Editorial

Pulmonary segmentectomy for early stage non-small cell lung cancer: when, for which cases and how

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Times have changed since lobectomy was considered a curative surgery for lung cancer (1), and segmentectomy is now beginning to be recognized as an alternative surgical procedure for early stage lung cancer. Detailed qualitative diagnosis with thin section helical computed tomography (CT) and improved imaging techniques, such as positron emission tomography (PET), have made it possible to detect smaller lung cancers and at an earlier stage. Attempts at limited surgery and preservation of pulmonary function for these lung cancers are a natural progression. Segmentectomy has been reported to be equivalent in radicality and less invasive compared with lobectomy (2-4). Moreover, the results of a Japanese randomized controlled trial comparing lobectomy with segmentectomy for patients with clinical stage IA non-small cell lung cancer (NSCLC) [tumor diameter ≤2 cm; consolidation-to-tumor (C/T) ratio >0.5] (JCOG0802/WJOG4607L) showed the benefits of segmentectomy versus lobectomy in terms of overall survival (5). Although the indications for segmentectomy are expected to expand, there are still differences between institutions regarding the indications for segmentectomy, including ground-glass opacity (GGO) dominant lesions, and the detailed surgical modalities (intersegmental identification and dissection methods, with or without lymph node dissection, etc.). Wang *et al.* reported the right apical segmentectomy under uniportal video-assisted thoracoscopic surgery for bilateral synchronous pure GGO lesions, and also raised some important questions about segmentectomy for early stage lung cancer (6), including when, for which cases and how to perform a segmentectomy.

With improvements in imaging technology, thin-section CT is now commonly available, and several attempts to identify early stage lung cancer with less invasiveness have been reported. The JCOG0201 trial investigated the association between pathological invasiveness and radiological findings in patients with clinical T1N0M0 peripheral (in the outer half of the lung field) lung cancer to determine the indications for limited surgery, and revealed that pathologically non-invasive cancer can be predicted by a cut-off value of a C/T ratio of 0.25 with a specificity of 98.7% [95% confidence interval (CI): 93.2–100.0%] for lung cancer ≤2.0 cm in size (7). Based on these results, a trial was conducted to evaluate the efficacy and safety of sublobar resection for GGO dominant peripheral lung cancers with ≤2.0 cm in size and with a C/T ratio ≤0.25 (JCOG0804/WJOG4507L trial) (8). In this trial, intraoperative confirmation of a macroscopic surgical margin of ≥5 mm and the histology of the primary tumor by frozen-section were mandatory, and conversion to segmentectomy or lobectomy from wedge resection was at the surgeon's discretion. Wedge resection was performed in 79.3% of the cases, resulting in a 5-year relapse free rate of 99.7% (90% CI: 98.3–99.9%), with no local relapse. These results suggest that wedge resection might be sufficient when the radiologically non-invasive lung cancer is located in the outer third of the lung field, while a segmentectomy is required when sufficient margins are not secured.

There is also the question of when to operate on radiologically non-invasive tumors. Multiple GGO lesions in multiple different lobes on both sides, as in the case presented by Wang *et al.* (6), are frequently experienced and are commonly resected from tumors of larger diameter or those with a solid component. In a multicenter study that observed the natural history of pulmonary subsolid nodules, the frequency of pure GGO lesions developing into part-solid nodules during a 5-year follow-up period was low, at 5.6%, although 24% of part-solid GGO tumors with a solid component of 3 mm or less at the time of first detection showed a trend towards increase in the solid component at 2.4±1.3 years (9). This suggest that pure GGO and part-solid GGO tumors differ in terms of the optimal surgical timing and surgical procedure. A follow-up observation study is currently underway in Japan for radiologically non-invasive tumors with a maximum tumor diameter of ≤2 cm and C/T ratio of ≤0.25 on thin-section CT (JCOG1906 trial), and the results of this trial will be an important indicator in the future regarding optimal surgical timing. Actually, the indications and the surgical procedure are likely to be determined by taking into account the location of the tumor and radiologic findings, as well as the patient's age, request, and cardiopulmonary function in general.

