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Commentary: The debate between surgery and stereotactic body radiation therapy in treatment of early non–small cell lung cancer: A new connotation is needed for an old topic

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CENTRAL MESSAGE

Although the debate on the choice of surgery or SBRT for early NSCLC is an old topic, it has new content, such as a smaller resection scope of surgery, the new GGO issues, and the concept of MRD.

Since the successful surgical treatment of lung cancer in the prior century, surgery has been the gold standard for treatment of early lung cancer. The concept of surgery seems unchanged, yet now there are many new theories (oncology), new knowledge, and new technologies (oncology and surgery). Thus, the connotation of surgery has changed greatly. Stereotactic body radiation therapy (SBRT) is an alternative to surgery for the treatment of early non–small cell lung cancer (NSCLC). SBRT can also provide favorable effect of local control, which poses a challenge to surgery in treating early NSCLC. However, the relative advantages and disadvantages of SBRT and surgery are still controversial. In 2015, Chang and colleagues[1] analyzed the data of 2 incomplete studies (STARS and ROSEL) and found that SBRT brought longer recurrence-free survival for stage I NSCLC with tumor diameter less than 4 cm; this report pushed the debate to a new height. At the same time, several retrospective studies performed by surgeons suggested that surgery was more effective. Obviously, the retrospective study by Littau and colleagues[2] also supported surgery, and the sample size was larger with more advanced statistical methods. The authors compared the efficacies of SBRT and surgery for patients with clinical stage I NSCLC who were treated between 2004 and 2016. Of the 26,080 eligible patients, 5465 received SBRT. The results showed that surgery had better efficacy for stage I NSCLC. The core of this topic is, after all, the oncological effect, whereas these studies were still based on the slightly old and single concept of anatomic "early lung cancer." In fact, there are many new data on the surgical treatment of early NSCLC that were not considered in previous studies.

RECONSIDERATION OF RESECTION SIZE OF EARLY NSCLC

Since 1995, lobectomy has been the standard of surgical resection for early NSCLC. In 2021 at the 101st annual meeting of the American Association for Thoracic Surgery, Asamura and colleagues[3] presented results of the long-awaited Japan Clinical Oncology Group (JCOG) 0802 study. The study compared the efficacies of segmentectomy and lobectomy in the treatment of peripheral NSCLC with tumor diameter 2 cm or less and consolidation/tumor ratio (CTR) 0.5 or greater. The primary end point was overall survival (OS), and secondary end points were postoperative pulmonary function, relapse-free survival, and rate of local recurrence. The study enrolled 1106 patients, of whom 554 underwent lobectomy and 552 underwent segmentectomy. There were 968 adenocarcinomas, including 923 patients with pathologically stage IA, and the mean diameter of

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the tumors was 1.6 cm (0.6-2.0 cm). There were 553 patients with CTR of 1. The median follow-up was 7.3 years. The 5-year OS after segmentectomy and lobectomy were 94.3% and 91.1%, respectively (hazard ratio, 0.663, 95% confidence interval, 0.474-0.927). The 5-year relapse-free survival between the 2 groups was not statistically different, being 88% and 87.9%, respectively. Compared with lobectomy, the death risk after segmentectomy reduced by 34%. The median decline rates of forced expiratory volume in the first second, 6 months and 1 year after segmentectomy were significantly better compared with that after lobectomy, namely, 10.4% versus 13.1% and 8.5% versus 12.0%, respectively. JCOG 0802 was the first phase III clinical trial that proved segmentectomy was statistically superior to lobectomy in the treatment of early-stage NSCLC in terms of OS and pulmonary function. The study also indicated that for peripheral NSCLC with tumor diameter 2 cm or less and CTR greater than 0.5, segmentectomy should be the standard treatment method. On the basis of the results of JCOG 0802, Japanese scholars are performing a prospective study on segmentectomy and large wedge resection in the same patient group that was examined in JCOG 0802 (tumor $\leq$2 cm, CTR >0.5)[4] and a repeat JCOG 0802 study of patients with 2- to 3-cm diameter tumors and CTR greater than 0.5. These studies indicate that the scope of surgery for early-stage NSCLC may be decreasing. In this context, it is not surprising that there is a local control method without surgery such as SBRT, and the results of the study by Chang and colleagues[1] are not surprising. There will still be room for debate on the choice of surgery or SBRT for the treatment of early NSCLC.

