Editorial: Pulmonology

Non-invasive diagnosis of the solitary pulmonary nodule: which way is right?

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Lung cancer is one of the most common and is one of the leading causes of cancer death. It is often identified late, in fact only about 20% of lung cancers are operable at the time of diagnosis. It can be seen occasionally and presents radiologically as a solitary pulmonary nodule (SPN). However, the radiological study is not sufficient to precisely define the characteristics of the SPN. Therefore the main challenge is to obtain a histological diagnosis and a preoperative staging, also through the study of the mediastinum, in the least invasive way possible. Technological progress provides new tools that allow us to achieve results that were unthinkable until a few years ago. In this special series we report the most recent techniques used in the diagnosis and staging of the pulmonary nodule.

The challenge to obtain preoperative histological diagnosis of pulmonary nodules is still open. Technological progress provides us with ever more precise and effective methods. Our task is to know how to use them correctly in order to achieve our goal.

The computed tomography (CT) detection of a SPN generates concern and questions about the best way to get a diagnosis. The first problem is the following: are there any predictive models of malignancy based on clinical imaging exclusively? Senent-Valero *et al.* (1) considered the most frequent independent (age, smoking history, nodule size and morphologic characteristics) and variable (race, nodule growth, prior lung disease, and exposure to harmful substances) factors of malignancy. Subsequently authors tried to set up an algorithm, but the methodological defects compromised the validity of the predictive model. Does the integration with positron emission tomography/computed tomography (PET/CT) allows to better define the nature of the SPNs? The trial by Weir-McCall *et al.* (2) on 355 patients highlighted not only the advantages of fluorine-18 fluorodeoxyglucose (18F-FDG) PET/CT but also many limitations. In fact, the specificity of this method not always allows to obtain a differential diagnosis between inflammatory and malignant nodules. In our VATS Group experience on 8,139 patients (3), we attempted to demonstrate the correlation between standardized uptake value (SUV)max, histopathology outcomes and tumor size in NSCLC. The key is to understand which are the factors that influence the SUV, codify them and correlate to a histological by type of patient. Undoubtedly, the histological diagnosis is essential to plan the most suitable treatment of pulmonary nodule. The CT-guided percutaneous biopsy is characterized by the high levels of diagnostic accuracy in peripheral lesions but is not indicated in small or centrally located nodules (4,5). Therefore, in recent years, new techniques have been developed using bronchoscopy platforms associated with optical fibers and able to reduce the risk of false negatives (6). The standard fiber-optic bronchoscopy (FB) associated with fluoroscopy (Flu) and transbronchial biopsy, for both peripheral and central nodules, showed several limitations and a low diagnostic yield for malignancy also because not all lesions are visible under Flu. Therefore, the problem is how to improve the diagnostic accuracy? Deng *et al.* (7), in 24 patients

