Original Article

Residual tumor descriptors proposed by the International Association for the Study of Lung Cancer may not be applicable to stage I and ground-glass opacity-featured non-small cell lung cancer

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Background: The International Association for the Study of Lung Cancer (IASLC) has proposed a residual tumor descriptor, essential for subsequent treatments. This study aimed to validate the prognostic effect of the proposed R descriptor and restrict its scope of clinical application in a large-scale cohort with non-small cell lung cancer (NSCLC).

Methods: Patients, who underwent lobectomy from January 2010 to May 2019, were retrospectively reviewed. Patients were categorized according to the different R classification standards proposed by Union for International Cancer Control (UICC) and IASLC.

Results: Among 5,200 enrolled patients with NSCLC, 1,727 and 9 cases of UICC-R0 were re-evaluated as uncertain resection [R(un)] and R1, respectively. After reclassification, there were 3,228 (62.1%) cases of R0, 1,727 (33.2%) cases of R(un), 151 (2.9%) cases of R1, and 94 (1.8%) cases of R2. Not performing rigorous systematic nodal dissection (SND) or lobe-specific SND (68.3%) was the main reason for the alteration from R0 to R(un). Patients with R(un) showed intermediate survival between those with R0 and R1. Further multivariable Cox analysis indicated that the proposed R descriptor was an independent prognostic factor for overall survival (OS) and recurrence-free survival (RFS). However, subgroup analysis of OS and RFS revealed that there was no significant difference between R0 and R(un) in patients with ground-glass opacity (GGO) or patients with tumor-node-metastasis stage I.

Conclusions: R(un) represented an intermediate type between R0 and R1. Our study provided an external validation for new residual tumor descriptors for NSCLC proposed by IASLC. Proposed residual tumor descriptors were applicable in radiologic solid NSCLC and stage II–III NSCLC, but were ineffective for GGO-featured or stage I NSCLC.

Keywords: Lung cancer staging; R descriptors; resection margin; systematic nodal dissection (SND)

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Introduction

Background

Surgical resection remains a crucial part of the treatments for most malignancies, and the completeness of surgical resection is an important variable in evaluating the therapeutic effect. In 1987, the Union for International Cancer Control (UICC) proposed the R classification: R0 (no residual tumor), R1 (microscopic tumor residual), and R2 (macroscopic tumor residual) (1). However, the clinical scenarios might be so complex that the above classification system could miss some important information. Therefore, the R classification was revised by the International Association for the Study of Lung Cancer (IASLC) in 2005 (2).

Rationale and knowledge gap

Previous studies have reported the prognostic effect of R classification from IASLC (3-7). Nevertheless, these studies did not include radiologic appearance, which is an emerging prognostic factor in lung cancer (8,9). In addition, most studies lack sub-group analyses to investigate the prognostic role of R classification. Thus, it is necessary to conduct a study in a large-scale cohort involving radiologic appearance and restrict its scope of clinical application.

Highlight box

Key findings

- Residual tumor descriptors proposed by the International Association for the Study of Lung Cancer (IASLC) may not be applicable to stage I and ground-glass opacity (GGO)-featured NSCLC.

What is known and what is new?

- Many studies have validated the prognostic value of the R descriptors proposed by IASLC.
- However, GGO was recently considered to be a special clinical subtype with excellent survival when compared to solid nodules, which was not considered or studied as a special subgroup in IASLC R proposal and subsequent validation study of proposed R descriptors.

What is the implication, and what should change now?

- Our study provided an external validation for new residual tumor descriptors for NSCLC proposed by IASLC. Proposed residual tumor descriptors were applicable in radiologic solid NSCLC and stage II–III NSCLC, but were ineffective for GGO-featured or stage I NSCLC.

Objective

This study verified the prognostic role of the uncertain resection [R(un)] classification proposed by IASLC and specified its scope of clinical application, which shed light on the stratification and treatments for patients with non-small cell lung cancer (NSCLC). We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-497/rc).

Methods

Patient cohort

The study was conducted by searching patients who underwent surgical resection from January 2010 to May 2019 in the Department of Thoracic Surgery, Fudan University Shanghai Cancer Center. Only patients with NSCLC were finally enrolled. Patients with the diagnoses of adenocarcinoma in situ (AIS)/minimally invasive adenocarcinoma (MIA) or receiving sublobar resection were excluded.

Ethics statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Institutional Review Board of Fudan University Shanghai Cancer Center (2008223-9). Due to the retrospective nature of this study, informed consent was waived.

Radiological and pathological evaluation

Thin-section computed tomography (CT) scans were reviewed by two senior radiologists to distinguish between the ground-glass opacity (GGO) groups (patients with GGO) and solid groups (patients with solid nodule) independently. Mostly solid with a small peripheral GGO component was classified as GGO group. GGO was defined as a nonspecific radiologic finding showing a hazy opacity without blocking underlying pulmonary vessels or bronchial structures, according to the Fleischner Society (10). For the cases with different opinions from radiologists, the agreement was reached through discussion. Intraobserver and interobserver agreements were reported in our previous studies (9,11). Postoperative pathologic

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reviews including diagnosis and staging were based on the IASLC/American Thoracic Society/European Respiratory Society classification and 8th tumor-node-metastasis (TNM) classification (12,13).

Re-classification of residual tumors descriptors

Residual tumor classification (R descriptors) was based on the 2005 IASLC proposal (2). Complete resection (R0 resection) was defined as follows: (I) the resection margin is negative under the microscope; (II) systematic nodal dissection (SND) or lobe-specific SND (LSND) is performed; (III) the tumor does not invade the tissues around the lymph nodes (LNs), and lung specimens; and (IV) the highest LN resected is negative. Incomplete resection (microscopic residual R1 resection and macroscopic residual R2 resection) was defined as follows: (I) the tumor involves the resection margin; (II) the tumor has extracapsular invasion; (III) there are known positive LNs but have not been resected; and (IV) pleural effusion cytology is negative. R(un) (resection) was defined as those with no tumor involvement at the resection margin under the microscope, but one of the following conditions: (I) there is no extensive SND or LSND; (II) the highest LN resected is positive; (III) the bronchial resection margin shows carcinoma in situ (CIS); and (IV) pleural lavage fluid is positive.

LN dissection

In our study, LN stations 10–14 were considered as N1, whereas stations 2–9 as N2 (14,15). LSND was performed according to tumor locations: (I) right upper and right middle lobes: LN stations of 2R, 4R, and 7; (II) right lower lobe: LN stations of 4R, 7, 8, and 9; (III) upper left lobe: LN stations of 5, 6, and 7; and (IV) lower left lobe: LN stations of 7, 8, and 9. In addition, at least three dissected LNs were required for both the N1 station and N2 station (16).

Follow-up strategy for patients

The follow-up protocol was made according to guidelines (17). The postoperative follow-up of the patient started from the completion of the operation, including chest CT scans, ultrasonography of abdominal and cervical/supraclavicular regions, head magnetic resonance imaging (MRI)/CT, and bone scans. Overall survival (OS) was defined as the interval from surgery to death from any cause. Recurrence-free survival (RFS) was defined as the time between surgery and recurrence of lung cancer or death. The sites of first recurrence were classified as "thorax", "abdomen", "neck", "brain", and "bone" according to the follow-up protocols.

