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C-Arm Cone-Beam CT-Guided Transthoracic Lung Core Needle Biopsy as a Standard Diagnostic Tool

An Observational Study

Marta Jaconi, MD, Fabio Pagni, MD, Francesco Vacirca, MD, Davide Leni, MD, Rocco Corso, MD, Diego Cortinovis, MD, Paolo Bidoli, MD, Francesca Bono, MD, Maria S. Cuttin, MD, Maria G. Valente, MD, Alberto Pesci, MD, Vittorio A. Bedini, MD, and Biagio E. Leone, MD

Abstract: C-arm cone-beam computed tomography (CT)-guided transthoracic lung core needle biopsy (CNB) is a safe and accurate procedure for the evaluation of patients with pulmonary nodules. This article will focus on the clinical features related to CNB in terms of diagnostic performance and complication rate. Moreover, the concept of categorizing pathological diagnosis into 4 categories, which could be used for clinical management, follow-up, and quality assurance is also introduced.

We retrospectively collected data regarding 375 C-arm cone-beam CT-guided CNBs from January 2010 and June 2014. Clinical and radiological variables were evaluated in terms of success or failure rate. Pathological reports were inserted in 4 homogenous groups (non-diagnostic-L1, benign-L2, malignant not otherwise specified-L3, and malignant with specific histotype-L4), defining for each category a hierarchy of suggested actions.

The sensitivity, specificity, and positive and negative predictive value and accuracy for patients subjected to CNBs were of 96.8%, 100%, 100%, 100%, and 97.2%, respectively. Roughly 75% of our samples were diagnosed as malignant, with 60% lung adenocarcinoma diagnoses. Molecular analyses were performed on 85 malignant samples to verify applicability of targeted therapy. The rate of ''nondiagnostic'' samples was 12%.

C-arm cone-beam CT-guided transthoracic lung CNB can represent the gold standard for the diagnostic evaluation of pulmonary nodules. A clinical and pathological multidisciplinary evaluation of CNBs was needed in terms of integration of radiological, histological, and oncological data. This approach provided exceptional performances in terms of specificity, positive and negative predictive values; sensitivity in our series was lower compared with other large studies, probably due to the application of strong criteria of adequacy for CNBs (L1 class rate). The satisfactory rate of collected material was evaluated not only in terms of merely diagnostic performances but also for predictive results by molecular analysis.

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Abbreviations: CI = confidence interval, CNB = core needle biopsy, CT = computed tomography, MDCT = multidetector CT, NOS = not otherwise specified, NPV = negative predictive value, NSCLC = nonsmall cell lung cancer, PET = positron emission tomography, PPV = positive predictive value.

INTRODUCTION

Lung core needle biopsy (CNB) is an invasive diagnostic procedure for nodules suspicious of malignancy that enables the collection of a large quantity of tissue for pathological analysis, mainly exploited by oncologists requiring an exhaustive histopathological diagnosis along with therapy-related biomolecular tests.[1–3] One of the most recent developments in this field is the Xper computed tomography (CT) (Philips, AmsterdamThe Netherlands) guide, an innovative software application of the newest interventional vascular surgery instruments in which the x-ray source and flat panel detector are mounted on a rotating C-arm stand, fully adjustable around the table, granting more flexibility in approaching the patient. The 270° or 360° cone-beam acquisition allows the CT-like reconstruction of images in all the 3 dimensions on which the most suitable path for the biopsy needle is planned; furthermore, fluoroscopy provides real-time monitoring of needle placement and complications. Starting from the retrospective evaluation of the largest monocentric European XperCT-guided lung CNB series, this article will focus on the clinical features related to CNB application in terms of diagnostic performance and complication rate. Pathological results will be grouped into 4 homogeneous diagnostic classes for the statistical evaluation of clinical management and follow-up.

