ORIGINAL ARTICLE

The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for Revision of the Classification of Residual Tumor After Resection for the Forthcoming (Ninth) Edition of the TNM Classification of Lung Cancer

Frank C. Detterbeck, MD,[a,*] Marcin Ostrowski, MD,[b] Hans Hoffmann, MD,[c] Ramón Rami-Porta, MD, FETCS,[d] Ray U. Osarogiagbon, M.B.B.S.,[e] Jessica Donnington, MD, MSCR,[f] Maurizio Infante, MD,[g] Mirella Marino, MD,[h] Edith M. Marom, MD,[i] Jun Nakajima, MD,[j] Andrew G. Nicholson, DM, FRCPath.,[k] Paul van Schil, MD,[l] William D. Travis, MD,[m] Ming S. Tsao, MD,[n] John G. Edwards, PhD, FRCS(C/Th),[o] Hisao Asamura, MD,[p] and the Members of the Staging and Prognostic Factors Committee and Advisory Boards[q]

[a]*Department of Surgery, Yale University School of Medicine, New Haven, Connecticut*
[b]*Department of Thoracic Surgery, Medical University of Gdansk, Gdansk, Poland*
[c]*Division of Thoracic Surgery, Department of Surgery, Klinikum Rechts der Isar, Technical University of Munich, Munich, Germany*
[d]*Department of Thoracic Surgery, Hospital Universitari Mutua Terrassa, University of Barcelona, Terrassa, Barcelona, Spain*
[e]*Oncology Research Group, Multidisciplinary Thoracic Oncology Program, Baptist Cancer Center, Memphis, Tennessee*
[f]*Department of Surgery, University of Chicago, Chicago, Illinois*
[g]*Department of Thoracic Surgery, Ospedale Borgo Trento, Verona, Italy*
[h]*Department of Pathology, IRCCS Regina Elena National Cancer Institute, Rome, Italy*
[i]*Department of Diagnostic Imaging, The Chaim Sheba Medical Center, Ramat Gan, Israel*
[j]*Department of Thoracic Surgery, The University of Tokyo, Tokyo, Japan*
[k]*Department of Histopathology, Royal Brompton and Harefield NHS Hospitals, Guy's and St. Thomas' NHS Foundation Trust and National Heart and Lung Institute, Imperial College, London, United Kingdom*
[l]*Department of Thoracic and Vascular Surgery, Antwerp University Hospital, Edegem (Antwerp), Belgium*
[m]*Department of Pathology, Memorial Sloan-Kettering Cancer Center, New York, New York*
[n]*Department of Pathology, The Princess Margaret Cancer Centre, Toronto, Ontario, Canada*
[o]*Department of Cardiothoracic Surgery, Sheffield Teaching Hospitals National Health Service Foundation Trust, Northern General Hospital, Sheffield, United Kingdom*
[p]*Division of Thoracic Surgery, Keio School of Medicine, Tokyo, Japan*

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ABSTRACT

Introduction: The goal of surgical resection is to completely remove a cancer; it is useful to have a system to describe how well this was accomplished. This is captured by the residual tumor (R) classification, which is separate from the TNM classification that describes the anatomic extent of a cancer independent of treatment. The traditional R-classification designates as R0 a complete resection, as R1 a macroscopically complete resection but with microscopic tumor at the surgical margin, and as R2 a resection that leaves gross tumor behind. For lung cancer, an additional category encompasses situations in which the presence of residual tumor is uncertain.

Methods: This paper represents a comprehensive review of evidence regarding these R categories and the descriptors thereof, focusing on studies published after the year 2000 and with adjustment for potential confounders.

*Corresponding author.

[q]See appendices

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Address for correspondence: Frank C. Detterbeck, MD, Division of Thoracic Surgery, Department of Surgery, Yale University School of Medicine, 330 Cedar Street, New Haven, Connecticut 06520-8062. E-mail: frank.detterbeck@yale.edu

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Results: Consistent discrimination between complete, uncertain, and incomplete resection is revealed with respect to overall survival. Evidence regarding specific descriptors is generally somewhat limited and only partially consistent; nevertheless, the data suggest retaining all descriptors but with clarifications to address ambiguities.

Conclusion: On the basis of this review, the R-classification for the ninth edition of stage classification of lung cancer is proposed to retain the same overall framework and descriptors, with more precise definitions of descriptors. These refinements should facilitate application and further research.

Keywords: Lung cancer; Surgery; Complete resection; Residual disease

Introduction

Surgical resection is well established as a treatment of localized cancers, including lung cancer. A fundamental principle of cancer surgery is complete resection of the tumor with a margin of normal tissue to ensure that no residual tumor remains. This is not only logical but also supported by decades of experience revealing high cure rates for many localized cancers when this is achieved. Reflecting this, the residual tumor (R) classification of resection completeness has been well established as a complement to the TNM classification of the anatomic extent of cancer since the first edition of the American Joint Committee on Cancer (AJCC) staging manual published in 1977.[1] The traditional R-classification designates as R0 a complete resection, as R1 a macroscopically complete resection with microscopic tumor at the surgical margin, and as R2 a resection that leaves gross tumor behind.

Increasing knowledge naturally leads to questions about finer details—the R-classification for lung cancer is no exception. The seventh edition of TNM classification of lung cancer marked a major upgrade through the International Association for the Study of Lung Cancer (IASLC) initiative to create an unprecedented large database, an international multidisciplinary expert panel (the Staging and Prognostic Factors Committee, SPFC), and extensive analysis to provide a solid basis for revisions in TNM classification.[2] This included refinements of the R-classification, such as designation of a resection in the face of a malignant pleural effusion as R1, a focus on extracapsular extension of involved lymph nodes as a potential source of residual disease, and proposal of an "uncertain" R category. This new category included limited node evaluation or finding involvement of the highest resected lymph node, designated as R0(un), and carcinoma in situ (CIS) at the bronchial margin or finding tumor cells in a pleural lavage (performed despite the absence of an effusion), designated respectively as R1(is) or R1(cy+).[3]

As with the seventh and eighth editions of TNM classification of lung cancer, the IASLC SPFC has been tasked with creating proposals for refinements for the ninth edition. This effort included an R-subcommittee, involving an international multidisciplinary group. This paper describes the proposals for R-classification for the ninth edition. Specifically, this paper provides a review and analysis of the available evidence regarding the R-classification and potential refinements of the descriptors of the R categories. Additional work by the R-subcommittee will be published elsewhere.

Methods

To inform potential revisions to the R-classification, a review of the available pertinent literature was undertaken. This involved the PubMed database and English-language articles using search terms related to lung cancer, surgery, completeness of resection, residual tumor, and resection margins. In addition, reference lists of relevant papers and reviews were assessed.

Papers were identified for inclusion if they provided information about the prognostic impact of the existing R categories and descriptors—specifically to evaluate between-category discrimination and within-category homogeneity. The inherent problem that prognosis is determined by multiple factors is accentuated when evaluating the R-status. There are clearly tumor-related differences associated with resection completeness and patient- and setting-related factors that can limit the ability to achieve a complete resection. Therefore, this review focused on reports that adjusted for at least some confounders. Study interpretation must also consider potential residual confounding; confidence that an observed difference is due to the question of interest (i.e., R-status) in a nonrandomized comparison is undermined by potential confounders that were not accounted for. It was deemed best to focus on studies with at least 100 patients, as the number of confounders that can be included and the strength of multivariate adjustment are diminished when the number of outcome events is limited. Inclusion criteria for each table are listed in the respective legends.

In addition, the R-subcommittee considered areas of ambiguity that have emerged during implementation of the eighth edition definitions. Areas for clarification stem in part from a survey conducted by the R-subcommittee, from assessing how the R-classification has been understood in published studies, and from a critical reassessment of the wording in the eighth edition classification. Results of the R-classification survey are the topic of a separate paper.

The proposed revisions were reviewed and discussed in the R-subcommittee and the SPFC steering committee. A refined document was then reviewed and approved by the entire SPFC according to the standard process of the SPFC.

Results

R-Status Categories

Definitions. The AJCC/Union for International Cancer Control (UICC) classification system defines R0 as a complete resection, R1 as a microscopically positive resection margin, and R2 as gross unresected tumor remaining.[4,5] Specifically for lung cancer, the IASLC and the UICC additionally recognize an uncertain resection category,[3,4,6] defined as resections that are microscopically and macroscopically complete but have potentially concerning features, that is, (1) a limited lymph node assessment was performed, (2) the highest node removed is involved, (3) CIS is found at the bronchial resection margin, and (4) a pleural lavage was performed and result was found to be cytologically positive.[3,6,7] The first two descriptors are designated as R0(un). The latter two are designated as R1(is) and R1(cy+)—because UICC defines these situations as R1[8] but with the addition of (is) and (cy+) to distinguish them from a standard microscopically positive margin or malignant pleural effusion. These two descriptors are referred to in this paper as R1(un); the four scenarios are collectively referred to as R(un).

At the time of resection, IASLC has recommended a minimum assessment of six nodes/station; this should include the subcarinal station, at least two other mediastinal nodes/station, and three nodes/station from the hilum or other N1 locations.[6] The eighth edition IASLC recommendation is not specific regarding nodes versus node stations, and presumably both preoperative and intraoperative assessments count (although not explicitly stated).