Statistical analysis

The statistical analysis of this study was performed in R software (version 4.0.3, R Foundation, Vienna, Austria). Survival analysis was conducted using the "survival" and "surviminer" packages in the R software, and the visualization was performed using the "ggplot2" package (18). Two categoric variables' correlations were analyzed using Fisher exact test or Pearson's chi-squared test. For the comparison of continuous variables between the two groups, the student's *t*-test was used. Kaplan-Meier plots were used for survival analysis (19), and the log-rank test was used to explore the differences between groups in univariate analysis. Multivariate Cox regression models were used to identify independent prognostic factors. Variables with a P value less than 0.1 in univariable analysis were used in the multivariable survival analysis. All tests were two-tailed and $P<0.05$ was defined as statistical significance.

Results

Patient characteristics

A total of 5,200 patients were included in our study (*Figure 1*). Average follow-up time was 40.1 months. The clinicopathological characteristics are shown in *Table 1* and Table S1. Solid nodules were found in 3,591 patients (69.1%), and the majority of this cohort had adenocarcinoma (75.6%). Stage I, stage II, and stage III disease accounted for 60.1%, 14.8%, and 25.1%, respectively (*Table 1*). Forty-five cases of other type of lung cancer included 28 adenosquamous carcinomas and 17 large cell carcinomas. There were significant differences in sex, age, smoking status, pathology types, pathological T (pT) stage, pathological N stage, number of resected LN, pathological TNM (pTNM) stage, and proposed R descriptors between GGO and solid nodule groups ($P<0.001$) (Table S1).

According to criteria released by UICC, 4,964 cases (95.5%) had R0 resection, 142 cases (2.7%) had R1 resection, and 94 cases (1.8%) had R2 resection. Furthermore, survival analyses demonstrated that the R0 group had significantly longer OS and RFS than R1 (OS, $P<0.001$; RFS,

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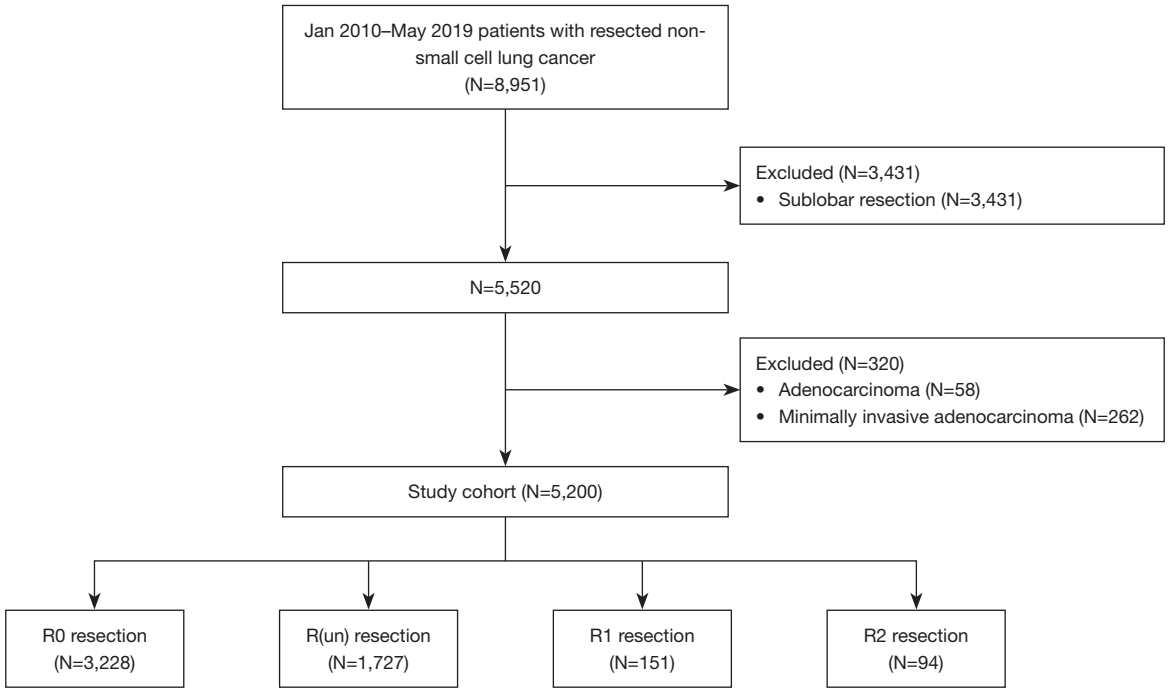

Figure 1 Flow diagram of the study cohort. R(un), uncertain resection.

1,380/4,964, P<0.001) (Figure S1).

Recategorization using R descriptors released by IASLC

After recategorization according to the R descriptors proposed by IASLC, 1,727 cases of R0 were recategorized as R(un), and 9 cases of R0 were recategorized as R1. As a result, there were 3,228 cases of R0 (62.1%), 1,727 cases of R(un) (33.2%), 151 (2.9%) cases of R1, and 94 (1.8%) cases of R2 using the new R descriptors. Details of recategorization were summarized (Table S2), and the main reasons for recategorization from R0 to R(un) were not performing SND/LSND (1,179 cases in total, 68.3%) and the positive highest LN (663 cases in total, 38.3%). Extracapsular invasion (9 cases, 100%) was the only reason for reclassification from R0 to R1. The details of LN dissection (Table S3) showed that N1 samples <3 & N2 samples <3, site-specific LNs not dissected, and neither standard met accounted for 50.2%, 24.9%, and 24.9% in 1,179 cases who were reclassified to R(un) due to not performing rigorous LSND/SND.

After recategorization according to the IASLC proposed R descriptors, patients were divided into R0, R(un), R1, and R2 groups. Compared with R0 groups and R1 groups, R(un) had superior OS to R1 (P<0.001) and inferior OS to R0 (P<0.001) (*Figure 2A*). Cox proportion hazard analyses demonstrated that R descriptor was an independent prognostic factor for OS in patients with NSCLC (Table S4). Similarly, R(un) had intermediate RFS, compared to R0 (P<0.001) and R1 (P<0.001) (*Figure 2B*). R descriptor also was an independent prognostic factor for RFS in patients with NSCLC (Table S5). The recurrence pattern between R0, R(un), R1, and R2 groups are shown in Table S6. First recurrence on thorax is the most frequent among all first recurrence sites in R0, R(un), R1, and R2 groups (57.8%, 48.4%, 58.3%, and 52.9%).

