ORIGINAL ARTICLE

Prognostic Significance of the Proposed Residual Tumor Classification in Patients With NSCLC After Sleeve Lobectomy

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ABSTRACT

Introduction: To validate the residual tumor (R) classification proposed by the International Association for the Study of Lung Cancer (IASLC) in NSCLC after sleeve lobectomy.

Methods: A total of 682 patients were analyzed. The R status, on the basis of the Union for International Cancer Control (UICC) criteria, was recategorized according to the IASLC descriptors. Recurrence-free survival (RFS) and overall survival (OS) among different R classifications were assessed for the entire cohort and pathologic node (pN) subgroups.

Results: All in all, 631 (92.5%), 48 (7.1%), and three patients (0.4%) were classified as R0, R1, and R2, respectively, by the UICC criteria, whereas 489 (71.7%), 110 (16.1%), and 83 patients (12.2%), received R0, uncertain resection (R[un]), and R1/2 resection, respectively, according to the IASLC criteria. There were 96 patients (15.2%) with UICC R0 who were reclassified as R(un), mainly because of the positive highest mediastinal node station (82 of 96, 85.4%). A total of 46 patients (7.3%) were reassigned from UICC R0 to IASLC R1/2 owing to extracapsular extension. For the entire cohort, patients with R(un) and R1/2 exhibited worse RFS (R[un], adjusted $p = 0.023$; R1/2, adjusted $p = 0.001$) and OS (R[un], adjusted $p = 0.040$; R1/2, adjusted $p = 0.051$) compared with R0. No significant differences were observed between R(un) and R1/2 (RFS, adjusted $p = 0.586$; OS, adjusted $p = 0.781$). Furthermore, subgroup analysis revealed a distinct prognostic impact of the IASLC R status—with prognostic significances in the pN1 and pN2 subgroups, but not in the pN0 subgroup.

Conclusions: The IASLC R descriptors helped to stratify the prognosis of NSCLC after sleeve lobectomy, with its prognostic impact varied among pN stages.

Keywords: Residual tumor classification; UICC; IASLC; Sleeve lobectomy; Non–small cell lung cancer

Introduction

The residual tumor (R) classification after surgical resection for NSCLC is mainly determined by the Union for International Cancer Control (UICC) criteria.[1–3] However, in patients with UICC-defined R0 resection, several factors—such as inadequacy of nodal dissection, positive highest mediastinal nodes, and extracapsular extension (ECE)—could still substantially compromise

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the prognosis of patients.[4–6] In such instances, the International Association for the Study of Lung Cancer (IASLC) proposed a new R classification for NSCLC in 2005 to further clarify the definition of surgical sufficiency,[7] which specified more rigorous standards for R0 resection and shifted cases with the inadequacy of nodal dissection or positive highest mediastinal nodes from R0 to the uncertain resection (R[un]) and cases with ECE to R1 resection.

Sleeve lobectomy, a well-established procedure to preserve lung function, has been an effective alternative to pneumonectomy for patients with centrally-located NSCLC,[8–12] considering the fact that a considerable proportion of patients who underwent sleeve lobectomy were represented with large tumor sizes, lymph node involvements, and locally advanced stages. Whether sleeve lobectomy could achieve R0 resection is crucial for the surgical decision to perform this challenging procedure and the prognosis of these patients.

Previous studies have reported the discriminatory ability of the R descriptors proposed by IASLC for the surgical population of NSCLC.[12,13] Nevertheless, existing results implied that the prognostic role of the R descriptors may vary from tumor stage and histologic subtype.[14,15] The study cohorts of the publications mentioned above mostly consisted of stage I (60.0%–66.9%) and adenocarcinomas (67.5%–73.3%), whereas patients who underwent sleeve lobectomy had mostly locally advanced stages and centrally-located squamous cell carcinomas. Therefore, it is important to clarify the distributions of R0 resections and explore the prognostic value of different R classifications in the population with sleeve lobectomy.

To the best of our knowledge, no study has validated the IASLC R descriptors in this special subset. Thus, our study aimed to investigate the prognostic role of the proposed R descriptors in patients with NSCLC after sleeve lobectomy.

Materials and Methods

Patients

Patients who underwent bronchial sleeve lobectomy at Shanghai Pulmonary Hospital between January 2013 and December 2018 for centrally-located lung cancer, which invaded the lobar bronchus and the artery and extended to the main bronchus were retrospectively collected. Clinical records were reviewed and extracted from the electronic medical system by two thoracic surgeons (T.C., Y.Z.). In total, 828 patients undergoing sleeve lobectomy were identified during this period. Subsequently, after multiple exclusions ([1] 66 patients with tumors other than NSCLC; [2] 17 patients with benign lesions; [3] 9 patients with carinal reconstruction; [4] 7 patients with metastatic disease; and [5] 47 patients lost to follow-up), 682 patients were finally included in the current study. Approval of the institutional review board of Shanghai Pulmonary Hospital and the waiver of informed consent were acquired.

Preoperative Evaluation and Surgical Technique

All patients received a thorough preoperative evaluation, including pulmonary function test, computed tomography (CT)/contrast-enhanced CT, abdominal/brain CT, and bone scan. Positron emission tomography (PET) and endobronchial ultrasound–guided transbronchial needle aspiration were performed when mediastinal involvement was suspected on CT images.

