Editorial

Sublobar resections—current evidence and future challenges

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Several factors have contributed to a heightened interest in the oncologic efficacy of sublobar resections versus lobectomies for patients with non-small cell lung cancer (NSCLC). Firstly, the increased detection of early-stage disease in targeted screening programs has identified a growing number of patients with smaller tumours, which are more amenable to sublobar resections compared to tumours of higher clinical stage (1). Secondly, with improved understanding of pathological behavior and availability of high-resolution imaging, disease entities such as lung adenocarcinomas are refined into prognostic subgroups based on histological and imaging patterns that directly impact on the resection approach (2,3). Thirdly, with an ageing cohort of patients who present for surgical evaluation and treatment, there is a growing proportion of surgical candidates who will not tolerate lobectomies and require lesser resections. The introduction of stereotactic radiotherapy has warranted additional considerations in the selection process for the optimal treatment modality (4,5).

Despite these pressing concerns, the current evidence for sublobar resections versus lobectomies for early-stage NSCLC is controversial, with the only published randomized trial dating back to the 1980s from the Lung Cancer Study Group (6). A recent systematic review and meta-analysis identified 54 studies in the existing literature, including 1 randomized trial, 3 propensity score matched studies, and 50 observational studies. Overall, 29,641 patients who underwent lobectomies were compared with 9,318 patients who underwent sublobar resections. Importantly, this analysis divided sublobar patients according to "intentionally treated patients" and "compromised patients" depending on whether the patient could tolerate a lobectomy. This distinction in the patient selection process is critical in data interpretation, as patients who underwent sublobar resections due to limitations such as diminished pulmonary reserve or significant comorbidities were a distinct subpopulation compared to patients who could have tolerated a lobectomy. Outcomes of this meta-analysis demonstrated that overall survival was not significantly different between "intentionally treated" sublobar resection patients compared to lobectomy, but worse survival outcomes were observed in the "compromised patients" who underwent sublobar resections because they were not able to tolerate a lobectomy (7).

More recently, Speicher and colleagues reported the clinical outcomes of patients with stage IA NSCLC from the National Cancer Data Base, which included 29,736 patients who underwent lobectomies and 9,667 patients who underwent sublobar resections in the United States from 2003–2011 (8). This database did not distinguish the patients according to intentionally selected versus compromised cohorts, and found that lobectomy was associated with significantly improved 5-year survival compared to sublobar resection (66.2% *vs.* 51.2%, P<0.001). Furthermore, of the patients who underwent sublobar resections, nodal sampling was associated with significantly

improved survival, although this was not performed in 28.8% of the study population. The authors of this study emphasized that nodal sampling was an integral part of the surgical management of NSCLC, and sublobar resections should be limited in the current clinical setting to patients who cannot tolerate a lobectomy. Similar conclusions were drawn by a propensity score analysis using the same database by Khullar *et al.* (9). Data from the Surveillance Epidemiology and End Results (SEER) database also reported worse outcomes for segmentectomy compared to lobectomy, even after adjusting to patient and tumour factors (10).

The recent publication by Dziedzic *et al.* further explored the outcomes of lobectomy versus sublobar resection in patients with stage I NSCLC from the Polish National Lung Cancer Registry (11). This retrospective study included 6,905 patients treated from 2007 to 2013, and a propensity score analysis matched 231 patients who underwent lobectomy, segmentectomy and wedge resection. Within the unmatched patients, the authors found no differences in perioperative mortality between the three treatment groups, but a long-term survival benefit for lobectomy and segmentectomy over the wedge resection group. After propensity matching according to gender, age, histology, grade and date of resection, a similar finding of superior long-term outcomes was identified for lobectomy compared to wedge resection, but the difference between segmentectomy versus wedge resection was less apparent. The strengths and weaknesses of this study largely reflected those of other national databases, with a large number of consecutive patients included for analysis, but potential selection bias for each treatment arm according to intrinsic patient factors. The authors did emphasize that data submission to the Polish National Lung Cancer Registry was mandatory, which was an advantage over some of the voluntary databases in the United States. Anatomical resection with lymphadenectomy were also standardized according to the authors, although important details of intraoperative lymph node management were not specified, and analysis of outcomes were not presented as they were for the National Cancer Data Base, which demonstrated superior outcomes for sublobar resections that underwent lymph node sampling (8). It should be noted there is currently a lack of standardized reporting on the intraoperative examination of intersegmental lymph nodes and resection margins. One recent study has demonstrated the important impact of intraoperative frozen sections on converting a planned segmentectomy into a lobectomy (12). Without such thorough examination, segmentectomy treatment groups may have worse outcomes due to misidentification of N1 disease. Although guidelines are in place for lymph node dissection for lobectomies, such recommendations are lacking for sublobar resections, and further investigations in this area are warranted.

A number of challenges hinder the data analysis and interpretation of clinical outcomes for lobectomy versus sublobar resections, especially in retrospective studies. One of the biggest challenges is mitigating the impact of selection bias. Sublobar resections are often performed based on the patient's inability to tolerate a lobectomy procedure, either due to limited pulmonary reserve or significant comorbidities. These patients will clearly have inferior overall survival outcomes due to non-cancer-related causes of death. Although Dziedzic *et al.* attempted to minimize the impact of potential confounders through propensity matching, the analysis did not match patients based on potentially prognostic factors such as respiratory function, functional status, or comorbidities. In addition, endpoints such as disease-free survival and cancer-specific survival were not assessed in the current analysis. Other potentially prognostic factors that may need to be considered when comparing sublobar resection to lobectomy include a wide range of tumour-related factors such as size, location, histopathologic subtype, presence of spread through air spaces (STAS), and standardized uptake value on positron emission test (8,13,14).

In summary, despite a heightened interest in the comparative oncological outcomes of sublobar resections versus lobectomies, there is limited robust clinical data in the current literature. National databases may offer the advantages of large patient cohorts and a "real world" view of outcomes in clinical practice, but are potentially flawed by selection bias. The only completed randomized controlled trial by the Lung Cancer Study Group was performed some three decades ago, but additional insight may come from the phase III Japanese randomized controlled trial (JCOG0802/WJOG4607L) (15), and the Cancer and Leukemia Group B Group (CALGB) 140503 trial (16). Until randomized data can present at least mid-term results of disease-free survival and local recurrence outcomes for patients who can tolerate either a sublobar resection or a lobectomy, the issue of oncological equivalence will likely remain controversial in the foreseeable future.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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