Subgroup analyses and survival analyses

To investigate the prognostic role of R descriptors proposed by IASLC in different groups that was utilized in daily practice, subgroup analyses were further performed (*Figure 3*). The prognostic effect of R descriptors manifested in most groups, except patients with GGO and stage I (*Figure 3*). Specifically, in patients with GGO, no statistical difference of OS and RFS between R0 and R(un) was observed [OS, hazard ratio (HR): 1.19, 95% confidential interval (CI): 0.78–1.81, log-rank P=0.4; RFS, HR: 1.19, 95% CI: 0.88–1.62, log-rank P=0.29] (*Figure 3* and Figure S2). As for stage I, patients with R(un) had similar OS to R0 patients (HR:

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Table 1 Clinical and pathological characteristics of 5,200 patients

Variables	All (n=5,200)	R0 (n=3,228)	R(un) (n=1,727)	R1 (n=151)	R2 (n=94)	P value
Sex						<0.001
Male	2,885 (55.5)	1,808 (56.0)	897 (51.9)	114 (75.5)	66 (55.5)	
Female	2,315 (44.5)	1,420 (44.0)	830 (48.1)	37 (24.5)	28 (44.5)	
Age						0.481
<60 years	2,478 (47.7)	1,519 (47.1)	842 (48.8)	68 (45.0)	49 (47.7)	
≥60 years	2,722 (52.3)	1,709 (52.9)	885 (51.2)	83 (55.0)	45 (52.3)	
Smoking						<0.001
Never	3,204 (61.6)	1,999 (61.9)	1093 (63.3)	64 (42.4)	48 (61.6)	
Former/current	1,996 (38.4)	1,229 (38.1)	634 (36.7)	87 (57.6)	46 (38.4)	
CT appearance						<0.001
GGO	1,609 (30.9)	1,052 (32.6)	531 (30.7)	17 (11.3)	9 (30.9)	
Solid	3,591 (69.1)	2,176 (67.4)	1,196 (69.3)	134 (88.7)	85 (69.1)	
Pathology types						<0.001
IAC	3,932 (75.6)	2,425 (75.1)	1,406 (81.4)	51 (33.8)	50 (75.6)	
SCC	1,223 (23.5)	771 (23.9)	311 (18)	99 (65.6)	42 (23.5)	
Others	45 (0.9)	32 (1.0)	10 (0.6)	1 (0.7)	2 (0.9)	
pT stage						<0.001
1a	377 (7.3)	234 (7.2)	134 (7.8)	6 (4.0)	3 (7.3)	
1b	1,637 (31.5)	1,072 (33.2)	530 (30.7)	23 (15.2)	12 (31.5)	
1c	1,147 (22.1)	738 (22.9)	367 (21.3)	32 (21.2)	10 (22.1)	
2a	1,052 (20.2)	605 (18.7)	380 (22.0)	44 (29.1)	23 (20.2)	
2b	379 (7.3)	216 (6.7)	129 (7.5)	24 (15.9)	10 (7.3)	
3	366 (7.0)	218 (6.8)	111 (6.4)	16 (10.6)	21 (7.0)	
4	242 (4.7)	145 (4.5)	76 (4.4)	6 (4.0)	15 (4.7)	
pN stage						<0.001
0	3,639 (70.0)	2,600 (80.5)	956 (55.4)	48 (31.8)	35 (70)	
1	487 (9.4)	366 (11.3)	73 (4.2)	30 (19.9)	18 (9.4)	
2	1,066 (20.5)	260 (8.1)	693 (40.1)	72 (47.7)	41 (20.5)	
3	8 (0.2)	2 (0.1)	5 (0.3)	1 (0.7)	0 (0.2)	
Number of LN resected	18.0±32.3	20.3±40.2	13.7±9.0	18.0±8.2	18.2±9.0	<0.001
pTNM stage						<0.001
Stage I	3,127 (60.1)	2,215 (68.6)	856 (49.6)	36 (23.8)	20 (60.1)	
Stage II	769 (14.8)	588 (18.2)	123 (7.1)	37 (24.5)	21 (14.8)	
Stage III	1,304 (25.1)	425 (13.2)	748 (43.3)	78 (51.7)	53 (25.1)	

Data are presented as n (%) or mean ± SD. R(un), uncertain resection; CT, computed tomography; GGO, ground-glass opacity; IAC, invasive adenocarcinoma; SCC, squamous cell carcinoma; pT, pathological tumor; pN pathological node; LN, lymph node; pTNM, pathological tumor-node-metastasis; SD, standard deviation.

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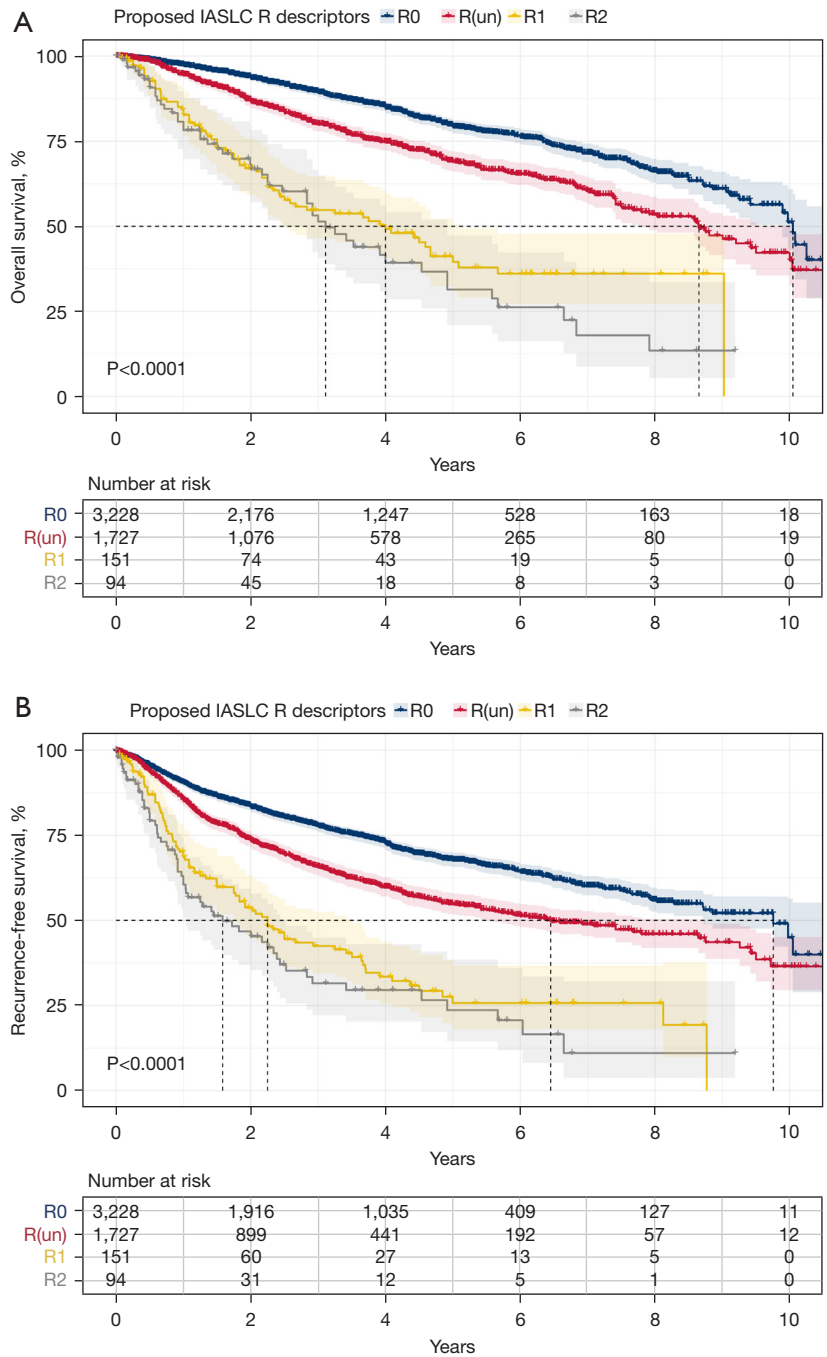

Figure 2 OS and RFS of IASLC R descriptors: (A) comparisons of OS between IASLC R0, R(un), R1, and R2; (B) comparisons of RFS between IASLC R0, R(un), R1, and R2. The 95% CIs are shown as shaded areas. IASLC, the International Association for the Study of Lung Cancer; R(un), uncertain resection; OS, overall survival; RFS, recurrence-free survival; CI, confidential interval.

