Endobronchial ultrasound: from lung cancer diagnosis and staging to translational research

Ultrassom endobrônquico: do diagnóstico e estadiamento do câncer de pulmão até a pesquisa translacional

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Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) is probably the most important advance in thoracic diseases in the last decade. EBUS-TBNA was first applied for the diagnosis of lymph node metastasis in lung cancer patients. Thereafter, its indications quickly evolved, and the method is currently used for the diagnosis of many thoracic diseases, including sarcoidosis, thymomas, tuberculosis, lymphomas, and metastatic diseases.[1]

In the oncological setting, EBUS-TBNA soon became a key tool in the evaluation of lung cancer patients. The uses of EBUS ranged from extended and bilateral mediastinal staging to the collection of specimens for molecular analyses—epidermal growth factor receptor (*EGFR*) mutations, *KRAS* mutations, and anaplastic lymphoma kinase (ALK) rearrangement—underpinning modern target therapy in lung cancer patients.[2]

In the diagnosis of peripheral pulmonary nodules or ground-glass opacities, EBUS-radial probe has improved the diagnostic yield of transbronchial biopsies and dramatically reduced the number of CT-guided transthoracic fine needle aspiration biopsies and their associated complications.

Mediastinal staging is fundamental for the evaluation of resectable lung cancer and indicates the type of treatment (induction chemotherapy, surgery, or definitive chemotherapy/radiotherapy). For many years, mediastinoscopy was the gold standard for mediastinal staging and was widely used in referral centers. Currently, EBUS-TBNA equals mediastinoscopy in terms of its sensitivity and specificity for the diagnosis of mediastinal lymph node metastasis, and EBUS-TBNA has all of the advantages of a minimally invasive procedure.[3]

In 2011, we performed 79 mediastinoscopies for mediastinal staging of lung cancer patients. In 2012, after the introduction of EBUS into our clinical practice, the number of mediastinoscopies dropped to 17, confirming the central role of EBUS-TBNA at a cancer referral center.

Rapid on-site evaluation (ROSE) and specimen handling are crucial to enhancing the diagnostic yield of EBUS-TBNA and to obtaining all mutational analyses in the final examination.[4] At our center, specimens are collected with a 22G dedicated needle (NA-201SX-4022; Olympus, Tokyo, Japan) and a small amount of material is smeared onto glass slides. Some of the slides are air-dried and stained immediately using MGG quick stain (Bio-Optica, Milan, Italy) so that the cytopathologist can immediately interpret and confirm the adequacy of cell specimens. "Mirror" slides are alcohol-fixed for H&E staining. Other needle passages and sustained material are fixed into a formalin-like solution in order to be processed as a cell block for histological evaluation.

In the last 15 months, we have performed 322 EBUS-TBNA procedures (EBUS Convex Probe BF-UC180F; Olympus). The overall sensitivity was 94.5%. The sensitivity among ROSE cases (n = 251) was 98.8%. Molecular analysis was possible in 62 of 71 cases of adenocarcinoma (87.3%). We found *EGFR* and *KRAS* mutations in 10 (16.1%) and 15 (24.2%) patients, respectively, whereas ALK rearrangement was detected (by fluorescence in situ hybridization) in 2 of the patients (3.2%). These data show that the molecular analysis on samples obtained by EBUS-TBNA is feasible and can be incorporated into daily clinical practice. The proportion of *EGFR* and *KRAS* mutations, as well as that of ALK rearrangements, corresponds to those reported in surgically resected specimens.

We have recently implemented a new protocol with EBUS-TBNA specimens for a whole-genome approach (DNA and RNA extraction) in order to identify novel markers of chemoresistance in stage IIIA pN2 non-small cell lung cancer. In the preliminary phase of this translational research, the harvested samples underwent cell culture (epithelial cell cultures), and samples with little cellularity identified by ROSE did not grow in the culture. This finding confirms the importance of ROSE and the need for a new

classification of specimen "adequacy", taking into account different degrees of cellularity in air-dried smears.

In the current issue of the Brazilian Journal of Pulmonology, Figueiredo et al. published a comprehensive review on EBUS-TBNA. The authors discuss the main aspects, technique, feasibility, and expected results of the procedure. They also describe the difficulties of using this new technology in Brazil, the extremely high cost of the procedure, and the need for the Brazilian Medical Association to establish a new classification system.[5]

Economic concerns also afflict many centers in Europe. EBUS-TBNA is an expensive procedure, and many centers in Italy still use blinded TBNA, with all its limitations. Despite the high cost of EBUS-TBNA, the clear advantages of the procedure should encourage its use in referral centers worldwide. We hope that the spread of the technology will lower the cost of EBUS-TBNA, making it available at many more centers.

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