Validation. The overall survival (OS) of patients in the R(un) category consistently falls in-between that of R0 and R1,2 cohorts (Table 1, Fig. 1).[9–15] In all studies, the uncertain category included all four uncertain descriptors. The OS differences were maintained after multivariate adjustment for potential confounders, which included tumor-related and demographic factors in all studies, and frequently also comorbidities[10,11,13,14] and/or treatment-related factors (e.g., adjuvant therapy, lobectomy versus wedge resection).[9–11,13] Subset analyses in particular cohorts (N category, stage) maintained consistent differences. Furthermore, taken together, the four validation studies reveal that the ordering and statistical differences between the R categories are generally consistent across various geographic regions and time periods. In addition, a multivariate analysis found statistical differences in OS and recurrence-free survival (RFS) by R categories in 910 stage III-N2 patients who underwent neoadjuvant therapy before resection.[16]

Only two studies noted no statistically significant difference between the R0 and R(un) cohorts although ordering consistent with other studies was maintained. One involved an unadjusted analysis of a prospective cohort from 1993 to 1997 (not included in Table 1).[15] In the other study, an unadjusted statistically significant

Table 1. Studies Evaluating the R(un) Category

First Author	n	Cohort	% Limited N Among R(un)	Adjusted HR for OS: R0 vs. R(un)	Adjusted HR for OS: R(un) vs. R1,2	Multivariate Adjustment	Data Source, Years
Ren[9]	5293	All	85%	1.41	1.23	10 factors	China 2009-2013
Osarogiagbon[10]	3361	All	98%	1.36	2.18	8 factors	MSQSR 2009-2019
Gagliasso[11]	1277	All	58%	1.69	1.70	9 factors	Torino 1998-2007
Edwards[12]	8839	pI	96%	1.22	-	4 factors	IASLC 1999-2010
Ren[9]	3733	N0	85%	1.76	2.38	10 factors	China 2009-2013
Osarogiagbon[10]	2453	N0	98%	1.31	1.81	8 factors	MSQSR 2009-2019
Edwards[12]	3494	N+	96%	1.27	1.36[a]	4 factors	IASLC 1999-2010
Ren[9]	1556	N+	85%	1.14	1.61	10 factors	China 2009-2013
Osarogiagbon[10]	682	N+	98%	1.24	2.15	8 factors	MSQSR 2009-2019
Kadomatsu[13]	119	N+	34%	2.66	-	6 factors	Japan 2014-2015
Yun[14]	1039	N2	10%	1.06	1.40	10 factors	Korea 2004-2018

Inclusion criteria: Studies comparing IASLC R categories: R0, R(un), R1, R2, published from 2000 to 2023, with at least 100 patients total, and using a method of adjustment for confounders. A HR of >1 indicates worse survival in the second of the two cohorts being compared.

[a]R1 only.

Color coding: green, statistically significant; yellow, not significant.

HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; limited N, limited node assessment (<6 nodes/station); MSQSR, Mid-South Quality of Surgical Resection database; N+, pathologically proven node involvement; OS, overall survival; pI, pathologic stage I; R(un), R-status uncertain, this includes insufficient node assessment, highest node station involved, positive pleural lavage cytology, carcinoma-in-situ at the bronchial margin.

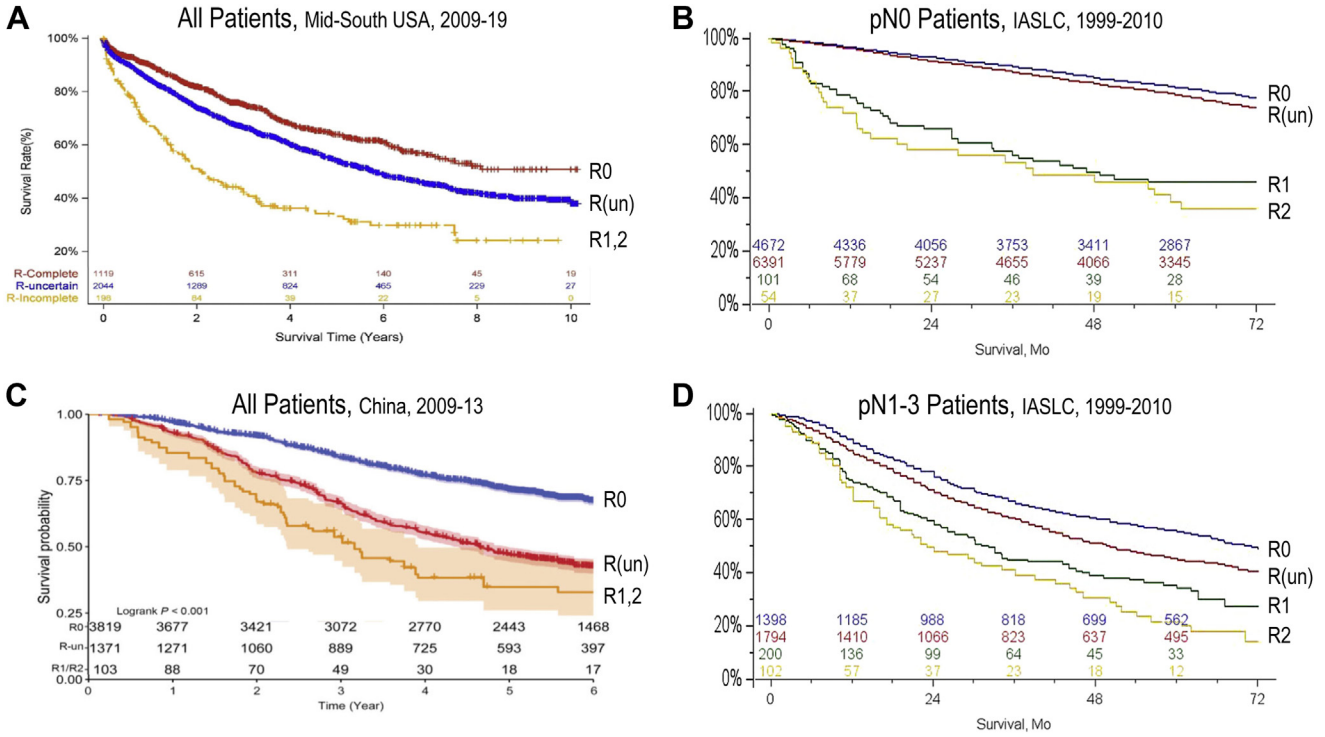

Figure 1. Prognostic impact of R-classification categories. *Overall survival in studies of the R-classification. (A) 3361 patients, 2009–2019, Mid-South Quality of Surgical Resection database*[10]*; (B, D) 11,218 and 3494 patients, respectively, 1999–2010, IASLC* eight *edition database*[12]*; (C) 5293 patients, 2009–2013, Shanghai Pulmonary Hospital*.[9] IASLC, International Association for the Study of Lung Cancer.

difference disappeared when adjustment for N2 subgroups was done (N2a with skip metastasis, N2a and N2b); furthermore, 90% of the R(un) cohort consisted of patients with highest node station involvement [most R(un) cases involved limited node assessment in other studies].[14]

Distinguishing gross residual disease (R2) from a microscopically positive margin (R1) that may or may not imply residual disease is based on a rationale that is intuitively reasonable. Nevertheless, few studies have compared the survival of R1 versus R2 cohorts. No difference was noted in a study considering all stages together[10] and in another that adjusted for T, N, histotype, and region.[12] In a stage-specific analysis, differences were noted but with some inconsistency (OS was better in patients undergoing an R1 versus R2 resection of pI and pIII tumors but lower after an R1 versus R2 resection of pII tumors).[17] Unstudied confounders include comorbidities and use of adjuvant therapy. The R2 cohort in all studies is small; presumably, imaging technology makes it unusual to encounter unexpected unresectable tumor.

Specific R(un) Descriptors

R0(un) - Limited Node Assessment. There is a discrepancy between the prevalence of limited node assessment and how well this descriptor has been studied. In Table 1, the vast majority of R(un) resections in most studies were classified as such because of a limited node assessment. The consistent ordering and statistical difference in OS support retention of this descriptor of R0(un). In all studies, the IASLC definition of adequate assessment was interpreted as pertaining to node stations (not the number of discrete nodes).

