

# Tiny lung adenocarcinomas: better prognosis with a word of caution

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The recent article published in the *European Journal of Cardio-Thoracic Surgery* by Zhu *et al.* (1) deals with the characteristics, surgical management and prognosis of resected lung adenocarcinomas  $\leq 1$  cm in size (micro-sized lung adenocarcinomas) and compares them with those adenocarcinomas  $>1$ – $\leq 2$  cm (small-size lung adenocarcinomas). From January 2007 to December 2013, 842 patients underwent surgical treatment for primary peripheral lung cancers at the Zhoushan Hospital, Zhejiang Province, China. After proper exclusions, 366 patients with lung adenocarcinomas (175  $\leq 1$  cm and 191  $>1$ – $\leq 2$  cm in size) remained for analyses. The tumours were staged with computed tomography (CT) and mediastinoscopy, brain magnetic resonance imaging or CT, bone scan and abdominal CT or ultrasound. Functional assessment of the patients included cardiopulmonary tests. Peripheral tumours underwent limited resection (segmentectomy or wedge) and intraoperative lymph node evaluation was performed according to the National Comprehensive Cancer Network guidelines. All patients were followed up for a mean of 36 months: 19 died from lung adenocarcinoma and 2 from other causes.

When the study variables were compared, in the micro-sized adenocarcinoma group, there were important statistically significant differences: patients were younger; there were more females and more patients with normal carcinoembryonic antigen (CEA) values; limited resection was more common; pleural invasion and nodal disease were very rare or absent, respectively; and all tumours were in stage 0 or IA, while those in the small-size group spanned all stages from 0 to IIIA (1).

The comparison of survival showed that micro-sized tumours had significantly better survival compared with small-size tumours: overall 5-year survival rates were 100% and 88.4%, respectively; and adenocarcinoma-specific 5-year survival rates were 100% and 89%, respectively. Female patients, those with normal CEA values, with adenocarcinoma *in situ* (AIS) and minimally invasive adenocarcinoma (MIA), without nodal disease, and those with stage 0 tumours had significantly better prognosis, considering both overall and adenocarcinoma-specific survival. Survival of younger patients ( $\leq 60$  years) had a marginally better prognosis when overall survival was considered, but not when cancer-specific survival was calculated. Although there were no statistically significant differences between lobectomy and limited resection in relation with overall and cancer-specific survival, limited resections had worse 5-year survival rates. At multivariate analysis, histopathological subtype, nodal disease and pathological stage were significant prognostic factors for overall and cancer-specific survival.

There are several issues that are worth commenting. Firstly, tumours  $\leq 1$  cm have now their specific category in the tumour, node and metastasis (TNM) classification of lung cancer: T1a (2). This fact will increase awareness of these tiny tumours that can be taken as the base ground for future studies. However, size is not the only tumour characteristic to take into account when making therapeutic decisions. Radiographic and pathologic features are important, too. In the series reported by Zhu *et al.*, more than two thirds of the patients with tumours  $\leq 1$  cm (117 or 67%) had AIS, a much higher rate compared with that of patients

with tumours  $>1$ – $\leq 2$  cm in size (45 or 24%). Micro-sized adenocarcinomas also had significantly higher rate of MIAs compared with small-size adenocarcinomas: 47 (27%) *vs.* 22 (11%) (1). AIS and MIAs also have their own coding in the 8<sup>th</sup> edition of the TNM classification: Tis (AIS) and T1mi, respectively. TisN0M0 (AIS) is stage 0 and T1miN0M0 is stage IA1, together with T1aN0M0 (3). In the article by Zhu *et al.*, these tumours were pathologically staged as such, but therapeutic decisions are taken based on clinical staging. Tis (AIS) commonly presents on high resolution CT as a ground glass opacity of  $\leq 3$  cm in size; and T1mi is a part-solid lesion of  $\leq 3$  cm in size consisting of a ground glass opacity part and a dense part seen on CT. The latter usually corresponds to the invasive part of the tumour and should not exceed 5 mm (3). Tis (AIS) and T1mi have very good prognosis, because they do not spread through stroma, vessels or visceral pleura. However, at clinical staging, their radiographic diagnosis is not absolutely certain. In addition, intraoperative diagnosis at frozen section may be difficult due to the intrinsic limitations of the technique (4). That is why caution should be exercised when choosing limited resections for these tumours, because they may show features of invasiveness larger than 5 mm in the definitive pathological study and a subsequent wider resection with systematic nodal dissection may be necessary. Caution should be taken, too, in solid micro-adenocarcinomas. The recently described spread through air spaces (STAS) is another factor to be considered when making the decision to perform a limited resection. This new pattern of invasion, in which tumour cells in the form of micropapillary structures, solid nests or single cells spread within air spaces beyond the edge of the main tumour, is associated with significantly higher recurrence rate in patients undergoing limited resection, but not in those undergoing lobectomy (5).