Surgical procedures for sleeve lobectomy have been described in our previous publications.[16,17] The surgery included resection of the primary tumor and systematic nodal dissection (SND) or lobe-specific nodal dissection (LSND). SND was defined as a dissection of at least three nodes from three N2 stations (including station 7) in addition to three nodes from three N1 stations (lobar, interlobar, or hilar).[7] LSND was defined as the evaluation of station seven and at least two of three other stations—station 2R, station 3, and station 4R for right upper or middle lobe tumors; station 4R, 8, and 9 for right lower lobe tumors; station 5 and 6 for left upper lobe tumors; and station 8 and 9 for left lower tumors.[7] The adequacy of nodal dissection for each patient was assessed using the criteria proposed by the IASLC Staging and Prognostic Factors Committee.[7] All lymph nodes were evaluated and classified on the basis of their anatomical location using the numbering system described in the Mountain-Dresler modification of the American Thoracic Society[18] and the IASLC lymph node map.[19] The pathologic staging was on the basis of the eighth edition of the TNM staging system.[20] Platinum-based two-drug adjuvant chemotherapy was routinely administrated for patients with stage II to III, and stage I with high-risk factors, if they could tolerate it.

Definition of Residual Tumor Descriptors by UICC and IASLC Criteria

On the basis of the UICC R status, no residual, microscopic, or macroscopic tumors were defined as R0, R1, and R2, respectively. Regarding the IASLC R status, R0 resection must meet all of the following conditions: (1) SND or LSND; (2) no ECE of the tumor in nodes located at the margin of the main lung specimen or in those removed separately; and (3) the highest mediastinal nodes removed must be negative. Failure to fulfill any of the conditions above was defined as R(un). Notably, patients with carcinoma in situ (CIS) at the bronchial resection margin (BRM) or a positive pleural

lavage cytologic were classified as R(un) rather than R1. Patients with ECE were classified as R1 instead of R0.[7,12]

In the current study, two experienced pathologists (L.H., C.W.) re-evaluated all positive nodes to determine the status of ECE. All disagreements were resolved by discussion.

Follow-Up Strategy

Chest CT scan and abdominal ultrasound/CT were performed at durations of 3, 6, and 12 months after surgery and annually after for 5 years. Magnetic resonance imaging for the cerebrum and bone scan were performed to exclude distant metastasis. The PET-CT scan and biopsy were recommended to confirm the recurrence. Locoregional recurrence was defined as a new lesion in the bronchial stump or residual lobe, ipsilateral lobar parenchyma, hilum, or mediastinal lymph node (N1/N2). Distant recurrence was defined as evidence of a tumor in the contralateral lung, contralateral mediastinal or supraclavicular lymph nodes (N3), ipsilateral or contralateral pleural disease, or somewhere outside the hemithorax. Follow-up data were acquired from outpatient clinic revisits and telephone. Recurrence-free survival (RFS) was defined as the time from surgery to recurrence, death, or last follow-up. Overall survival (OS) was defined as the time from surgery to either death for any cause or the last follow-up.

Statistical Analysis

Categorical variables were presented as numbers (percentage) and compared with the Pearson chi-square test. Continuous variables were reported as mean and SD or median and interquartile range on the basis of the normal distribution of the data and compared by one-way analysis of variance or Kruskal-Wallis H test, as appropriate.

We first validated the prognostic role of the proposed R descriptors for the entire cohort and then investigated whether there was a distinct prognostic impact of the R descriptors in subsets according to the pathologic N (pN) stage. Survival analysis was performed with the Kaplan-Meier method and compared by log-rank test. Multivariable Cox regression analysis was performed to identify independent predictors for RFS and OS. A two-sided p value less than 0.05 was considered significant. All statistical analysis was performed using the Statistical Package for the Social Sciences version 25.0 (IBM SPSS Statistics, IBM Corp., Armonk, NY) and R version 4.1.2 (R Core Team, Vienna, Austria).

Results

Patient Characteristics

A total of 682 patients were included in the current study. For the IASLC criteria, 489 (71.7%), 110 (16.1%), and 83 patients (12.2%) received R0, R(un), and R1/R2 resections, respectively. Patient characteristics according to the IASLC R descriptors are listed in Table 1. Patients with R(un) had younger age (R0, 64 y; R[un], 61 y; R1/R2, 63 y, $p = 0.013$), more women (R0, 9.0%; R[un], 18.2%; R1/R2, 8.4%, $p = 0.014$), lower proportion of smoking history (R0, 64.2%; R[un], 47.3%; R1/R2, 66.3%, $p = 0.003$), more right-sided tumors (R0, 51.9%; R[un], 64.5%; R1/R2, 43.4%, $p = 0.010$), higher proportion of neoadjuvant therapy (R0, 9.2%; R[un] 18.2%; R1/2, 12.0%, $p = 0.023$), more video-assisted thoracic surgery performed (R0, 47.2%; R[un] 52.7%; R1/2, 30.0%, $p = 0.005$), and more adenocarcinomas (R0, 12.9%; R[un] 33.6%; R1/2, 22.9%, $p < 0.001$). Notably, more pN2 diseases were observed in patients with R(un) resections (R0, 5.9%; R[un] 80.9%; R1/2, 47.0%, $p < 0.001$). According to the UICC criteria, 631 (92.5%), 48 (7.1%), and three patients (0.4%) were classified as R0, R1, and R2, respectively. The clinicopathologic characteristics on the basis of the UICC system were summarized in Supplementary Table 1.

The distribution of the R classification between the IASLC and UICC systems is presented in Table 2. For UICC R0 patients (n = 631), 489 patients (77.5%) maintained R0, 96 patients (15.2%) were reclassified as R(un), and 46 patients (7.3%) were reclassified as R1/R2 after IASLC classification. For UICC R0 to R(un) (n = 96), 82 patients (85.4%) were reclassified owning to the positive highest mediastinal lymph node. There were 46 patients (7.3%) who were reassigned from R0 to R1 because of ECE; 14 patients (29.2%) redistributed from R1 to R(un) because of CIS at BRM.