0.88, 95% CI: 0.68–1.14, log-rank P=0.34) (*Figure 3* and Figure S3A). Surprisingly, patients with R(un) had better RFS than those with R0 (HR: 0.81, 95% CI: 0.61–0.98, log-rank P=0.024) (*Figure 3* and Figure S3B). Number of events for OS and RFS is shown in *Figure 3*. Specially, in stage I radiographical solid adenocarcinoma, patients with

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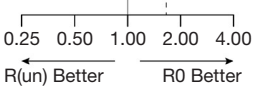
A

Subgroup analysis of overall survival

Subgroup	Patients	R(un)	R0	Hazard ratio (95% CI)
	no. (%)	no. of events/total no. (%)		
All patients	4,955 (100.0)	406/1,727 (23.5)	489/3,228 (15.1)	1.66 (1.45–1.91)
Sex				
Male	2,705 (54.6)	258/897 (28.8)	340/1,808 (18.8)	1.66 (1.40–1.97)
Female	2,250 (45.4)	148/830 (17.8)	149/1,420 (10.5)	1.79 (1.42–2.28)
Age				
<60 years	2,361 (47.6)	182/842 (21.6)	183/1,519 (12.0)	1.89 (1.53–2.35)
≥60 years	2,594 (52.4)	224/885 (25.3)	306/1,709 (17.9)	1.54 (1.28–1.84)
Smoking				
Never	3,092 (62.4)	198/1,093 (18.1)	243/1,999 (12.2)	1.54 (1.27–1.87)
Former/current	1,863 (37.6)	208/634 (32.8)	246/1,229 (20.0)	1.85 (1.51–2.25)
CT appearance				
GGO	1,583 (31.9)	37/531 (7.0)	61/1,052 (5.8)	1.19 (0.78–1.81)
Solid nodule	3,372 (68.1)	369/1,196 (30.9)	428/2,176 (19.7)	1.74 (1.50–2.02)
Lobe				
Single lobe	4,058 (81.9)	332/1,373 (24.2)	415/2,685 (15.5)	1.67 (1.43–1.95)
≥2 lobes	897 (18.1)	74/354 (20.9)	74/543 (13.6)	1.60 (1.15–2.23)
Pathology				
Adenocarcinoma	3,831 (77.3)	292/1,406 (20.8)	311/2,425 (12.8)	1.73 (1.47–2.05)
Squamous	1,082 (21.8)	110/311 (35.4)	174/771 (22.6)	1.70 (1.31–2.20)
pTNM stage				
Stage I	3,071 (62.0)	71/856 (8.3)	214/2,215 (9.7)	0.88 (0.68–1.14)
Stage II/III	1,884 (38.0)	335/871 (38.5)	275/1,013 (27.1)	1.54 (1.32–1.81)



B

Subgroup analysis of recurrence-free survival

Subgroup	Patients	R(un)	R0	Hazard ratio (95% CI)
	no. (%)	no. of events/total no. (%)		
All patients	4,955 (100.0)	588/1,727 (34.0)	786/3,228 (24.3)	1.55 (1.38–1.73)
Sex				
Male	2,705 (54.6)	356/897 (39.7)	507/1,808 (28.0)	1.62 (1.40–1.87)
Female	2,250 (45.4)	232/830 (28.0)	279/1,420 (19.6)	1.53 (1.28–1.84)
Age				
<60 years	2,361 (47.6)	282/842 (33.5)	335/1,519 (22.1)	1.70 (1.44–2.01)
≥60 years	2,594 (52.4)	306/885 (34.6)	451/1,709 (26.4)	1.44 (1.24–1.68)
Smoking				
Never	3,092 (62.4)	315/1,093 (28.8)	418/1,999 (20.9)	1.49 (1.27–1.73)
Former/current	1,863 (37.6)	273/634 (43.1)	368/1,229 (29.9)	1.68 (1.42–1.99)
CT appearance				
GGO	1,583 (31.9)	68/531 (12.8)	119/1,052 (11.3)	1.19 (0.88–1.62)
Solid nodule	3,372 (68.1)	520/1,196 (43.5)	667/2,176 (30.7)	1.63 (1.44–1.84)
Lobe				
Single lobe	4,058 (81.9)	468/1,373 (34.1)	668/2,685 (24.9)	1.53 (1.35–1.73)
≥2 lobes	897 (18.1)	120/354 (33.9)	118/543 (21.7)	1.65 (1.27–2.15)
Pathology				
Adenocarcinoma	3,831 (77.3)	447/1,406 (31.8)	549/2,425 (22.6)	1.56 (1.34–1.78)
Squamous	1,082 (21.8)	137/311 (44.1)	231/771 (30.0)	1.66 (1.22–2.09)
pTNM stage				
Stage I	3,071 (62.0)	122/856 (14.3)	400/2,215 (18.1)	0.81 (0.61–0.98)
Stage II/III	1,884 (38.0)	466/871 (53.5)	386/1,013 (38.1)	1.58 (1.38–1.81)

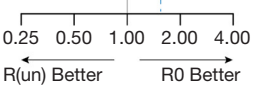


Figure 3 Subgroup analysis of survival between R0 patients and R(un) patients. (A) OS; (B) RFS. R(un), uncertain resection; CI, confidential interval; CT, computed tomography; GGO, ground-glass opacity; pTNM, pathological tumor-node-metastasis; OS, overall survival; RFS, recurrence-free survival.

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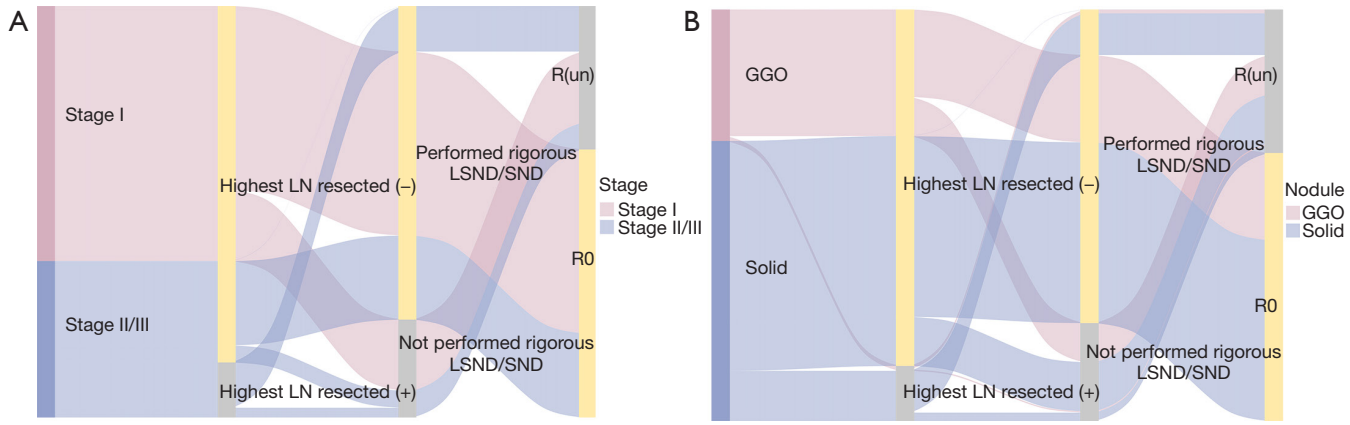

Figure 4 Alluvial diagram of the relationship (A) between TNM stage and proposed R descriptors; (B) between GGO/solid nodule and proposed R descriptors. Pink and blue bands, passing through yellow and grey rectangles, were reclassified into R(un) and R0 groups. LN, lymph node; LSND, lobe-specific systematic nodal dissection; SND, systematic nodal dissection; GGO, ground-glass opacity; TNM, tumor-node-metastasis.

