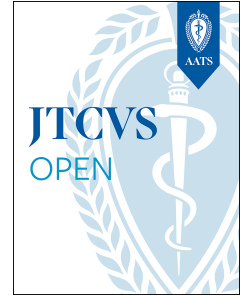


Journal Pre-proof

Surgery for patients with cTisN0M0 NSCLC: it's time to say less is more.

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23 **Central Picture Legend:** Dr. Ming Li, MD, and Dr. Qun Wang, PhD

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27 We read with great interest the retrospective study by Perez Holguin RA et al., reporting
28 that there is no difference in overall survival between sublobar resection and lobectomy
29 in patients with cTisN0M0 non-small cell lung cancer (NSCLC) with tumors ≤ 2 cm in
30 the cohort of the National Cancer Database¹. However, this study aroused our enormous
31 interest and caused a heated discussion: "What are the practical implications of this
32 study?" and "May these findings impact clinical practice?". Recently, results of
33 JCOG0802/WJOG4607L showed the benefits of segmentectomy versus lobectomy in
34 the overall survival of patients with small-peripheral NSCLC (tumor diameter ≤ 2 cm;
35 consolidation-to-tumor ratio > 0.5)². Similarly, results of another phase 3 trial,
36 CALGB140503, suggested that sublobar resection was not inferior to lobectomy for
37 disease-free survival in patients with peripheral NSCLC with a tumor size of 2 cm or
38 less and pathologically confirmed the node-negative disease in the hilar and mediastinal
39 lymph nodes³. It is worth noting that the number of patients with carcinoma in situ may
40 be minimal in these two trials. Interestingly, the latest results of JCOG1211 showed that
41 segmentectomy should be considered as part of standard treatment for patients with
42 predominantly ground-glass opacity NSCLC with a tumor size of 3 cm or less in
43 diameter⁴. Thus, we need to rethink whether a patient with carcinoma in situ should
44 undergo the procedure. Previous studies have reported that tumors of ≤ 2 cm with a

45 consolidation/tumor ratio of ≤ 0.25 were considered radiologically non-invasive
46 cancers with a low risk of metastasis⁵. Thus, although these tumors can be cured by
47 lobectomy or sublobar resection, surgical resection for some of these lesions that are
48 stable over a long period may not improve the prognosis. Lung resection leads to a loss
49 of lung capacity, even in partial resections, and is associated with a risk of adverse
50 events. Thus, observation can potentially avoid surgical resection, which may be the
51 least invasive approach for patients.

52 Therefore, we would appreciate it if the authors could answer the following questions
53 so that we could better understand this question.

54 **a.** Although the authors mentioned that TNM status was determined based on editions
55 6 and 7 in this study, how to define "cTis" is still very important. According to the 8th
56 edition TNM staging, "cTis" is defined as pure ground-glass lesions without solid
57 components. However, surgery is unnecessary for such patients with pure ground-glass
58 lesions.

59 **b.** If the "cTis" is defined as pure ground-glass lesions, or at least some patients have
60 pure ground-glass lesions, how are these lesions defined in imaging? Whether primary
61 lesions were evaluated using thin-section CT images.

62 **c.** What is the lung cancer-specific mortality of the two groups? Lung cancer-specific
63 mortality is one of the most important indicators for better comparison.

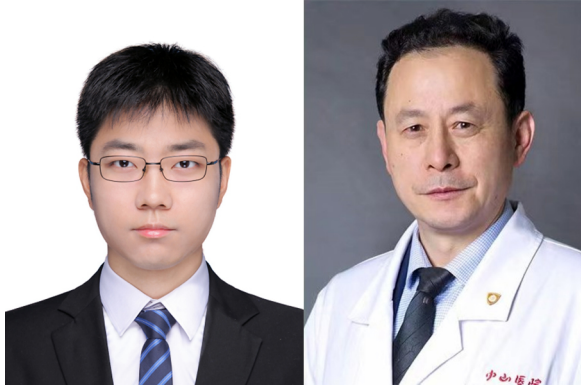
64 Given the opportunity, we are more than willing to share our data and outcomes of
65 patients with c-stage IA NSCLC presenting as ground-glass opacity. Let's agree to
66 disagree and base our arguments on further convincing studies.

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