Survival Outcomes for the Entire Cohort

All patients completed the follow-up survey before September 15, 2022. The median follow-up time was 57.4 months. Concerning the IASLC R descriptors, patients with R0 resection exhibited favorable RFS (5-y RFS, 60.3% versus 37.1% versus 30.0%, $p < 0.001$, Fig. 1*A*) and OS (5-y OS, 67.6% versus 49.8% versus 45.7%, $p < 0.001$, Fig. 1*B*), compared with R(un) and R1/2, with no significant differences between R(un) and R1/2 for RFS ($p = 0.401$, Fig. 1*A*) and OS ($p = 0.616$, Fig. 1*B*). Multivariable Cox analysis revealed that the IASLC R descriptors were independent predictors of RFS ($p = 0.002$; R(un) versus R0, hazard ratio [HR] = 1.59, 95% confidence interval [CI] 1.09–2.31, $p = 0.023$; R1/2 versus R0, HR = 1.77, 95% CI: 1.27–2.47, $p = 0.001$; R(un) versus R1/2, HR 0.90, 95% CI: 0.61–1.33, $p = 0.586$). Although the IASLC R descriptors were not statistically significant predictors of OS ($p = 0.059$; R(un) versus R0, HR = 1.54, 95% CI: 1.02–2.33, $p = 0.040$; R1/2 versus R0, HR = 1.45, 95% CI: 1.00–2.11, $p = 0.051$; R(un) versus

Table 1. Clinicopathological Characteristics of Patients With NSCLC Underwent Sleeve Lobectomy on the Basis of the IASLC Criteria

Variables	Total (N = 682)	IASLC			p
		R0 (n = 489)	R(un) (n = 110)	R1/R2 (n = 83)	
Age, y, median (IQR)	63 (58-68)	64 (58-68)	61 (54-66)	63 (59-69)	0.013
Sex, n (%)					0.014
Male	611 (89.6)	445 (91.0)	90 (81.8)	76 (91.6)	
Female	71 (10.4)	44 (9.0)	20 (18.2)	7 (8.4)	
Smoking history, n (%)	421 (61.7)	314 (64.2)	52 (47.3)	55 (66.3)	0.003
CCI, n (%)					0.533
0	26 (3.8)	17 (3.5)	8 (7.3)	1 (1.2)	
1	116 (17.0)	79 (16.2)	22 (20.0)	15 (18.1)	
2	257 (37.7)	184 (37.6)	42 (38.2)	31 (37.3)	
3	226 (33.1)	168 (34.4)	30 (27.3)	28 (33.7)	
4	54 (7.9)	39 (8.0)	8 (7.3)	7 (8.4)	
5	3 (0.4)	2 (0.4)	0	1 (1.2)	
FEV1, liter, mean (SD)	2.3 (0.5)	2.3 (0.5)	2.3 (0.6)	2.2 (0.5)	0.185
FEV1 (%), mean (SD)	82.5 (16.6)	82.2 (17.2)	84.8 (14.9)	81.5 (14.3)	0.277
Location, n (%)					0.010
Left	321 (47.1)	235 (48.1)	39 (35.5)	47 (56.6)	
Right	361 (52.9)	254 (51.9)	71 (64.5)	36 (43.4)	
Neoadjuvant chemotherapy, n (%)	75 (11.0)	45 (9.2)	20 (18.2)	10 (12.0)	0.023
Surgical approach, n (%)					0.005
VATS	314 (46.0)	231 (47.2)	58 (52.7)	25 (30.1)	
Thoracotomy	368 (54.0)	258 (52.8)	52 (47.3)	58 (69.9)	
Operative techniques, n (%)					0.526
Bronchial sleeve	534 (78.3)	386 (78.9)	87 (79.1)	61 (73.5)	
Bronchial sleeve plus angioplasty	148 (21.7)	103 (21.1)	23 (20.9)	22 (26.5)	
pT stage, n (%)					0.705
T1	35 (5.3)	25 (5.1)	8 (7.3)	3 (3.6)	
T2	490 (71.8)	354 (72.4)	79 (78.1)	57 (68.7)	
T3	115 (16.9)	82 (16.8)	18 (16.4)	15 (18.1)	
T4	41 (6.0)	28 (5.7)	5 (4.5)	8 (9.6)	
pN stage, n (%)					<.001
N0	400 (58.7)	362 (74.0)	16 (14.5)	22 (26.5)	
N1	125 (18.3)	98 (20.0)	5 (4.5)	22 (26.5)	
N2	157 (23.0)	29 (5.9)	89 (80.9)	39 (47.0)	
Pathologic stage, n (%)					<.001
I	271 (39.7)	244 (49.9)	10 (9.1)	17 (20.5)	
II	200 (29.4)	170 (34.8)	11 (10.0)	19 (22.9)	
III	211 (30.9)	75 (15.3)	89 (80.9)	47 (56.6)	
Histology, n (%)					<.001
Squamous cell carcinoma	519 (76.1)	395 (80.8)	65 (59.1)	59 (71.1)	
Adenocarcinoma	119 (17.4)	63 (12.9)	37 (33.6)	19 (22.9)	
Others	44 (6.5)	31 (6.3)	8 (7.3)	5 (6.0)	
Adjuvant chemotherapy, n (%)	446 (65.4)	298 (60.9)	79 (71.8)	69 (83.1)	<.001
Recurrence pattern					<.001
No	414 (60.7)	331 (67.7)	50 (45.5)	33 (39.8)	
Locoregional	80 (11.7)	48 (9.8)	18 (16.4)	14 (16.9)	
Distant	168 (24.6)	99 (20.2)	38 (34.5)	31 (37.3)	
Both	20 (2.9)	11 (2.2)	4 (3.6)	5 (6.0)	

CCI, Charlson comorbidity index; FEV1, forced expiratory volume in 1 second; IASLC, International Association for the Study of Lung Cancer; IQR, interquartile range; pN, pathologic N; pT, pathologic T; R, residual tumor; R(un), uncertain resection; VATS, video-assisted thoracic surgery.