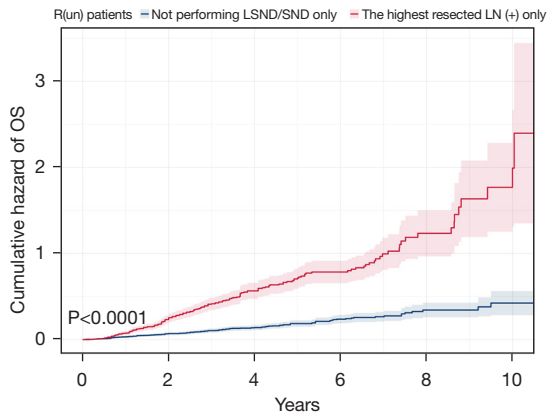

Figure 5 Comparison of cumulative hazard of OS between R(un) patients with the highest LN resected (+) only *vs.* R(un) patients with not performing rigorous LSND/SND only. The 95% CIs are shown as shaded areas. R(un), uncertain resection; LSND, lobe-specific systematic nodal dissection; SND, systematic nodal dissection; LN, lymph node; OS, overall survival; CI, confidential interval.

R(un) had similar OS to R0 patients (HR: 1.07, 95% CI: 0.75–1.53, P=0.7), while in stage II/III radiographical solid adenocarcinoma, patients with R(un) had worse OS to R0 patients (HR: 1.46, 95% CI: 1.18–1.80, P<0.001) (Figure S4).

To further look into the possible causes behind this phenomenon, we summarized the reasons for reclassification from R0 to R(un) in patients with stage I disease and GGO. Not performing rigorous LSND/SND was the only reason for the re-evaluation from R0 to R(un) in patients with stage I, while the main reason for the re-evaluation from R0 to R(un) in patients with stage II/III was the metastasis of highest LN resected positive [highest LN resected (+)] (*Figure 4A*). The situation was similar for patients stratified by GGO and solid nodule. Not performing rigorous LSND/SND resulted in the recategorization from R0 to R(un) in patients with GGO, whereas the highest LN resected (+) remained the main reason for recategorization in patients with solid nodules (*Figure 4B*). Next, we investigated the survival difference between patients not performing rigorous LSND/SND and patients with the highest LN resected (+). R(un) patients with the highest LN resected (+) had a worse OS than those without performing rigorous LSND/SND only (*Figure 5*).

In the different subgroups, multivariable analysis demonstrated the prognosis impact of performing rigorous LSND/SND and highest LN resected (+) (Tables S7,S8). In squamous cell carcinoma group and TNM stage II/III group, performing rigorous LSND/SND was an independent prognostic factor on OS. In all analyzed subgroups, highest LN resected (+) was an independent prognostic factor on OS.

Discussion

As a pan-cancer variable about the residual tumor, the R descriptors proposed by UICC might miss some important information for lung cancer, such as the status of LSND/SND and the metastasis of the highest LN resected.

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Therefore, in 2005, IASLC proposed a new category of R(un), integrating pathological results of the resection margin, completeness of LN dissection, tumor extracapsular invasion, and status of LN dissection (2). Our study carried out an external validation of proposed R descriptors with a sizable cohort. The main findings of this study included two points. One point was that the complete resection, R(un), and incomplete resection proposed by IASLC were associated with significant differences in survival, which was consistent with previous studies (3-6). The other point was that we firstly demonstrated that proposed residual tumor descriptors were ineffective in GGO-featured NSCLC.

For the R(un) classification advocated by IASLC had not been officially included in the 8th edition of the TNM staging of lung cancer, studies on the R(un) classification proposed by IASLC were sparse. Several previous studies validated the prognostic effect of R(un) (3-6) in OS. However, these studies lacked the information on RFS, and the prognostic effect of R(un) in RFS had not been validated. Some studies investigated incomplete resection as a whole without differentiating between R1 and R2 resection (3,5,6). Nevertheless, with the widespread use of thin-section CT scans, more GGOs were encountered and GGO was recently considered to be a special clinical subtype with excellent survival when compared to solid nodules (11), which was not considered or studied as a special subgroup in IASLC R proposal (2) and subsequent validation study of proposed R descriptors.

After the validation of proposed residual tumor descriptors in OS and RFS, we conducted a subgroup survival analysis to investigate the prognostic impact in various subgroups of NSCLC. The R descriptors proposed by IASLC was found to be applicable to NSCLC as a whole, and to the majority of various subsets of NSCLC, but was ineffective in GGO-featured NSCLC and stage I NSCLC.

The difference in the distribution of the reasons for recategorization, compared with solid nodule NSCLC and pTNM stage II/III NSCLC, may have contributed to the poor prognostic effect of proposed R descriptors in GGO-featured NSCLC and pTNM stage I NSCLC. The reclassification from R0 to R(un) in patients with pTNM stage I, was entirely due to not performing rigorous LSND/SND, whereas in patients with pTNM stage II/III, a large part of the reclassification from R0 to R(un) was due to resected highest LN (+). Compared with highest LN resected (+), not performing rigorous LSND/SND was found to have a smaller effect on survival, which may account for the similar OS between R0 and R(un) in patients with pTNM stage I. Similar findings were made by Edwards and his colleagues: in patients with pN0, OS between R(un) and R0 was nearly identical (4).

The similar reasons might lead to similar OS and RFS outcomes between R0 and R(un) in patients with GGO. For GGO-featured NSCLC, the incidence of LN involvement was relatively low. For GGO with consolidation tumor ratio (CTR) of less than 0.5, no LN metastasis was discovered (20), while only 15–34% of patients with CTR from 0.5 to 1 had LN involvement (20,21). Therefore, some surgeons might not choose to conduct rigorous LSND/SND for selected patients with GGO. Nevertheless, these who were considered to have better prognosis were classified as R(un) according to the IASLC R classification system. In addition, patients with GGO had favorable outcomes, which covered the survival effect of R description.

In this study, we excluded the patients with AIS/MIA, because AIS/MIA was reported to have an excellent prognosis (22-24) and LN dissection was not routinely recommended. The main reasons for the recategorization to R(un) were not performing rigorous LSND/SND and positive status in the highest station of LN resected. In fact, there are two reasons why rigorous LSND/SND is not performed. The one reason is that the surgeons were planned to perform LSND/SND, but for some reason did not meet the criteria for rigorous LSND/SND (e.g., it was quite challenging for patients with an inherent LN number of less than three to meet the rigorous LSND/SND standard, even though the surgeons resected certain LN stations entirely). The other reason is that not performing LSND/SND is surgeons' choice based on the judgement of no LN metastases and a better prognosis in some patients. LN involvement was reported to be one of the most important prognostic factors on survival (25), performing rigorous LSND/SND had potential benefit. On the other hand, considering there was no consensus about the extent of LN dissection, the definition of R(un) needs to be altered in GGO-featured or pTNM stage I patients. According to the definition of TNM stage, R(un) patients with the highest LN resected (+), would be diagnosed as pN1+ or pTNM stage II/III/IV, which caused the difference in the distribution of R(un) between early-stage patients and advanced-stage patients, and may have an impact on the prognostic effect of proposed R descriptors as discussed above.

