



Appropriate treatment strategy for ground glass opacity—dominant non-small cell lung cancer

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Lobectomy with lymph node dissection long has been the standard surgical treatment for non-small cell lung cancer (NSCLC). A landmark study by the Lung Cancer Study Group in 1995 made comparison between lobectomy and sublobar resection (segmentectomy or wedge resection) of stage IA NSCLC, and demonstrated that sublobar resection was associated with inferior overall survival (OS) and three times the local recurrence rate compared to lobectomy (1). Two years later, another prospective, multicenter nonrandomized study demonstrated a similar trend for increased local recurrence in patients undergoing sublobar resection (2). Consequently, sublobar resection has been applied only in patients unable to tolerate lobectomy as a “somewhat poor quality” substitute. Over the decades, lung cancers, especially many small lung cancers consisting of ground glass opacity (GGO), are increasingly diagnosed at early stages through the widespread use of high resolution computed tomography (HRCT) and low-dose helical CT for screening (3). Accordingly, mainly after 2000, many reports have demonstrated that patients with lung adenocarcinoma consisting of GGO component have good prognoses, and could be candidates for sublobar resection (4-6). Asamura *et al.* (4) demonstrated that patients who diagnosed with GGO dominant lung adenocarcinoma have an excellent prognosis. This prospective, multi-institutional study [Japan Clinical Oncology Group (JCOG) 0201] has shown that the 5-year OS was 96.7% for patients with a consolidation/tumor ratio (CTR) ≤ 0.5 and a ≤ 30 mm tumor, and 97.1% for those with CTR ≤ 0.25 and a ≤ 20 mm

tumor. In addition, we demonstrated that patients with GGO-dominant (CTR ≤ 0.5) and ≤ 30 mm lung adenocarcinomas rarely had pathologically invasive tumors and had an excellent prognosis (5). This study showed that the 3-year recurrence-free survival (RFS) and the OS rates after sublobar resection were comparable to those after lobectomy, without significant differences in the GGO-dominant and ≤ 30 mm lung adenocarcinoma. Additionally, sublobar resection reportedly improves postoperative quality of life by preserving the pulmonary function (7,8). We emphasized that preserving as much healthy lung tissue as possible should result in less frequent operative morbidity and better postoperative quality of life. Moreover, the possibility for further resections is increased because patients with GGO-dominant lung cancers survive long enough to be at risk for next lung cancer (7). The lesser the amount of the initial resection, the more unrestricted the treatment options for subsequent lung cancers. Together with these situations, the speculation became whether patients with small lung cancer with GGO should undergo lobectomy, which is a more aggressive procedure than sublobar resection is. However, there is no clear evidence, because most of the previous reports were retrospective studies and their follow-up periods did not reach 5 years. To evaluate the validity of limited pulmonary resection for small adenocarcinomas with GGO clearly, Sagawa *et al.* (9) began a multi-institutional, prospective study in 2006 (JNETS 0601). With their criteria using HRCT, positron emission tomography imaging with 18F-fluorodeoxyglucose

(FDG-PET) and intraoperative pathologic examination, limited resection was performed safely without any recurrence after a 5-year follow-up, and with well-preserved postoperative pulmonary function. The outcomes of this study were satisfactory.

They included a maximum tumor diameter of 8–20 mm, GGO ratio >80%, lower FDG accumulation than the mediastinum (grade 1 FDG accumulation), and an intraoperative pathologic diagnosis of bronchoalveolar carcinoma. After 5 years of follow-up (60.0–126.3 months), the original lung cancer had not recurred postoperatively. The 5-year disease-specific and OS rates were 100% and 98.1%, respectively, and pulmonary function was minimally reduced after limited resection. Their results were more distinct than those of the previous studies and indicated that patients who met their protocol criteria did not require pulmonary lobectomy, and that limited resection, mainly wedge resection, was sufficient.

One concern about this study is that their inclusion criteria were so strict, including not only the HRCT findings, but also the FDG-PET findings and the intraoperative pathologic examination. Namely, they enrolled tumors with grade 1 FDG accumulation and Noguchi A or B according to an intraoperative pathologic diagnosis. They explained that they set these strict criteria because a nonnegligible number of invasive cancers can evade the HRCT check, even in pure GGO cases (10,11). But, such tumors are less frequent, thus, they could not collect a sufficient number of cases even as a multi-institutional study. Especially, an intraoperative pathologic diagnosis seems to be difficult in general, and it would not be completely accurate due to difficulties in examination with limited conditions of specimen processing. Actually, six of the 53 eligible patients (11.3%) had been diagnosed intraoperatively as having bronchoalveolar carcinoma, but were diagnosed ultimately with adenocarcinoma with mixed subtype. These six patients neither had recurrence nor died at 62.1–99.7 months after wedge resection. Additionally, in this study, of the 14 patients diagnosed intraoperatively with adenocarcinomas with mixed subtype, nine underwent wedge resections and have suffered neither recurrence nor death. These facts might indicate that intraoperative pathologic examinations are not always necessary, and preoperative HRCT findings (GGO ratio, CTR) are simple and useful tools to identify good prognosis NSCLC candidates for sublobar resection.