R1/2, HR = 1.06, 95% CI: 0.69–1.63, $p = 0.781$), a clear trend was observed (Supplementary Table 2). Survival analysis regarding the UICC system for the whole cohort revealed that R1 resection defined by UICC revealed no significant difference compared with UICC R0 (Supplementary Fig. 1).

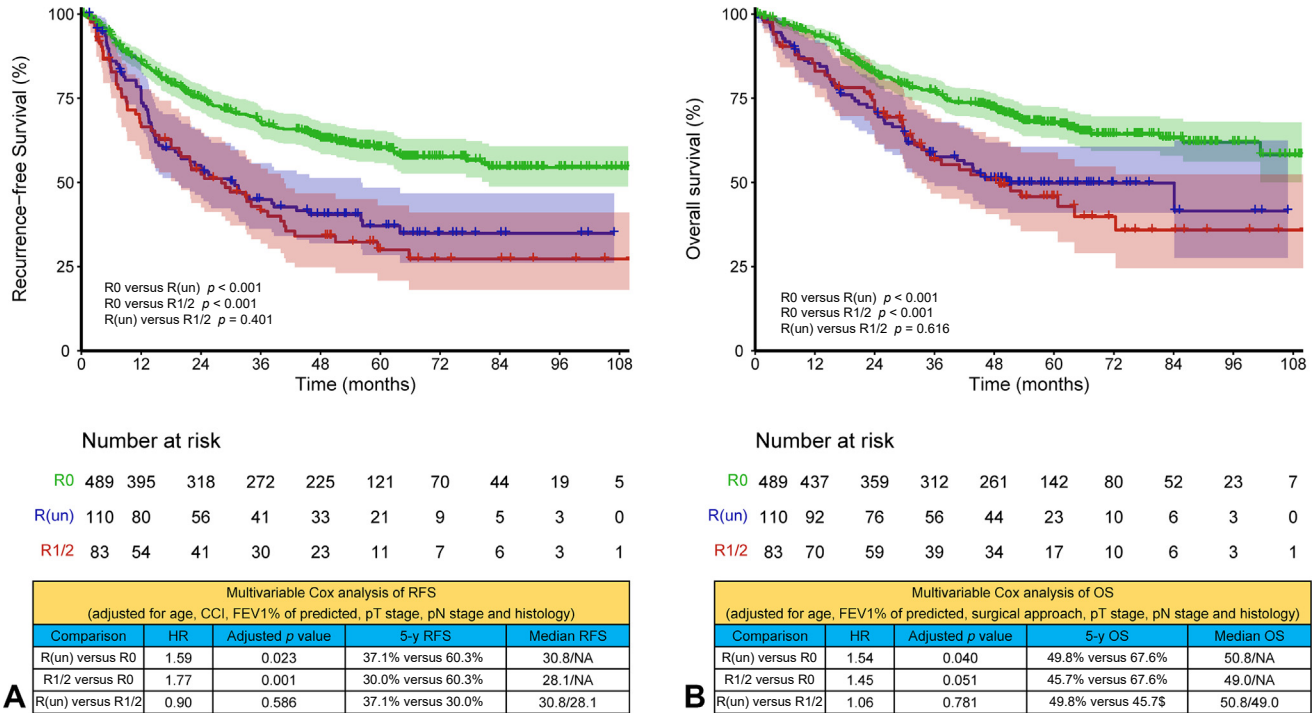
Table 2. Relationship of Resection Status Between the UICC and IASLC Criteria

	UICC			
IASLC	R0	R1	R2	Total (%)
R0	489 (77.5)[a]	-	-	489 (71.7)[a]
R(un)	96 (15.2)[a]	14 (29.2)[a]	-	110 (16.1)[a]
Incomplete lymph node dissection	14 (14.6)[b]	-	-	14 (12.7)[b]
<3 N1 or <3N2	10 (10.4)[b]	-	-	10 (9.1)[b]
No station 7	4 (4.2)[b]	-	-	4 (3.6)[b]
Positive highest mediastinal lymph node only	82 (85.4)[b]	-	-	82 (74.5)[b]
Carcinoma in situ at bronchial resection margin	-	14 (100)[b]	-	14 (12.7)[b]
Pleural lavage cytology positive	0	-	-	0
R1/R2	46 (7.3)[a]	34 (70.8)[a]	3 (100)[a]	83 (12.2)[a]
Residual tumor at resection margin	-	34 (100)[b]	3 (100)[b]	37 (44.6)[b]
Extracapsular extension	46 (100)[b]	0	-	46 (55.4)[b]
Within N1	27 (58.7)[b]	0	-	27 (32.5)[b]
Within N2	19 (41.3)[b]	0	-	19 (22.9)[b]
Positive nodes not removed	0	0	-	0
Positive cytology of pleural or pericardial effusions	0	0	-	0
Total (%)	631 (92.6)	48 (7.0)	3 (0.4)	682

[a]Percentage of column total.
[b]Percentage of category total.
IASLC, International Association for the Study of Lung Cancer; R, residual tumor; UICC, Union for International Cancer Control.