Few studies have focused specifically on the impact of the extent of node assessment (Table 2).[10,18] One study found incrementally lower survival as the degree of node assessment diminishes (Fig. 2).[10] The OS differences are statistically significant after multivariate adjustment between patients who underwent a fully compliant node assessment (R0), a partially compliant assessment (at least one mediastinal station sampled), no node assessment (NX), and an incomplete resection (R1,2); a further group with only N1 nodes assessed falls in-between the partially compliant and NX cohorts, although the differences are not statistically significant. In contrast, another study found a trend toward better survival with more limited node assessment, but differences in adjusted OS rates were not statistically significant between patients who underwent a completely compliant node assessment (R0), a partially compliant assessment (at least one mediastinal station was

Table 2. Studies Evaluating the Limited Node Assessment R0(un) Descriptor

First Author	n	Cohort	% cI	Adjusted HR for OS: R0 vs. R0(un)	Adjusted HR for OS: R0(un) vs. R1,2	Multivariate Adjustment	Data Source, Years
R0(un) = partially compliant node assessment							
Osarogiagbon[10]	3357	All	69%	1.28	1.7	8 factors	MSQSR 2009-2019
Lee[18]	4765	All	74%	1.07	-	6 factors	Korea 2008-2016
R0(un) = Nx (no nodes assessed)							
Osarogiagbon[10]	3357	All	69%	1.74	1.25	8 factors	MSQSR 2009-2019
Lee[18]	3158	All	72%	0.99	-	6 factors	Korea 2008-2016

Inclusion criteria: Studies comparing the IASLC R0(un) limited node assessment descriptor versus other R categories, published from 2000 to 2023, with at least 100 patients total, and using a method of adjustment for confounders. A HR of >1 indicates worse survival in the second of the two cohorts being compared. Color coding: green, statistically significant; yellow, not significant.
cI, clinical stage I; HR, hazard ratio; MSQSR, Mid-South Quality of Surgical Resection Database; OS, overall survival.

sampled in >90%), and no node assessment (NX).[18] The latter study involved an increasing proportion of cI tumors and lepidic tumors in the partially compliant and NX cohorts. Unfortunately, only total size was collected, leaving the proportion of ground-glass tumors unclear, and hampering multivariate adjustment for T size. The study noted no differences by degree of node assessment in subgroup analyses involving adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma, pIA1 and pIA2 tumors; however, among pIA3 tumors, better OS was observed when patients underwent fully compliant versus partially compliant node assessment.

These findings suggest that although there is general support for the six-station node assessment R0(un)

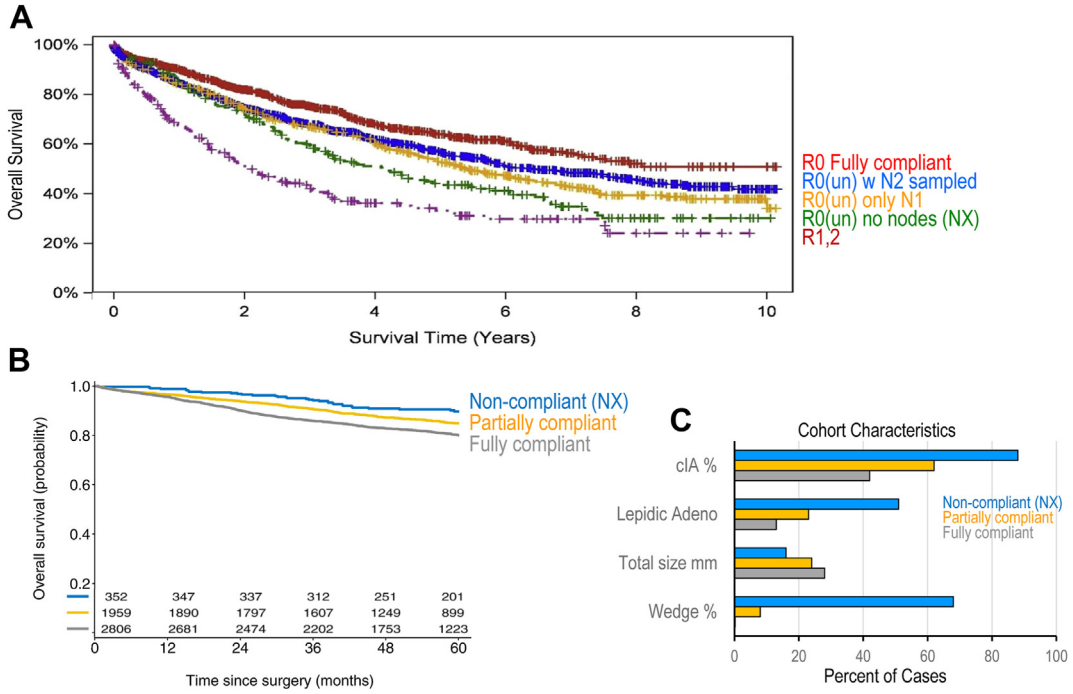

Figure 2. Prognostic *impact of extent of node evaluation*. Overall survival of patients by extent of node evaluation at the time of resection. (*A*) 3359 patients, 2009-2019, Mid-South Quality of Surgical Resection database[10]; (*B*) 5117 patients, 2008-2016, Samsung Medical Center, Seoul, South Korea, and (*C*) cohort characteristics of the cases in panel *B*.[18] The impact of a more limited node evaluation is diametrically opposed in the two studies. The dramatically better survival in all groups in *B* compared with those in *A* suggests that the tumors involved in *A* and *B* are fundamentally different; the variable incidence of characteristics in *C* suggests that confounding by these characteristics may explain the better survival of the NX versus the compliant cohorts in *B*. Adeno, adenocarcinoma; fully compliant, 6-station minimum as recommended by the eight edition R-classification; partially compliant, some nodes assessed but less than the 6-station minimum; noncompliant, no nodes sampled.

descriptor, this does not apply to all types of tumors (e.g., small and ground-glass tumors). In addition, it seems prudent to clarify that the definition refers to node stations (not nodes); this reflects how the descriptor has been interpreted around the world for almost two decades.

R0(un) - Highest Node Station Involvement. Studies addressing involvement of the highest node removed have used the highest node station assessed (most cephalad) as a surrogate. Among N2-positive cases, data are conflicting regarding a survival difference among cohorts with versus without highest node station involvement—that is, R0(un) versus R0 (Table 3).[9,10,12,14,19–21] No clear reason for the discrepancy is apparent. All studies involved some adjustment for potential confounders. Results do not correlate with adjustment for the N2 subcategories; only one study adjusted for comorbidities.[14]

One study[20] explored a definition of "most distant" node involvement (e.g., station 9) following an earlier suggestion.[15] No difference was noted between R0 and R0(un) as defined by either highest or most distant node involvement in multivariate analyses of N2 tumors.[20] Another study explored laterality and found similar significant adjusted differences between R0 versus R0(un) cohorts among right- and left-sided tumors, using R2 and L4, respectively, as the definition of the highest station.[19]

Unrecognized factors seem to be contributing to the conflicting results; further study is warranted. Nevertheless, it seems reasonable to include highest station involvement as an R0(un) descriptor. Furthermore, defining the descriptor as highest station instead of highest individual node is practical and reflects how data are collected.

R1(is) - Carcinoma In Situ at the Bronchial Margin. CIS at the bronchial resection margin is reported infrequently. A systematic SPFC review in 2011 found 136 cases, with almost all patients diagnosed 20 to 40 years ago, and limited availability of details.[22] The incidence of CIS was 0.9%. Little additional data have emerged since then. The IASLC 1999–2010 database contained 13 cases.[12] The IASLC ninth edition database was not assessed regarding CIS in time for this review. The most informative contemporary study involves 18 patients with bronchial margin CIS [R1(is)] and 42 with extramucosal microscopic residual cancer at the bronchial margin (R1).[23]

Stump recurrences are rare after R1(is) resection (6% at 5 years in the recent study).[23] This is corroborated by others, although less specifically,[22,24] and is consistent with studies revealing that CIS may regress or may never progress in a substantial portion of cases.[25] Adjuvant radiotherapy was often administered in R1(is) cases, but the impact is unclear. Some studies report a higher rate of death from radiation toxicity than from cancer recurrence.[26,27]

Surveillance studies of untreated preinvasive endobronchial lesions provide additional evidence. Moderate inter- and intra-observer variability in classification of preinvasive squamous bronchial lesions (degrees of dysplasia versus CIS) suggests some uncertainty.[28] In addition, a prospective study noted sustained regression in 63% of foci of severe dysplasia and regression in 31%

Table 3. Studies Evaluating the Highest Node Station Positive R0(un) Descriptor

			Adjusted HR for OS				
First Author	n	Cohort	R0 vs. R0(un)-HN+	R0(un)-HN+ vs. other R(un)	Multivariate Adjustment	Adjusted for N2 Subtype?	Data Source, Years
Edwards[12]	1820	N2	1.32	-	4 factors	-	IASLC 1999-2010
Ren[9]	1207	N2	1.23	0.94	10 factors	-	China 2009-2013
Yun[a,14]	1039	N2	1.06	(1.40)[b]	10 factors	Yes	Korea 2004-2018
Zheng[19]	549	N2	1.58	-	13 factors	Yes	China 1999-2005
Park[20]	339	N2	1.02	-	10 factors	Yes	Korea 2000-2015
Osarogiagbon[10]	231	N2	1.08	1.07	8 factors	-	MSQSR 2009-2019
Wang[c,21]	218	N2	1.00	-	6 factors	-	China 2004-2015

Inclusion criteria: Studies comparing the highest node station positive R0(un) descriptor with other R categories/descriptors, published from 2000 to 2023, with at least 100 patients total, and using a method of adjustment for confounders. A HR of >1 indicates worse survival in the second of the two cohorts being compared.

[a]90% of the R(un) cohort were so classified due to HN+; data are reported for entire R(un) cohort.

[b]Reported for HR compared with R1,2 cohort, in parentheses, because not directly comparable to R(un) by other descriptors.

[c]Unclear if patients with insufficient node assessment were included.

Color coding: green, statistically significant; yellow, not significant; blue, statistically significant but versus a different end point.

