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 Bonia, MD, Maria S. Cattin, MD, Maria G. Valentia, 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.

(Medicine 94(12):e698)

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. 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 interventionally 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 semi-automatic biopsy needles (Biopsybell SRL, Mirandola, Modena, Italy)
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 acquisition 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 biopptic 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 guidelines4 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 recategorized 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 |
| | ALK-1 |
| | KRAS |
| | ROS-1 |

| 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 |
| Acute pulmonary injury/ interstitial pneumonia, n = 25 |
| Reactive/replicative fibrotic nodules, n = 15 |
| Nodular fibrosis pleurisy, n = 3 |
| Wegener granulomatosis, n = 1 |
| Hamartoma, n = 1 |
| Lymphoproliferative, NOS, n = 3 |
| Non-small cell lung cancer, NOS, n = 2 |
| 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 |

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

**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
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 χ² 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%)  | 40 (87%)          |           |
| L2                          | 6 (13%)       | 2 (22.2%)  |                   |           |
| L3                          | 7 (77.8%)     | 38 (13.8%) | 236 (86.2%)       |           |

*Three patients (6.5%) were subjected to no further testing due to poor clinical conditions.
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 $12.4 \pm 6.3$ 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 ($12.9 \pm 6.1$ and $10.7 \pm 7.2$ 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 $\kappa$ 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 ($\text{EGFR} = 71$, $\text{EML4} / \text{ALK} = 50$, $\text{K/NRAS} = 14$, $\text{ROS1} = 1$); 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-fluodeoxyglucose 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.\textsuperscript{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.\textsuperscript{10} The rate of complications is also lower, with the considerable advantage of real-time monitoring of needle insertion and progression; moreover, the use of semi-automated 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.\textsuperscript{11,12} Moreover, there is a significant reduction in the operator’s exposure to radiations when compared with fluoroscopy guidance alone\textsuperscript{13–15} and traditional CT. Koyama et al\textsuperscript{16} reported a factor 1–3 lower organ and effective doses for cone-beam CT in comparison with multi-detector CT (MDCT). Damet et al\textsuperscript{17} found that the dose for cone-beam CT with XperCT was reduced by a factor 2.6 for the detector CT (MDCT). Koyama et al\textsuperscript{16} reported a factor 1–3 lower organ and effective doses for cone-beam CT in comparison with multi-detector CT (MDCT). Damet et al\textsuperscript{17} found that the dose for cone-beam CT with XperCT was reduced by a factor 2.6 for the detector CT (MDCT). Koyama et al\textsuperscript{16} reported a factor 1–3 lower organ and effective doses for cone-beam CT in comparison with multi-detector CT (MDCT). Damet et al\textsuperscript{17} found that the dose for cone-beam CT with XperCT was reduced by a factor 2.6 for the detector CT (MDCT). Koyama et al\textsuperscript{16} reported a factor 1–3 lower organ and effective doses for cone-beam CT in comparison with multi-detector CT (MDCT). Damet et al\textsuperscript{17} found that the dose for cone-beam CT with XperCT was reduced by a factor 2.6 for the detector CT (MDCT).

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\textsuperscript{22} or breast,\textsuperscript{23} 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 together 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),\textsuperscript{28} where the Papanicolau Society of Cytopathology’s classification for cytological smears\textsuperscript{29} was applied to improve coordination between pulmonologists and pathologists and multidisciplinary effectiveness, or in the study by Saqi et al\textsuperscript{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.

ACKNOWLEDGMENT

The authors would like to thank Andrew Smith, BSc, University Milan Bicocca, for the English revision of this article.

REFERENCES

1. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer. 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e93S–e120S.

2. Winer-Muram HT. The solitary pulmonary nodule. Radiology. 2006;239:34–49.

3. Heck SL, Blom P, Berstad A. Accuracy and complications in computed tomography fluoroscopy-guided needle biopsies of lung masses. Eur Radiol. 2006;16:1387–1392.

4. Travis WD, Brambilla E, Muller-Hermelink HK, et al. Pathology and Genetics of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press; 2004.

5. Socinski MA, Evans T, Gettiger S, et al. Treatment of stage IV non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e341S–e685S.

6. Killock D. Alternative rearrangements—targeting ROS1 in NSCLC. Nat Rev Clin Oncol. 2014;11:624. doi: 10.1038/nrclinonc.2014.180. Epub 2014 Oct 14.

7. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. American College of Chest Physicians - Medical Specialty Society. Treatment of stage I and II non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e278S–313S.

8. Ramnath N, Dilling TJ, Harris LJ et al. American College of Chest Physicians - Medical Specialty Society. Treatment of stage III non-small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e314S–40S.

9. Jett JR, Schuld SE, Kesler KA, Kalenkerian GP. American College of Chest Physicians - Medical Specialty Society. Treatment of small cell lung cancer: diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e400S–19S.

