

Does less equal more? The curious issue of small-sized lung cancer

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Lung cancer is the leading cause of cancer-related death and continues to be a major global health problem (1). Nevertheless, as a result of advances in imaging techniques and the introduction of screening programs, significant progress in early stage diagnosis and reduction in mortality is observed (2). The increasing detection numbers of early staged non-small cell lung cancer (NSCLC) elicit multiple questions concerning the appropriate treatment approach in these patients.

Lobectomy with R0 resection and lymph node dissection is considered a standard surgical procedure for patients with NSCLC (3,4). However, according to multiple studies, sub-lobar resections, particularly segmentectomy, seem to provide equivalent survival rates for small peripheral lung cancer (5-7), especially for patients with limited life expectancy (7-9). Still, limited resection is associated with an increased risk of positive surgical margins and inadequate lymphadenectomy (10), which should be taken into consideration. The question whether the limited resection might be considered oncologically equivalent to lobectomy in early-stage NSCLC still remains unanswered.

Furthermore, some authors suggested that systematic lymph node dissection could be limited or even avoided in case of small peripheral lung cancer. However, the lymph node involvement, including N1 and N2 stages, in sub-centimetre tumours has been reported in a range of 0-15% (11-13). As a result, the lymph node dissection still remains the standard approach. Nonetheless, the search for reliable N0 stage predictive factors continues (13,14).

The fourth edition of the WHO classification of Tumours of the Lung, Pleura and Thymus introduced the new classification for lung adenocarcinoma, as proposed by the International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society

(IASLC/ATS/ERS). The histological subtyping has been proven to be of prognostic significance and the introduced subtypes: adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA) are associated with a near 100% disease-specific survival after complete resection (15,16). Therefore, histological subtyping might be useful to determine the type of surgical management in stage I lung adenocarcinoma. However, the correct recognition of the predominant histological subtype in preoperative biopsy or intraoperative frozen section remains a challenge (17).

In the article 'Clinical characteristics and advantages of primary peripheral micro-sized lung adenocarcinoma over small-sized lung adenocarcinoma' by Zhu *et al.*, the authors retrospectively analysed data of 366 patients with primary peripheral lung adenocarcinoma and tumour size <2 cm in maximum diameter, treated in the period from 2007 to 2013. The objective of the study was to estimate the overall survival and lung cancer-specific survival in these patients (18).

The authors propose a new term 'micro-sized lung adenocarcinoma' defined as a tumour of 1.0 cm or less in maximum diameter, which seems unnecessary considering that these tumours have recently been defined as T1a in the eighth edition of the TNM Classification for Lung Cancer. According to Rami-Porta *et al.*, a progressive degradation of survival is observed for each 1-cm cut-point in tumour size and therefore a subclassification of present pT1 category into T1a (≤ 1 cm), T1b (>1 and ≤ 2 cm) and T1c (>2 and ≤ 3 cm) based on tumour size was proposed (19). Taking these results into consideration, the study by Zhu *et al.* confirmed that lung adenocarcinoma patients with a tumour of 1.0 cm or less in diameter had better 5-year overall and disease-specific survival rates than patients with a tumour of 1.1-2.0 cm (100% *vs.* 88.4% and 100% *vs.* 89%, $P < 0.001$, respectively).

Noticeably, the authors observed no significant difference in the overall and lung adenocarcinoma-specific survival rates with regard to the surgical procedure undergone. However, even though the 5-year overall and disease-related survival rates of 92.2% and 94.0% for patients who had lobectomy and 95.9% and 81.0% for patients who had limited resection ($P=0.349$, 0.124 , respectively) are statistically insignificant, these differences should be taken into consideration. Moreover, no significant differences between the tumour size and surgical procedure with regard to 5-year survival rates were observed. Perhaps it would have been interesting to include in the analysis the information about the limited resection type, i.e., to examine the postoperative survival after lobectomy *vs.* segmentectomy *vs.* wedge resection in patients with T1a and T1b tumours.

In the study, the patients routinely received chest CT scans and mediastinoscopy before surgical treatment. According to the Revised ESTS guidelines for preoperative mediastinal lymph node staging for NSCLC by De Leyn *et al.*, the mediastinal nodal staging in patients with suspected or proven NSCLC should include positron emission tomography (PET) and endosonography: endobronchial ultrasound with real-time guided transbronchial needle aspiration (EBUS-TBNA) and esophageal ultrasound with fine needle aspiration (EUS-FNA), which is recommended over surgical staging as the initial procedure. Moreover, in patients with suspected or proven <3 cm peripheral NSCLC with normal mediastinal and hilar nodes at CT and/or PET, direct surgical resection with systematic nodal dissection, without further preoperative mediastinal staging is advised (20). These recommendations seem applicable for patients included in the study by Zhu *et al.*

The authors suggested that lung adenocarcinoma tumours smaller than 1.0 cm in diameter and a subtype of AIS evaluated by CT images or intraoperative frozen section may be appropriate candidates for limited resection without mediastinal lymph node dissection. In the study the lymphatic metastasis rates for patients with a tumour size of 1.0 cm or less and 1.1–2.0 cm were 0 and 9%, respectively. However, the patients only underwent mediastinal sampling and systematic lymph node dissection was not performed. Therefore the results regarding the N stage may not be reliable and the proposal of omitting mediastinal lymph node dissection seems not justified—this important issue warrants further studies.

Additionally, the authors admitted that lack of the

recurrence data for the disease is a limitation of the study. Indeed, it would be of great interest to know the pattern of recurrence (local, mediastinal, distal) with respect to the size of the tumour and type of resection (segmentectomy, wedge), in order to determine the type of resection allowing to minimize the risk of recurrence.

In conclusion, the article ‘Clinical characteristics and advantages of primary peripheral micro-sized lung adenocarcinoma over small-sized lung adenocarcinoma’ by Zhu *et al.* confirms the findings of previous publications and re-opens the debate on the reassessment of the optimal treatment approach for small-sized lung cancer. Will the limited resection replace the today’s golden standard of early-stage NSCLC treatment: lobectomy with systematic lymph node dissection? The debate is open, the controversies remain. Many questions still need answering and further investigation is required.

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Footnote

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