METHODS

Patients and Procedures

We collected data regarding 375 consecutive XperCT-guided (Philips Allura Xper FD20, Philips, AmsterdamThe Netherlands) lung CNBs performed from January 2010 to April 2014 on 355 patients. Ethical approval was not necessary as all data were rendered anonymous. The 18-gauge semiautomatic biopsy needles (Biopsybell SRL, Mirandola, Modena, Italy)

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From the Department of Pathology (MJ, FP, FB, MSC, MGV), University Milan Bicocca; Department of Radiology (FV, DL, RC); Department of Oncology (DC, PB); Department of Health Sciences (AP), Pneumology Unit, University Milan Bicocca; Department of Thoracic Surgery (VB), San Gerardo Hospital, Monza; and Department of Pathology (BEL), Desio Hospital, University Milan Bicocca, Desio, Italy.
Correspondence: Fabio Pagni, Department of Surgery and Translational Medicine, Section of Pathology, University Milan Bicocca, San Gerardo Hospital, 20900 Monza, Italy (. e-mail: fabio.pagni@unimib.it).
MJ and FP equally contributed to this work.
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with a 17-gauge coaxial needle were used. CNB procedures were performed by 2 highly specialized interventional radiologists with previous experience in lung imaging. The needle path was planned on the first 180° to 270° CT-like acquisition with the C-arm in order to define the shortest and the safest trajectory, which could be checked on multiplanar reconstructions. In fluoroscopy, ''bull's eye'' approach was used to guide the entry point and perpendicular approach to monitor the needle progression. CT-like and fluoroscopy images were merged in real time to provide guidance on hybrid images. A second and third CT-like acquisitions were performed to check needle placement and postprocedural complications, respectively. For all the patients, the main clinical and radiological variables were recorded in Table 1, including the site of the lesion, diameter, number of nodules, and contingent complications of the bioptic procedures. CNB-related pathological variables (number of passes and length of sampled cores) were also reported in Table 1. Pathological analysis was performed by a team of 3 expert lung-committed pathologists; International Agency for Research on Cancer and World Health Organization guidelines[4] were applied for the standardization of the histological report. Samples were fixed in neutral-buffered formalin, embedded in paraffin blocks, and sectioned followed by staining with hematoxylin and eosin or immunohistochemical markers; cytological samples were stained with Papanicolaou or Giemsa. For the purpose of the study, CNBs were reevaluated and reclassified in blind into the 4 categories shown in Table 2 by an external team of 3 lung-experienced pathologists, who were not involved in the original diagnosis. If there was a disagreement regarding the assignment of the diagnostic class, a collegial discussion took place in order to make a definitive decision on the case. Cohen κ was used to evaluate the agreement between the pathologists in the assignment of the CNB-based diagnosis.

TABLE 1. Clinical and Pathological Variables

Clinical Imaging Variables	Results (n = 375)
Mean lesion size	3.9 ± 2.5 cm
Range	0.7–19 cm
Single nodules	212 (57%)
Upper lobes location	210 (56%)
Right lung	119
Left lung	91
Procedural complications rate	140 (37.5%)
Pneumothorax	80 (21.5%)
Hemorrhage	60 (16%)
Pathological variables	**Results**
Mean number of cores	2 (1–3)
Mean size	12.4 ± 6.3 mm
Immunohistochemistry application	72.3%
Mean number of markers	4 (1–21)
Type of molecular analysis requested	
EGFR	71
ALK-1	50
KRAS	14
ROS-1	1

EGFR = epidermal growth factor receptor.

Nondiagnostic (Lung Class ''L1'')

The category included biopsies for which a definitive diagnosis and biological characterization of the lesion could not be established due to the suboptimal quality and/or quantity of the sample (Figure 1). Patients in this category underwent (Table 3) repeat biopsy with careful clinical–radiological correlation and diagnostic resection.

Benign (''L2'')

The category included qualitatively and quantitatively adequate biopsies that were given a final diagnosis of benignity. The suggested actions in these cases were clinical–radiological follow-up after an additional multidisciplinary discussion and possible diagnostic/therapeutic resection.