HN+, highest mediastinal node station involved; HR, hazard ratio; IASLC, International Association for the Study of Lung Cancer; MSQSR, Mid-South Quality of Surgical Resection database; OS, overall survival.

of CIS lesions at 3 months (mostly to normal epithelium) which was sustained in 71% during further surveillance.[29] Although a review reported development of invasive cancer in approximately 50% of patients with CIS (over 2–8 years),[30] this may be misleading because several studies report that most invasive cancers do not occur at the site of the CIS.[31–33] In a large prospective study, the 10-year rate of progression to invasive cancer at a site of CIS/severe dysplasia was 11% (among patients with a prior respiratory cancer undergoing bronchoscopic surveillance of a preinvasive endobronchial lesion).[32]

Good OS is generally reported for R1(is)—in the 2011 SPFC review the 5-year OS was approximately 70%[22]; this is corroborated by others.[11,23] Survival of patients with R1(is) and similar-stage R0 tumors is not clearly different. A contemporary study noted no difference in OS by multivariate analysis for patients undergoing R1(is) versus either R0 or R1 resections with microscopic invasive cancer at the bronchial margin, analyzed separately for stage I–II and stage III tumors.[23] The sample size limits the certainty of this observation.

In conclusion, CIS at the bronchial margin is rare but has a good prognosis. It is intuitively difficult to ignore clear demonstration of CIS at the margin. Nevertheless, lack of progression and regression of bronchial CIS is well documented, making the impact unclear. It is reasonable to designate this as an R1(un) descriptor.

R1(cy+) – Positive Pleural Lavage Cytology. Pleural lavage cytology has been studied frequently, especially in Japan; a 2016 meta-analysis included 28 studies and more than 20,000 patients worldwide.[34] Pleural lavage cytology result is positive in approximately 5% of patients.[35–40] Several meta-analyses have consistently found that positive cytology result is associated with lower OS and higher recurrence.[34,41] Nevertheless, meta-analyses of nonrandomized comparisons obscure the impact of confounders.[42]

Large multivariate studies involving routine pleural lavage report that positive cytology result is independently associated with lower OS and RFS with few exceptions (versus negative cytology result, Table 4).[35–40,43–50] Most studies have adjusted for tumor-related factors (positive lavage cytology result increases with greater anatomic

Table 4. Studies Evaluating the Positive Pleural Lavage R1(cy+) Descriptor

First Author	n	Cohort	% cI	Lavage Timing	Adjusted HR R0 vs. R1(cy+) OS	Adjusted HR R0 vs. R1(cy+) RFS	Multivariate Adjustment	Data Source, Years
Lim[a,37]	8763	All	-	-	1.47	-	13 factors	IPLCC -
Kameyama[a,35]	4171	All	65%[b]	-	1.57	-	7 factors	Japan LCR 2004
Kaneda[a,43]	3231	All	60%[b]	Pre	1.44	1.36	6 factors	Japan[c] 2000-207
Aokage[36]	2178	All	87%	Pre	1.54	1.45	14 factors	Japan 1992-2006
Nakao[39]	1572	All	79%	Pre	1.23	-	8 factors	Japan 1991-2009
Hokka[44]	1317	All	64%	Pre	1.54	-	11 factors	Japan 1987-2004
Mizuno[38]	1293	All	63%[b]	Pre	1.34	1.7	7 factors	Japan 2002-2014
Shintani[45]	1271	All	57%[b]	Pre	1.07	-	8 factors	Japan 1985-2005
Nakagawa[a,46]	1025	All	68%	Pre	3.42	-	6 factors	Japan 1993-2005
Okada[47]	1000	All	59%[b]	Pre	1.63	-	8 factors	Japan 1987-2001
Tomizawa[a,40]	754	All	69%	Pre	2.25	-	10 factors	Japan 2007-13
Shoji[48]	700	All	77%	Pre	-	1.14	10 factors	Japan 1994-2011
Higashiyama[49]	679	All	57%[b]	Pre	1.67	-	15 factors	Japan 1988-1997
Kawachi[50]	597	All	71%[b]	Pre	2.96	-	5 factors	Japan 1993-2006
Mizuno[38]	818	pI	-	Pre	1.91	2.68	7 factors	Japan 2002-2014
Higashiyama[49]	395	pI	-	Pre	1.75	-	9 factors	Japan 1988-1997
Aokage[36]	2178	All	87%	Post	1.77	1.55	14 factors	Japan 1992-2006
Shintani[45]	1271	All	57%[b]	Post	2.31	-	8 factors	Japan 1985-2005
Shoji[48]	700	All	77%	Post	-	1.56	10 factors	Japan 1994-2011

Inclusion criteria: Studies comparing the IASLC R1(cy+) positive pleural lavage descriptor versus other R categories, published from 2000 to 2023, with at least 500 patients total, and using a method of adjustment for confounders. A HR of >1 indicates worse survival in the second of the two cohorts being compared.
[a]Not explicitly stated that all cases were considered R0 (other than the lavage).
[b]Pathologic stage.
[c]12-center collaboration.
Color coding: green, statistically significant; yellow, not significant.
cI, clinical stage I; HR, hazard ratio; IPLCC, international pleural lavage cytology collaborators; LCR, Lung Cancer Registry; OS, overall survival; pI, pathologic stage I; Pre, pre-resection lavage (immediately on entering the thorax); Post, post-resection lavage (before closure); RFS, recurrence-free survival.

tumor extent), approximately half have adjusted for surgical extent, and few have adjusted for patient-related factors (e.g., performance status, comorbidities) or treatment-related factors (e.g., adjuvant therapy). Although the incidence is lower, R1(cy+) is found even in stage pI tumors. Most studies involve careful stage evaluation by imaging and node dissection. The data from multivariate-adjusted studies suggest an impact of R1(cy+) on long-term outcomes in stage I tumors, but this is less certain.

Most studies performed lavage before any lung manipulation. A few studies have assessed lavage cytology pre- and post-resection,[36,45,48] and found that in approximately half of cases with positive pre-resection cytology result, the post-resection lavage result is negative, and vice versa (Supplementary Fig. 1).[36,45,48] These studies have also suggested that prognosis correlates more strongly and consistently with post- than pre-resection lavage.[36,45,48]

In a large multicenter study, the 5-year OS for patients without and with positive cytology result, respectively, was 77% and 54% for stage pI, 50% and 29% for stage pII, and 35% and 21% for pIII (fifth/sixth edition TNM).[37] Positive lavage cytology result clearly has an impact on outcomes, but it does not indicate that resection is futile. Several studies have also compared R0 and R1(cy+) cases with patients with pleural dissemination who underwent resection (Fig. 3).[39,44,46,47] These have revealed that outcomes for R1(cy+) cohorts fall in-between R0 cohorts and patients with pleural dissemination undergoing resection (R1). Among patients with pleural dissemination who underwent resection, approximately two-thirds had pleural nodules and one-third a malignant pleural effusion. These studies provide the best available comparison to R1,2 resections; no studies have compared R1(cy+) and general R1,2 resection cohorts.

Positive lavage cytology result is associated with a higher risk of recurrence (approximately twofold overall, approximately twofold for distant, approximately fivefold for pleural recurrence; rates not adjusted for potential confounders).[34,35,41] The pleural recurrence rate is 15% to 20% versus 2% to 3%, respectively, after R1(cy+) versus R0 resections in two meta-analyses. In addition, pleural recurrences are involved in approximately 30% of all recurrences after R1(cy+) resection.[34,41] A small study (n = 17) of intrapleural chemotherapy for R1(cy+) cases suggested a benefit.[51]