Therefore, more thought and consideration should be given to the application of proposed R descriptors in patients with GGO and pTNM stage I. As the clinical T

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descriptors in GGO-featured patients have been modified by the 8th edition of TNM classification, perhaps the definition of R(un) in GGO-featured patients should be changed (26). Performing rigorous SND/LSND, one of the criteria in R(un)'s definition may be modified or relaxed in patients with GGO, because GGO is a significantly different type compared with solid nodules, and GGO was not widely encountered or studied during the period when the concept of R(un) was proposed. These findings reflected the limitation of residual tumor descriptors proposed by IASLC in GGO-featured NSCLC and stage I NSCLC and the necessity of careful application of proposed R descriptors.

There were several limitations in our research. Firstly, pleural lavage cytology is not an established practice in our institution, our data in this study did not include the results of pleural lavage cytology, which may lead to the inadequacy of this study. Secondly, our study was retrospective and was based on a single center. Thirdly, positron emission tomography (PET)/CT was only performed in a small proportion, for PET/CT was not covered in Chinese medical insurance. It would be more meaningful to include PET/CT results in further studies. Fourthly, the number of patients in the R1 and R2 groups was relatively small compared to the R0 and R(un) groups, thus affecting the results of the comparison. At last, follow-up information after 4 to 6 years become really limited and therefore there is still uncertainty around impact on long-term outcome. We are looking forward to a multi-center study to validate our results.

Conclusions

In conclusion, R(un) represented an intermediate type between R0 and R1. Our study provided an external validation for new residual tumor descriptors for NSCLC proposed by IASLC. Proposed residual tumor descriptors was applicable in radiologic solid and stage II–III NSCLC, but was ineffective in GGO-featured NSCLC and stage I NSCLC.

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Footnote

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-23-497/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by Institutional Review Board of Fudan University Shanghai Cancer Center (2008223-9). Due to the retrospective nature of this study, informed consent was waived.

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Supplementary

Table S1 Clinical and pathological characteristics in patients with GGO and solid nodules

Variables	All (n=5,200)	GGO (n=1,609)	Solid nodules (n=3,591)	P value
Sex				<0.001
Male	2,885 (55.5)	611 (38.0)	2,274 (63.3)	
Female	2,315 (44.5)	998 (62.0)	1,317 (36.7)	
Age				<0.001
<60 years	2,478 (47.7)	809 (50.3)	1,669 (46.5)	
≥60 years	2,722 (52.3)	800 (49.7)	1,922 (53.5)	
Smoking				<0.001
Never	3,204 (61.6)	1,281 (79.6)	1,923 (53.6)	
Former/current	1,996 (38.4)	328 (20.4)	1,668 (46.4)	
Pathology types				<0.001
IAC	3,932 (75.6)	1,543 (95.9)	2,389 (66.5)	
SCC	1,223 (23.5)	56 (3.5)	1,167 (32.5)	
Others	45 (0.9)	10 (0.6)	35 (1.0)	
pT stage				<0.001
1a	377 (7.3)	222 (13.8)	155 (4.3)	
1b	1,637 (31.5)	841 (52.3)	795 (22.1)	
1c	1,147 (22.1)	274 (17.0)	872 (24.3)	
2a	1,052 (20.2)	161 (10.0)	891 (24.8)	
2b	379 (7.3)	30 (1.9)	349 (9.7)	
3	366 (7.0)	39 (2.4)	327 (9.1)	
4	242 (4.7)	41 (2.5)	201 (5.6)	
pN stage				<0.001
0	3,639 (70.0)	1,463 (90.9)	2,176 (60.6)	
1	487 (9.4)	52 (3.2)	435 (12.1)	
2	1,066 (20.5)	93 (5.8)	93 (2.6)	
3	8 (0.2)	1 (0.1)	7 (0.2)	
Number of LN resected	18.0±32.3	14.7±26.5	19.5±34.5	<0.001
pTNM stage				<0.001
Stage I	3,127 (60.1)	1,379 (85.7)	1,748 (48.7)	
Stage II	769 (14.8)	96 (6.0)	673 (18.7)	
Stage III	1,304 (25.1)	134 (8.3)	134 (3.7)	
R descriptors				<0.001
R0	3,228 (62.1)	1,052 (65.4)	2,176 (60.6)	
R(un)	1,727 (33.2)	531 (33.0)	1,196 (33.3)	
R1	151 (2.9)	17 (1.1)	134 (3.7)	
R2	94 (1.8)	9 (0.6)	85 (2.4)	

GGO, ground-glass opacity; IAC, invasive adenocarcinoma; SCC, squamous cell carcinoma; pT, pathological tumor; pN pathological node; LN, lymph node; pTNM, pathological tumor-node-metastasis.

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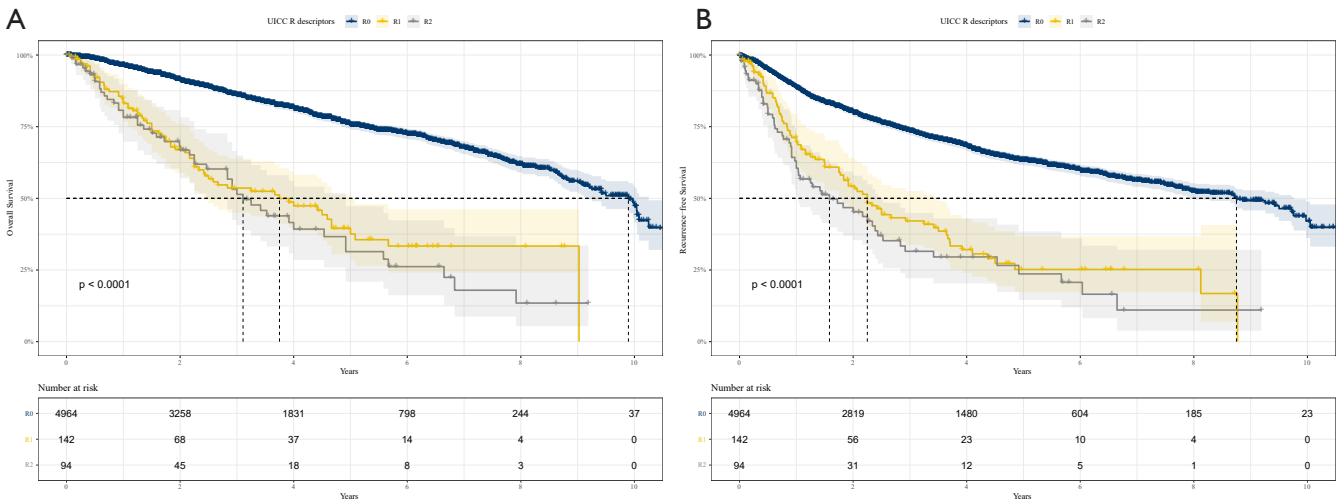

Figure S1 OS and RFS of UICC R descriptors: (A) comparisons of OS between UICC R0, R1, and R2; (B) comparisons of RFS between UICC R0, R1, and R2. The 95% CIs are shown as shaded areas. UICC, Union for International Cancer Control; OS, overall survival; RFS, recurrence-free survival; CI, confidential interval.

