

PERSPECTIVE

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Several problems in the progression of lung adenocarcinoma manifesting as ground-glass opacity

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Lobectomy can be traced back to 1960 [1]. For over half a century, lobectomy has been the standard surgical procedure for early-stage lung cancer. In 1995, Ginsberg retrospectively compared the impact of procedures on the survival of patients with stage T1N0 non-small cell lung cancer (NSCLC) [2]. The study established the gold standard position of lobectomy in the surgical treatment of lung cancer. In the latest National Comprehensive Cancer Network guidelines, segmentectomy or wedge resection is only an optional procedure for some patients. However, it has become clear that nothing can be set in stone.

With low-dose CT screening, the number of patients with early-stage lung cancer with ground-glass opacity (GGO) is increasing rapidly, especially in East Asian countries, and this form of lung cancer is becoming very common. The clinical oncology group at the National Cancer Center Hospital conducted a series of clinical studies on the imaging features, pathological subtypes, and prognosis of GGO. The first and most significant study was JCOG0201 [3]. The main study in Europe and America was still based on TNM staging to determine

surgical procedures. The Japan Clinical Oncology Group has conducted extensive studies on the differences in CT imaging manifestations. The results suggested that the postoperative prognosis and pathology (adenocarcinoma in situ, AIS; minimally invasive adenocarcinoma, MIA; invasive adenocarcinoma) were completely different depending on differences in CT imaging manifestations, especially consolidation to tumor ratio (CTR); furthermore, the results indicated that rather than conducting lobectomy on all patients, the surgical procedure should be individualized [4]. From these findings, the concept of determining surgical procedures based on CT imaging was proposed, and a series of prospective randomized controlled studies was subsequently initiated. JCOG0201 is thus considered a landmark study and has established non-invasive radiological criteria for lung adenocarcinoma on the basis of tumor maximum diameter and CTR, revising the position of lobectomy as the main treatment of early-stage lung adenocarcinoma.

The Japan Clinical Oncology Group further refined the grouping from the results of JCOG0201 and conducted a series of studies lasting 10 years (and longer): the JCOG0802, JCOG0804, and JCOG1211. The earliest studies conducted were JCOG0802 and JCOG0804, with a boundary of "0.25" because according to the results of JCOG0201, CTR less than 0.25 is considered a radiological non-invasive tumor. JCOG0804 is a single-arm phase II study that explored intentional lobectomy (including wedge resection and segmentectomy) in a population of patients with peripheral tumors with a maximum diameter of less than 2 cm and a solid component of less than 25% [5]. The preliminary results of JCOG0804 were unexpected, so the researchers further

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expanded the scope to distinguish the population with a $0.25 < \text{CTR} \leq 0.5$ from the JCOG0802 and added patients with a maximum tumor diameter between 2–3 cm and a $\text{CTR} \leq 0.5$; the tumor location was not limited to the peripheral type. This new study population was analyzed as the JCOG1211 [6]. A common issue with JCOG0804 and JCOG1211 is that neither challenges the existing guidelines. The critical study is JCOG0802, a randomized controlled phase III clinical trial comparing the differences between lobectomy and segmentectomy in long-term outcomes and lung function protection [7]. In April 2023, the results of JCOG0802 were published online: for patients with clinical stage IA NSCLC (tumor diameter ≤ 2 cm; $\text{CTR} > 0.5$), segmentectomy should be the standard surgical procedure, which will be the biggest challenge faced by lobectomy as the gold standard. For the intention-to-treat population, at a median follow-up of 7.3 years, the 5-year overall survival was 94.3% for segmentectomy and 91.1% for lobectomy (HR = 0.663; 95% CI: 0.474–0.927; one-sided $P < 0.0001$ for non-inferiority; $p = 0.0082$ for superiority). However, the 5-year recurrence-free survival was 87.9% for segmentectomy and 88.0% for lobectomy (HR = 0.998, 95% CI: 0.753–1.323, $P = 0.9889$), with no significant difference. Moreover, at the 1-year follow-up, the difference in the reduction of median forced expiratory volume in 1 s between the two groups was 3.5% ($P < 0.0001$), which did not reach the predefined threshold for clinical significance of 10%. Thus, following the criteria set in the study protocol, because of the superior 5-year survival and significant advantages in lung function protection of segmentectomy compared with lobectomy, segmentectomy should become the standard surgical procedure for small peripheral invasive lung adenocarcinoma. The JCOG0802 study is the first randomized controlled trial to show the benefits of segmentectomy versus lobectomy in overall survival. Notably, how to distinguish patients who are not suitable for segmentectomy remains an unanswered question. For patients with high-risk pathological subtypes, early occult lymph node metastasis, positive STAS during the procedure, and different radiological forms of ground-glass nodules, the refinement and differentiation of surgical procedures is a crucial issue, and there is currently a lack of relevant studies. The results of another multicenter, non-inferiority, phase III trial for patients with clinically stage T1aN0 tumors (GALGB140503) also suggested that sublobar resection was not inferior to lobectomy, and the outcomes were similar with the two procedures [8]. More importantly, this trial broadens the population and procedure: not only for patients with GGO, and the wedge resection is also included. Studies have shown that a higher proportion of solid components indicates a greater risk of tumor invasion and metastasis

