-2.28)	.232	1.44 (0.86-2.42)	.162
		CKD	2.56 (0.36-18.34)	.348	1.43 (0.18-11.56)	.735	1.46 (0.18-12.03)	.724
		CVA	1.88 (1.13-3.13)	.015	1.45 (0.85-2.49)	.173	1.46 (0.85-2.50)	.170
	Pathologic stage	I	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		II	1.32	.077	1.44 (1.04-1.98)	.027	1.55 (1.09-2.20)	.014
		III	2.16	<.001	2.31 (1.65-3.22)	<.001	2.42 (1.66-3.53)	<.001
		IV	3.22	.006	4.06 (1.72-9.61)	.001	4.09 (1.73-9.38)	.001
	Margin	**R0**	**1 (Reference)**	**–**	**1 (Reference)**	**–**	**1 (Reference)**	**–**
		R-is/dysplasia	**0.91 (0.34-2.44)**	**.844**	**0.84 (0.31-2.30)**	**.740**	**0.00 (0.00-∞)**	**.995**
		R1-invasion	**1.26 (0.73-2.16)**	**.401**	**1.12 (0.64-1.95)**	**.694**	**2.19 (0.77-6.23)**	**.142**
	Adjuvant treatment	None	1 (Reference)	–			1 (Reference)	–
		CTx	0.93 (0.67-1.28)	.652			0.82 (0.57-1.17)	.269
		RTx	1.37 (0.99-1.91)	.060			1.23 (0.84-1.81)	.289
		Both	1.32 (0.85-2.05)	.220			0.97 (0.56-1.67)	.915

Model 1 was adjusted for age, sex, tumor location, preoperative pulmonary function tests (ie, FEV1 and DLco), comorbidities, and pathologic stage. Model 2 was further adjusted for adjuvant treatment and an interaction term of margin:adjuvant treatment (margin:adjuvant were not significant; *P* for interaction = .846 by Wald test). *HR*, Hazard ratio; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl mono-oxide; *HTN*, hypertension; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *CVA*, cerebrovascular accident; *CTx*, chemotherapy; *R0*, complete resection; *R1*, microscopic residual tumor; *RTx*, radiotherapy.

TABLE E4. Cox-proportional hazard model for recurrence-free survival after bronchial sleeve resection: A sensitivity analysis II (margin variable with 3-levels)

Outcome	Variable		Crude model		Multivariable model 1		Multivariable model 2	
			HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Recurrence-free survival								
	Age	(continuous)	1.02 (1.01-1.04)	.005	1.02 (1.01-1.04)	.005	1.02 (1.00-1.04)	.010
	Sex	Female	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Male	0.95 (0.60-1.51)	.834	0.85 (0.52-1.38)	.509	0.89 (0.55-1.46)	.653
	Tumor location	Left	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		Right	1.12 (0.87-1.45)	.373	1.01 (0.75-1.37)	.924	0.98 (0.73-1.33)	.902
	FEV1 (L)	(continuous)	1.11 (0.89-1.37)	.349	0.97 (0.75-1.26)	.815	0.96 (0.74-1.25)	.776
	DLco (%)	(continuous)	1.00 (0.99-1.00)	.487	1.00 (0.99-1.00)	.409	1.00 (0.99-1.00)	.509
	Comorbidities	HTN	1.11 (0.81-1.52)	.501	0.97 (0.70-1.36)	.879	0.98 (0.69-1.38)	.900
		DM	1.42 (1.01-2.01)	.046	1.34 (0.92-1.94)	.123	1.37 (0.94-2.00)	.098
		COPD	0.60 (0.28-1.27)	.181	0.70 (0.33-1.52)	.372	0.69 (0.32-1.51)	.356
		Heart failure	1.25 (0.68-2.30)	.468	1.01 (0.54-1.90)	.966	1.05 (0.56-1.99)	.872
		CKD	0.00 (0.00-∞)	.993	0.00 (0.00-∞)	.994	0.00 (0.00-∞)	.997
		CVA	1.47 (0.78-2.77)	.239	1.31 (0.68-2.52)	.416	1.37 (0.71-2.64)	.351
	Pathologic stage	I	1 (Reference)	–	1 (Reference)	–	1 (Reference)	–
		II	1.22 (0.85-1.77)	.281	1.16 (0.80-1.69)	.438	1.32 (0.88-1.99)	.185
		III	2.61 (1.82-3.73)	<.001	2.54 (1.76-3.67)	<.001	3.09 (2.02-4.72)	<.001
		IV	4.50 (1.79-11.32)	.001	4.97 (1.93-12.78)	<.001	5.61 (2.17-14.52)	<.001
	Margin	**R0**	**1 (Reference)**	**–**	**1 (Reference)**	**–**	**1 (Reference)**	**–**
		R-is/dysplasia	**0.24 (0.03-1.71)**	**.155**	**0.20 (0.03-1.45)**	**.111**	**0.00 (0.00-∞)**	**.997**
		R1-invasion	**1.34 (0.74-2.40)**	**.331**	**1.14 (0.63-2.08)**	**.667**	**1.73 (0.42-7.16)**	**.453**
	Adjuvant treatment	None	1 (Reference)	–			1 (Reference)	–
		CTx	0.96 (0.68-1.37)	.836			0.78 (0.53-1.15)	.214
		RTx	1.23 (0.82-1.83)	.319			0.88 (0.55-1.39)	.576
		Both	1.37 (0.85-2.18)	.193			0.65 (0.36-1.16)	.142

Model 1 was adjusted for age, sex, tumor location, preoperative pulmonary function tests (ie, FEV1 and DLco), comorbidities, and pathologic stage. Model 2 was further adjusted for adjuvant treatment and an interaction term of margin:adjuvant treatment (margin:adjuvant were not significant; *P* for interaction = .971 by Wald test). *HR*, Hazard ratio; *CI*, confidence interval; *FEV1*, forced expiratory volume in 1 second; *DLco*, diffusion capacity of carboxyl mono-oxide; *HTN*, hypertension; *DM*, diabetes mellitus; *COPD*, chronic obstructive pulmonary disease; *CKD*, chronic kidney disease; *CVA*, cerebrovascular accident; *R0*, complete resection; *R1*, microscopic residual tumor; *CTx*, chemotherapy; *RTx*, radiotherapy.

TABLE E5. The results of frozen section analyses

Variable	R1 group (n = 40)	R0 group (n = 496)	*P* value
Frozen section analyzed	40 (100)	466 (94.0)	.984
Frozen section result			<.001
Positive	31 (77.5)	0 (0.0)	
Equivocal or undetermined	6 (15)	23 (4.9)	
Negative	3 (7.5)	443 (95.1)	

Values are presented as n (%). *R1*, Microscopic residual tumor; *R0*, complete resection.