Editorial Commentary

Is it time to revise the International Association for the Study of Lung Cancer definitions of completeness of lung cancer resection?

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In a recent article published in the *Journal of Thoracic Oncology*, Lee *et al*. suggest that the International Association for the Study of Lung Cancer (IASLC) criteria for categorizing completeness of lung cancer resection should be revised and adapted to the pathologic type of the tumour, its biologic behaviour and its risk profile (1). Their conclusion is based on a detailed single tertiary care institution retrospective cohort study of 5,117 patients who had undergone complete (2,806 patients) or uncertain (2,311 patients) resections based on the IASLC definitions (2). Deconstructing their analysis cohort according to three lymph node evaluation criteria (adequate examination of mediastinal, hilar/intrapulmoary and subcarinal lymph nodes), they categorized resections meeting all three criteria as 'fully compliant' (meaning they met the IASLC definition of R0 resection; 2,806 patients), 'partially compliant' (met one or two, but not all three criteria; 1,959 patients), 'noncompliant' (did not meet any of the three criteria; 352 patients). The latter two groups met IASLC criteria for uncertain resection [R0(un)]. They focused attention solely on the intraoperative nodal assessment because an inadequate nodal assessment by IASLC criteria, that is, less than the minimum requirements for systematic nodal dissection or lobe-specific systematic nodal dissection (2), was the criterion for reclassification from R0 (no residual tumour) resection, as judged by the Union for International Cancer Control (UICC) criteria (3), to R0(un) in 97.4% of patients.

The comparative recurrence free survival (RFS) and overall survival (OS) results were paradoxical: the partially compliant and noncompliant [R0(un)] cohorts had significantly better survival than the fully compliant (R0) cohort (*Fig. 2* in Lee *et al*.) (1). That is, patients in the cohorts with a less rigorous lymphadenectomy lived longer than those whose nodal assessment fulfilled the recommended requirements. Those significant differences held in the aggregate groups of patients and in the clinical stage I, and adenocarcinoma subsets (*Table 1*). RFS and

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Table 1 Five-year survival of fully compliant, partially compliant and noncompliant groups

Survival	FCG	PCG	NCG	P value
Five-year survival: global				
RFS	69.7%	74.5%	86%	<0.001
OS	80.1%	84.5%	89.9%	<0.001
Five-year survival: clinical stage I				
RFS	75.2%	79.5%	87.5%	<0.001
OS	75.2%	87.2%	88.6%	<0.001
Five-year survival: adenocarcinoma				
RFS	86.3%	88.3%	96.9%	<0.001
OS	92.4%	95.3%	97.6%	<0.001

FCG, fully compliant group; PCG, partially compliant group; NCG, noncompliant group; RFS, recurrence free survival; OS, overall survival.

OS were worse in the noncompliant group with clinical stage II. Moreover, when adenocarcinomas with no lepidic component were analysed separately, OS did not differ among the three groups. Furthermore, when stratified according to pathologic stage, RFS and OS did not differ in the comparison of adenocarcinoma in situ (AIS) combined with minimally invasive adenocarcinoma (MIA), stages IA1 and IA2, but OS was significantly worse (P=0.021 for the 3-cohort comparison) in the noncompliant group with stage IA3 (*Fig. S2* in Lee *et al.*) (1).

The authors recognize that major imbalances in key prognostic characteristics between the cohorts accounted for the appearance of better survival in the groups with inadequate nodal assessment. For example, 51.4% of patients in the noncompliant group had adenocarcinomas with lepidic component, compared to 13.3% and 22.6% of patients in the fully compliant and partially compliant groups, respectively (P=0.001); 20.3%, 2.5% and 4.9% of the non-, fully- and partially-compliant groups, respectively, were clinical stage IA1 (P=0.001); and 52.3%, 18.4% and 31.9%, respectively, were clinical stage IA2 (P=0.001); and pathologic stage I tumours were 91.5%, 58.2% and 75.2%, respectively (P=0.001). Consequently, the comparative wedge resection rates were 68.2%, 0.2% and 7.7%, respectively (P=0.001).

Given the foregoing, should we revise the IASLC definitions of completeness of lung cancer resection as the authors suggest? Is there sufficient evidence to support tailoring the definition to clinico-pathologic characteristics? If so, what characteristics? A careful consideration of these questions is in order, starting with brief historical context. When the IASLC proposed the definitions of complete, incomplete and uncertain resections in 2005 (2), there was no universally accepted classification of lung adenocarcinomas. The Noguchi classification, the forerunner of the IASLC/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification, although published 10 years before the IASLC completeness of resection definition, was not universally applied, and hard evidence on the indolence and excellent long-term survival of Noguchi types A and B was lacking (4). A multidisciplinary group of specialists from the IASLC, the ATS and the ERS proposed a new classification of lung adenocarcinomas, including the new entities AIS, MIA and lepidic predominant adenocarcinoma, in 2011 (5), which was incorporated into the World Health Organization book of thoracic pathology in 2015 (6).

