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► To cite this version:

Anne-Claire Toffart, Stéphane Asfari, Anne Mc Leer, Emilie Reymond, Adrien Jankowski, et al.. Percutaneous CT-guided biopsy of lytic bone lesions in patients clinically suspected of lung cancer: Diagnostic performances for pathological diagnosis and molecular testing. *Lung Cancer*, 2020, 140, pp.93 - 98. 10.1016/j.lungcan.2019.12.012 . hal-03489699

HAL Id: hal-03489699

<https://hal.science/hal-03489699>

Submitted on 21 Jul 2022

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Percutaneous CT-guided biopsy of lytic bone lesions in patients clinically suspected of lung cancer: diagnostic performances for pathological diagnosis and molecular testing

Running title: Percutaneous CT-guided biopsy of lytic bone lesions

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Abstract

Objectives

Bone is a common location for lung cancer metastasis. Clinicians are often reluctant to biopsy bone metastases, as they are known to require a decalcification process that damages nucleic acids, which makes it incompatible with molecular testing. We performed this study to assess the diagnostic performance of histopathology and molecular testing of computed tomography (CT)-guided percutaneous bone biopsies of lytic bone lesions during the initial assessment or during the progression of lung cancer.

Materials and Methods:

This retrospective study included all patients suspected of having or known to have primary lung cancer and CT-guided percutaneous bone biopsies of lytic bone from January 2010 to June 2017. The main judgment criterion was the diagnostic performance of the pathological analysis. Secondary endpoints were the diagnostic performance of molecular testing and incidence of complications.

Results:

Fifty patients were included. The yield of CT-guided percutaneous bone biopsies for pathological analysis was 100%, allowing for a diagnosis of certainty in all cases. The percentage of tumor cells in samples was higher than the 20% threshold in 83.9% of cases. The yield of molecular analysis was 94.6%. A mutation was found in 60% of cases; most frequently in *KRAS* (Kirsten rat sarcoma viral oncogene homolog) (28.6%) and *EGFR* (epidermal growth factor receptor) (14.3%). The complication rate was 2%, i.e. a minor undrained pneumothorax.

Conclusion:

CT-guided percutaneous biopsies of lytic bone is associated with a very low complication rate and high diagnostic performance for histopathology and mutation testing.

Key words: lung cancer; bone metastasis; core biopsy; computed tomography; CT-guided biopsy; histopathology; molecular biology; tumor genotype.

Introduction

The management of advanced stage non-small cell lung cancer (NSCLC) has significantly improved in the last decades with the introduction of personalized treatments showing better efficacy than chemotherapy [1,2]. However, such treatments require precise histopathological subtyping of the tumor, molecular testing and PD-L1 (Programmed death-ligand 1) immunohistochemistry (IHC) to predict immune checkpoint inhibitor response. In cases of tumor progression, a rebiopsy is often performed with specific molecular testing to detect mechanisms of EGFR (epidermal growth factor receptor) or ALK (anaplastic lymphoma kinase) inhibitor resistance. Finally, this multistep approach for the biological diagnosis of lung cancer requires sufficient quantity and optimal quality of material [3]. Alternatively, while the number of biological tests has increased, sample size has decreased with the growing development of small biopsies under local anesthesia, such as those provided by computed tomography (CT)-guided biopsies.

The contribution to the histopathological diagnosis and molecular testing of CT-guided biopsies of NSCLC bone metastases (initial diagnosis or rebiopsy at progression) is, however, poorly understood. Indeed, whereas bone is a frequent or exclusive site of lung cancer metastasis, biopsies frequently require decalcification, with acidic reagents leading to degradation of nucleic acids and DNA, incompatible with molecular testing [4].

Nonetheless, it has been shown that biopsies of lytic bone lesions perform better, regarding diagnosis and theranostics, than biopsies of sclerotic bone lesions [5,6]. To our knowledge, no studies have specifically examined the performances and complications of CT-guided percutaneous bone biopsies in patients with suspected or known advanced lung cancer.

Complications of bone biopsies are on the order of 0.2 to 1.6% for percutaneous biopsies, compared to 6 to 16% for open surgical biopsies [7], including hematomas, pneumothorax and neurological complications. In a meta-analysis involving 9,500 patients,

Murphy [8] recorded severe neurological complications (paralysis, meningitis) in 0.08% of cases and death in 0.02%. The theoretical risk of dissemination on the path of biopsy is low.

The purpose of our study was to determine the diagnostic performance and complication rate of imaging-guided percutaneous needle core biopsy in patients with lytic bone metastases and known or suspected lung cancer.

