Commentary

Microsized lung adenocarcinoma *vs.* small-sized lung adenocarcinoma: clinical characteristics, advantages and surgical implications

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Owing to the advances in imaging techniques such as thin-section computed tomography (CT) and 3D imaging, lung cancer can now be diagnosed at an early stage. The detection of small-sized lung cancer, including the 1 cm in diameter or less, is remarkably increasing. As a consequence, in 2015 the International Association for the Study of Lung Cancer (IASLC) proposed the new TNM staging system of lung and pleural tumours, in which T1 (≤3 cm) non-small-cell lung cancer (NSCLC) tumors were divided based on tumour size into T1a (≤1 cm), T1b (>1 and ≤2 cm) and T1c (>2 and ≤3 cm) (1). In this scenario several studies have investigated the role of limited resections, such as wedge and segmentectomy, in the treatment of small size lung cancer (<2 cm). Particularly, the hypothesis zero is the assumption that, in this type of lung cancer, no significant differences in survival rate are identified when patients who underwent lobectomy and those who were subjected to a limited resection are compared.

Recently, Zhu *et al.* (2) focused on the pathological characteristic as well as on the differences among patients with micro-sized (<1 cm) lung adenocarcinoma and small-sized (1.1–2.0 cm) lung adenocarcinoma undergoing either lobectomy or limited resection. Zhu and colleagues reported that, in their series, adenocarcinoma of 1.0 cm or less, defined as micro-sized lung cancer, has specific clinical characteristics and more favorable survival rates than a tumour of 1.1–2.0 cm. The authors identified several favorable predictors of overall survival of small lung adenocarcinoma including the adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) subtypes, the absence of nodal metastases and a pathological stage 0. Moreover, no significant differences between lobectomy and limited resection were observed in patients with small lung adenocarcinoma. Based on this evidence, the authors concluded that lung adenocarcinomas smaller than 1.0 cm in diameter and the AIS subtype evaluated by CT imaging or intraoperative frozen section may represent appropriate candidates for limited resection without proceeding to mediastinal lymph node dissection. However, several issues need to be considered prior to accepting these results.

First of all, the retrospective nature of the study by Zhu and coworkers represents a major limitation. Furthermore, the analysis was limited to a small series (366 patients) and for a short overall follow-up ranged from 2 to 73 months with a mean of 36 months (median: 29 months) (2). All oncological survival in the field of oncological surgery should be reported at least 5 years.

Also, all patients underwent mediastinal lymphadenectomy and the reported nodal metastasis for patients with a tumour size of 1.0 cm or less and 1.1–2.0 cm were 0 and 9%, respectively (2). However it should be noted that other studies report N1 and N2 involvement even in sub-centimeter lung cancer patients (3,4). In this setting, Riquet *et al.* (5) observed that pN1 and pN2 disease could be associated to <5 mm tumors, in up to 29.3% of their 187 patients with small lung cancer measuring 1 cm or less. Zhu *et al.* in the text reported that all patients were undergone to mediastinal lymphadenectomy according to NCCN but the median number of resected nodes was not reported. Can the type of lymphadenectomy performed or the pathological

sample assessment be the reason for this difference in pN involvement?

One of the major concerns in performing sublobar resections for small adenocarcinomas lies in the availability and the accuracy of frozen section. The authors supported in this study the importance of frozen section to confirm the presence of AIS in order to perform limited resection without mediastinal node dissections. Recently, He *et al.* (6) reported on a series of 136 patients diagnosed by either frozen sections or paraffin-embedded sections. In this series, the diagnostic yield was concordant in 86 (63.24%) of the cases intraoperatively diagnosed with AIS or MIA. Conversely, in 44 patients (32.35%) the intraoperative diagnosis was of mere adenocarcinoma as the extent of the infiltration could not be determined from frozen section. In the remaining six patients (4.41%), the frozen section and paraffin-embedded section diagnoses were discordant (6). Several reasons may explain frozen section errors and diagnostic delay including location of the tumor too close to the visceral pleura, the presence of interstitial inflammation or fibrosis, the absence of prominent atypia and the differential morphology in the deeper levels of the paraffin block. For this reason the frozen section can not be a discriminant for making a surgical and therapeutic choice.

On the other hand, with respect to the role of CT to confirm the AIS subtype, it should be recognized that CT can only provide a probability of identification based on retrospective series. Only one retrospective study reported by Cohen identified a 100% sensitivity of CT only for a solid component larger than 5 mm in diameter between several preoperative CT-features (7). We think that the high-resolution computed tomography may help to the preoperative and differential diagnosis of AIS and MIA from invasive adenocarcinomas (IACs) as recently reported by Zhang *et al.* (8).

Recently a new phenomenon, called "spread through air spaces" (STAS), has been reported in the pathology literature (9). STAS is defined as spread of lung cancer tumor cells into air spaces in the lung parenchyma adjacent to the main tumor (10). In a recent series, Kadota *et al.* have investigated the clinical implication of STAS in the pathological specimens of resected small (≤2 cm) stage I lung adenocarcinomas (n=411). Indeed, STAS was observed in 155 cases (38%). Interestingly, in the limited resection group (n=120), the risk of any recurrence was significantly higher in patients with STAS-positive tumors than that of patients with STAS-negative tumors (P<0.001). The presence of STAS correlated with higher risk of distant (P=0.035) and locoregional recurrence (P=0.001) (10). However, in the lobectomy group (n=291), presence of STAS was not associated with either any (P=0.50) or distant recurrence (P=0.76) (10). This study supports the evidence of the presence of STAS as a significant risk factor of recurrence in small lung adenocarcinomas treated with limited resection. Unfortunately, Zhu *et al.* did not analyze this important prognostic factor that should be taken into account in the future studies. Finally, another important prognostic factor that was not considered by Zhu *et al.* is the micropapillary histologic subtype (MIP). The MIP has been reported to be a high-grade morphologic pattern in lung adenocarcinoma and was associated with lymphovascular invasion (11). Some authors have wondered whether histologic subtyping can predict recurrence after limited resection (LR) *vs.* lobectomy (LO) (12). Nitadori *et al.* identified in a series of 734 consecutive patients the presence of an MIP component of 5% or greater as independently associated with the risk of recurrence in patients treated with LR (13).

In conclusion, lobectomy with hilar and mediastinal lymph node dissection is the current gold standard for treatment of early-stage lung cancers. Despite multiple studies have suggested that peripheral small (≤2 cm) lung cancers could be treated by limited resection alone, there are no established criteria for choosing limited resection over lobectomy for the treatment of lung adenocarcinomas to date (14-16).

However, a final answer will originate from for the RCT's currently active in the US and Japan.

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Footnote

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