Malignant, Not Otherwise Specified (''L3'')

The category accounted for those cases that were certainly malignant but were unable to be assigned an exact histotype (Figure 2). The suggested actions in these cases were surgical resection, especially if the patient, once the diagnosis of

TABLE 2. Histological Results of 375 Core-Needle Biopsy Procedures

L1. Nondiagnostic (n = 46, 12.2%)	Fibrosis/scattered acute and chronic inflammatory infiltrate (tumor capsule), n = 18
	Normal parenchyma samples, n = 18
	Necrosis, n = 10
L2. Benign (n = 46, 12.2%)	Acute pulmonary injury/ interstitial pneumonia, n = 25
	Reactive/reparative fibrotic nodules, n = 15
	Nodular fibrosing pleurisy, n = 3
	Wegener granulomatosis, n = 1
	Sarcoidosis, n = 1
	Hamartoma, n = 1
L3. Malignant, NOS (n = 9, 2.5%)	Malignant nonepithelial, NOS, n = 4
	Lymphoproliferative, NOS, n = 3
	Nonsmall cell lung cancer, NOS, n = 2
L4. Diagnostic for specific malignant histotype (n = 274, 73.1%)	Lung adenocarcinomas, n = 157
	Lung squamous cell carcinomas, n = 51
	Lung large cell carcinoma, n = 12
	Lung carcinoids, n = 10
	Lung small cell carcinomas, n = 9
	Mesotheliomas, n = 5
	Rare histotypes and metastases, n = 30

L3 class included the following: suboptimal quality of the sample that prevents further specification beyond a generic diagnosis of ''malignant'' NOS (small biopsy, excessive fragmentation, necrosis, and paucity of neoplastic foci); optimal quality but insufficient quantity of the sample that prevents further specification beyond a generic diagnosis of ''malignant'' NOS (after application of immunohistochemistry panel, no specific tumor type is expressed); optimal quality but insufficient quantity of the sample that prevents further specification beyond a generic diagnosis of ''nonsmall cell lung carcinoma'' (after application of immunohistochemistry panel). NOS = not otherwise specified.

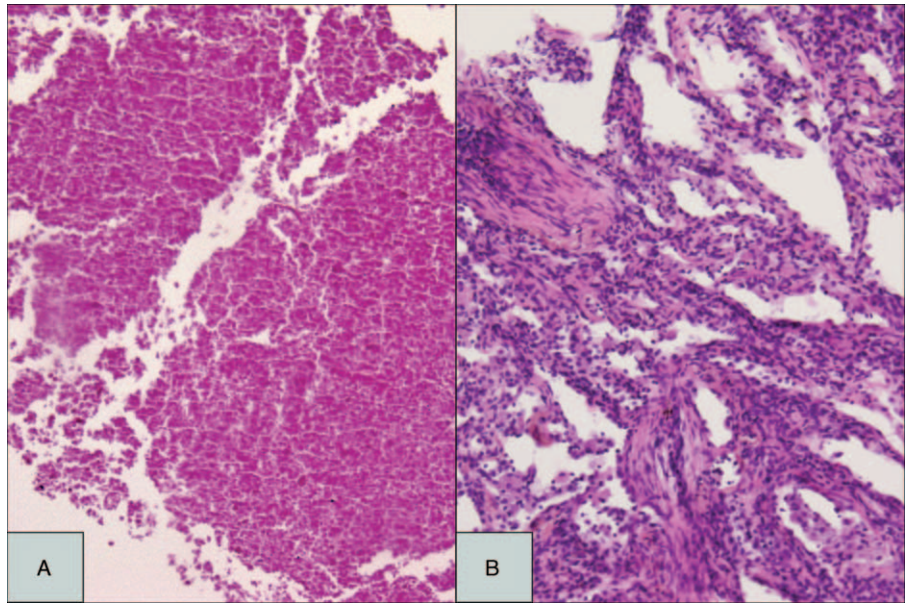

FIGURE 1. ''Nondiagnostic'' class: histological criteria. (A) Suboptimal sample due to fragmentation and extensive necrosis (Hematoxylin and Eosin H&E, 20×). (B) Sampling from tumor capsule with fibrosis and inflammatory infiltrate (H&E, 20×). H&E = hematoxylin and eosin.

malignant disease was confirmed, was eligible for surgery, and repeat biopsy.