Materials and Methods

Subjects and study design

This monocentric retrospective study was conducted at the University Hospital of Grenoble Alpes, France. All patients known or suspected of having lung cancer who received CT-guided percutaneous bone biopsies of a lytic bone between January 2010 and June 2017 were included. Lytic bone lesions were detected by regular contrast enhanced CT of the thorax, abdomen and pelvis and defined as a bone defect filled with tissue density material, with or without cortical rupture. Patients with lytic bone metastases of known extra-pulmonary origin were excluded as well as those with entirely sclerotic bone lesions. The main endpoint of this study was the diagnostic performance of the pathological analysis. Secondary endpoints were the diagnostic performance of molecular testing and incidence of complications.

According to the French regulations for retrospective non-interventional clinical research, written information was delivered to the last known postal address to all selected patients, with the possibility of sending back, within the specified time limits (1 month), their opposition to the anonymous collection of their data. This study was registered at www.ClinicalTrials.gov with the identifier NCT03386916. Study ethics approval was obtained on 25 September 2019 (CECIC Rhône-Alpes-Auvergne, Clermont-Ferrand, IRB 5891).

Data

Data for each CT-guided percutaneous bone biopsies were collected from our hospital's computerized patient record and the radiology information system (RIS-PACS). The patients' electronic medical records were reviewed to obtain clinical history.

Collected data included characteristics of the patient, biopsied lesion (location, size), occurrence of a complication during and after the biopsy, histopathological and molecular biology results and the resulting therapeutic impact.

Biopsy procedure

Prior to each CT-guided percutaneous bone biopsy, the risks and benefits of percutaneous biopsies were discussed and written informed consent was obtained from each patient.

All CT-guided percutaneous bone biopsies were performed by a board-certified radiologist (with 3 to 27 years of experience) or by a radiology resident under direct senior radiologist supervision.

Coagulation screening was performed before all procedures (exclusion criteria were an international normalized ratio > 1.5 or a platelet count $< 50,000/L$). For all patients, the biopsy was performed percutaneously under CT scan guidance.

All patients underwent a CT of the chest-abdomen-pelvis prior to biopsy to confirm the site of biopsy and calculate the optimal trajectory of the needle. At the time of biopsy, selected images were obtained in the area of interest with 1 mm-thick contiguous CT sections. The procedure was performed with the patient in a prone, supine, or lateral position, depending on the location of the lesion (Figure 1). The position allowed the easiest access route to avoid neurovascular structures and viscera. All CT-guided percutaneous bone

biopsies were performed using a local anesthetic (20 mL of 1% lidocaine). We used a coaxial biopsy system consisting of a 15- or 17-gauge (G) outer needle (Angiotech coaxial introducer needle; Medical Device Technologies Inc., Gainesville, FL, USA) and a 16- or 18-G core biopsy needle (Angiotech BioPince™ full core biopsy instrument), respectively, which allows for 13-mm or 23-mm or 33-mm long core tissue biopsies. The coaxial technique allows for acquisition of multiple samples using only one transgression through the skin. The number of samples depended on the will of the radiologist in charge of the patient according to the visual quality and quantity of the material obtained. After the biopsy, the patients were transferred to the chest unit for a 3-hour clinical follow-up. A chest radiograph was performed 3 hours after the procedure in cases of thoracic biopsy. Biopsies were immediately fixed in formalin and embedded in paraffin within 24 hours.

Histopathological and molecular biology analysis

As mentioned in our prescription form, pathologists received the information of a lytic bone lesion to preclude decalcification.

Hematoxylin–eosin–safran (HES) sections of formalin-fixed and paraffin-embedded TTNB were analyzed histologically. The lengths of biopsies and the average percentage of tumor cells present on the slides were recorded.

For nonsquamous NSCLC, samples were tested by pyrosequencing or NGS (next generation sequencing) for *EGFR*, *KRAS*, *BRAF* (BRAF proto oncogene), and *HER2* (human epidermal growth factor receptor 2), and screened for *ALK* and *ROS1* (ROS1 proto oncogene) rearrangement by IHC and by FISH (Fluorescence in situ hybridization) for *MET* amplification in cases of EGFR TKI (Tyrosine kinase inhibitor) resistance. Detection of *MET* (hepatocyte growth factor receptor) exon 14 mutation was performed when requested by the

oncologist. PD-L1 IHC (using the 22C3 assay) was performed starting in May 2015 and only for requested patients.

Complications

Immediate complications were collected on the radiologist's report. The clinical files were reviewed for complications.