with 24 lesions of which 12 were not visible under Flu, determined the core point of nodule detecting the longest diameter of length, width and height by CT scan; the cross point of three perpendicular planes (sagittal, coronal and horizontal) marked on the chest wall individuated the core point of the lesion. The diagnostic accuracy was 66.7% and 58.3% in visible and not visible lesion under Flu, with an average yield of Flu-FB rate of 62.5%. These results were compared with those obtained in a third group of 23 patients with peripheral pulmonary nodules undergoing radial endobronchial ultrasound (rEBUS). In this group the results in terms of diagnostic accuracy were similar (65.2%). However, if we consider that the execution time is superimposable, the Flu-FB has lower costs than the rEBUS and this represents an advantage undoubtedly. The limitation of this technique is represented by the impossibility to identify endoscopically the lesions due to the difference in caliber between the instrument and the subsegmental bronchi. The solution may be to use a thin bronchoscope. Tanner *et al.* (8) carried out a multicenter study involving 197 patients with lung lesions ranging from 1.5 cm to 5 cm. All patients underwent Flu-FB but only in 85 of these was it possible to identify the lesion, allowing the subsequent biopsy. In 112 patients the Flu-FB did not allow a diagnosis. Therefore, these patients underwent thin bronchoscopy (TB) by an instrument with a diameter of 4.2 mm associated with rEBUS. In fact, the 2 mm radial probe reaches and identifies even the most peripheral lesions. The authors conclude that the TB-rEBUS showed higher diagnostic accuracy than Flu-FB, obtaining a diagnosis in 32 Flu-FB patients (37%) and in 55 TB-rEBUS patients (49%); also, in patients undergoing TB-rEBUS the identification of lesion displayed a percentage rate of 97% by transbronchial biopsy. Obviously, if there is an afferent bronchus the biopsy forceps have the priority; in case of lack of bronchus sign, the transbronchial biopsy needles are more useful. Virtual fluoroscopy (VF) is a novel guided technique that provides Ray-summation images of target lesions like X-ray Flu, without the limitations attributable to this method such as the lack of identification of ground-glass nodules (GGNs). Through a workstation it is possible to obtain virtual reconstructions starting from the CT acquisitions. A virtual path that can be followed with the bronchoscope to the exact point of the lesion is traced; also, it is possible to further improve the diagnostic yield of this technique associating it with EBUS. Nakai *et al.* (9) studied 74 patients affected by GGNs not visible at X-ray Flu. All patients underwent thin-section CT (TSCT), X-ray Flu, endobronchial ultrasound with a guide sheath (EBUS-GS) and virtual bronchoscopy (VB). Two groups of patients were established on the basis of the use of VF (35 patients) or not (39 patients), in addition to the other methods described. The lesions showed an average size of 18.8 mm and the bronchus sign in a percentage rate of 60%. The diagnostic yield in VF Group was 77% while in the Not-VF Group was 51%. Casal *et al.* (10) suggested the combined use of the thin/ultrathin bronchoscope, radial-probe endobronchial ultrasound (rEBUS) and cone beam computed tomography (CBCT). This technique allows to reach the peripheral nodules, determining a low risk of patient to radiological exposure. The method involves the use of a C-shaped mobile arm that orbits around the patient, allowing to acquire images of a precise anatomical area and to obtain detailed reconstructions through the software. Once the lesion was identified, it was reached by a 4.2 mm thin bronchoscope equipped with a 2 mm service channel. Twenty patients with peripheral pulmonary nodules ranging from 1.1 to 3 cm in size and with an average distance from the pleura of 2.1 cm were studied. Thirteen patients (65%) showed a solid lesion while 7 patients (35%) a subsolid nodule; only 12 patients (60%) displayed the "bronchus sign". Eleven patients (55%) received a single CBCT scan while 9 patients (45%) two scans in order to achieve a valid and accurate identification of the lesion. The diagnostic accuracy without and with CBCT was 50% and 70% respectively, with a very low risk of complications (authors noted only one pneumothorax). The mean duration of procedure was 62.5 minutes, with a radiation exposure of 64.57 Gy-cm^2. Currently, an important role in the diagnosis of pulmonary nodules is played by the robotic-assisted navigation bronchoscopy (RANB). This method involves the use of a robotic platform and allows, through 3D reconstructions carried out by CT scans, to reach the most distal bronchi by a 4 mm endoscopic probe, identifying small and peripheral nodules with a very high precision. Benn *et al.* (11) applied the combined use of CBCT and RANB in 52 patients, for 59 pulmonary nodules (9 GGO) between 10 and 33.8 mm in diameter. The "bronchus sign" was noted in 27 of these (46%). CBCT played an important role in checking the right position of the needle, even when it was necessary to correct the orientation, and in verifying complications at the end of the procedure. Diagnosis was obtained in 83% of nodules (49 out of 59), with an overall diagnostic yield of 86% (51 out of 59); sensitivity and diagnostic accuracy were 84% and 86%, respectively.

In conclusion, the challenge to obtain preoperative

histological diagnosis of pulmonary nodules is still open. Technological progress provides us with ever more precise and effective methods. Our task is to know how to use them correctly in order to achieve our goal.

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