Review Article

Biopsy and re-biopsy in lung cancer: the oncologist requests and the role of endobronchial ultrasounds transbronchial needle aspiration

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Abstract: As the leading cause of death worldwide, lung cancer has proven itself incurable in the advanced stages. For early stages, endobronchial ultrasounds transbronchial needle aspiration (EBUS-TBNA) is now considered the standard to assess mediastinal lymph node, to define the multimodality therapeutic approach. In recent years, EBUS-TBNA has extended its use also in the metastatic and locally recurrent disease. New molecules, with specific mutations that give resistance to current target therapies, have made re-biopsy at disease progression an important assessment, with therapeutic and clinical implication. Here we present the oncologist's point of view on EBUS-TBNA in the staging process, at recurrence and progression.

Keywords: Endobronchial ultrasounds (EBUS); re-biopsy; T790M; lung cancer; review

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Introduction

Lung cancer

Lung cancer is one of the leading causes of cancer deaths worldwide. The main histological types of cancers are squamous cell carcinoma (SCC), adenocarcinoma (ADC), large cell carcinoma (LCC) and small cell lung cancer (SCLC). In Western countries, the ADC frequency is increasing (>50%), while SCC and small cell are significantly reduced (1).

Accurate staging of the disease is mandatory to determine the prognosis and appropriate treatment. The most significant treatment decision lies on the distinction between those patients who can benefit from surgical resection and those who should receive chemotherapy and radiation therapy or both (2).

Biopsy

Diagnosis

In case of suspected lung cancer it is recommended a sequential approach that involves physical examination, radiogram of the chest, chest computed tomography (CT scan) with medium contrast enhancement, bronchoscopy, and cyto-histological definition of the lesion. For central lesions endoscopically visible, histological diagnosis is obtained through cyto-histological samples such as biopsy, brushing, transbronchial needle aspiration (TBNA). Peripheral lesions can be approached percutaneously. The transbronchial approach has lower incidence of complications (especially pneumothorax) and it provides the possibility, during the diagnostic procedure, to sample the lymph nodes by TBNA (3).

The clinical staging is usually performed with non-invasive diagnostic modalities, such as total body CT scan with medium contrast, and/or positron emission tomography (PET). The imaging obtained from these techniques is used to assess the primary lung malignancy, to characterize the mediastinal involvement and to search for distant metastases. Accurate mediastinal staging is a crucial part of the diagnostic workup of every patient with lung cancer, for its prognostic value and for planning optimal treatment. In many cases, the status of these nodes determines whether the disease is surgically resectable. The existence of metastatic contralateral adenopathy (N3) or distant metastasis (M1) contraindicates surgery. Patients with mediastinal ipsilateral lymph node metastasis (N2) may be considered for neoadjuvant therapy followed by surgery based on studies reporting improved survival with this treatment approach (2).

In patients with an abnormal mediastinum (lymph nodes enlargement at CT, with or without a PET increased activity), or with a radiologically normal mediastinum associated with a central lung tumor or with a N1 disease, histological samples of the suspected lymphonodular metastasis are required (4).

Mediastinoscopy and video-assisted thoracoscopy have been the methods of choice to invasively stage the mediastinum before the introduction of endoscopic ultrasounds needle aspiration techniques. Endobronchial ultrasounds transbronchial needle aspiration (EBUS-TBNA) is minimally invasive, safe and well-tolerated method to stage the mediastinum. Furthermore, because its accuracy and cost-effectiveness, endoscopic staging is now the recommended method for invasive mediastinal evaluation (5).

EBUS-TBNA has to be performed in moderate or deep sedation, with a needle of 21 or 22 gauge. The tissue sampling may be run with or without the pathologist's assessment in the endoscopic room (rapid on-site evaluation, ROSE); however, in the absence of ROSE a minimum of three separate steps to sample each lymph-node is suggested (6).

Relapsed disease

Even patients with early disease are at relatively high risk of disease recurrence. Cisplatin-based chemotherapy regimens have decreased the risk of recurrence after surgery and provided modest survival gains. An updated meta-analysis from the non-small cell lung cancer (NSCLC) Collaborative Group demonstrated an average survival benefit of 5.4% at 5 years for patients with resected stage I to III disease (7).

Greater than 50% of disease recurrences occurring after surgery for early stage NSCLC involve local sites (8); detecting mediastinal involvement is crucial for the curative treatment of recurrent NSCLC (9).

EBUS-TBNA can be used for the diagnosis of mediastinal recurrence as a non invasive approach.

Guidelines recommend the acquisition of additional samples to perform not only the diagnosis of relapse but also additional molecular analysis (6).

Role of molecular profile

In recent years studies on molecular characteristics of lung cancers showed a role for specific genes that proved to be important therapeutic targets. In NSCLC (especially in 10–15% of the ADC of Caucasian patients and in 40% of Asian patients) activating mutations of EGFR (exons 18, 19, 20 and 21) have been identified. The presence of these mutations is the most important predictive factor for targeted therapies with specific EGFR tyrosine kinase inhibitors (9,10). In fact, only patients with EGFRm+ have good responses to the treatment with first-generation EGFR TKIs, such as erlotinib and gefitinib (11), with improvements in progression free survival, overall response rate and clinical benefit.