We now know that AIS and MIA have a postoperative disease-free survival of 100% (7,8), because, by definition, AIS does not invade surrounding tissues and MIA does not invade beyond 5 mm; AIS and MIA do not disseminate distally via haematogenous or lymphatic spread; and adenocarcinomas with lepidic component have better survival than other subtypes (9). Therefore, lymphadenectomy may be unnecessary for AIS and MIA, and the lack of the recommended systematic nodal dissection or lobe-specific systematic nodal dissection should not preclude a complete resection. However, the diagnosis of AIS and MIA requires pathologic examination of the whole specimen and frozen section examination may be inadequate. The concordance of frozen section and definitive pathologic diagnosis varies, seemingly dependent on the number of studied cases, that is, the experience of the pathologist. He *et al.* reported a concordance of 63.24% in a series of 136 patients (10). The concordance reported by Shima *et al.* was 82.7% in 151 patients (11). With 803 patients, Liu *et al.* reported a concordance of 84.4% (12). Su *et al.* and Zhang *et al.* with 2,006 and 3,031 patients, respectively, reported the highest concordance of 86.4% and 93.7%, respectively (13,14). AIS and MIA of ≥1 cm are at risk of being upstaged at definitive pathologic examination to invasive adenocarcinomas, and, if no further treatment is indicated (completion lobectomy or anatomical segmentectomy, if not performed, or adjuvant chemotherapy, if appropriate), local recurrence is possible (13). Although others have reported 100% 5-year disease-free survival for invasive adenocarcinomas

previously diagnosed as atypical adenomatous hyperplasia, AIS or MIA during frozen section examination (14), these discordant results nevertheless indicate the need for caution in using the results of frozen section examination to decide on the extent of lung resection and intraoperative nodal assessment.

Spread through air spaces (STAS) is another important consideration. Kadota *et al.* triggered alarm when they reported significantly increased local recurrence in patients with lung adenocarcinomas of ≤2 cm who had undergone sublobar resections and whose specimens had STAS (15). Since then, many others have reported that the presence of STAS, whether understood as a true way of cancer dissemination or an artefact related to cell subtypes of intrinsically poor prognosis (16), is associated with worse prognosis in all cell types (17). There is currently no code for STAS in the tumour, node and metastasis (TNM) classification. Based on the anatomic extent of cancers, the TNM classification is supported by cytological or histologic confirmation of tumour extent: malignant cells in the pleural or pericardial fluids indicate M1a; in the bronchial secretions with no other evidence of tumour, TX; in the lymph nodes or bone marrow, as N0(i/mol+) and M0(i/mol+), respectively, the 'i' indicating their identification by morphological analysis, such as immunohistochemistry, and 'mol' indicating their identification by non-morphological tests, such as molecular analysis; finally, when found in pleural lavage fluid, the resection is deemed microscopically incomplete (R1cy+) (18). No code has yet been assigned to STAS, discussions are ongoing whether it should be a descriptor of the T or of the M component of the classification, whether it should be coded in a similar way to vascular invasion (V), lymphatic permeation (L) or perineural invasion (Pn), or whether STAS should be a qualifier of uncertain or incomplete resections. No decision has been made at the time of this writing, but there is every reason to think that STAS will have its place in the forthcoming 9th edition of the TNM classification.

Circulating cancer cells or tumour DNA (ctDNA) can be found in the blood stream, persistence or recurrence of which connotes a poor prognosis after treatment, including after radiotherapy or resection (19-23). This indication of minimal residual disease was not considered when IASLC definitions were published, but the final paragraph of that article stated that the definitions were not static and that they were subject to revision as new information was generated 'especially in the field of molecular biology, to identify residual disease'. Some have proposed that the presence of cancer cells or ctDNA in the blood should be considered a new component of the TNM classification that should be added as B for blood—TNMB—with two categories: B0 (no cancer cells in the blood) and B1 (cancer cells in the blood) (24). Perhaps, it is too early to consider the presence of cancer cells in the blood as a criterion of incomplete resection or as a new component of the TNM classification, given the lack of universal availability even in developed countries, but it will be considered in future revisions of the classification and of the IASLC definitions of completeness of resection as more data becomes available and the test becomes more generally used in clinical practice.

Lee *et al.* raise the possibility of using radiologic/pathologic tumour characteristics to tailor the intraoperative nodal assessment in early lung cancers. However, the revision of the IASLC definitions should be more comprehensive and not limited to this one technical aspect of the lung cancer resection. The revision should take into account the new pathologic findings of local invasiveness, such as STAS, and the presence of circulating cancer cells or ctDNA. This is a natural progression: from macroscopic assessment and procedural requirements to refinements in the microscopic examination of the resected specimen and the assessment of minimal residual disease by means of blood-based 'liquid' biopsy. With the emerging evidence, the definitions of completeness of resection will evolve. Any revision must be thoughtful and evidence-based. Emerging biomarkers might minimize the uncertainty in determining the completeness of lung cancer resection. Until then, the prognostic value of the existing definitions having been widely validated in large multi-institutional datasets, the *status quo* seems appropriate (25-28).

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Footnote

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