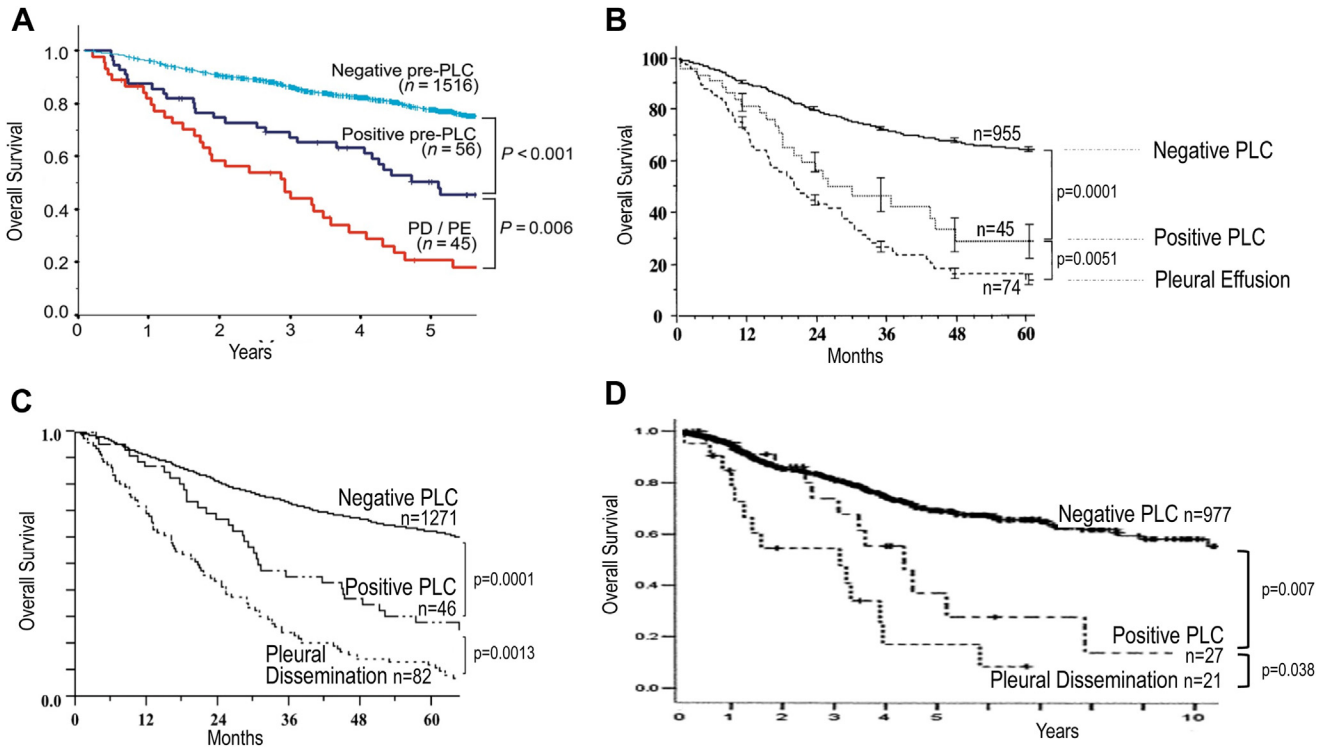

Figure 3. Overall survival of R0, R1(cy+), and pleural dissemination cohorts. Overall survival of patients undergoing R0 resection with negative pleural lavage cytology result *or resection in the face of a positive lavage cytology* result *or evidence of pleural dissemination (malignant pleural nodules or effusion)*. (*A) 1572 consecutive surgical patients, 1991–2009, Tokyo Cancer Institute Hospital*[39]; (*B) 1000 consecutive surgical patients, 1987–2001, Hyogo Medical Center*[47]; (*C) 1317 surgical patients, 1987–2004, Kobe University and Hyogo Cancer Center*[44]; (*D) 1025 retrospective surgical patients, 1993–2005, Kurashiki Central Hospital.*[46] PD/PE, pleural dissemination/pleural effusion; PLC, pleural lavage cytology; Pre, pre-resection.

Nevertheless, a randomized controlled trial (n = 49, closed prematurely due to poor accrual) of intrapleural chemotherapy for cytology-positive cases found no difference in OS but a dramatic reduction in pleural recurrences.[52]

In summary, there is substantial evidence that positive pleural lavage cytology result is associated with worse survival than R0 resection and consistent evidence that outcomes fall in-between R0 resections and patients with pleural dissemination who underwent resection. Positive pleural lavage result is associated with a higher risk of pleural recurrence, but this occurs in a minority of patients. Classification of R1(cy+) as an R(un) descriptor is appropriate. If no lavage was performed, the R1(cy+) descriptor does not apply.

Specific R1 Descriptors

R1 – Microscopically Positive Resection Margin. Depending on how specific the desired evidence is, there is either extensive or somewhat limited data regarding the impact of microscopic invasive cancer at a resection margin. Numerous reports document lower OS (unadjusted) for R1 versus R0 resections. Large database studies using the basic UICC definitions reveal a meaningful difference between R1 and R0 resection (5-year OS approximately 35% versus approximately 60%).[10,12,17,27] Table 1 documents that numerous adjusted studies consistently find significant differences for R1,2 versus R(un) resections, and versus R0 resections.[9–15] Most of these incomplete resections were R1, and most of the R1 resections involved the positive margin descriptor (among studies reporting such details).

Fewer studies have specifically evaluated the R1 microscopic margin descriptor. Table 5 depicts studies involving multivariate adjustment or reporting results stratified by stage.[10,17,23,27,53,54] The outcomes of R1 versus R0 cohorts support the microscopic margin descriptor as a useful differentiator; comparisons to R(un) or R2 cohorts have not been reported. In smaller studies, the difference is less consistent. Some studies have focused specifically on the bronchial margin.[23,54] Although the bronchial margin is most common, other margins (e.g., hilar tissues, vascular or parenchymal margins) account for a substantial minority of microscopically positive resections. Some data suggest worse outcomes with a positive extrabronchial versus a bronchial or peribronchial margin.[53] This may be due to node involvement, but studies have not adjusted for this.

R1 – Extracapsular Extension of Involved Lymph Nodes. In the seventh and eighth edition manuals, extranodal extension of involved lymph nodes was not clearly defined.[3,6] This feature is mentioned both under microscopic- and macroscopic-positive margin headings, suggesting extranodal extension merely refers to the surgical margin around a resected node or node packet. Nevertheless, the specific mention of extracapsular extension implies that it is different than other resection margins.

Studies addressing this topic do not mention whether extranodal extension was present at a resection margin or contained within a packet of surrounding normal

Table 5. Studies Evaluating the Microscopically Positive Margin R1 Descriptor

First Author	n Total	Cohort	n R1 Cases	% Recur at Margin	Adjusted HR for OS		Multivariate Adjustment	Data Source, Years
					R0 vs. R1	R1 vs. R2		
Multivariate adjusted								
Riquet[53]	4026	All	216	-	NR	-	7	France 1984-2006
Osarogiagbon[10]	3316	All	153	-	2.08	-	8	MSQSR 2009-2019
Lee[23]	1249	pI,II	16	12%[a]	2.21[b]	-	9	Korea 1994-2012
Lee[23]	533	pIII	26	12%[a]	1.05[b]	-	9	Korea 1994-2012
Stratified by stage, but unadjusted								
Osarogiagbon[27]	112,998	pI-III	3041	-	NR	-	-	NCDB 2004-2011
Hancock[17]	54,512	pI-III	1688	-	NR	-	-	NCDB 2003-2006
Lequaglie[54]	4530	pI-III	56	-	NR[b]		-	Italy 1998-1998

Inclusion criteria: Studies comparing the R1 microscopically positive margin descriptor versus other R categories, published from 2000 to 2023, with at least 500 patients total, and using a method of adjustment for confounders or reporting results stratified by stage. A HR of >1 indicates worse survival in the second of the two cohorts being compared.

[a]Rate for all stages combined.

[b]Included only cases involving bronchial/peribronchial margin.

Color coding: green, statistically significant; yellow, not significant.

HR, hazard ratio; MSQSR, Mid-South Quality of Surgical Resection database; NCDB, National Cancer Database (USA); NR, not reported (but statistical significance reported); OS, overall survival; pI,II or pIII, pathologic stage I, II, or III; recur, recurrence.

tissue (presumably reflecting that this information was not collected). Therefore, this paper assesses whether extracapsular extension (without information on the surrounding margin) has prognostic implications similar to a microscopically positive margin. Cases of direct primary tumor invasion of an adjacent node are excluded.

Studies evaluating extranodal extension reveal mixed results (Table 6).[10,55–61] The largest study suggests distinctly worse outcomes among resections with versus without extranodal extension (among resections otherwise meeting R0 criteria).[10] Furthermore, the outcomes are similar to that of patients undergoing R1,2 resection[10]; this is corroborated by an unadjusted comparison in another study.[59] A meta-analysis found that extracapsular extension was associated with lower OS and higher recurrence rates, although most studies did not adjust for confounders and spanned four decades.[62]

The reason for conflicting results is unclear. The incidence of extranodal extension varies dramatically between studies, also unexplained. Most studies have not adjusted for N2 subcategories. One study found incrementally worse survival when more nodes exhibit extranodal extension, but whether extranodal extension involved N1 or N2 nodes had little impact.[57]

Although the microscopic presence of extranodal extension seems straightforward, what this represents regarding the surgical procedure is unclear. One can envision (1) a node with extranodal extension within a node packet, surrounded by a margin of normal tissue, (2) microscopically visible extranodal tumor extension at a resection margin of the node/node packet, or (3) extranodal extension in nodes that have been removed in pieces (making margin assessment impossible). The first scenario is mostly a tumor burden issue, the second a margin issue (already addressed by R1 and R2 margin descriptors), and the third a technical issue and communication issue between the surgeon and pathologist. This third scenario is presumably most common. Because nodes are friable and lie within loose tissue, they are often removed in pieces—rendering it impossible to ascertain a margin. The pathologist's only recourse is the capsule of an intact node as a surrogate—the resection margin is presumably negative if tumor lies within a node with an intact capsule, but potentially positive if extracapsular extension is found. A problem remains when nodes are removed in pieces—the resection margin cannot be assessed (and identification of extranodal extension is compromised). From a practical perspective, the pathology report provides some information about extranodal extension, whereas information on how nodes were removed or the nodal resection margin is rarely available.

In summary, more research is needed to clarify the impact of the extranodal extension descriptor. Perhaps more importantly, better definition of the issue of interest is needed so appropriate data are gathered.

One can argue that uncertainty about the impact and ambiguity about what it reflects suggests that extranodal extension fits as an R(un) descriptor. A general SPFC principle is to avoid changes unless there is strong evidence that change is needed. Because addressing the uncertainties will take time, it is best to retain extranodal extension as an R1 descriptor.