Malignant, With Specific Histotype (''L4'')

In this category, samples were adequate for quality/quantity and allowed for the precise morphological and immunohistochemical evaluation and execution of molecular biology analyses for patients eligible for medical therapy. For adenocarcinomas, the standard predictive panel included epidermal growth factor receptor (EGFR, exons 18, 19, 20, 21) mutations detected with Sanger sequencing and Echinoderm microtubule-associated protein-like 4 (*EML4*)/activin receptor-like kinase (*ALK*) translocation detected with fluorescence in situ hybridization analysis. Patients were treated according to the most recent international guidelines.[5]

Optional mutation analysis included in selected cases proto-oncogene tyrosine-protein kinase (*ROS1*) or Kirsten rat sarcoma viral oncogene homolog (*KRAS*).[6] The operative consequences of the diagnosis were always managed by a multidisciplinary team, that included pulmonologists, oncologists, radiotherapists, and thoracic surgeons. Management of these cases varied depending on tumor stage and type and included therapeutic resection (for nonsmall cell lung carcinoma [NSCLC] up to stage II), radiotherapy, traditional chemotherapy, molecular targeted therapy, radiofrequency ablation, or other palliative treatments.[7–9]

Statistical Analysis

CNB sensitivity was defined as the percentage of correctly identified malignant neoplasms (CNB diagnostic category of L3 and L4). CNB specificity was defined as the percentage of correctly identified benign entities (CNB diagnostic category of L2). Statistical differences between the ''diagnostic success'' and ''diagnostic failure'' groups (including L3 or L4 and L1 in presence of malignancy, respectively) were evaluated with Student *t* test for the following variables: age, lesion size, number, and size of cores. Pearson χ^2 test was used in the evaluation of the following variables: sex, lesion site, number of nodules, presence of procedure complications, and frequency of immunohistochemical staining. For statistical variables, confidence interval (CI) 95% was calculated. Management of data and statistical operations were performed with Microsoft Office Excel (MS Office 2010; Microsoft Corporation, Redmond, Washington, USA).

RESULTS

Clinical Performance of CNB

Globally, mean patient age was 68.3 ± 11.5 years, 67.5% of which were male. Mean nodule size ranged within 3.9 ± 2.5 cm, single nodules were the majority (57%) with the right upper lobe being the most frequent location (56%, Table 1). The rate of

TABLE 3. Patient Management

Core-Needle Biopsy Class	Repeat Biopsy	Surgery	Medical Treatment	Follow-Up
L1*	36 (78.3%)	7 (15.2%)		
L2		6 (13%)		40 (87%)
L3	7 (77.8%)	2 (22.2%)		
L4		38 (13.8%)	236 (86.2%)	

* Three patients (6.5%) were subjected to no further testing due to poor clinical conditions.