Another important molecular alterations that has been documented for ADC is the rearrangement of anaplastic lymphoma kinase (ALK) that activates a specific receptor tyrosine kinase involved in the processes of proliferation and cell survival; it is found in approximately 3–7% of ADC (12,13).

The determination ALK rearrangement is necessary to select patients for treatment with specific tyrosine-kinase inhibitors [crizotinib and ceritinib, approved by European Medicines Agency (EMA) for patients pre-treated with crizotinib] (14,15).

Other molecular alterations that can be tested in ADC, with promising therapeutic implication are the rearrangement of the *ROS1* gene (about 1–2% of ADC) and RET gene. Activating mutations of BRAF (V600E is that non-V600E), amplification of HER2, mutation of PI3KCA and PTEN, amplification and mutations of PDGFR are molecular changes that could have future therapeutic implications in SCC (16).

Currently, only EGFR and ALK represent molecular targets with specific available target therapy and therefore

they must be tested in case of metastatic disease. While EGFR and KRAS mutations are usually mutually exclusive, the ALK rearrangement was detected in 1–2% of EGFR mutated tumors (17). The role of KRAS mutation is still uncertain. Therefore, the determination of KRAS remains optional.

EGFR and ALK analysis can be performed on surgical specimens, cytology, and biopsy of the primary tumor and/or metastases.

Re-biopsy

Re-biopsy is a growing trend in oncology. This is due to many factors, chiefly: (I) finer molecular characterization, through next generation sequencing (18); (II) new drugs capable of overcoming specific resistance mutations (19); (III) less invasive technique to obtain tissue specimen (20). Up until recent years, re-biopsy was a practice confined to cancer that, even in advanced stages, were still managed by surgeons, and/or presented easily accessible sites, such as prostate cancer and breast cancer (21). Things started to change with the advent of target therapy, with many clinical trials having mandatory re-biopsy, and also with the development of less invasive and safer technique to collect tissue specimens. Still, for some years the interest for re-biopsy was confined mostly to research, without it entering clinical practice. It is only in very recent times that re-biopsy is acquiring a growing importance, with practical implication not only for the clinician but also for the patient. As of today, awaiting validation of the liquid biopsy, re-biopsy represents the only instrument to discover specific transformation and targetable mutation in patient experiencing progressive disease.

Histology shift

A known mechanism of resistance to therapy, especially tyrosine kinase inhibitors targeting EGFR, is the transformation of NSCLC, generally ADC, in SCLC (22). One of the first cases of resistance to erlotinib due to the transformation in SCLC was described in 2006 (23). Since then, several others have been reported. Case series give variable percentage for this phenomenon, between 5% and 14%, among patients with EGFR mutated ADC (24,25): although rare, it can still affect at least one patient in twenty. The mutation of the driver gene EGFR, still present after histological shift supports the hypothesis that these are transformation regarding the same tumour and not the growth of a new neoplasm (26). Current understanding still leaves some open questions: is the SCLC already present at diagnosis, in combined-histology tumour, and grows under the selective pressure of therapy for the NSCLC? Or is it a transformation at the molecular level, with candidate gene RB1 as a key player that triggers the histological shift (22)? While further studies enlighten the basis of this transformation, the clinician should keep this event in mind, considering re-biopsy for those patients affected by ADC with rapid progression or unusual behaviour, especially EGFR-mutated ones. The importance of pathological demonstration of a histological shift is due to the mixed response to anti EGFR observed in these patients (27,28), thus recommending SCLC treatment as the main therapeutic option.

Acquired resistance

A common concept, in microbiology as in oncology, is that a prolonged exposition to certain drugs can select a resistant population, either a bacterium or a neoplastic cell. In the cytotoxic era, the usual strategy to overcome this phenomenon was to combine different chemotherapeutics, with only partial success, limited to haematological malignancies. Acquired resistance was also the limit to the great hopes of target therapy: the majority of patients experience, after a variable interval of time, the ensuing of a resistant clone that causes disease progression. The silver lining to this event is that our deeper understanding of molecular biology has made possible in some cases to identify the specific mechanisms behind acquired resistance. One of the finest example is T790M in EGFR mutated lung ADC (29): this mutation is one of the main mechanism of acquired resistance, generally present only in a minority of cells at diagnosis, and much more expressed at disease progression. Beside identifying the mutation, we now have also new tyrosine kinase inhibitors that specifically target T790M, osimertinib (19). In the following years, molecular profiling will become a key part of patient re-evaluations, along radiological assessments and physical examinations, making re-biopsy at progression mandatory.

Conclusions

Lung cancer represents one of the leading causes of death worldwide, especially in the advanced stages of the disease.

For early stage lung cancer, EBUS-TBNA represents a fundamental evaluation to assess correctly mediastinal

involvement. The extent of lymph node invasion is key information, for the oncologist as well as for the surgeon and the radiotherapist, to better define the therapeutic approach.

In recent years, because of better understanding of molecular biology, EBUS-TBNA has gained a role also in the metastatic and locally recurrent disease. New target therapies, aimed at specific resistance mutation, have made re-biopsy a usual assessment at disease progression. This is of paramount importance for the oncologist, to detect histological shift or specific mutation such as T790M for EGFR-mutated ADC. While re-biopsy was, up until recent years, mainly confined to research, as of today it has therapeutic implication and actively change patients' outcome.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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