The nonrandomized confirmatory phase III study (JCOG 0804/WJOG 4507L) conducted by the JCOG and West

Japan Oncology Group (WJOG) evaluated the efficacy and safety of sublobar resection for GGO-dominant lung cancer defined with HRCT only by prospective, multicenter, and large cohort analysis (333 registered patients). The inclusion criteria were maximum tumor diameter ≤ 2 cm, CTR ≤ 0.25 , and no recurrence of the original lung cancer, and the 5-year RFS rate was 99.7% after limited resection, mainly wedge resection. Their results were more definite and indicated that HRCT is sufficient for choosing patients suitable for limited resection (12). It might be reasonable that limited resection should be performed as “standard therapy” for GGO-dominant lung adenocarcinomas with a maximum tumor diameter ≤ 2 cm.

Sublobar resection generally is considered for ≤ 20 mm lung cancer (7,13,14). However, the excellent prognosis of GGO-dominant lung cancer allowed us to consider expansion of adaptation for sublobar resection. We demonstrated that GGO-dominant and 21–30 mm tumors rarely showed pathologic invasiveness also, and there were no differences in survival analysis between patients with GGO-dominant and 21–30 mm tumors who underwent lobectomy and those who underwent sublobar resection. Thus, we indicated that GGO-dominant and 21–30 mm tumors also could be candidates for sublobar resection (5). It was necessary to distinguish between wedge resection and segmentectomy to clarify which procedure was used. We recommended segmentectomy and not wedge resection for sublobar resection of 21–30 mm tumors because these tumors could metastasize to lymph node, and taking a sufficient surgical margin often is difficult in a 21–30 mm tumor. In our study, two of the 84 patients (2.4%) with GGO-dominant and 21–30 mm tumors metastasized to lymph node, whereas no lymph node metastases were found in those with GGO-dominant, ≤ 20 mm tumors. Segmentectomy can approach hilar lymph nodes, whereas wedge resection cannot. In dissecting hilar lymph nodes and taking a sufficient surgical margin, segmentectomy would be superior to wedge resection. Currently, since September 2013, a nonrandomized confirmatory trial of segmentectomy (JCOG 1211) is ongoing with the aim of confirming the efficacy of segmentectomy for clinical T1N0 GGO-dominant lung cancer based on HRCT (15). Patient accrual already finished in November 2015 and the primary analysis will be performed in 2021. This study will be a pivotal trial of lung segmentectomy for early lung cancer. Further investigations on sublobar resection in the treatment of 21–30 mm lung cancer will be needed.

Some small-sized lung cancers with GGO have been

reported to have no pathologic invasiveness, and also have markedly longer doubling times than typical lung adenocarcinomas (16,17). Such tumors might not require surgical resection itself. Therefore, future studies will need to evaluate the validity of follow-up for GGO-dominant small lung cancer (maximum tumor diameter ≤ 2 cm and CTR ≤ 0.25) without pulmonary resection. Sublobar resection, even if wedge resection, is a surgical procedure requiring general anesthesia, and involves a considerable risk of adverse events. If surgery itself could be avoided, it might be said to be the least invasive treatment for patients. Ultimately, lung cancers that do not require surgery should be identified in the future.

Finally, Sagawa *et al.* (9) evaluated the validity of limited resection for small GGO-dominant lung adenocarcinomas prospectively and in a multi-institutional manner, and the outcomes were excellent and informative. From their results and JCOG 0804 mentioned above, we consider it reasonable that sublobar resection should be performed as “standard therapy” for GGO-dominant lung adenocarcinomas with a maximum tumor diameter of ≤ 20 mm. Regarding treatment for GGO-dominant lung adenocarcinomas with a maximum tumor diameter of ≥ 20 and ≤ 30 mm, we must wait for the results of JCOG 1211. Ultimately, lung cancers not requiring lung resection might be identified in the future. Further investigations in the treatment of GGO-dominant lung cancer will be needed.

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appropriately investigated and resolved.

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