

## A complicated clinical problem: surgical treatment decisions for patients with early-stage lung cancer

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Toste *et al.* raise several concerns in their editorial. To our knowledge, the forthcoming eighth edition of TNM classification proposed that T1 disease could be subdivided into T1a ( $\leq 1$  cm), T1b ( $>1$  to 2 cm) and T1c ( $>2$  to 3 cm) (1). This suggests that the size of tumor becomes a more important factor for the prognosis of early stage lung cancer. Not only the subdivision into  $<1$  cm, 1 to 2 cm, and  $>2$  cm, but in addition, a recognition of the importance of component within the tumour, both clinically and pathologically by IASLC (2). In recent years, early CT screening for lung cancer has detected an increasing number of tumors, most of which have been small lung nodules ( $\leq 2$  cm). The focus of the ongoing debate among surgeons in this regard is the choice of surgical procedure (lobectomy, segmentectomy or wedge resection) for patients with early stage non-small cell lung cancer (NSCLC). To identify the appropriate surgical treatment for those with NSCLC ( $\leq 2$  cm), we conducted a retrospective study by using the Surveillance, Epidemiology, and End Results (SEER) database (3).

In this study, we confirmed that lobectomy remains the gold standard of treatment for early-stage NSCLC ( $\leq 1$  cm), and there has been no significant survival difference in tumors  $\leq 1$  cm that have undergone sublobar (segmentectomy and wedge) pulmonary resection (4). With the development of medical science, the evaluation of early

lung tumors' biologic behavior and prognosis only by tumor size has hardly satisfied clinicians, because imaging findings and the multidisciplinary pathological classification (5) stated by the International Association for the Study of Lung Cancer (IASLC), the American Thoracic Society (ATS), and the European Respiratory Society (ERS) have also played a crucial role in the prognosis.

As Toste *et al.* have mentioned, Maeyashiki and colleagues demonstrated that the solid component of imaging performance is a more unfavourable prognostic factor than the tumor size of ground-glass opacity (GGO) (6). Based on the IASLC/ATS/ERS classification, previous studies have shown that the prognosis of the micropapillary, papillary and solid predominant lung adenocarcinoma was poorer than lepidic predominant adenocarcinoma (7). Unfortunately, the relevant data on imaging and new lung adenocarcinoma classification have not been available for further analysis in the SEER database. Additionally, the SEER database also lacks data on preoperative cardiopulmonary function and complications, which could lead to the patients being compromised with sublobar resection. We hope that the ongoing prospective randomized controlled study on the effect of lobectomy compared with sublobar resection for early NSCLC could answer these questions (8,9).

Here and now, one problem is that the evaluation of prognosis between lobectomy and sublobar resection, which needs to be verified imperatively, especially for early stage NSCLC with CT performance, showed pure GGO (mainly for adenocarcinoma in situ or minimally invasive adenocarcinoma) and the lepidic predominant adenocarcinoma. Perhaps even a solid or micropapillary non-dominant component could have negative impact on survival (10,11). Another problem is how to make a rational clinical decision with the recurrence or relapse of early lung cancer patients who have been diagnosed at a very early stage. If the curative effect of lobectomy and sublobar resection for pure GGO and the lepidic predominant adenocarcinoma patients is similar, these patients will be able to preserve more lung function and have a second opportunity for surgery.

The main outcome in this study is overall survival (OS) and lung cancer-specific survival (LCCS), with no information of tumor recurrence and metastasis (progression free survival, PFS cannot be assessed) and adjuvant therapy (such as postoperative chemotherapy and targeted therapy). However, the assessment of tumor recurrence and metastasis is very important for the option of different surgical procedure. We recommend that future related researches should take PFS as the primary end point. Although it is common sense that the prognosis of early stage patients is very good, there are also many patients who have been experienced tumor recurrence and metastasis after surgery. So, it is particularly important to recognize these patients and ensure effective treatment.

Lymphadenectomy is a crucial and relevant topic during the treatment of early stage NSCLC between lobectomy and sublobar resection. It may lead to underestimating the stage of some patients on whom sublobar resection was conducted with hilar/intraparenchymal lymph node sampling, while others routinely received lobectomy with systematic lymph node dissection. But so far, there is no universal standard for lymph node sampling conducted by sublobar resection, and the assessment of lymph node metastasis mainly on the frozen section of the hilar and mediastinal lymph node.

Sublobar resection composed of intentional and compromised sublobar resection, and in compromised resection, maybe both margin and resection lymph node dissection (RLND) will be compromised, this was totally different from the intentional sublobar resection study designed by CALGB140503 and also JCOG 0802. Even in intentional type of sublobar resection, still much rooms

to be improved including indication, margin, LND, so our current study implies that if we not proper select the indication (GGO), margin, cell type, LND, the surgical results of lobectomy is still better than sublobar resection even in stage IA lung cancer in the real world.

We think the future of choosing whether to perform lobectomy, anatomical sublobar resection or even other forms of therapy (stereotactic body radiation therapy/local catheter based ablation) will be determined not just by measurements of survival or disease-free survival, but also by quality of life & functional measurements during and after therapy, particularly for high risk groups (the very elderly, poor pre-morbid). Therefore measurement of quality of life and functionality following oncological treatment in future better conducted study will be useful. This data is sadly lacking at the moment (12,13).

In conclusion, although our study has several limitations, it does serve as a meaningful guide for the treatment of early stage NSCLC. Moreover, we looking forward to the research results from the United States (CALGB 140503) and Japan (JCOG0802/WJOG4607L) could provide more clinical evidence for our puzzle of surgical treatment for early lung cancer (8,9).

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### Footnote

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

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