Table S2 Reasons for recategorization

R0 → R(un)	Value (n=1,727)
Summary	
Rigorous LSND/SND not performed	1,179 (68.3)
The highest LN resected (+)	663 (38.3)
CIS at margin	3 (0.2)
Details	
Rigorous LSND/SND not performed only	1,061 (61.4)
The highest LN resected (+) only	546 (31.6)
CIS at margin only	2 (0.1)
Rigorous LSND/SND not performed & highest LN resected (+)	117 (6.8)
Rigorous LSND/SND not performed & CIS at margin	1 (0.1)

Values are presented as n (%). R(un), uncertain resection; LSND, lobe-specific nodal dissection; SND, systematic nodal dissection; LN, lymph node; CIS, carcinoma in situ.

Table S3 Details of LSND/SND

Not performing rigorous LSND/SND	Value (n=1,179)
N1 samples <3 & N2 samples <3	592 (50.2)
Site-specific LNs not dissected	293 (24.9)
Neither standard met	294 (24.9)

Values are presented as n (%). LSND, lobe-specific nodal dissection; SND, systematic nodal dissection; LN, lymph node.

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Table S4 Univariable and multivariable analysis of OS

Variables	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Gender (female *vs.* male)	0.564	0.494–0.643	<0.001	0.743	0.622–0.887	0.001
Age (≥60 *vs.* <60 years)	1.428	1.260–1.618	<0.001	1.424	1.256–1.615	<0.001
Smoking history (current/former *vs.* never)	1.749	1.546–1.978	<0.001	1.031	0.875–1.215	0.717
CT appearance (solid nodules *vs.* GGO)	3.873	3.167–4.737	<0.001	2.182	1.761–2.705	<0.001
Pathological types						
SCC *vs.* IAC	1.813	1.594–2.064	<0.001	0.981	0.845–1.138	0.801
Others *vs.* IAC	1.940	1.039–3.624	0.038	1.085	0.579–2.032	0.799
pTNM stage (stage II/III *vs.* stage I)	4.195	3.668–4.798	<0.001	2.954	2.554–3.417	<0.001
Proposed R descriptors						
R(un) *vs.* R0	1.661	1.456–1.895	<0.001	1.400	1.223–1.603	<0.001
R1 *vs.* R0	4.123	3.209–5.297	<0.001	2.608	2.019–3.368	<0.001
R2 *vs.* R0	5.164	3.849–6.929	<0.001	3.483	2.587–4.690	<0.001

OS, overall survival; HR, hazard ratio; CI, confidence interval; CT, computed tomography; GGO, ground-glass opacity; SCC, squamous cell carcinoma; IAC, invasive adenocarcinoma; pTNM, pathological tumor-node-metastasis; R(un), uncertain resection.

Table S5 Univariable and multivariable analysis of RFS

Variables	Univariable			Multivariable		
	HR	95% CI	P	HR	95% CI	P
Gender (female *vs.* male)	0.658	0.592–0.730	<0.001	0.801	0.695–0.923	0.002
Age (≥60 *vs.* <60 years)	1.166	1.054–1.290	0.003	1.139	1.029–1.260	0.012
Smoking history (current/former *vs.* never)	1.570	1.419–1.736	<0.001	1.030	0.899–1.180	0.668
CT appearance (solid nodules *vs.* GGO)	3.384	2.917–3.927	<0.001	2.263	1.930–2.654	<0.001
Pathological types						
SCC *vs.* IAC	1.420	1.272–1.586	<0.001	0.758	0.667–0.862	<0.001
Others *vs.* IAC	1.287	0.728–2.273	0.385	0.681	0.384–1.206	0.188
pTNM stage (stage II/III *vs.* stage I)	3.597	3.238–3.995	<0.001	2.690	2.398–3.019	<0.001
Proposed R descriptors						
R(un) *vs.* R0	1.538	1.382–1.712	<0.001	1.285	1.151–1.434	<0.001
R1 *vs.* R0	3.229	2.587–4.030	<0.001	2.158	1.720–2.707	<0.001
R2 *vs.* R0	4.151	3.178–5.422	<0.001	2.647	2.021–3.468	<0.001

RFS, recurrence-free survival; HR, hazard ratio; CI, confidence interval; CT, computed tomography; GGO, ground-glass opacity; SCC, squamous cell carcinoma; IAC, invasive adenocarcinoma; pTNM, pathological tumor-node-metastasis; R(un), uncertain resection.

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Table S6 The recurrence pattern between R0, R(un), R1, and R2 groups

Variables	All (n=5,200)	R0 (n=3,228)	R(un) (n=1,727)	R1 (n=151)	R2 (n=94)
Any sites	1,123	595	446	48	34
Thorax	606	344	216	28	18
Neck	44	20	22	1	1
Abdomen	71	35	27	6	3
Bone	204	90	97	9	8
Brain	198	106	84	4	4

R(un), uncertain resection.

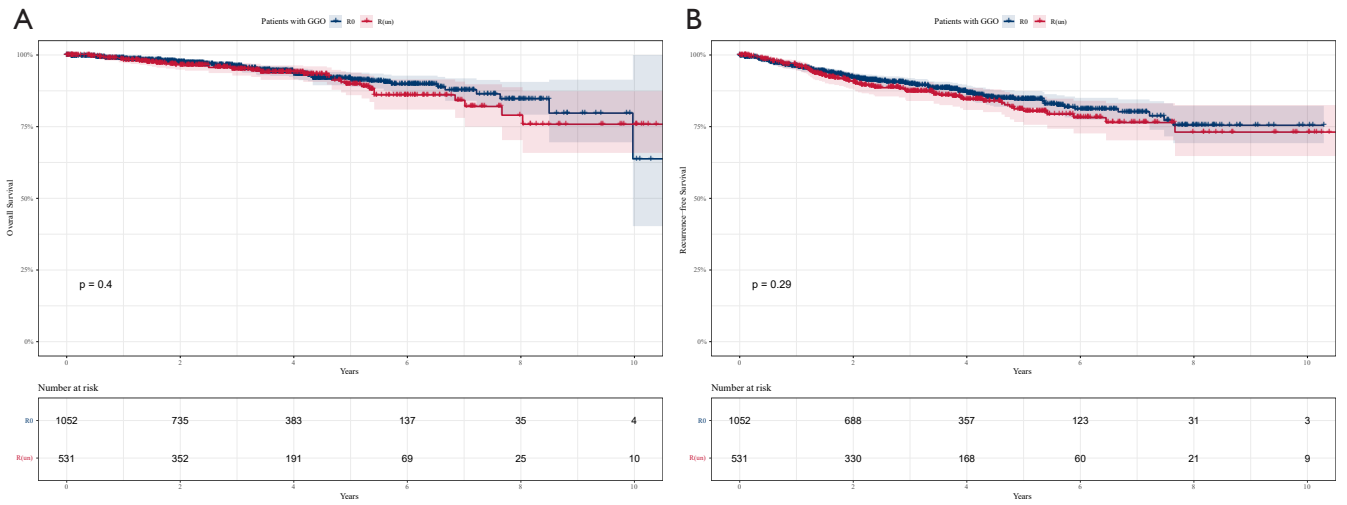

Figure S2 Comparisons of survival in patients with GGO. (A) OS; (B) RFS. The 95% CIs are shown as shaded areas. R(un), uncertain resection; GGO, ground-glass opacity; R(un), uncertain resection; OS, overall survival; RFS, recurrence-free survival; CI, confidential interval.