Subgroup Analysis According to pN Status

For patients with pN0 (N = 400), the relationship of R status between IASLC and UICC was listed in Supplementary Table 3. Eight of 362 patients (2.2%) with UICC R0 were reassigned to R(un) because of inadequate nodal dissection. A total of 8 of 28 patients (28.6%) with



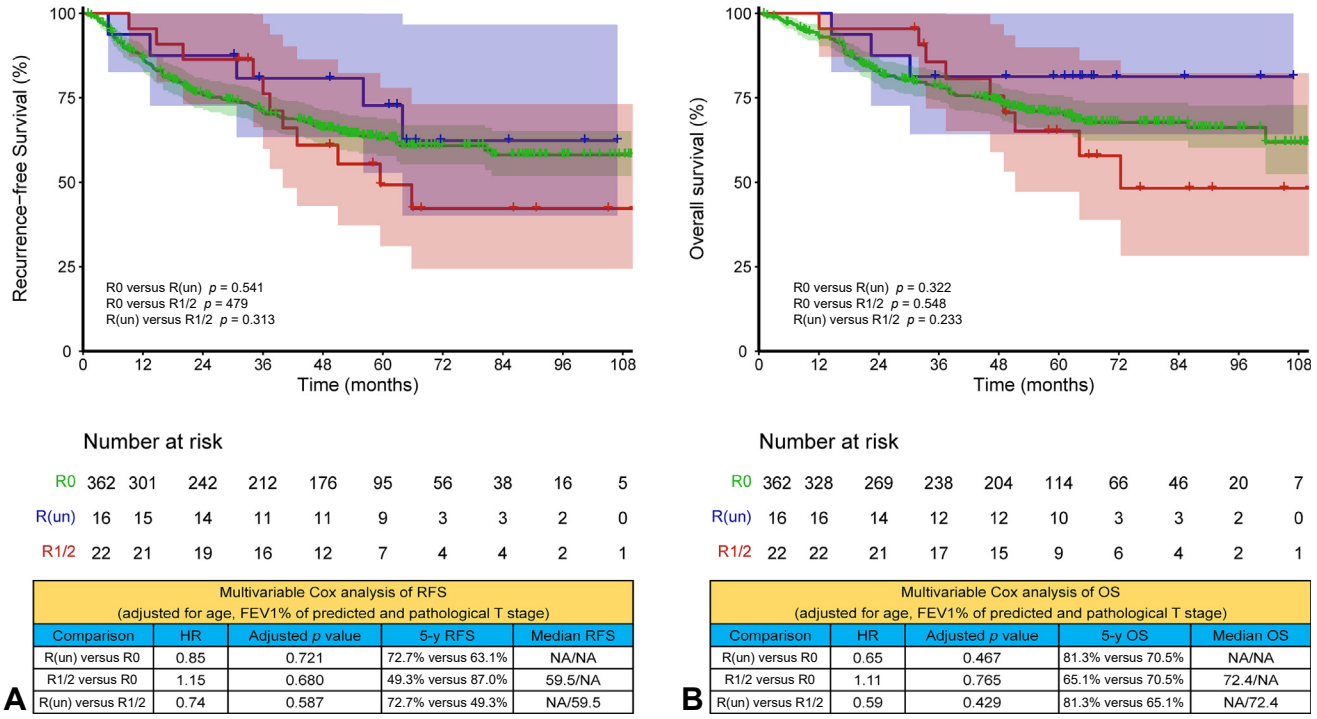
A

Multivariable Cox analysis of RFS (adjusted for age, CCI, FEV1% of predicted, pT stage, pN stage and histology)				
Comparison	HR	Adjusted *p* value	5-y RFS	Median RFS
R(un) versus R0	1.59	0.023	37.1% versus 60.3%	30.8/NA
R1/2 versus R0	1.77	0.001	30.0% versus 60.3%	28.1/NA
R(un) versus R1/2	0.90	0.586	37.1% versus 30.0%	30.8/28.1

B

Multivariable Cox analysis of OS (adjusted for age, FEV1% of predicted, surgical approach, pT stage, pN stage and histology)				
Comparison	HR	Adjusted *p* value	5-y OS	Median OS
R(un) versus R0	1.54	0.040	49.8% versus 67.6%	50.8/NA
R1/2 versus R0	1.45	0.051	45.7% versus 67.6%	49.0/NA
R(un) versus R1/2	1.06	0.781	49.8% versus 45.7$	50.8/49.0

Figure 1. Survival analysis of RFS (*A*) and OS (*B*) regarding the IASLC R descriptors for the entire cohort. CCI, Charlson comorbidity index; FEV1, forced expiratory volume in 1 second; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; NA, not applicable; OS, overall survival; R, residual tumor; R(un), uncertain resection; RFS, recurrence-free survival.