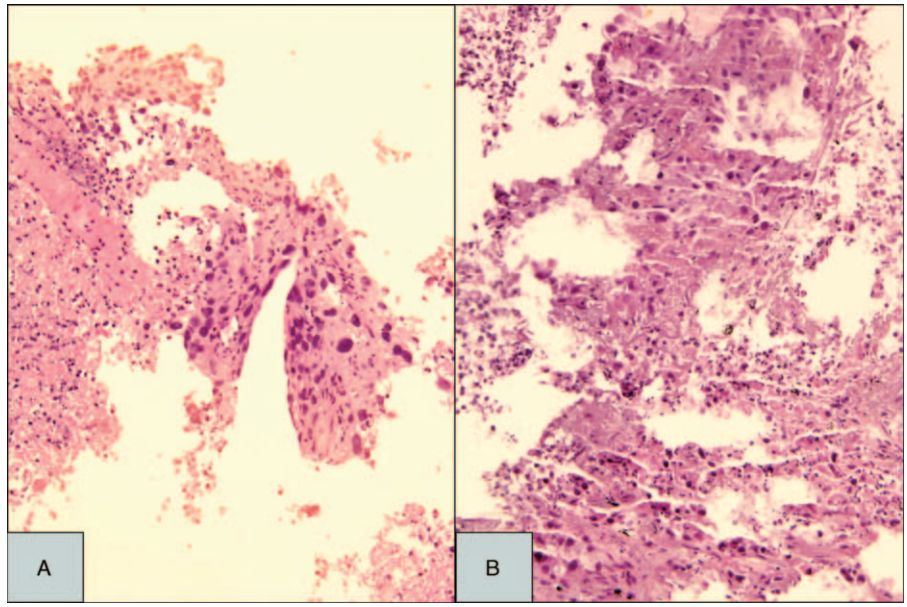

FIGURE 2. ''Malignant, NOS'' class: histological criteria. (A and B) Poorly preserved and necrotic cores showing infiltration by nonsmall cell lung carcinoma (H&E, 10×). The specimen was enough for an obvious diagnosis of malignancy but insufficient both for the exact evaluation of the histotype and the biological characterization. H&E = hematoxylin and eosin, NOS = not otherwise specified.

complication was 37.5%. A localization different from the upper lobes was significantly correlated with a higher risk of pneumothorax ($P < 0.03$). Interestingly, the placement of a drainage tube was required for the treatment of this condition in only 4 cases (3 in upper right lobe and 1 in upper left lobe). Moreover, hemorrhagic suffusion along the needle path was quite a frequent event, but there was hemoptysis in only 8 cases (4 in upper right lobe, 2 in upper left lobe, and 2 in lower right lobe). This occurrence was managed with accurate patient observation until resolution or, if needed, with an operative bronchoscopy (n = 3) and the administration of antifibrinolitics (n = 5). No patient died as a consequence of the procedure. Self-limiting subcutaneous emphysema occurred in rare cases (n = 2). Mild thoracic pain was often recorded.

For CNB sampling, the radiologist carried out an average number of 2 passes per nodule, with rare exceptions (<0.5%) where only 1 core was obtained due to technical issues (hemorrhage after the first needle passage). Cores had a mean length of 12.4 ± 6.3 mm. Fragmentation of the sample was a frequent occurrence, and a statistically significant difference was found for the mean size of cores between the diagnostic success and diagnostic failure group (12.9 ± 6.1 and 10.7 ± 7.2 mm, $P = 0.04$). Sensitivity and specificity were 87.5% (95% CI 0.820–0.893) and 100% (95% CI 0.987–1.000), respectively. Positive predictive value (PPV), negative predictive value (NPV), and overall accuracy were 100%, 100%, and 87.7%, respectively. Sensitivity was significantly lower for small lesions (57.1%, $P < 0.01$ for lesions $\leq$10 mm); above 20 mm, our diagnostic performance reached 90% in terms of sensitivity. It must be highlighted that on 36 of the 46 patients with a biopsy report of L1, a repeat biopsy was performed; thus, although single procedure sensitivity is relatively low, patient sensitivity increases to 96.8% (305 correctly diagnosed patients of the 315 with malignant disease) and overall accuracy to 97.2%.

Pathological Diagnosis on CNB and Clinical Management

We decided to group all the histological reports together into 4 diagnostic classes (L1–L4, Table 2). Lung CNB was found to be a technique with a high diagnostic reproducibility, because the relabeling of biopsies, in blind, into categories had a κ of agreement in above 75% of the cases (Cohen $\kappa = 0.77$, $P < 0.05$). The large majority of our series were assigned to the malignant (L4) class (73.1%, Table 2) and 86.2% of them required medical treatment (Table 3). The immunohistochemical panel for tumor typing usually included a mean of 4 markers (with a maximum of 21). The most frequent histotype was pulmonary adenocarcinoma (57.3% of malignant disease cases). In 85 of the 274 CNB (L4) cases, the oncologists requested molecular tests (EGFR = 71, *EML4*/*ALK* = 50, *K/NRAS* = 14, *ROS1* = 1); 5 patients already diagnosed with adenocarcinoma were subjected to a repeat biopsy specifically for molecular testing. In CNBs for which a molecular analysis was requested, the mean percentage of tumor tissue was around 50% of total cellularity, with samples up to 90% and a minimum of 5%; however, DNA extraction and analysis was highly satisfying (roughly 10% of failures). In the 9 ''malignant, not otherwise specified'' cases (L3), surgery was performed in 2 NSCLC cases. Almost all (87%) of the benign (L2) cases were subjected to follow-up with contrast-enhanced CT or ^{18}F-fludeoxyglucose positron emission tomography; no false negatives were noted during the subsequent observation period (average of 24 months). In the majority of inconclusive cases (L1), a repeat biopsy (78.3%) confirmed the malignant nature of the lesion, except for 3 cases in which no further testing was performed due to the patients' poor clinical conditions.