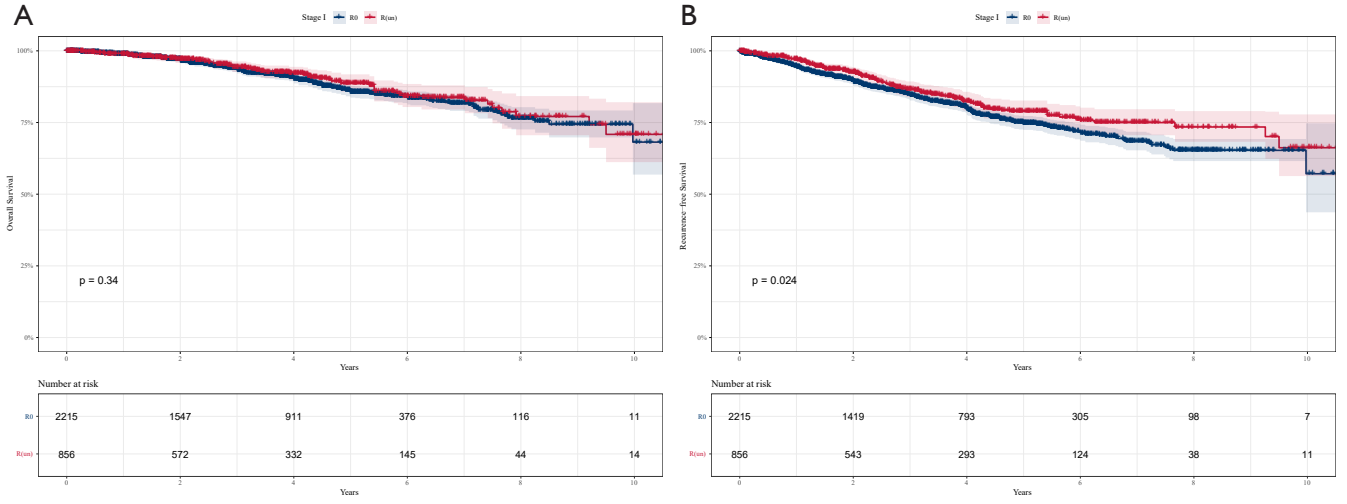

Figure S3 Comparisons of survival in patients with TNM stage I. (A) OS; (B) RFS. The 95% CIs are shown as shaded areas. R(un), uncertain resection; TNM, tumor-node-metastasis; OS, overall survival; RFS, recurrence-free survival; CI, confidential interval.

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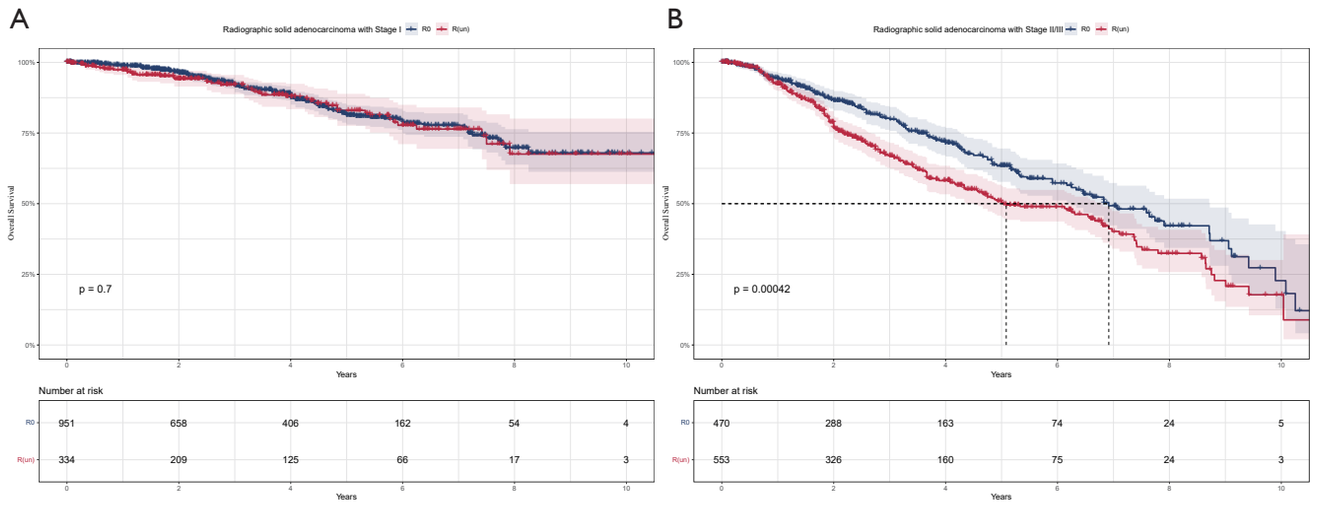

Figure S4 Comparisons of survival in radiographic solid adenocarcinoma patients with TNM stage I and with TNM stage II/III. The 95% CIs are shown as shaded areas. R(un), uncertain resection; TNM, tumor-node-metastasis; CI, confidential interval.

Table S7 HR, 95% CI, and P value of performing rigorous LSND/SND on multivariable analysis in different subgroups

Different subgroups	Multivariable analysis of OS		
	HR	95% CI	P
CT appearance			
GGO	NR	NR	NR
Solid	NR	NR	NR
Pathology types			
IAC	1.138	0.941–1.376	0.182
SCC	1.290	1.014–1.641	0.038
pTNM stage			
I	N0	N0	N0
II/III	1.314	1.098–1.571	0.003

NR means not reaching the criteria of P value <0.1 in univariable analysis; N0 means highest LN resected (–). HR, hazard ratio; CI, confidence interval; LSND, lobe-specific systematic nodal dissection; SND, systematic nodal dissection; OS, overall survival; CT, chest tomography; GGO, ground-glass opacity; IAC, invasive adenocarcinoma; SCC, squamous cell carcinoma; pTNM, pathological tumor-node-metastasis; LN, lymph node.

Table S8 HR, 95% CI, and P value of highest LN resected (+) on multivariable analysis in different subgroups

Different subgroups	Multivariable analysis of OS		
	HR	95% CI	P
CT appearance			
GGO	2.182	1.248–3.817	0.006
Solid	1.689	1.441–1.980	<0.001
Pathology types			
IAC	1.138	1.354–1.981	<0.001
SCC	1.679	1.286–2.192	<0.001
pTNM stage			
I	NR	NR	NR
II/III	1.650	1.419–1.918	<0.001

NR means not reaching the criteria of P value <0.1 in univariable analysis. HR, hazard ratio; CI, confidence interval; LN, lymph node; OS, overall survival; CT, computed tomography; GGO, ground-glass opacity; IAC, invasive adenocarcinoma; SCC, squamous cell carcinoma; pTNM, pathological tumor-node-metastasis.

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