Perspective

Lung cancer screening in China: early-stage lung cancer and minimally invasive surgery 3.0

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Lung cancer remains the leading cause of death worldwide (1). In China, lung cancer is also the most common incident cancer and the leading cause of cancer death (2). Every year in China, over seven hundred thousand new lung cancers were diagnosed and over six hundred thousand lung cancer patients died (2). The International Early Lung Cancer Action Project (I-ELCAP) established in 1992 is an international, collaborative group consisting of experts on lung cancer and related issues from around the world. Its research showed that annual low-dose computed tomography (LDCT) screening allows at least 80% of lung cancers to be diagnosed at clinical stage I, and the curability of Stage I lung cancers is 80–90% (3). Later, the National Lung Screening Trial (NLST) in the US from 2002 demonstrated that low-dose CT increased lung cancer incidence by 13% and reduced lung cancer mortality by 20% (4).

In the last decade, LDCT is becoming more and more popular in China. In 2008, our group joined in I-ELCAP and conducted the first community-based LDCT screening project for early-stage lung cancer in China. Based on community health service, screening with LDCT could improve the early diagnosis rate of lung cancer in both smokers and nonsmokers with feasibility and validity. Surprisingly, in the traditionally defined high-risk populations of lung cancer which mainly include elder smokers, we detected a high incidence of lung cancer in females and non-smokers (5). Similarly, LDCT screening in hospital employees in different regions of China revealed a high frequency of females and non-smokers were diagnosed with lung cancer. And in Shanghai, lung cancer incidence in women increased significantly since 2005. Data of lung cancer patients in Fudan University Shanghai Cancer Center (FUSCC) also showed an increased proportion of lung cancer patients with females, non-smokers, young and early-stage populations in the last decade. Collectively, an increased trend of lung cancer was found in the young, females, non-smokers in China.

LDCT in China is relatively cheap and convenient. It costs less than three hundred CNY (less than fifty dollars) and can be performed within a week after an appointment. These advantages make LDCT popular and widely covered nationwide. As a consequence, the incidence of early-stage lung cancer increases. And in the long run, it is expected that the mortality rate of lung cancer will also decrease.

Why does an increasing population of young, female, non-smoking patients have lung cancers? Should the traditional high-risk population of lung cancer screening be redefined? On the other hand, will Western countries have more young, female, non-smoking lung cancer patients if LDCT screening was widely performed in these population? Unfortunately, till now we still do not know the etiology. Although there are environmental risk factors such as smoking, second-hand smoke, kitchen fumes, radon, asbestos, hormones, or air pollution. However, a large fraction of lung cancers occurring in never smokers cannot be definitively associated with these established environmental risk factors (6). The further epidemiologic research in this area is warranted. The association between genetic alterations and lung cancers may bring insights to these questions.

Most of the CT detected lung cancers are early-stage lung cancers and presented as small ground glass opacity (GGO). However, it should be noted that not all GGOs are early-stage lung cancers. CT presented GGO can have a variety of pathological findings: benign lesions such as inflammation or

hemorrhage, precancerous lesion like atypical adenomatous hyperplasia and finally lung cancer. Therefore, not every patient has GGO after CT scan needs surgical intervention. Our data showed that nearly 80% of the GGOs turned out to be malignant tumors, and the rest were the benign disease. How to accurately distinguish these two groups of patients and give the right treatment remains a big challenge in clinical practice. We have encountered some patients, after three to six months of follow-up, their GGOs significantly reduced or disappeared. We also have encountered some patients, with the same period of follow-up, their GGOs enlarged or remain the same. We believe that a period of follow-up (3–6 months) may be the optimal differential diagnosis. During follow-up, benign GGOs always reduced or disappeared, whereas malignant GGOs persistent or developed.

In FUSCC, for small lung nodules found by CT screening, we developed a set of treatment procedures that can achieve the most accurate diagnosis. For solid or sub-solid lung nodules more than 5 mm, we strongly recommend a percutaneous needle aspiration biopsy. And for small GGOs, we suggest a period of follow-up. If GGOs persist after a period of follow-up, surgical intervention is always performed, especially for young patients with peripheral GGOs. Of course, there was a small part of patients with small GGOs, they did not want surgery at that time, or the doctors considered their GGOs more likely a benign disease. For these patients, we recommended a close CT follow-up.