R1 – Malignant Pleural or Pericardial Effusion. Patients with malignant pleural/pericardial nodules or

Table 6. Studies Evaluating the Extranodal Extension Descriptor

First Author	n	Cohort	% With ENE	Adjusted HR for OS		Multivariate Adjustment	Adjusted for N2 Subtype?	Data Source, Years
				R0 vs. ENE	ENE vs. R1,2			
Osarogiagbon[10]	3181	All	.6%	3.03	NR	8 factors	-	MSQSR 2009-2019
Liu[55]	388	II, IIIA	22%	1.23	-	13 factors	-	China 2008-2009
Shih[56]	282	N2	30%	1.63[a]	-	15 factors	Yes	Korea 2005-2018
Lee[57]	199	II, IIIA	63%	NR	-	9 factors	-	Taiwan 1990-1999
Müller[58]	118	N2	43%	NR	-	17 factors	-	Germany 2013-2018
Yoon[59]	862	N1	15%	1.34	-	10 factors	-	Korea 2004-2018
Shin[60]	305	N1	21%	1.59	-	8 factors	-	Korea 2003-2009
Borghetti[61]	202	N1	9%	NR	-	17 factors	-	Italy 2001-2011

Inclusion criteria: Studies comparing the extranodal extension descriptor versus other R categories, published from 2000 to 2023, with at least 100 patients total, and using a method of adjustment for confounders. A HR of >1 indicates worse survival in the second of the two cohorts being compared.
[a]HR is for recurrence-free survival.
Color coding: green, statistically significant; yellow, not significant.
ENE, extranodal extension; HR, hazard ratio; MSQSR, Mid-South Quality of Surgical Resection database; NR, not reported (but statistical significance reported); OS, overall survival.

effusion are generally not considered appropriate for resection, but in the select patients who do, the resection is classified as R1 (if otherwise meeting R0 criteria). This seems intuitively logical, but data directly comparing this with other R1 descriptors are limited. Survival was similar among patients with a malignant effusion who underwent resection (R1) and those with a positive margin (90% microscopic, 10% macroscopic residual, R1,2) in one study (adjusted for eight potential confounders, but involving a limited number of malignant effusion cases).[10] In addition, reasonable long-term outcomes are consistently reported in patients with pleural dissemination undergoing resection. The eighth and ninth edition analyses have not addressed this, but in the seventh edition analysis, such patients had a 5-year OS of 31% if N0 R0 (22 patients) and 24% if N0 R-any (87 patients).[63] Similar results are found in Figure 3 among patients undergoing resections meeting criteria for R0 other than the pleural dissemination.[39,44,46,47] Many studies corroborate this.[64–73] A substantial proportion of these patients never experience a pleural recurrence (or recurrence at any site). Although not well defined, approximately two-thirds of patients undergoing resection of pleural M1a tumors involved pleural tumor nodules, and outcomes may be better after macroscopic complete resection of pleural nodules versus when a malignant effusion is present.[65–67,70] Limited data have been reported regarding resection of tumors with pericardial dissemination.[70]

Thus, consistent data suggest that outcomes are similar in patients with pleural dissemination undergoing macroscopic complete resection and those undergoing an R1 resection defined by other criteria (but comparisons across studies should be interpreted cautiously). Moreover, it is intuitively logical to consider a resection in the face of pleural dissemination as R1—concern of microscopic residual exists despite no visible tumor remaining.

R2 Descriptors

The R2 category denotes macroscopic tumor remaining after resection. It is intuitively logical to distinguish this from a complete (R0) or a microscopic margin positive (R1) resection. Data on outcomes after R2 resections are limited (see R-Status Categories section).

The seventh and eighth edition R-classifications specifically mention macroscopic residual disease at the site of extranodal extension or pleural nodules. Nevertheless, this is not meant to imply anything other than macroscopic residual at such sites. It would avoid potential confusion to focus the R2 descriptor on the gross residual tumor (without mention of extranodal extension or pleural nodules).

Finally, R2 includes lack of resection of involved nodes.[6] This seems intuitively logical, but limited data exist. A cohort of 14 such patients exhibited similar survival after resection as those undergoing an R1 or R2 resection as defined by other descriptors.[10] Good communication between the surgeon and pathologist is needed to avoid confusion with respect to R2 status.

Proposed Ninth Edition R-Classification

On review of the evidence and considerations discussed in the previous sections, some modifications to the R-classification are proposed (Table 7). The table includes changes from the eighth edition intended to improve clarity and a summary assessment of the basis for the descriptors.

The uncertain descriptors of positive pleural lavage cytology result or CIS at a bronchial margin are more explicitly identified as R1(un) descriptors. Highest node involvement is interpreted to mean that tumor is present in the highest (most cephalad) node station (lowest node station number) assessed, rather than an individual node.

The recommendation regarding a complete node assessment is clarified to apply to node stations rather than individual nodes ($\geq$6 stations, with at least station #7 and two additional mediastinal stations). It is important that the surgeon labels nodes (e.g., #10, #11), whether submitted separately or en-bloc with the specimen. Node stations invasively assessed preoperatively (e.g., endobronchial ultrasound, mediastinoscopy) and intraoperatively count collectively toward this descriptor. Actual dissection of a node station that documents absence of any nodes (e.g., #L2) counts as a station that was evaluated (if clearly documented in the operative report). The same applies regarding N1 node stations dissected by the pathologist (with documentation in the pathology report). For endobronchial ultrasound, documentation of no nodes or only nodes less than 5 mm within a node station counts as an assessment. If the tissue submitted from a node station reveals no nodal tissue, or there is insufficient tissue (e.g., aspiration cytology) to allow a definitive diagnosis, it counts as a negative assessment of that station (this assumes that clinicians will exercise judgment and consider a second assessment of the station if the negative/nondiagnostic result is suspected to be a false negative).

If a limited node assessment reveals no involved nodes, the tumor is classified as N0 by IASLC, AJCC, and UICC; if no nodes at all are assessed, it is classified as NX.[4–6] The resection in both of these scenarios is

Table 7. Residual Tumor After Surgical Resection

Symbol	Name	Descriptor	Evidence Basis[a]
R0	No residual	No identifiable tumor remaining, negative surgical margins, adequate node assessment,[b] and highest node station assessed is negative	Reference
R0(un)	Uncertain residual	Limited node assessment[b]	Moderate[c]
		Highest station assessed is positive	Conflicting
R1(un)		R1(is) carcinoma in situ at the bronchial margin	Conflicting
		R1(cy+) pleural lavage performed with malignant cytology	Strong
R1	Microscopic residual	Microscopically positive surgical margin but no visible tumor remaining[d]	Good
		Extranodal extension of an involved hilar or mediastinal node[e]	Conflicting
		Malignant pleural or pericardial nodules or effusion[f]	Moderate
R2	Gross residual	Gross (visible or palpable) tumor remaining[d]	Intuitive
		Involved nodes not resected	Intuitive
RX	Unknown	Margin cannot be assessed	Intuitive

[a]Overall assessment of amount, consistency, and strength (e.g., accounting for confounders, generalizability) of evidence of within-category homogeneity and between-category discrimination regarding the descriptor.
[b]Recommended assessment is ≥6 node stations (including subcarinal and two other mediastinal stations).
[c]Appears generally justified, but not defined across tumor subgroups.
[d]Applies to any site of tumor resection (i.e., primary tumor, involved nodes, resected pleural implants, resected extrathoracic metastasis).
[e]Applies when identified microscopically, regardless of how the nodes are resected (individually, in fragments, en-bloc packet of an entire node station)—provided there is no gross tumor remaining.
[f]This classification (R1) applies if a resection has been accomplished that meets criteria for R0 in a patient with a malignant pleural (or pericardial) effusion or resected nodules.

classified as R0(un) (provided the resection meets other criteria for R0).

The seventh and eighth edition descriptions of the R-classification[3,6] mentioned a lobe-specific node dissection as defined by the European Society of Thoracic Surgeons[74] as an alternative to the 6-station definition of a complete node assessment. Nevertheless, the technical difference is limited—the lobe-specific assessment still requires 6 node stations; the difference is in which mediastinal stations are recommended based on the lobe involved. A recent detailed study found identical OS comparing resections defined as R0 by the IASLC 6-node/station definition or by a lobe-specific definition (n = 1119; 2009–2019).[10] Another detailed study found involvement of N2 node stations not included in the lobe-specific definition in a substantial minority of resections, in both single N2 (N2a) and multistation (N2b) cohorts (n = 1779; 1980–2009).[75] Implementation of a general system is easier than a lobe-specific system. Therefore, the R-subcommittee recommends the more general 6-station definition of a complete node assessment, with the assumption that knowledgeable surgeons will include the stations most likely to be involved in an individual patient.

Extranodal extension is defined as a finding on pathologic evaluation of hilar and mediastinal nodes. This applies (provided there is no gross tumor remaining) regardless of how the nodes were resected (as intact individual nodes, in fragments, or as a node packet involving an entire node station). Extranodal extension is not contingent on identification of a resection margin around the nodes (or whether there is extension to a resection margin). It does not apply to intraparenchymal nodes, which presumably are surrounded by a margin of the resected lung. The definition of extranodal extension includes tumor that is directly extending beyond the node capsule into perinodal tissue, including discontinuous tumor deposits in lymphatics or perinodal fatty tissue. By the general UICC/AJCC rules, isolated tumor cells (defined as isolated cells or clumps of cells <0.2 mm in diameter, often identified by special staining techniques) are not counted toward the TNM categories or stage group assignment. Such a finding in hilar/mediastinal tissues is not included in the R-classification. Nevertheless, micrometastases (tumor deposits 0.2–2 mm in largest dimension) in perinodal tissues count as extranodal extension.

