Uncertain resection for localized cN0M0 non small cell-lung cancer: the crucial prognosis of suboptimal lymph node assessment

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Introduction

Surgery remains the gold standard in the treatment of early stages of lung cancer.To achieve longer overall survival, complete resection of the tumor and careful lymphadenectomy are essential. Thus, incomplete resection, defined as residual disease within the resection margin, is associated with poor survival. However, this definition does not take into account inadequate and limited surgery where examination does not ensure that all disease has been removed, particularly with regard to lymph node assessment.

The concept of uncertain resection R(un) was defined in 2005 by IASLC to highlight inadequate and limited resections and focused on intraoperative lymph node assessment. Although complete lymphadenectomy is recommended even in cN0M0 patients, the effect of R(un) in these patients has never been studied.

The main objective was to compare the overall survival of complete resections (R0), uncertain resections R(un) and incomplete resections (R1) for cN0M0 patients. The secondary objective was to develop a classification that predicts the long-term survival of these patients by identifying the most important predictors of survival for R(un) patients.

Methods

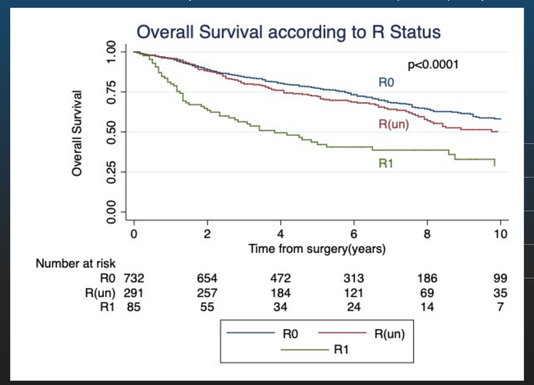
We include **cN0M0 patients** who underwent an anatomical lung resection for NSCLC from 2008 to 2018 at Toulouse University Hospital. We retrospectively reclassified tumours according to 8th edition of TNM stage and IASLC R-status based on pathologist reports.

According to the IASCLC definition, **complete resection** R0 was defined by **free resection** margins (bronchial, vascular, peribronchial, around the tumor, or at the margins of any resected tissue). Lung resection had to be accompanied by **systematic nodal dissection or lobe-specific nodal dissection**. The minimum number of lymph nodes removed was considered to be, at least, six with three from the intrapulmonary and hilar nodal stations and three from the mediastinal nodal stations, always including the subcarinal. **No extracapsular lymph node extension** was found and the **highest mediastinal lymph node removed might be tumor-free**. **Otherwise, tumors were declared as uncertain resection R(un).**

The primary outcome was overall survival according to the R classification system. Secondary outcomes were to determine whether uncertain resection was an independent factor in mortality, to identify specific criteria affecting R(un) and R1 survival, to perform subcategorization of R classification predicting survival.

Results

Of the 1108 cN0M0 patients, we identified 732 (66.1%) R0 patients, 291 (26.2%) R(un) patients, and 85 (7.7%) R1 patients.



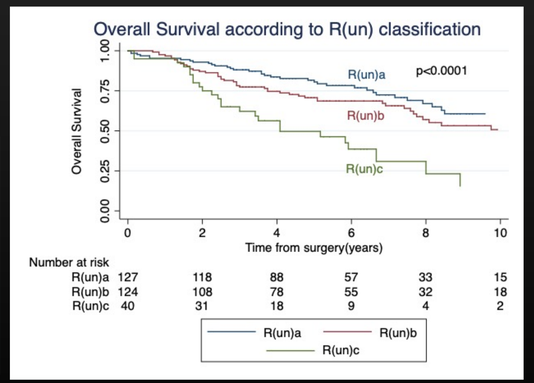
Survival characteristics of the study population

	All Patients n=1108	R0 n=732	R(un) n=291	R1 n=85
Median Survival (months) [95%CI]	137[118-153]	NA[126-NA]	**122[96-148]**	46[28-78]
3-Year Survival rate (%) [95%CI]	81[79-84]	85[82-87]	**81[76-85]**	56[45-66]
5-Year Survival rate (%)[95%CI]	73[71-76]	77[74-80]	**73[67-77]**	44[32-54]
10-Year Survival rate (%) [95%CI]	54[50-58]	58[53-63]	**50[42-58]**	29[17-42]
Adjusted HR* [95%CI]	-	1.0(Reference)	**1.26[1.01-1.59]**	2.41[1.76-3.30]

*Adjusted HR for age at operation, sex, obesity, histology, extent of resection, cardiac and respiratory comorbidities, and pathologic T- category

We found substantial heterogeneity among R(un) patients with significantly different survival according to the R(un) definition criteria.
Therefore, we defined 3 new subgroups of R(un) to discriminate between populations of homogeneous survival.

R(un)c included all patients with lymph node involvement of the highest mediastinal node.
R(un)b included patients with less than 3 mediastinal lymph node sites examined or no station 7 nodes examined (without positivity of the highest mediastinal lymph node).
R(un)a included all other patients who did not meet the above criteria.



This difference was confirmed after adjustment with an adjusted hazard ratio of 1.31 (95%CI : 0.85-2.05) between R(un)a and R(un)b, of 3.88 (95%CI : 2.23-6.76) between R(un)a and R(un)c, and of 2.52(95%CI :1.50-4.22) between R(un)b and R(un)c.

Conclusion

Our study demonstrated the validity of the IASLC R classification in **cN0M0 patients**. By demonstrating the **heterogeneity of R(un)patients**, it pointed out the critical problem of suboptimal assessment of lymph nodes**. We proposed the creation of subcategories to identify high-risk patients and suggest closer follow-up.**

The goal is to spread knowledge about uncertain resection and its prognosis among surgeons and pathologists. If used in routine practice and included in pathologists' reports (which may be facilitated by the **introduction of the new R status in the next version of the TNM)** , it could also serve as **quality marker in anatomic resections for lung cancer**. It should be considered when planning and performing a resection to reduce recurrence and ultimately improve the prognosis of patients with NSCLC.

Take-home message

Uncertain resection is a prognostic factor and could become a quality marker in anatomic resections for lung cancer.
In our opinion, it should be included in the new TNM classification and used in routine practice.

We propose a new subclassification of R(un) that could lead to a closer follow-up

Disclosure :

All authors declare no conflict of interest

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