THE THINKING ON GROUND-GLASS OPACITY–LIKE ADENOCARCINOMA

The concept of ground-glass opacity (GGO) appeared with the advent of high-resolution CT. GGO is not only a new imaging concept but also a new clinical issue. According to the prognosis and follow-up results of GGO, the 8th TNM staging system and new classification of adenocarcinoma by the World Health Organization in 2015 clearly stated that the diameter of pure GGO and heterogeneous GGO with a diameter 3 cm or less should not be calculated in the T stages of the patients.[5] The measurement of T descriptor for semi-solid GGO is according to the solid component of the tumor. Therefore, pure GGO with a diameter 3 cm or less is not classified as T1a, but it belongs to carcinoma in situ. Histopathology has always been the only gold standard to decide the nature of a tumor, determine the treatment plan, and predict prognosis. However, with progress and deeper understanding of GGO-like lung adenocarcinoma, the black and white thinking of tumor histopathology has been challenged in the diagnosis of GGO-like lung adenocarcinoma; the clinician needs multidimensional indicators to judge the malignant behavior of GGO-like lung adenocarcinoma. Therefore, the 2011 multidisciplinary classification of pulmonary adenocarcinoma,[6] accepted by the World Health Organization in 2015, has excellently demonstrated the advantages of a multidisciplinary perspective. This histopathological classification based on multidisciplinary discussion is the first new classification of lung adenocarcinoma in the history of lung cancer pathology. The disciplines involved in the discussion included pathologists, imaging physicians, surgeons, respiratory disease experts, molecular biologists, and oncologists. The multidisciplinary approach has changed from "differentiation degree" of lung adenocarcinoma to "growth pattern," including precursor lesions, carcinoma in situ, minimally invasive adenocarcinoma, invasive adenocarcinoma, and variants of invasive adenocarcinoma. The pathology experts have associated each growth pattern with a specific degree of malignancy. More important, the new classification compares, under the microscope, the possible imaging manifestations for each growth pattern, it emphasizes the weight of imaging manifestations in judging the malignant biological behavior and prognosis of GGO-like lung adenocarcinoma. Again, it points out the importance of solid components in reflecting the malignant biological behavior of tumors, which is a great progress of lung cancer in recent years. Unfortunately, in the real world of clinical practice, some clinicians still do not fully understand the work of experts in multidisciplinary pathological classification. Instead, clinicians instinctively, consistently, and solely rely on the pathological reports to determine treatment strategies, neglecting the importance of multidisciplinary factors outside the microscope, especially the imaging in tumor malignant biology and prognosis.

The results of JCOG0201[7] showed that if the pulmonary tumors with a diameter 3 cm or less have a GGO component, the 5-year OS could be 90% or greater regardless of the T staging, and the tumor diameter only influences the survival of patients with solid tumors. The JCOG0201 investigators concluded that the index with best specificity to predict the microscopic histopathology of noninvasive lung adenocarcinoma was CTR. The specificity of tumor diameter 2 cm or less and CTR 0.25 or less in predicting pathological noninvasive lung adenocarcinoma was 97.5%. Although most scholars still use the microscope to determine whether a pulmonary tumor is invasive adenocarcinoma, the imaging findings seem to better reflect the infiltration at the level of clinical outcome. In a sense, the subtext of the new classification of multidisciplinary lung adenocarcinoma is if the pure GGO with a diameter of 3 cm or less was diagnosed under thin-layer, high-resolution, and standard-dose CT. Regardless of the growth pattern of the tumor under the microscope, it should be regarded as carcinoma in situ to avoid overtreatment caused by overdiagnosis and overstaging. Moreover, the results of JCOG 0804[8] implied that when a tumor of GGO-like

lung cancer was peripheral, then anatomic resection was not necessary, and wedge resection with a 5-mm margin could cure patients. Therefore, the GGO component is an independent favorable prognostic factor for early-stage NSCLC.