When a resection involves several R descriptors, the overall R designation is based on the highest R descriptor that applies. Direct communication between the surgeon and pathologist is encouraged to resolve questions whether or not a surface with exposed tumor represents a surgical margin.

The R-subcommittee recommends using the R-classification only in the context of a surgical resection and not consider expansion to describe response to nonsurgical treatment modalities, as was previously suggested[8]; this is congruent with current UICC policy.[76] The definitions and descriptors are clearly focused on a surgical setting. Issues regarding the definition of response in other settings are not addressed (e.g., response after stereotactic body radiosurgery, pseudoprogression after immunotherapy). The meaning of a complete response after targeted therapy (with frequent emergence of resistance) is different than complete tumor resection. Classification systems of response designed specifically

for nonsurgical treatment modalities should be used instead of the R-classification.

The R-subcommittee recommends that the R-classification applies to tumor resection at any site (i.e., the primary tumor, intrathoracic lymph nodes, pleural nodules, or distant metastases). Specifically, if resection of oligometastatic distant metastases is undertaken (e.g., adrenal, brain metastases), the R-classification should apply to describe the completeness of the procedure. The R-subcommittee recommends following the UICC policy[76] of recording the site of resection—for example, R0 (thorax) or R0 (adrenal).

With the increasing use of definitive local therapy for oligometastatic disease, it is important to define how the R-classification applies when definitive local therapy is not delivered to all sites of disease simultaneously. The eighth edition AJCC and UICC books contain statements that are internally conflicting and ambiguous[5,76]; IASLC has not addressed the issue in the past.[6] The R-subcommittee proposes that the R-classification applies to a specific surgical procedure—and not count tumor in another site that is to be addressed at another time (perhaps with another treatment modality). It is important to clearly communicate the completeness of a resection, even if it is only one part of the treatment plan. It is also critical to acknowledge that another site of tumor remains to be addressed; this is essential for accurate recording in databases. Recording the site of resection—for example, R0 (thorax) and the M1 category—accomplishes this. This approach would be able to accommodate separate steps in the management strategy, a combination of treatment modalities, and communicate the completeness of a specific step.

Discussion

In conjunction with proposed revisions for the ninth edition TNM classification of lung cancer, the R-subcommittee has undertaken refinement of the R-classification. In general, the existing classification is supported by available evidence, although in many areas, it is limited. Many clarifications align with how studies have been applying the R-classification. Therefore, we anticipate that the ninth edition R-classification can be implemented easily. We hope that these revisions facilitate consistent recording of the R-status in health care records around the world.

We believe that this review provides as solid a basis for refinement of the R-classification as is currently possible despite limitations in the available data. Understanding whether an observed difference reflects the resection completeness or simply an association with a confounding anatomic-, patient-, or setting-related factor is a particular challenge. This review addressed this by emphasizing studies that have adjusted for at least some confounders. As a crude measure, the tables list the number of factors used. Nevertheless, this does not shed light on unaddressed domains of confounding, how closely the factors used approximate the actual potential confounders, and statistical limitations when the number of events is low.

The R-classification is not part of a prognostic model. Outcomes are assessed only to judge whether a potential R-descriptor is consequential enough to include. The R-status is a categorization of the physical presence of residual tumor after resection. Thus, the purpose of the R-classification allows conclusions to be drawn despite ambiguities in the available data on outcomes. Furthermore, by providing clear definitions, the R-classification establishes a universal way that terms are understood, data are collected, and results are reported. This facilitates ongoing research and the day-to-day ability to communicate and evaluate the applicability of clinical trials and guidelines to individual patients.

There are clearly areas of ambiguity that require more work. For example, although a thorough node evaluation is generally supported, this does not apply to all tumors. Several considerations need to be evaluated to figure out how best to address this. The increased complexity would hamper implementation if the R-classification only applied to some tumors or involved different definitions depending on tumor characteristics. Analysis of the impact of the extent of node assessment in the ninth edition IASLC database is planned. The Japan Clinical Oncology Group has completed accrual ($n = 1500$) to a randomized trial of systematic versus selective node dissection for cI–II NSCLC; results are anticipated in 2027.[77]

Although the recommendation for assessment of six node stations to fully define the pathologic stage remains, this should not be interpreted as a quality metric. Designing (and implementing) quality metrics is not the purview of the SPFC and requires consideration of factors such as validity (consistency of linkage to improved outcomes), feasibility (ability to measure and translate into practice), and relevance (variability in existing practice and applicability of the indicator).

The extranodal extension descriptor also requires improvement. Current data are conflicting and likely influenced by unaccounted confounders. Particularly with the subdivision of the N2 category in the ninth edition (N2a and N2b), this needs to be studied more thoroughly to understand whether extranodal extension itself is important or simply a marker of tumor burden or technical challenges during node dissection.

Aspects of the parenchymal margin assessment need additional attention, particularly as sublobar resection is

gaining importance and peripheral tumors have replaced central endobronchial tumors as the predominant tumor location. The SPFC has decided that "spread through air spaces" (STAS, a microscopic finding adjacent to the primary tumor) should be an additional histologic descriptor and not a component of the T- or R-classification.[78] Should finding foci of AIS at a parenchymal margin be included in the R-classification? Arguments against this include the fact that, when observed, most foci that likely are AIS histologically do not progress in 10 years.[79–81]

Techniques that can detect evidence of tumor in the bloodstream (e.g., circulating tumor cells, cell-free DNA) are not addressed in this paper. A thoughtful exploration is needed to define what role, if any, this should play in a classification of the completeness of surgical resection. Considerations include assay availability, standardization, false negative rates, broad applicability versus only with specific molecular markers, and context (e.g., immediately postoperatively, long-term surveillance). The most important issue is probably whether it is appropriate to view tumor detection in the blood as a measure of a surgical procedure, anatomic tumor extent, a prognostic factor, or a useful marker to guide patient management.

In conclusion, the R-subcommittee has assembled available evidence to inform revisions to the R-classification of lung cancer. Although the evidence generally has upheld the R categories—R0, R(un), R1, and R2—the review has also pointed out opportunities to clarify the definition of some descriptors in these categories. We hope that the proposed refinements of the R-classification will facilitate communication about the type of resection accomplished as the ninth edition becomes implemented. We also hope that review of the available data and knowledge gaps will stimulate research by the global thoracic community and promote continued progress.

CReDIT Authorship Contribution Statement

Frank C. Detterbeck: Conceptualization; Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing-original draft; Writing-review and editing.

Marcin Ostrowski: Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing-original draft; Writing-review and editing.

Hans Hoffmann: Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing-original draft; Writing-review and editing.

Ramón Rami-Porta: Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing-original draft; Writing-review and editing.

Ray U. Osarogiagbon: Investigation; Methodology; Supervision; Validation; Visualization; Roles/Writing-original draft; Writing-review and editing.

Jessica Donnington: Writing-review & editing.

Maurizio Infante: Writing-review & editing.

Mirella Marino: Writing-review & editing.

Edith M. Marom: Writing-review & editing.

Jun Nakajima: Writing-review & editing.

Andrew G. Nicholson: Writing-review & editing.

Paul van Schil: Writing-review & editing.

William D. Travis: Writing-review & editing.

Ming S. Tsao: Writing-review & editing.

John G. Edwards: Writing-review & editing.

Hisao Asamura: Writing-review & editing.

Disclosure

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from AstraZeneca, personal fees from GE Healthcare, personal fees from Eli Lilly, personal fees from Gilead Sciences, personal fees from Pfizer, outside the submitted work; In addition, Dr. Osarogiagbon has a patent Lymph node specimen collection kit issued, and a patent Method for collecting lymph nodes issued and Board Chair, Hope Foundation for Cancer Research (SWOG); Board of Scientific Advisors, National Cancer Institute; Steering Committee, National Lung Cancer Roundtable; Scientific Advisory Board, Lung Cancer Foundation of America; Scientific Advisory Board, GO2 Foundation; Scientific Advisory Board, Druckenmiller Center for Lung Cancer Research, Memorial Sloan Kettering Cancer Center; Scientific Advisory Board, LUNGevity Foundation. Founder, Oncobox Devices, Inc.