A

Multivariable Cox analysis of RFS (adjusted for age, FEV1% of predicted and pathological T stage)

Comparison	HR	Adjusted *p* value	5-y RFS	Median RFS
R(un) versus R0	0.85	0.721	72.7% versus 63.1%	NA/NA
R1/2 versus R0	1.15	0.680	49.3% versus 87.0%	59.5/NA
R(un) versus R1/2	0.74	0.587	72.7% versus 49.3%	NA/59.5

B

Multivariable Cox analysis of OS (adjusted for age, FEV1% of predicted and pathological T stage)

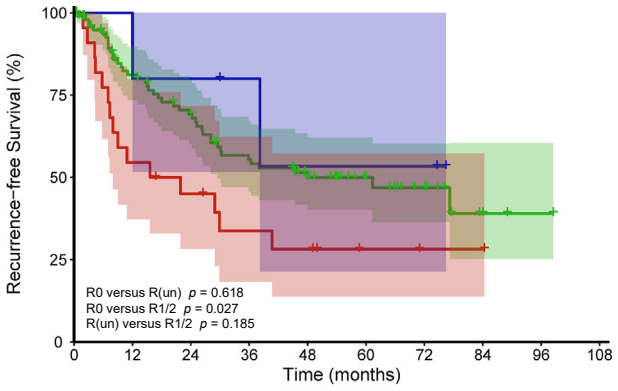
Comparison	HR	Adjusted *p* value	5-y OS	Median OS
R(un) versus R0	0.65	0.467	81.3% versus 70.5%	NA/NA
R1/2 versus R0	1.11	0.765	65.1% versus 70.5%	72.4/NA
R(un) versus R1/2	0.59	0.429	81.3% versus 65.1%	NA/72.4

Figure 2. Survival analysis of RFS (*A*) and OS (*B*) regarding the IASLC R descriptors for patients with pN0. FEV1, forced expiratory volume in 1 second; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; NA, not applicable; OS, overall survival; pN0, pathologic N0; R, residual tumor; R(un), uncertain resection; RFS, recurrence-free survival.

UICC R1 were reclassified to R(un) owing to CIS at BRM. Survival analysis revealed no prognostic impact of the IASLC R status for RFS (R[un] versus R0, adjusted $p = 0.721$; R1/2 versus R0, adjusted $p = 0.680$; R[un] versus R1/2, adjusted $p = 0.587$, Fig. 2*A*) and OS (R[un] versus R0, adjusted $p = 0.467$; R1/2 versus R0, adjusted $p = 0.765$; R[un] versus R1/2, adjusted $p = 0.429$, Fig. 2*B*) of this subset of patients. Similarly, survival analysis also revealed no prognostic impact of the UICC system for RFS (Supplementary Fig. 2*A*) and OS (Supplementary Fig. 2*B*) in patients with pN0.

For patients with pN1 (n = 125), the relationship of R status between IASLC and UICC was listed in Supplementary Table 4. A total of 2 of 114 patients (1.7%) with UICC R0 were reclassified to R(un) because of inadequate nodal dissection. There were 14 patients (12.3%) who were reassigned from R0 to R1 because of ECE; 3 of 11 patients (27.3%) with R1 were reclassified from R1 to R(un) owing to CIS at BRM. Regarding the IASLC R descriptors, survival analysis revealed that significant differences existed between R1/2 and R0 (5-y RFS 28.1% versus 50.0%, adjusted $p = 0.009$, Fig. 3*A*; 5-y OS 39.9% versus 60.1%, adjusted $p = 0.025$, Fig. 3*B*), but there were no significant differences between R(un) and R0 (5-y RFS 53.3% versus 50.0%, adjusted $p = 0.490$, Fig. 3*A*; 5-y OS 50.0% versus 60.1%, adjusted $p = 0.180$, Fig. 3*B*), R(un) and R1/2 (5-y RFS 53.3% versus 28.1%, adjusted $p = 0.673$, Fig. 3*A*; 5-y OS 50.0% versus 39.9%, adjusted $p = 0.770$, Fig. 3*B*). In addition, survival analysis revealed no significant differences between UICC R1 and R0 for RFS (Supplementary Fig. 3*A*) and OS (Supplementary Fig. 3*B*).

For patients with pN2 (n = 157), the relationship of R status between UICC and IASLC was listed in Supplementary Table 5. A total of 86 of 147 patients (58.5%) with R0 were reclassified as R(un); among them, four patients (4.7%) were reassigned because of inadequate nodal dissection, and 82 patients (95.3%) were reclassified owing to the positive highest mediastinal lymph node. There were three of nine patients (33.3%) with R1 were reclassified to R(un) because of CIS at BRM. As for the IASLC R status, survival analysis revealed that significant differences existed between R(un) and R0 (5-y RFS 29.1% versus 59.1%, adjusted $p = 0.010$, Fig. 4*A*; 5-y OS 43.5% versus 56.6%, adjusted $p = 0.010$, Fig. 4*B*), R1/2 and R0 (5-y RFS 20.8% versus 59.1%, adjusted $p = 0.002$, Fig. 4*A*; 5-y OS 38.3% versus 56.6%, adjusted $p = 0.036$, Fig. 4*B*), but there was no difference between R(un) and R1/2 (5-y RFS 29.1% versus 20.8%, adjusted $p = 0.360$, Fig. 4*A*; 5-y OS 43.5% versus 38.3%, adjusted $p = 0.698$, Fig. 4*B*). A trend for worse prognosis was observed for UICC R1 resection compared with R0 resection, but not statistically significant (Supplementary Fig. 4*A* and *B*).