10. Choo JY, Park CM, Lee NK, et al. Percutaneous transthoracic needle biopsy of small (1 cm) lung nodules under C-arm cone-beam CT virtual navigation guide. Eur Radiol. 2013;23:712–719.

11. Halloush RA, Khawseh FA, Saleh HA, et al. Fine needle aspiration cytology of lung lesions: a clinicopathological and cytopathological review of 150 cases with emphasis on the relation between the number of passes and the incidence of pneumothorax. Cytopathology. 2007;18:44–51.

12. Ko JP, Shepard JO, Drucker EA, et al. Factors influencing pneumothorax rate at lung biopsy: are dwell and angle of pleural puncture contributing factors? Radiology. 2001;218:491–496.

13. Lee SM, Park CM, Lee KH, et al. C-arm cone-beam CT-guided percutaneous transthoracic needle biopsy of lung nodules: clinical experience in 1108 patients. Radiology. 2014;271:291–300.

14. Hiraki T, Mimura H, Gohara H, et al. CT fluoroscopy-guided biopsy of 1,000 pulmonary lesions performed with 20-gauge coaxial cutting needles: diagnostic yield and risk factors for diagnostic failure. Chest. 2009;136:1612–1617.

15. Choi MJ, Kim Y, Hong YS, et al. Transthoracic needle biopsy using a C-arm cone-beam CT system: diagnostic accuracy and safety. Br J Radiol. 2012;85:e182–187.

16. Koyama S, Aoyama T, Oda N, et al. Radiation dose evaluation in tomosynthesis and cone-beam CT examinations with an anthropomorphic phantom. Med Phys. 2010;37:4298–4306.

17. Damet J, Sans-Merce M, Méville F, et al. Comparison of organ doses and image quality between CT and flat panel XperCT scans in wrist and inner ear examinations. Radiat Prot Dosim. 2010;139:164–168.

18. Cheung JY, Kim Y, Shim SS, et al. Combines fluoroscopy- and CT-guided transthoracic needle biopsy using a C-arm cone-beam CT system: comparison with fluoroscopy-guided biopsy. Korean J Radiol. 2011;12:89–96.

19. Kurbang, Gallow BL, Leveridge M, et al. Needle core biopsies provide ample material for genomic and proteomic studies of kidney cancer: observations on DNA, RNA, protein extractions and VHL mutation detection. Pathol Res Pract. 2012;208:22–31.

20. Cheung YC, Chang JWC, Hsieh JJ, et al. Adequacy and complications of computed tomography-guided core needle biopsy on non-small cell lung cancers for epidermal growth factor receptor mutations demonstration: 18-gauge or 20-gauge biopsy needle. Lung Cancer. 2010;67:166–169.

21. Brega E, Brandao G. Non-small cell lung carcinoma biomarker testing: the pathologist’s perspective. Front Oncol. 2014;4:182.

22. Sharma SV, Bell DW, Settleman J, et al. Epidermal growth factor receptor mutations in lung cancer. Nat Rev Cancer. 2007;7:169–181.

23. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol. 2012;13:1011–1019.

24. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363:1693–1703.

25. Tuononen K, Mäki-Nevala S, Sarhadi VK, et al. Comparison of targeted next-generation sequencing (NGS) and real-time PCR in the detection of EGFR, KRAS, and BRAF mutations on formalin-fixed, paraffin-embedded tumor material of non-small cell lung carcinoma-superiority of NGS. Genes Chromosomes Cancer. 2013;52:503–511.

26. Pagni F, Prada M, Goffredo P, et al. “Indeterminate for malignancy” (Tir3/Thy3 in the Italian and British systems for
classification) thyroid fine needle aspiration (FNA) cytology reporting: morphological criteria and clinical impact. Cytopathology. 2014;25:170–176.

27. Pagni F, Bosiso FM, Salvioni D, et al. Application of the British National Health Service Breast Cancer Screening Programme classification in 226 breast core needle biopsies: correlation with resected specimens. Ann Diagn Pathol. 2012;16:112–118.

28. Bonifazi M, Sediari M, Ferretti M, et al. The role of the pulmonologist in rapid on-site cytologic evaluation of transbronchial needle aspiration: a prospective study. Chest. 2014;145:60–65.

29. Suen KC, Abdul-Karim FW, Kaminsky DB, et al. Guidelines of the Papanicolaou Society of Cytopathology for the examination of cytologic specimens obtained from the respiratory tract. The Papanicolaou Society of Cytopathology Task Force on Standards of Practice. Mod Pathol. 1999;12:427–436.

30. Saqi A, Coley SM, Crapanzano JP. Granulomatous inflammation and organizing pneumonia: role of computed tomography-guided fine needle aspirations, touch preparations and core biopsies in the evaluation of common non-neoplastic diagnoses. Cytojournal. 2014;11:2.