Commentary

Early detection and early treatment of lung cancer: risks and benefits

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The paper by Zhu and colleagues (1) on the clinical characteristics of primary peripheral lung adenocarcinomas is notable for showing that lesions up to 1 cm in diameter have different clinical characteristics to, and better survival than, lesions 1.1–2.0 cm. The authors coined the term "micro-sized" to describe these adenocarcinomas up to 1 cm, and suggested they might be adequately treated by sublobar resection without mediastinal lymph node dissection.

Potentially malignant lung nodules as small as few mm in diameter are now routinely identified by CT screening in high risk populations (2), resulting in improved lung cancer cure rates at a time when lung cancer is the still main cause of cancer death, and has reached epidemic proportions in developing countries (3). However large-scale lung cancer screening is not without risks, including high number of potentially harmful diagnostic procedures carried out for benign disease, and excessive treatment for overdiagnosed cancers. It is therefore essential that screening programs implement diagnostic and management protocols to reduce these risks.

In this regard, there is considerable controversy as to the best management policy for cancers detected in ground-glass opacities (GGOs) and many investigators are concerned that these lesions are often overtreated (4-6). A recent paper by Yankelevitz *et al*. (7) analyzed the frequency, treatment and prognosis of adenocarcinomas presenting as nonsolid nodules (mainly GGOs) within the large International Early Lung Cancer Action Program (IELCAP). They concluded that nonsolid nodules of any size could be safely followed by CT at 12-month intervals, and should be treated surgically only when a solid component appears; in general the rate of malignant evolution of these nodules was low. The authors further suggested (7) that "cancer" was an inappropriate term for such nodules and should be replaced by "indolent lesions of epithelial origin" (IDLE), not simply because adenocarcinomas presenting as nonsolid nodules behave much like benign disease, but also because the change in terminology might reduce anxiety in screened patients.

The study of Zhu and colleagues (1) showed that surgical removal of adenocarcinomas less than 1 cm had important benefits: 5-year overall survival was 100% (compared to 88.4% for adenocarcinomas 1.1–2.0 cm), and a sublobar surgical approach was feasible. These findings are consistent with the IELCAP finding that patients with stage I disease had 90% lung cancer-specific survival (7). Nevertheless it is worrying that 67% of Zhu and colleagues' (1) cases were (premalignant) adenocarcinomas *in situ*. This is a high proportion compared to other studies (8,9) including our own (10,11). It is therefore possible that some of Zhu and colleagues' micro-sized cases were overtreated, even though more received limited resection than lobectomy. For some cases, continued follow-up may have been appropriate, as the data of Yankelevitz *et al*. suggest (7).

In our own experience (10,11), most screening-detected lesions less than 1 cm were invasive or minimally invasive adenocarcinomas. This is because we only performed surgical biopsy when lesions increased in size (volume doubling size less than 600 days) or were CT-PET positive by visual assessment (11). We did not usually operate on stable GGOs. Thus, differences in indication for surgery could well explain the high proportion of in situ adenocarcinomas in Zhu and colleagues' series (1); however the authors did not state their criteria for going to surgery. It is also possible that pathological criteria for recognizing invasiveness, in the various types of lesion with lepidic

growth pattern, varied between studies.

Deciding on surgery is not a trivial matter. CT-guided biopsy for non-solid lesions is not always reliable, as an invasive component can be missed; in which case the decision to treat is normally based on nodule characteristics—volume doubling time, standard uptake value, nodule density, margin characteristics, size, etc.—and, for indolent lesions, age, comorbidities and patient preference (12).

Clearly, less invasive and more reliable methods of assessing nodule status are required to better inform the decision for surgery. Various biomarkers have been investigated for their ability to indicate the presence of lung cancer in asymptomatic persons, and provide evidence as to whether indeterminate nodules are malignant and aggressive, or indolent. However, to our knowledge, only two miRNA signatures (the miR-Test for serum and the MSC test for plasma) are under validation in prospective screening trial (13,14). Other promising modalities are the detection of circulating tumor cells (CTCs) from lung cancer in blood (15) and improved detection of CTCs in sputum using automated 3-dimensional morphologic analysis (16).

When the decision is for surgery, standard treatment for any adenocarcinoma is still lobectomy, although, as noted, accumulating data (1,7) indicate that lobectomy is overtreatment for very early stage lung tumors. Alternative surgical approaches are segmentectomy and wedge resection.

Stereotactic ablative radiotherapy (SABR) is an alternative non-invasive treatment that should be discussed with patients presenting with multiple lung nodules or a second primary after lung resection. Patients at high risk of surgical complications should also be informed of the merits of SABR, since for them surgery may be overtreatment. The 2014 study of Takeda *et al.* (12) investigated the relation of pretreatment maximum standard uptake values (SUVmax on FDG-PET-CT) of lung lesions in patients treated by SABR for early (T1a-2N0M0) non-small cell carcinoma. They found that SUVmax above optimum thresholds significantly predicted poor outcomes, indicating that PET can be used to select patients for SABR and that those with high SUVmax should be directed to surgery. However, for many patients with screening-detected lung cancer it is unclear whether surgery or SABR is best approach; and such patients would be ideal candidates for a randomized trial comparing the two approaches (17).

As regards surgery, it is encouraging that minimally invasive approaches like video-assisted thoracic surgery (VATS) and robot-assisted surgery—that avoid division of major thoracic muscles and rib-spreading—are increasingly used for lung cancer resections. VATS is associated with equivalent cancer survival, reduced pain, and better quality of life compared to open surgery (18). Robotic surgery is easier for the surgeon than VATS, while retaining all the advantages of VATS over open surgery.

In the near future we can expect robotic surgery to be integrated with virtual reality and augmented reality techniques that superimpose a previously acquired three dimensional model of the patient's anatomy onto the intraoperative view of the patient provided by the robot visual system. This will allow the surgeon to navigate virtually through the patient's anatomy to identify target structures, surgical planes, and resection margins, resulting in improved lesion targeting and improved ability to identify critical structures such as blood vessels that are not visible in the surgeon's real field of view. These techniques will also greatly improve preoperative planning, but will require radical changes in surgical practice, and operating room and setup procedures (19).

To return to the present, the paper of Zhu and colleagues (1) has shown that patients with micro-sized (1.0 cm or less) lung adenocarcinomas have better survival than those with somewhat larger cancers (1.1–2.0 cm), and suggests that these small lung cancers are adequately treated by limited resection without mediastinal lymph node dissection. We caution, however, that most of the patients turned out to have adenocarcinomas *in situ*, raising questions as to the criteria for going to surgery, and leading to the surmise that many of these lesions were probably overtreated. We expect that prognostic markers may soon become available to better distinguish aggressive from indolent lesions. For indolent lesions, sublobar resection (preferably by minimally invasive approach), non-invasive SABR, and even careful follow-up are possibilities that need to be evaluated. A name change from "cancer" to something like "IDLE" for these small lesions would be useful to better reflect their behavior and to alleviate patient anxiety.

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Footnote

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