Appendix

IASLC Staging and Prognostic Factors Committee

Hisao Asamura (chair), Keio University, Tokyo, Japan; Valerie Rusch (chair elect), Memorial Sloan Kettering Cancer Center, New York, New York, USA; Ramón Rami-Porta (past chair), Hospital Universitari Mútua Terrassa, Terrassa, Spain; Luiz Henrique Araujo, Brazilian National Cancer Institute, Rio de Janeiro, Brazil; David Beer, University of Michigan, Ann Arbor, Michigan, USA; Pietro Bertoglio, IRCCS Azienda Ospedaliero Universitaria di Bologna, Bologna, Italy; Ricardo Beyruti, University of São Paulo Medical School, Sao Paolo, Brazil; Andrea Bille, Guy's Hospital, London, United Kingdom; Souheil Boubia, Department of Thoracic Surgery, University Hospital Ibn Rochd, Laboratoire de Pathologie Cellulaire et Moléculaire Hassan II University of Casablanca, Casablanca, Morocco; Elisabeth Brambilla, Centre Hospitalier Universitaire, Grenoble, France, University of Grenoble Alpes, Grenoble, France; A. K. Cangir, Ankara University Faculty of Medicine, Ankara, Turkey; David Carbone, The Ohio State University, Columbus, Ohio, USA; Vanessa Cilento, Cancer Research And Biostatistics, Seattle, Washington, USA; Casey Connolly, IASLC, Denver, Colorado, USA; Gail Darling, University of Toronto, Toronto, Canada; Frank Detterbeck, Yale University School of Medicine, New Haven, Connecticut, USA; Daniel Dibaba, Cancer Research And Biostatistics, Seattle, Washington, USA; Xavier Benoit D'Journo, Aix-Marseille University, Marseille, France; Jessica Donington, University of Chicago, Chicago, Illinois, USA; Wilfried Eberhardt, West German Cancer Centre, University Hospital Essen, Essen, Germany; John Edwards, Northern General Hospital, Sheffield, United Kingdom; Megan Eisele, Cancer Research And Biostatistics, Seattle, Washington, USA; Jeremy Erasmus, M. D. Anderson Cancer Center, Houston, Texas, USA; Wentao Fang, Department of Thoracic Surgery, Shanghai Chest Hospital, Jiaotong University Medical School, Shanghai, People's Republic of China; Dean Fennell, Leicester Cancer Research Centre, Department of Genetics and Genome Biology, University of Leicester and University Hospital of Leicester National Health Service Trust, Leicester, United Kingdom; Kwun Fong, University of Queensland Thoracic Research Centre, Brisbane, Australia; Françoise Galateau-Salle, Centre Hospitalier Universitaire, Caen, France; Oliver Gautschi, Cancer Center, Cantonal Hospital Lucerne, Lucerne, Switzerland; Ritu R. Gill, Beth Israel Lahey Health, Boston, Massachusetts, USA; Dorothy Giroux, Cancer Research And Biostatistics, Seattle, Washington, USA; Meredith Giuliani, The Princess Margaret Cancer Centre/University Health Network, Toronto, Ontario, Canada; Department of Otolaryngology - Head and Neck Surgery, The University of Toronto, Toronto, Ontario, Canada; Jin Mo Goo, Seoul National University, Seoul, Republic of Korea; Seiki Hasegawa, Hyogo College of Medicine, Nishinomiya, Japan; Emily Goren, Cancer Research And Biostatistics, Seattle, Washington, USA; Fred Hirsch, Center for Thoracic Oncology, Tisch Cancer Institute, Mount Sinai Health System, New York, New York, USA; Antje Hoering, Cancer Research And Biostatistics, Seattle, Washington, USA; Hans Hoffman, Technical University of Munich, Munich, Germany; Wayne Hofstetter, M. D. Anderson Cancer Center, Houston, Texas, USA; James Huang, Memorial Sloan Kettering Cancer Center, New York, New York, USA; Philippe Joubert, Quebec Heart and Lung Institute, Quebec, Canada; Kemp H. Kernstine, The University of Texas Southwestern Medical Center, Dallas, Texas, USA; Keith Kerr, University of Aberdeen, School of Medicine and Dentistry, Aberdeen, United Kingdom; Young Tae Kim, Seoul National University, Seoul, Republic of Korea; Hong Kwan Kim, Samsung Medical Center, Seoul, Republic of Korea; Hedy Kindler, The University of Chicago Medical Center, Chicago, Illinois, USA; Yolande Lievens, Radiation Oncology Department, Ghent University Hospital and Ghent University, Ghent, Belgium; Hui Liu, Sun Yat-Sen University Cancer Center, Guangdong Sheng, People's Republic of China; Donald E Low, Virginia Mason Medical Center, Seattle, Washington, USA; Gustavo Lyons, Buenos Aires British Hospital, Buenos Aires, Argentina; Heber MacMahon, University of Chicago, Chicago, Illinois, USA; Alyson Mahar, School of Nursing, Queen's University, Ontario, Canada; Mirella Marino, IRCCS Regina Elena National Cancer Institute, Rome, Italy; Edith M. Marom, University of Tel Aviv, the Chaim Sheba Medical Center, Tel Aviv, Israel; José-María Matilla, Valladolid University Hospital, Valladolid, Spain; Jan van Meerbeeck, Antwerp University and Antwerp University Hospital, Antwerp, Belgium; Luis M. Montuenga, Center of Applied Medical Research, University of Navarra, Pamplona, Spain and Centro de Investigación Biomédica en Red de Cáncer,

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APPENDIX 2. Chairpersons and Members of the Subcommittees of the Lung Cancer, Thymic Epithelial Tumors, Pleural Mesothelioma and Esophageal Cancer Domains of the IASLC Staging and Prognostic Factors Committee

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Lung Cancer Domain Vice Chair. Kemp H. Kernstine.

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Lung Cancer Domain Neuroendocrine Tumors Subcommittee. Ming Tsao (chair), Andrew G. Nicholson, (co-chair), Ricardo Beyruti, Frank Detterbeck, Wilfried Eberhardt, Pier Luigi Filosso, Yolande Lievens, Eric Lim, Geoffrey Liu, José-María Matilla, Natasha Rekhtman, William Travis, Jeff Yang, Yasushi Yatabe.

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Lung Cancer Domain Lymph Node Chart Subcommittee. Shun-ichi Watanabe (chair), Jin Mo Goo (co-chair), Hisao Asamura, Hans Hoffman, James Huang, Kemp H. Kernstine, Yolanda Lievens, Raymond U. Osarogiagbon, Paul Martin Putora, Ramón Rami-Porta, Valerie Rusch, Paul Van Schil, Jeff Yang.

Lung Cancer Domain Validation and Methodology Subcommittee. Frank Detterbeck (chair), Alyson Mahar (co-chair), Hisao Asamura, Meredith Giuliani, Mirella Marino, Raymond U. Osarogiagbon, Valerie Rusch.

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Lung Cancer Domain Database. Paula Ugalde (chair), Pietro Bertoglio (co-chair), Sarit Appel, Philippe Joubert, Catherine Labbe, Hongxu Liu, Gustavo Lyons, José-María Matilla, Robert Samstein, Ricardo Terra, Maria Teresa Ruiz Tzukazan, Benny Weksler.

Cancer Research And Biostatistics. Vanessa Cilento, Daniel Dibaba, Megan Eisele, Dorothy Giroux, Emily Goren, Antje Hoering, Katie Nishimura, Adam Rosenthal.

Thymic Epithelial Tumors Domain

Enrico Ruffini (chair), James Huang (co-chair), Usman Ahmad, Sarit Appel, Andrea Bille, Souheil Boubia, Cecilia Brambilla, A. K. Cangir, Frank Detterbeck, Conrad Falkson, Wentao Fang, Pier Luigi Filosso, Giuseppe Giaccone, Nicolas Girard, Francesco Guerrera, Maurizio Infante, Dong Kwan Kim, Marco Lucchi, Mirella Marino, Edith M. Marom, Andrew Nicholson, Meinoshin Okumura, Andreas Rimner, Anja Roden, Charles B. Simone II.

Thymic Domain T descriptor. Andrew Nicholson (chair), Cecilia Brambilla, A. K. Cangir, Maurizio Infante, Mirella Marino, Edith M. Marom, Meinoshin Okumura.

Thymic Domain N descriptor. Wentao Fang (chair), Frank Detterbeck, Pier Luigi Filosso, Marco Lucchi, Edith M. Marom, Charles B. Simone II.

Thymic Domain M descriptor. Nicolas Girard (chair), Usman Ahmad, Sarit Appel, Conrad Falkson, Wentao Fang, Giuseppe Giaccone, Dong Kwan Kim, Edith M. Marom, Andreas Rimner.

Thymic Domain Database subcommittee. Pier Luigi Filosso (chair), Usman Ahmad, Andrea Billè, Souheil Boubia, Frank Detterbeck, Wentao Fang, Nicolas Girard, Francesco Guerrera, James Huang, Dong Kwan Kim, Meinoshin Okumura, Enrico Ruffini.

Pleural Mesothelioma Domain

Valerie Rusch (chair), Anna K. Nowak (co-chair), Pietro Bertoglio, Andrea Billè, Ayten K. Cangir, Dean Fennell, Françoise Galateau, Ritu R. Gill, Seiki Hasegawa, Hong Kwan Kim, Hedy Kindler, Joseph Friedberg, Jan van Meerbeeck, Isabelle Opitz, Harvey Pass, Marc de Perrot, David Rice, Andreas Rimner, Robert T. Ripley, Jennifer Sauter, Ming S. Tsao, David Waller, Andrea Wolf.

Esophageal Cancer Domain

Wentao Fang (chair), Xavier D'Journo (co-chair), Gail Darling, Jeremy Erasmus, Mark Ferguson, Wayne Hofstetter, Hong Kwan Kim, Donald Low, Paula Ugalde.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *Journal of Thoracic Oncology* at www.jto.org and at https://doi.org/10.1016/j.jtho.2024.03.021.

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