DISCUSSION

In the last years, CNB has confirmed its pivotal role for the transthoracic evaluation of lung nodules. Despite its theoretical

and dreaded invasiveness, the current technological support of the procedure is free from a significant rate of complications and shows good diagnostic performance.[1] The current article reports the largest European series of CNBs (375 procedures in 4 years) performed with the C-arm cone-beam CT guidance, and one of its aims is to definitively show the value of lung CNB, especially as a multidisciplinary tool for radiologists, pathologists, and oncologists. The first fundamental step required for a good lung CNB result is the careful planning of the radiological sampling. C-arm cone-beam CT guidance is currently the best approach, with high diagnostic performance on lesions down to around 10 mm diameter, which is considered the cutoff in the most important case series found in literature.[10] The rate of complications is also lowered, with the considerable advantage of real-time monitoring of needle insertion and progression; moreover, the use of semiautomatic needle provides a quick and immediate sampling of the lesion with a minimal rate of pneumothorax. This is one of the most important advantages in comparison with fine-needle aspiration biopsy series, possibly due to a prolonged sampling time and linear excursions of the needle.[11,12] Moreover, there is a significant reduction in the operator's exposure to radiations when compared with fluoroscopy guidance alone[13–15] and traditional CT. Koyama et al[16] reported a factor 1–3 lower organ and effective doses for cone-beam CT in comparison with multidetector CT (MDCT). Damet et al[17] found that the dose for cone-beam CT with XperCT was reduced by a factor 2.6 for the petrous bone when compared with MDCT. Other advantages of the C-arm cone-beam technique lie in the combination of static and dynamic imaging, that allows real-time surveillance on the procedure and increases operator confidence, unlike traditional CT-guided transthoracic biopsies or fluoroscopy-guided biopsies.[18] C-arm cone-beam CT-guided lung CNB has, in the major studies conducted on this technique, a specificity of 100% and a sensitivity over 95%.[13] Our series reached 100% in specificity, PPV, and NPV, whereas sensitivity and overall accuracy settled at 87.5% and 87.7%, respectively; however, it is to be noted that, when considering patients and not procedures, sensitivity and accuracy noticeably increased (96.8% and 97.2%). This was due to the repeating of the biopsy, which exposed the patient to the already discussed minor (or otherwise easily treatable) complications and did not imply a delay in the oncological management (all repeat biopsies were carried out within 2 months from the first sampling). We believe that the reason behind the low procedure-related sensitivity is the strictness of histopathological inclusion criteria for biopsies containing only foci of suspect cells that were, if necrotic or poorly preserved, labeled as unsatisfactory. Moreover, in our study, although no variables influenced specificity, sensitivity was significantly lower for small lesions (57.1%, $P < 0.01$ for lesions ≤ 10 mm); Lee et al[13] also found a significant decrease in performance under this size ($P < 0.028$). However, technical approach to these lesions is possible and was performed by our team in the case series (16 cases with a size of 15 and below and 4 of them below 10 mm). Along with the radiologist, the second professional figure related with lung CNBs is the pathologist, who is responsible for the correct management of the precious cores. Generally, mean core size ranged from 10 mm to around 30 mm in length, with variable fragmentation due to sample handling. Fragmentation was a cause for the report resulting as unsatisfactory ($P = 0.04$ between mean core size in diagnostic success and diagnostic failure groups; 12.9 ± 6.1 vs 10.7 ± 7.2 mm). The 2 cores were usually obtained in every single procedure. Thus, there was a good availability of material for immunohistochemical staining (up to 21 in our series for the evaluation of particularly complex lesions) or molecular testing (such as EGFR mutational analysis with Sanger sequencing).[19,20] Due to the peculiar behavior of lung malignancies, CNB finds its best application in evaluating advanced lung carcinoma; moreover, the lung is one of the major target organs of metastases. Therefore, the third specialist, who is the final user of the CNB, is the oncologist. In our series, malignancy accounted for 75.6% of the cases with 73.1% correctly typed. Of these, 31% were sent for molecular testing, which is now an indispensable additional tool[21] when administering a targeted therapy with drugs such as erlotinib (for EGFR mutations)[22] or crizotinib (in case of *EML4*/*ALK* translocations).[23,24] Currently, due to the importance of genetic profiling, the possibility of a second biopsy specifically for molecular testing is contemplated (as was done for 5 cases of our series). The application of lung CNB for a molecular and potentially ''patient-tailored'' target therapy of cancer is surely one of the most peculiar factors. This field, due to the recent innovations brought about by next-generation sequencing technology, is bound to undergo substantial changes, and it is likely that the technical management of the sampled material could be more sophisticated.[25]