THE TECHNOLOGY OF SBRT MUST BE IMPROVED AND THE HOMOGENIZATION STANDARD MUST BE GUARANTEED

Surgeons often criticized the data of STARS and ROSEL for the poor quality of their surgical group (44% of grade 3-4 postoperative complication rate), which may have led directly to the results of Chang and colleagues.[1] As in surgery, the technical level of radiotherapy will also directly affect the prognosis of patients. Therefore, any comparative study of SBRT and surgery needs to balance the completion quality of the 2 treatment groups, which requires more data and, at least, data for the complications related to the 2 treatments.

THE DRAWBACKS OF THE NATIONAL CANCER DATA BASE (NCDB) DATABASE

The NCDB database has the following drawbacks: 1. The inherent confounding variables of retrospective analysis cannot be avoided. Therefore, it is impossible to assess the relationship between OS and disease-specific survival after surgery. 2. Whether the results showed that surgery is better than SBRT or SBRT is better than surgery, possible selection bias could not be excluded. Although the study by Littau and colleagues[2] excluded patients with comorbidities, patients in the surgical group may have been healthier. 3. The sample size of the SBRT group was small, the efficiency of research and analysis may have been insufficient, and there may have been type II errors. 4. There were many missing or incomplete data in both NCDB and Surveillance Epidemiology and End Results databases: (1) There were data that the authors could not confirm, such as the staging and treatment methods; (2) Because the pathological tissues could not be reevaluated, there was a lack of imaging and pathological review of patients and an absence of key pathological variables, such as margin status, lymphatic or vascular infiltration, resection completeness, and lymph node dissection extent. (3) NCDB and Surveillance Epidemiology and End Results databases do not include information on chemotherapy regimen, drugs, doses, and toxicities; (4) Although there are approximate anatomic targets of radiotherapy, there is a lack of information for further specific types of radiotherapy. (5) There is no information in the database about recurrence, so it is difficult to analyze the recurrence pattern. (6) There is a lack of preoperative evaluation information, such as general physical condition, weight loss, smoking status, and cardiopulmonary function (echocardiography and pulmonary function). Therefore, it is impossible to assess the true reason for sub-lobectomy.

THE ASSESSMENT OF MINIMAL RESIDUAL DISEASE

Even after curative surgery, a considerable proportion of patients with early NSCLC die of recurrence and metastasis. Recently, the concept of minimal residual disease (MRD) has attracted attention. MRD refers to the molecular abnormalities of cancer origin that cannot be found by traditional imaging (including positron emission tomography/computed tomography) or laboratory methods after treatment, but found by liquid biopsy, which represents the possibility of the persistence and clinical progress of lung cancer. Currently, the most common indicator for MRD is circulating tumor DNA.[9] Molecular abnormalities of lung cancer refer to the stable detection of circulating tumor DNA with 0.02% or greater in peripheral blood, including lung cancer driver genes or other class I/II gene variants.[10] The basic technology of MRD includes tumor-informed assays, an NGS panel, and tumor agnostic assays. However, these technologies are in the exploratory stage, and prospective studies are needed to determine their sensitivity, specificity, and predictive value. The possible use of MRD in early NSCLC is that a positive MRD after curative resection indicates a high risk of recurrence that requires follow-up management. MRD monitoring is recommended every 3 to 6 months postoperatively. Perioperative clinical trials of resectable NSCLC based on MRD are recommended and provide accurate perioperative treatment as much as possible. The activity of MRD in driver gene-positive and driver gene-negative patients should be evaluated. However, all of these are in the phase of clinical research and have not yet entered clinical practice.

Although the debate on the choice of surgery or SBRT for early NSCLC is an old topic, it has new content, such as a smaller resection scope of surgery, the new GGO issues, and the concept of MRD. All these factors will affect the choice of treatment for early NSCLC.

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