and a greater similarity of their clinical manifestations and prognosis to pure-solid nodules; however, from the results of the prospective and retrospective studies in our center [9], nodules with ground-glass components and pure-solid nodules are significantly different in terms of tumor biological behavior, pathological subtype distribution, prognosis, and tumor immune microenvironment, which indicates that the two may be different types of lung cancer. Similarly, CTR itself is not a perfect indicator, and “ $\text{CTR} = 0.5$ ” is not strictly used to define the boundary between “GGO dominated” and “solid component dominated,” nor is it the boundary between pathological “AIS or MIA” and “invasive adenocarcinoma.” The presence of GGO itself may be an indication of sublobar resection, regardless of CTR. The significance of CTR or above trials lies in determining the surgical procedures from a clinical perspective, rather than relying on the intraoperative pathological assessment using a frozen section.

In the past few years, many studies on ground-glass nodules seem to have been confirming that for pulmonary GGO, especially those with low-solid components, radiological findings and pathological diagnosis are consistent, and the long-term survival of those nodules with pathological diagnosis of AAH/AIS/MIA is excellent. Based on these results, it is evident that the current management could be improved. Will surgical procedures be replaced by more “minimally invasive” procedures, thermal ablation or SBRT? Although thermal ablation (including microwave ablation and radiofrequency ablation) or SBRT is currently being explored in the treatment of pulmonary nodules, its indications are still very limited. We now do not have a definite answer, and perhaps it will take time and ongoing cohort studies to answer.

Early-stage lung cancer diagnosis and treatment modes in the past decade seem to be undergoing changes. However, some nodules without or with small solid components underwent complete resection because they were considered early-stage lung cancer and many even underwent lobectomy. The tumor’s development process has been considered linear, following the development from carcinoma in situ to minimally invasive and then to invasive status [10]. However, this linear process may be debatable because pathological diagnosis is a cross-sectional description. There is no effective method to linearly track a carcinoma in situ to confirm its eventual development into an invasive lesion. The observation of lesions by CT scan can be continuous and linear. In a prospective, observational clinical trial (NCT03723629), we followed up 3,000 patients with ground-glass nodules for up to 5 years. We found that that only a small number of nodules progressed; there was an increase in solid

components, which may mean that the tumor progressed from carcinoma in situ to minimally invasive or invasive adenocarcinoma, but this process still could not be confirmed by pathology. However, it is inevitable that these nodules' solid components—that is, the invasive components—have indeed increased. Several problems arise. First, not all nodules will progress; that is, the solid components may not increase. The nodules with increased solid components do not progress at the same speed; the driving and influencing factors and how to further analyze them remain unclear. Second, whether the change of corresponding pathological subtypes accompanies the increase of solid components is very important. For example, how the lepidic predominant subtype develops to the acinar, papillary, or even micropapillary solid subtypes is unknown. The sources and driving factors for the emergence of these different pathological subtypes are also unknown. Finally, in the latest WHO classification, as carcinoma in situ was described as a spectrum of pre-invasive lesions, questions remain as to the significance of adenocarcinoma with pure lepidic growth for adenocarcinoma presenting as pure GGO and whether there is a necessary correlation between the two.

In summary, the standard surgical procedures for early-stage lung cancer have undergone revolutionary changes. In the past 30 years, procedures have not only gradually shifted from open to minimally invasive approaches but have also been continuously refined and improved on the basis of staging and oncological characteristics. The understanding of surgery for lung cancer has also shifted from rough to standard and then to detailed. More research is required to determine the most effective strategy for surgical treatment of lung cancer.

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Authors' contributions

Ming Li, Junjie Xi, Qun Wang: Conceptualization; Ming Li: Writing—Original draft preparation; Junjie Xi, Qun Wang: Supervision, Writing—Reviewing and Editing.

Availability of data and material

Not applicable.

Declarations

Ethics approval and consent to participate

Not applicable.

Competing interests

The authors have no financial or other interests regarding the submitted manuscript.

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