Secondly, Zhu *et al.* report no nodal disease in adenocarcinomas  $\leq 1$  cm in size (1). This low rate of nodal disease is more likely to be due to the nature of the tumours—Tis (AIS) and T1mi—than to their size. Riquet *et al.*, in a series of 187 patients who had undergone lung resection for lung cancers of  $\leq 1$  cm in size (98 or 52.4% adenocarcinomas), found pathologic (p) N1 in 18 (9.7%) and pN2 in 20 (10.7%). When the rate of nodal disease was analyzed in those patients whose tumours were  $< 5$  mm in size, it was found in 12 (29.3%) of 41, while it was present in 26 (17.8%) of 146 patients with tumours  $> 5$ – $\leq 10$  mm in size. Although the differences were not statistically significant, this report clearly shows that nodal disease can still be found

in very small tumours and that a proper systematic nodal dissection cannot be avoided (6).

Thirdly, limited resection (segmentectomy and wedge resection) for lung cancer is in constant debate. The only prospective randomized trial completed to date showed that limited resection was associated to a significant increase in recurrence. Mortality was also higher in the limited resection group, but did not reach statistical significance (7,8). The study is more than 20 years old, but a recent meta-analysis has confirmed that lobectomy is still better than limited resection for stage IA  $\leq 2$  cm tumours (9). This also has been observed in a recent population-based study comprising 15,760 patients with T1aN0M0 non-small cell lung cancers (10,493 or 66% adenocarcinomas) from the Surveillance, Epidemiology and End Results database who underwent lobectomy, segmentectomy or wedge resection. Lobectomy was associated with better survival than limited resection both in patients with  $\leq 1$  cm tumours and in those with tumours  $> 1$  to 2 cm in size. Segmentectomy was better than wedge resection in the group of patients with larger tumours, but not in those with tumours  $\leq 1$  cm in size. In this subgroup of patients the choice of wedge resection should imply consideration of surgical experience, patient profile and tumour characteristics (10). On the other hand, when the temporal trends are analysed, it is obvious that the survival after lobectomy and limited resection seems to be getting very similar when performed for tumours  $< 2$  cm in size, although this may be due to different selection criteria along the decades (11). In the study of Zhu *et al.*, overall and adenocarcinoma-specific survival was invariably worse for limited resections compared with lobectomies. The fact that the differences were not statistically significant seems little consolation for those patients who died in excess in the limited resection group. There are several facts that may explain this worse prognosis. Segmentectomies are associated with a significant better cancer-related survival than that of wedge resections in patients with stage IA tumours, even when the subgroup of tumours  $\leq 2$  cm in size is analysed independently; and recurrence is significantly lower for segmentectomies (12). Recurrence is significantly higher when the resection margin is  $< 1$  cm and this is found more frequently in wedge resections than in segmentectomies (13). This may be because other sites of field cancerization in the same lobe are not included in the resected specimen, to STAS, as described above, or to suboptimal intraoperative nodal assessment, which tends to be more limited in wedge resections (12). There is no doubt that segmentectomies and wedge resections are different

operations that we tend to put together in the same box. Perhaps it is time to abandon the terms 'limited' and 'sublobar' resection, call them by their specific names and analyse them separately.

The paper by Zhu *et al.* is of value because it clearly shows that tumour size separates lung adenocarcinomas of different prognosis, even in the early stage of the disease; that non-invasive or MIAs are more frequently encountered in tiny tumours; and that the size and the nature of the tumour may lead the type of resection of choice. Wedge resection seems to be adequate for these early subsolid tumours, but caution should be taken when the tumours are solid, even if they are small. Hopefully, the North American (14) and the Japanese (15,16) trials that are now in progress will clarify the resection of choice for each tumour size and type.

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