Another important issue is the extent of lymph node dissection. Katsumata *et al*. compared the result of preoperative CT imaging with the pathological results in completely resected early stage lung cancer, and reported that lung cancer that is clinically T1a or less or with a C/T ratio of 0.5 or less is usually pathologically noni-invasive, with no nodal involvement and no vessel invasion (10). Zhang *et al.* analyzed the data on 2,749 patients with invasive NSCLC who underwent pulmonary resection with systemic lymph node dissection, and reported that tumors with a C/T ratio of ≤0.5 had no lymph node involvement (11). In the aforementioned JCOG0804/WJOG4507L trial (8), lymph node dissection was not mandatory for hilar and mediastinal nodes, and in more than 70% of cases no lymph nodes were removed. Based on these results, it can be said that lymph node dissection is not necessary for radiologically non-invasive tumors (≤2.0 cm in size and C/T ratio of ≤0.25). However, for tumors with C/T ratio >0.5 covered by the JCOG0802/WJOG4607L trial, intraoperative confirmation of the absence of metastases in the hilar lymph nodes is essential. If metastases are found in the hilar lymph nodes, a change of surgical procedure should be considered. The results of trials of segmentectomy for tumors with C/T ratio >0.25 to ≤0.5 are currently awaited (JCOG1211 trial).

Now that thoracoscopic surgery is more common, it is important to ensure an adequate surgical margin in addition to the correct intersegmental dissection when performing segmentectomy for lesions that cannot be palpated intraoperatively. As far as limited surgery is concerned, preventing local recurrence is of paramount importance. Various methods for intersegmental identification have been reported (12-16), such as intravenous indocyanine green (ICG) injection and near infrared thoracoscopy, which are now widely used to identify the intersegmental plane (12,13,17). Intravenous ICG administration is simple and rapid, and identification with ICG does not require the lung to be inflated and does not obstruct the surgeon's view during thoracoscopic surgery. The ICG method identifies the intersegmental planes along the course of blood flow, but methods for identifying the planes along the airways, such as inflation-deflation and jet ventilation, are also commonly used, and a combination of both might be even more useful. Moreover, it has been reported that more than one-third of p-T1N0M0 NSCLCs extend beyond one segment regardless of size (18), suggesting that attempts should be made to resect two segments or combine subsegmentectomy to ensure sufficient margins.

Currently, there is a transition in surgical approaches from thoracotomy to multiportal video-assisted thoracoscopic surgery (VATS), with further uniportal and robot-assisted thoracoscopic surgery (RATS). Uniportal VATS segmentectomy is now widely performed and satisfactory perioperative results have been reported (19-21). Uniportal VATS requires unique surgical techniques, and Wang *et al.* described the surgical procedure for uniportal thoracoscopic segmentectomy in detail, with excellent results (6). Whatever the approach, it is important that surgical margins around the tumor are ensured, correct intersegmental (and sometimes subsegmental) dissection is achieved, and residual lung function is preserved as much as possible by preserving the intersegmental veins. With regard to lung function, there is still room for debate on the effect of segmentectomy on preservation of lung function. In a randomized controlled trial confirming the noninferiority of segmentectomy to lobectomy (JCOG0802/WJOG4607L) (5), the median reduction in forced expiratory volume in 1 second (FEV1) at 1 year postoperatively was 12.0% in the segmentectomy group and 8.5% in the lobectomy group (between-group difference: 3.5%, P<0.0001), although the difference did not reach the predefined threshold for clinical significance of 10% at 1-year follow-up. However, various factors

that cannot be determined by lung function data alone might also contribute to long-term survival, such as improved subjective symptoms due to less residual lung and mediastinal excursion, better general condition, and easier access to treatment for a second cancer. The relationship between preservation of lung parenchyma and long-term survival will require further investigation.

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