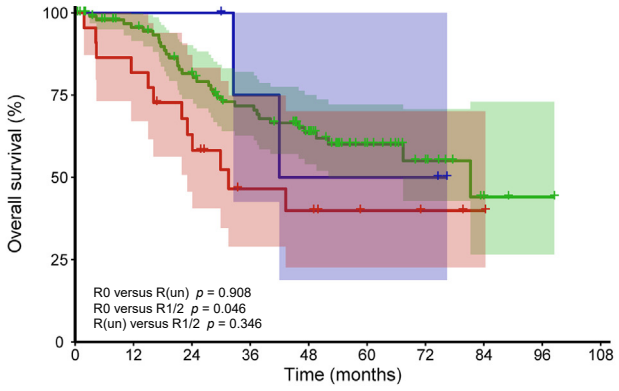


Number at risk

R0	98	70	57	43	34	17	10	3	1	0
R(un)	5	5	4	3	2	2	2	0	0	0
R1/2	22	12	9	6	5	2	1	1	0	0

A

Multivariable Cox analysis of RFS (adjusted for age, sex, smoking history, CCI, FEV1% of predicted, location, neoadjuvant therapy, approach, surgical technique, pathological T stage, histology and adjuvant chemotherapy)				
Comparison	HR	Adjusted *p* value	5-y RFS	Median RFS
R(un) versus R0	1.71	0.490	53.3% versus 50.0%	NA/48.0
R1/2 versus R0	2.40	0.009	28.1% versus 50.0%	15.6/48.0
R(un) versus R1/2	0.71	0.673	53.3% versus 28.1%	NA/15.6



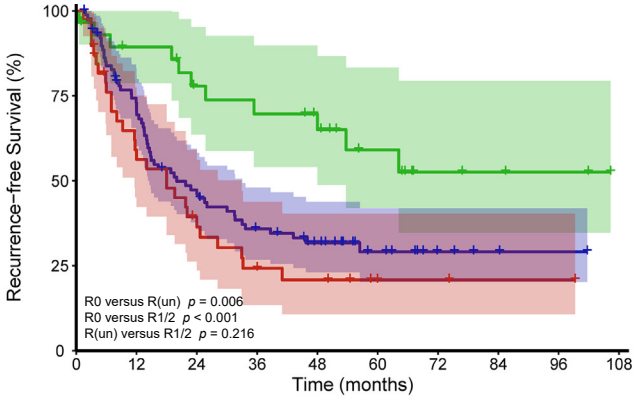
Number at risk

R0	98	84	69	56	41	19	10	3	1	0
R(un)	5	5	5	3	2	2	2	0	0	0
R1/2	22	18	13	7	6	3	2	1	0	0

B

Multivariable Cox analysis of OS (adjusted for age, sex, smoking history, CCI, FEV1% of predicted, location, neoadjuvant therapy, approach, surgical technique, pathological T stage, histology and adjuvant chemotherapy)				
Comparison	HR	Adjusted *p* value	5-y OS	Median OS
R(un) versus R0	2.94	0.180	50.0% versus 60.1%	42.0/81.3
R1/2 versus R0	2.30	0.025	39.9% versus 60.1%	31.5/81.3
R(un) versus R1/2	1.28	0.770	50.0% versus 39.9%	42.0/31.5

Figure 3. Survival analysis of RFS (*A*) and OS (*B*) regarding the IASLC R descriptors for patients with pN1. CCI, Charlson comorbidity index; FEV1, forced expiratory volume in 1 second; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; NA, not applicable; OS, overall survival; pN1, pathologic N1; R, residual tumor; R(un), uncertain resection; RFS, recurrence-free survival.

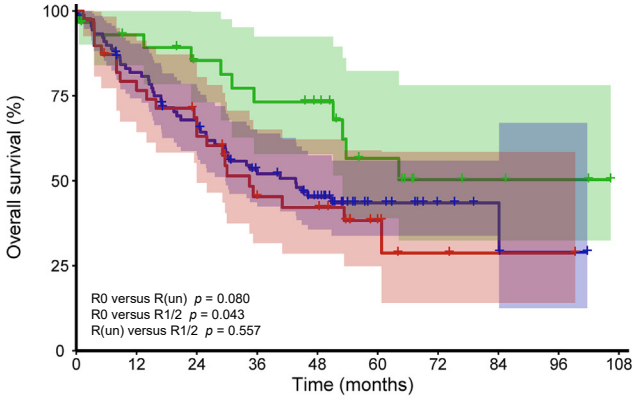


Number at risk

R0	29	24	19	17	15	9	4	3	2	0
R(un)	89	60	38	27	20	10	4	2	1	0
R1/2	39	21	13	8	6	2	2	1	1	0

A

Multivariable Cox analysis of RFS (adjusted for age, CCI, neoadjuvant therapy, pathological T stage and histology)				
Comparison	HR	Adjusted *p* value	5-y RFS	Median RFS
R(un) versus R0	2.44	0.010	29.1% versus 59.1%	20.0/NA
R1/2 versus R0	3.08	0.002	20.8% versus 59.1%	18.0/NA
R(un) versus R1/2	0.79	0.360	29.1% versus 20.8%	20.0/18.0



Number at risk

R0	29	25	21	18	16	9	4	3	2	0
R(un)	89	71	57	41	30	11	5	3	1	0
R1/2	39	30	25	15	13	5	2	1	1	0

B

Multivariable Cox analysis of OS (adjusted for age, CCI, neoadjuvant therapy, pathological T stage and adjuvant chemotherapy)				
Comparison	HR	Adjusted *p* value	5-y OS	Median OS
R(un) versus R0	2.46	0.010	43.5% versus 56.6%	43.7/NA
R1/2 versus R0	2.22	0.036	38.3% versus 56.6%	34.5/NA
R(un) versus R1/2	1.11	0.698	43.5% versus 38.3%	43.7/34.5

Figure 4. Survival analysis of RFS (*A*) and OS (*B*) regarding the IASLC R descriptors for patients with pN2. CCI, Charlson comorbidity index; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; NA, not applicable; OS, overall survival; pN2, pathologic N2; R, residual tumor; R(un), uncertain resection; RFS, recurrence-free survival.

