

# Strategy of intentional limited resection for lung adenocarcinoma in situ

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Dr. Gang Shen (The Second Affiliated Hospital Zhejiang University School of Medicine, Hangzhou, China).

*Comment on:* Sagawa M, Oizumi H, Suzuki H, *et al.* A prospective 5-year follow-up study after limited resection for lung cancer with ground-glass opacity. *Eur J Cardiothorac Surg* 2018;53:849-56.

Submitted Apr 23, 2018. Accepted for publication May 01, 2018.

doi: 10.21037/jtd.2018.05.41

**View this article at:** <http://dx.doi.org/10.21037/jtd.2018.05.41>

The current issue of *European Journal of Cardio-Thoracic Surgery* published the remarkable work of Sagawa and associates (1), which demonstrated excellent postoperative outcomes following limited resection for small-sized lung ground-glass opacity (GGO) with an intraoperative pathological diagnosis of bronchioloalveolar carcinoma (BAC). The authors conducted a prospective, multi-institutional study of limited resection for these tumors. In their report, 39 of the 53 patients with an intraoperative pathological diagnosis of BAC underwent wedge resection, and the 5-year disease-specific and overall survival rates were 100% and 98.1%, respectively.

BAC is a subtype of lung adenocarcinoma that grows and replaces alveolar epithelial cells (2), and Noguchi and associates (3) defined localized BAC (type A) and localized BAC with foci of collapse (type B) as pathologically and biologically in situ noninvasive peripheral carcinomas. They reported that no cases of types A and B showed lymph node metastasis, and the 5-year survival rate for patients with these tumors was 100%. Noguchi's type A/B adenocarcinomas were almost equivalent to BAC in the third edition the World Health Organization histological classification, as well as adenocarcinoma in situ (AIS) in the new classification for adenocarcinoma (4). Because these noninvasive adenocarcinomas should develop no lymph node metastasis, these tumors are thought to be a good

indication for limited resection (5). In the study by Sagawa *et al.* (1), 73 patients with a tumor having a GGO ratio  $\geq 80\%$ ,  $\leq 2$  cm in size, and lower <sup>18</sup>F-fluorodeoxyglucose accumulation than in the mediastinum on positron emission tomography combined with computed tomography (CT) were enrolled, and 53 patients with an intraoperative pathological diagnosis of BAC and a negative surgical margin were ultimately considered eligible. During the follow-up period, two patients died because of bladder cancer and ileus, and the 5-year overall survival rate was 98.1%. The follow-up period of living patients ranged from 60 to 126 (average, 73) months, and there were no events during the observation period. The results of the study by Sagawa *et al.* seem similar to those of previous limited resection trials that addressed small GGO lesions with an intraoperative pathological diagnosis of noninvasive adenocarcinomas (6-10), and even in these studies, no recurrence was observed following limited resection during a median follow-up of 29-51 months. However, Yoshida *et al.* reported a few cases with postoperative surgical resection margin recurrence, which was detected approximately 5 years after limited resection in their trial (9,11). Moreover, we experienced a case with mediastinal lymph node recurrence detected 3 years after resection in our previous trial of limited resection, and re-evaluation of the patient's pathological specimens showed small cell

clusters in the air space (6,12). Thus, improved follow-up with closer attention may be required for definitive determination as to whether small GGO lesions with an intraoperative pathological diagnosis of noninvasive adenocarcinoma can be cured with limited resection.

Although many studies have documented strong correlations between pure GGO lesions on CT and noninvasive adenocarcinomas (13,14), pure GGO lesions could pathologically include invasive components and would not correspond to AIS (15). Previous studies reported that even among pure GGO lesions measuring  $\leq 2$  cm, 26–39% of lesions were pathologically diagnosed as invasive adenocarcinomas (15,16). Thus, many studies of limited resection, including the study by Sagawa *et al.*, which addressed small GGO lesions, utilized intraoperative pathological examinations with frozen sections for the pathological diagnosis of noninvasive adenocarcinomas, such as Noguchi's type A/B adenocarcinomas, BAC, or AIS (1,6-10). In the study by Sagawa *et al.* (1), 14 of the 72 enrolled patients (19%) were intraoperatively diagnosed with invasive adenocarcinoma, and these patients were treated as ineligible patients. However, discrepancies can occur between the results of intraoperative frozen section diagnosis and the final pathologic diagnosis, and there is a possibility that some patients with an intraoperative diagnosis of noninvasive adenocarcinoma undergoing limited resection would have a final diagnosis of invasive adenocarcinoma based on permanent pathological examination. In fact, in the study by Sagawa *et al.* (1), 6 of the 53 patients (11%) who underwent limited resection based on the intraoperative pathological diagnosis of BAC were diagnosed with invasive adenocarcinoma on permanent pathological examination. Although the surgeons offered completion lobectomy to these 6 patients with revised a pathological diagnosis of invasive adenocarcinoma, they decided not to undergo additional surgery. According to the studies of limited resection for intraoperatively diagnosed noninvasive adenocarcinomas, including the study by Sagawa *et al.* (1,6-10), the predictive values of intraoperative frozen section examination for noninvasive adenocarcinoma were ranged from 89–100%. The effects of various outcome factors, namely the skill of the pathologist, the cut portion of the tumor, and the definition of noninvasiveness, must be understood for intraoperative pathological examination of noninvasive adenocarcinomas (17), and this may be a major limitation for such limited resection strategies based on the intraoperative frozen section examination of noninvasive adenocarcinoma. Moreover, because AIS

may present as a part-solid GGO lesion due to alveolar collapse (18), some part-solid GGO lesions might include AIS, even though its proportion should be small. Thus, the limited resection strategy that addresses pure or high proportion GGO lesions might overlook patients with noninvasive adenocarcinomas presenting with a relatively low proportion of the GGO component on CT.