According to guidelines, lung cancer patients should undergo chest and abdominal CT, bronchoscopy, cranial MRI, bone scan, whole body PET-CT, and invasive mediastinal lymph node biopsy as preoperative examinations to determine the size, location biological characters, and stage of the tumor. The design of these examination strategies is mainly based on data from patients with locally advanced lung cancers. On the other hand, these examinations both consume medical resources and cause physical and psychological trauma to patients. After that, traditional lobectomy or pneumonectomy plus mediastinal lymph node dissection must be performed as standard surgical procedures for every patient. Is it possible to streamline and individualize the preoperative examination and operation for patients with early-stage lung cancer?

Data in FUSCC showed that some early-stage lung cancer patients who meet certain conditions will not have positive findings in preoperative bronchoscopy, bone scans, and cranial MRI (7,8). Therefore, for selected patients, the preoperative examination such as bronchoscopy, bone scans, and cranial MRI can be waived. For patients considering mediastinal lymphadenopathy, we also performed EBUS-TBNA minimally invasive biopsy to replace the traditional Mediastinoscopic lymph node biopsy. This technique is more minimally invasive and safer, with a diagnostic accuracy of 97%, and can be a replacement for most mediastinoscopic procedures (9).

In the optimization of surgical procedures, we firstly systematically analyzed the law of lymph node metastasis in early-stage lung cancer and established a quantitative prediction model of mediastinal lymph node metastasis. By four variables: age, tumor size, location, and intraoperative frozen pathological type. We can four accurately predict the metastasis rate of mediastinal lymph nodes in a specific patient with lung cancer. Clinical data of lung cancer patients also confirmed that lung adenocarcinoma, micro-invasive adenocarcinoma, adherent subtype adenocarcinoma, and peripheral squamous cell carcinoma less than 2 cm all had no lymph node metastasis. For these patients, mediastinal lymph node dissection can be waived (10,11).

Is sub-lobular resection feasible for these early-stage lung cancer without lymph node metastasis? By analyzing patients with stage I peripheral lung adenocarcinoma, we found that if divide tumor into pre-invasive adenocarcinoma and invasive adenocarcinoma, the 5-year recurrence-free survival rate of patients with pre-invasive lung adenocarcinoma is 100%. These patients may be feasible for sub-lobular resection. The next question is how to distinguish between pre-invasive and invasive tumors before or during surgery. Further analyses revealed that the diagnostic accuracy of intraoperative frozen pathology and postoperative paraffin pathology in distinguishing pre-invasive adenocarcinoma from invasive adenocarcinoma was as high as 96%. This led us innovatively proposed the selection of an individualized surgical plan based on the precise frozen pathology results during the operation. We firstly propose that an intraoperative frozen diagnosis of adenocarcinoma and micro-invasive adenocarcinoma is an accurate indication for sub-lobar resection (12).

The ability to accurately locate tumor is fundamental for sub-lobular resection. Since 2008, we firstly conduct CT-guided Hookwire localization and VATS pulmonary nodule resection in China. For patients with lung nodules, less than 1.5 cm in diameter or even less than 1cm in diameter, the nodules can be accurately localized and removed. 99% of these surgeries were succeeded. And this technique can greatly shorten the operation period and ensure enough margins while retaining normal lung tissue (13).

Given the current alterations in the high-risk population

of lung cancer, and the increasing proportion in early-stage lung cancer patients, the traditional lung cancer diagnosis and treatment strategies are not well adapted to the development of the times. Our improvement and innovative contribution to the traditional diagnosis and treatment system of lung cancer can better serve these early-stage lung cancer patients. Enable them to reduce surgical trauma and improve postoperative survivals and quality of life. We call this system minimally invasive thoracic surgery 3.0, which means improving MIS by reducing systemic damage. MIS 3.0, compared with the previous MIS 1.0 (improving surgical outcomes by reducing incisional injury) and MIS 2.0 (improving MIS by reducing extent of resection), is a concept that better reflects the essence of minimally invasive thoracic surgery (14).

In conclusion, we found an increasing trend of young, female, non-smoking and early-stage lung cancer in China. For these patients, we innovatively proposed the concept of MIS 3.0, with the aim of reducing systemic trauma, to provide individualized treatment strategies from preoperative, intraoperative, and postoperative care. This paradigm shift in lung cancer diagnosis and treatment not only saves medical resources, reduces the patient's trauma, but also effectively prolongs the patient's survival time and improves the patient's quality of life.

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Footnote

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