Discussion

In the current study, we validated the prognostic discriminatory ability of the R descriptors proposed by IASLC for patients with NSCLC after sleeve lobectomy.

The results from our study suggested that the prognostic impact of the R descriptors varied within pN stages for NSCLC after sleeve lobectomy.

In our study, 15.2% of patients with UICC R0 were reassigned to R(un) mainly because of the positive highest mediastinal node station (85.4%), followed by the inadequacy of nodal dissection (14.6%). In contrast, more than half of the patients (56.0%–63.8%) with UICC R0 were reclassified to R(un), and failure to attain dissection criteria accounts for the main reason (95.7%–98.0%).[12,13] It may be attributed to the differences in the study populations. These studies focused on the overall cohorts of surgically resected NSCLC, with stage I and peripheral adenocarcinomas accounting for most patients. Whereas patients who underwent sleeve lobectomy had mostly locally advanced and centrally-located squamous carcinomas. Surgeons may strictly adhere to the requirements of SND to ensure the accuracy of the pN stage during a sleeve lobectomy, which accounts for the rarity of R(un) because of incomplete nodal dissection.

Notably, 7.3% of patients (46 of 631) with UICC R0 were reclassified as R1/2 because of ECE. Specifically, 12.3% (14 of 114) of patients with pN1 and 21.8% (32 of 114) of patients with pN2 were reclassified from UICC R0 to IASLC R1/2. Yun et al.[14] reported that patients reassigned from having a UICC R0 to IASLC R1/2 owing to ECE had a marginally better prognosis than those with UICC R1/2 status as the prognosis of patients with R0 and R(un) are much favorable than R1/2, it seems reasonable to classify ECE from UICC R0 to IASLC R1/2. Previous evidence has also confirmed ECE as a risk factor for poor prognosis.[5,6,21] In our subgroup analysis regarding pN1, the prognosis of patients having IASLC R1/2 was worse than those with R0 and R(un); the joint influence of positive margin and ECE may cause this.

Compared with the UICC R criteria, the IASLC R descriptors are more comprehensive and consider several variables affecting the quality of surgical procedures, emphasizing the thorough intraoperative evaluation of nodal status. With only considering the effect of margin status (UICC criteria) on postoperative prognosis for patients with NSCLC after sleeve lobectomy, our results were similar but not identical to the study of Hong et al.[22] UICC R1 resection occurred in 7.0% of all patients in our study, similar to the 7.5% reported by Hong et al.[22] In the meantime, CIS at BRM accounts for 29.2% of all UICC R1 resection in our study, close to 30.0% reported by Hong et al.[22] No significant differences were observed between UICC R1 and UICC R0 resection in our study, consistent with the results of Hong et al.[22] Ending a sleeve lobectomy with R1 resection may be a viable option when adequate nodal dissection and proper adjuvant therapy are performed.

For the entire cohort, the IASLC R descriptors were independent predictors of long-term survival (OS not statistically significant) after adjusting for covariates such as age, pT stage, pN stage, histology subtype, and adjuvant therapy. The TNM staging system remains the most powerful prognostic factor for the whole cohort. It is potentially owing to the fact that most (74.5%, 82 of 110) patients with R(un) were reclassified because of the positive highest mediastinal nodes station (pN2 patients). In addition, most (55.4%, 46 of 83) patients with R1/2 were reassigned owing to ECE (pN1 and pN2 patients). Therefore, combining the IASLC R status and the TNM staging system may better guide surgical decision-making and postoperative treatment for patients undergoing sleeve lobectomy. Meanwhile, better application of preoperative staging projects such as PET/CT and endobronchial ultrasound–guided transbronchial needle aspiration, and even proper use of intraoperative frozen section may all help thoracic surgeons to avoid inadequate resection during their surgeries.

Our study has some inevitable limitations. First, selection and statistical bias are inherent because of the retrospective nature, especially for lost follow-up information in our study cohort. Second, pleural lavage cytology and cytology of pleural or pericardial effusions were not routinely performed during the study period at our center, which would have helped better understand the impact of R descriptors among this surgical population. Third, although two experienced pathologists at our center reviewed all positive nodes to determine the status of ECE, some uncertainty occurred during the review process. Despite discussions to resolve this problem, bias still existed because the results may not represent real conditions.

In summary, our study revealed that the IASLC R descriptors could independently predict long-term survival for the entire cohort. Furthermore, subgroup analysis revealed that the IASLC R descriptors had prognostic significances in patients with pN1 and pN2 but not in those with pN0.

CRediT Authorship Contribution Statement

Tao Chen: Conceptualization, Data curation, Formal analysis, Writing original draft.

Yifan Zhong: Investigation, Methodology, Writing original draft.

Jialiang Wen: Investigation, Methodology, Software.

Jiajun Deng: Methodology, Supervision, Writing-review & editing.

Yunlang She: Methodology, Supervision, Writing-review & editing.

Yuming Zhu: Data curation, Investigation, Resources.

Qiankun Chen: Methodology, Supervision, Writing-review & editing.

Chunyan Wu: Supervision, Resources, Writing-review & editing.

Likun Hou: Supervision, Resources, Writing-review & editing.

Lei Jiang: Supervision, Resources, Writing-review & editing.

Chang Chen: Supervision, Resources, Writing review & editing.

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Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100574.

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