In the study by Sagawa *et al.* (1), 39 of the 53 eligible patients (74%) underwent wedge resection, and recurrence was not observed during the follow-up period of 73 months. Even in the previous studies of limited resection for intraoperatively diagnosed noninvasive adenocarcinoma (6,8-10), the majority of patients (93%) underwent wedge resection, and neither recurrence nor cancer-related death were observed during the median follow-up period of 30–51 months. These results suggested a possibility for curative treatment with limited resection, particularly with wedge resection, for intraoperative frozen section diagnosed AIS. However, wedge resection for small tumors is often challenging because of the small size and minimal palpability of the tumor, and it is crucial to obtain a clear surgical margin, especially surrounding the barely palpable GGO components (19). Furthermore, less invasive video-assisted thoracic surgery (VATS) has made tumor identification even more difficult. Although in an old study of limited resection for intraoperatively diagnosed noninvasive adenocarcinoma (6), pulmonary resection was performed via a conventional thoracotomy, in the study by Sagawa *et al.* (1), 48 of the 53 limited resections (91%) were performed using a VATS approach. In fact, one patient required an additional wedge resection because of positive cancer cells at the surgical margin identified on intraoperative pathological examination following the first wedge resection. General thoracic surgeons may find it stressful to perform wedge resection while securing an adequate surgical margin for minimally palpable small tumors through a VATS approach. Thus, identification of the location of such minimally palpable tumors in thoroscopic surgery using a novel lung-marking technique may be required; such methods include virtual assisted lung mapping, in which a preoperative bronchoscopic lung dye-marking technique utilizes three-dimensional virtual images based on thin-slice CT (19).

In some previous reports (20-22), prospective limited resection trials for small-sized non-small cell lung cancer (NSCLC) were conducted based on a concept different from that of wedge resection for GGO lesions with intraoperative diagnosis of noninvasive adenocarcinoma.

In these trials, patients with peripheral small NSCLC measuring  $\leq 2$  cm, regardless of the proportion of the GGO component on CT, were enrolled, and the majority of the enrolled patients underwent anatomical segmentectomy. Non-inferior postoperative outcomes in patients who underwent limited resection were demonstrated when compared with patients who underwent current standard surgical treatment with lobectomy. Thus, the authors concluded that limited resection, basically segmentectomy, should be considered as an alternative treatment approach for small-sized peripheral NSCLC, regardless of radiological characteristics and histological tumor subtypes, in low-risk patients with adequate pulmonary function for lobectomy. This limited resection strategy for small-sized peripheral NSCLC may be an option to solve the issues regarding wedge resection for small GGO lesions with an intraoperative diagnosis of noninvasive adenocarcinoma. Compared with wedge resection, anatomic segmentectomy has the theoretic advantages of evaluating hilar lymph nodes and a wider resection of the draining lymphatics, including intersegmental planes, commonly referenced as a source of residual cancer cells (17,23). Because of the reported superior locoregional control and postoperative prognosis of segmentectomy compared with wedge resection (24), patients who could be treated by wedge resection, such as patients with AIS or pure GGO lesions, are thought to show excellent postoperative outcome even after segmentectomy. Recent study demonstrated similar postoperative outcomes after lobectomy and segmentectomy even in patients with NSCLC having radiologically pure solid, small-sized tumor, which indicates invasive and aggressive carcinomas. However, the postoperative prognosis may have been poorer than that reported in previous limited resection trials, in which patients with NSCLC with GGO lesions were included (25). Therefore, non-inferior postoperative outcomes of patients with NSCLC other than AIS who undergo segmentectomy may be expected when compared to patients who undergo lobectomy, as previous studies of limited resection for small-sized NSCLC demonstrated (20-22). The limited resection strategy based solely on small tumor size can eliminate the need for intraoperative pathological examination, risk of preoperative patient exclusion based on a low proportion of the GGO component on CT, and the need for additional surgery based on the pathological diagnosis on permanent pathological examination. Moreover, segmentectomy can provide a sufficient surgical margin and reduce technical limitations for achieving appropriate margins compared

with wedge resection (17,23). Thus, segmentectomy should be an easier surgical procedure to secure negative and adequate surgical margins for minimally palpable small tumors through a VATS approach, rather than wedge resection.

Sagawa and associates reported the results of a prospective multi-institutional study of limited resection for GGO lesions with an intraoperative pathological diagnosis of BAC (1). In their report, 39 of the 53 patients underwent wedge resection, and the 53 eligible patients were postoperatively followed-up for a relatively longer period, that is, 73 months, than in the previous similar limited resection trials (6-10). No recurrence was observed during the follow-up period and thus it was suggested that small GGO lesions with an intraoperative pathological diagnosis of noninvasive adenocarcinoma can be cured by wedge resection. However, the limited resection strategy that addresses small GGO lesions with an intraoperative pathological diagnosis of noninvasive adenocarcinoma has some limitations, such as accuracy of intraoperative frozen section examination for noninvasive adenocarcinoma and technical difficulty in performing wedge resection for minimally palpable small GGO lesions with adequate surgical margins through the less invasive VATS approach. Although we still need to await for the results of ongoing prospective, randomized trials on lobar versus sublobar resection in patients with small peripheral NSCLC, segmentectomy based solely on small tumor size regardless of the proportion of GGO component may be the treatment of choice to solve these issues.

### Acknowledgements

None.

### Footnote

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

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**Cite this article as:** Koike T, Koike T, Nakamura M, Shimizu Y, Goto T, Sato S, Tsuchida M. Strategy of intentional limited resection for lung adenocarcinoma in situ. *J Thorac Dis* 2018;10(Suppl 17):S2018-S2021. doi: 10.21037/jtd.2018.05.41