The final pathological report of lung core biopsies reflects the increased complexity of the field, with more accurate but sometimes more complex differential diagnoses. This is particularly true in doubtful cases, when only a multidisciplinary approach including many other specialists, such as surgeons and pulmonologists, could solve the issues. In the multidisciplinary discussion, as already largely validated in other fields of pathology, such as thyroid[26] or breast,[27] the introduction of final diagnostic categories in the pathological report could provide the clinician with information that has an immediate and practical impact on the management of the patients. For the purpose of our study, we grouped the pathological findings of our series in a 4-tiered system with classes that had homogeneous and preferred actions in patient management. This decision simplified the statistical analysis using categories as indicators of diagnostic success or failure; other institutions could also use these classes in order to compare their diagnostic performances with an immediate view of procedure adequacy and quality control. This necessity was recently expressed in the literature on transbronchial fine needle aspiration (FNA),[28] where the Papanicolaou Society of Cytopathology's classification for cytological smears[29] was applied to improve coordination between pulmonologists and pathologists and multidisciplinary effectiveness, or in the study by Saqi et al[30] study on pathology reports of nonneoplastic lung diseases, in which a 4-tiered system was used.

In the L3–L4 classes, we grouped together successful biopsies in which histology revealed a definitively malignant lesion. However, only a diagnostic category of L4 was immediately informative of complete adequacy (also for molecular testing). Interestingly, although biopsies assigned to the L3 class were not fully typed, the 2 resectable NSCLC cases in this category underwent surgery, showing the usefulness and communication immediacy of this class between the various professional figures of multidisciplinary teams.

In L1–L2 patients, histology had to be matched together with imaging features for a final diagnostic class assignment. In this sense, lung pathologists must have a radiological background, and the pathological report has to be more than a ''histological report.'' Only the integration between the radiology and pathology results in our series could solve the challenge of differential diagnosis between a reactive fibrotic

process (L2) and sampling of a tumor capsule (L1, Figure 1B) with a repeat biopsy as the subsequent action.

In conclusion, we believe that CNB, guided by the modern imaging techniques, is a powerful option for the nonsurgical evaluation of pulmonary nodules, both for diagnostic and predictive purposes. Its great reliability allows for the application of a classification system whose main goal is to improve the effectiveness of multidisciplinary teams, which are the basic unit of modern medicine. Our monocentric experience, in which limitations are represented by the fact that it is a retrospective case series (with a relatively low standardization of data collection) and by the already discussed low procedure-related sensitivity, should be compared with other institutions with different epidemiological characteristics and disease prevalence. The pathological findings included in our series were surely not exhaustive of the entire possibilities related with lung pathology; however, future studies could validate this kind of methodological approach and evaluate the opportunity of a routine introduction of a classification system for the reporting of lung CNB.

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