Complications were classified as minor or major according to the Society of Interventional Radiology (SIR) Guidelines [9]. Minor complications consisted of pneumothorax without need for intervention, ground glass opacity around the target diagnosed as pulmonary hemorrhage, and transient hemoptysis. Major complications consisted of pneumothorax requiring intervention, hemothorax, air embolism, needle tract seeding, and death. Intervention was defined as treatment consequences (manual aspiration, chest tube placement, or pain control) or hospital admission.

Statistical analysis

The diagnostic performance of CT-guided percutaneous bone biopsies of lytic bone for histopathology was calculated by the number of samples that could be analyzed / total number of bone biopsies performed x100. The diagnostic performance of molecular analysis was calculated as the number of analyzable samples / total number of samples sent for molecular testing x 100.

Tumor size is the sum of the larger tumor axis and the larger perpendicular axis divided by two [10]. The percentage of tumor cells collected was classified according to the following threshold values: less than 20%, between 20 and 50% and greater than 50%, acknowledging that a minimum rate of 10 to 20% is commonly necessary for genetic testing.

Quantitative variables were expressed as median [interquartile (IQR) 25%-75%] and qualitative variables as n (%).

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA).

Results

Patients

A total of 773 biopsies were collected in the thoracic imaging unit of our hospital during the study period (Figure 2). Of these, 58 (8%) involved suspected bone metastases in patients with known or suspected primary lung cancer. Eight patients were excluded because the suspected bone lesions were not lytic. Finally, data from 50 patients with biopsies of lytic bone were included.

The main characteristics of biopsies are reported in Table 1. The characteristics of the biopsied lesions in terms of morphology and location are reported in Table 2. The average size of the biopsied lesions was 33 mm (IQR 25%-75%, 24-43 mm), located 27 mm deep (IQR 25%-75%, 20-36 mm). Bone lesions affecting the thoracic region (41 biopsies / 50, 82%) were at a median distance of 0 mm from the pleura (IQR 25%-75%, 0-6). Costal location predominated (28 cases (56%)), followed by sternum and iliac bone locations. A median of 3 biopsy samples were taken (1 to 5 samples, IQR 25%-75%, 2-3) with a median sampling length of 13 mm [IQR 25%-75%, 13-23]. A majority of biopsies were performed with a 16G needle (n=33, 66%).

Performance of histopathology and molecular analyses

The biopsy was informative in 100% of cases. Lung adenocarcinoma accounted for the majority of the cases (31 patients (62%)). Table 3 summarizes the main results.

For 31 (62%) patients, the percentage of tumor cells was mentioned in the pathological report. Among them, 26/31 (84%) patients had a tissue sample with more than 20% tumor cells and higher than 50% in 58.1%, allowing for reliable molecular analysis.

Molecular testing was requested for 37 of the 50 patients (74%), consistent with the current recommendations according to histological subtype of the tumor, i.e. adenocarcinomas and non-small cell carcinoma NOS (Table 3). In 35/37 cases, the molecular analyses could be performed. Two samples were not analyzable due to insufficient tissue material. In 21 patients, mutations were identified, mainly *KRAS* mutations (n=10; 29%) and *EGFR* mutations (n=6; 17%). In one patient, an adenocarcinoma was diagnosed on a biopsy performed during fibroscopy, but due to insufficient material for molecular testing, a biopsy of the metastatic bone was subsequently performed and showed an *EGFR* mutation.

Complications

Only one (2%) complication was detected. The complication was a pneumothorax of low abundance (13 mm thick) complicating a biopsy of a rib and requiring no drainage or specific management and therefore was minor according to the SIR classification.

Therapeutic Impact

Following the bone biopsy analyses, 8 patients received a specific targeted therapy, 28 received chemotherapy and 3 received immunotherapy. No follow-up information was found for 1 patient.

In 8 patients, an *EGFR* mutation or *ALK* translocation was identified. Six received a new targeted therapy. For the other 2 patients, no new targeted therapy could be proposed, and the patients received chemotherapy.

Discussion

Our retrospective study showed a 100% yield for histopathological diagnosis. Forty-five biopsies (90%) showed metastases from a primary lung cancer, of which adenocarcinoma was the most common subtype (62%). The diagnostic yield for molecular biology was 94.6% (35/37). A mutation was found in 60% of cases, and the most frequent were in *KRAS* (28.6%) and *EGFR* exons 19-21 (14.3%), in accordance with the literature [11]. The percentage of tumor cells in samples (mentioned in 31/50 cases) was higher than the usually recommended 20% threshold [12] in 83.9% of cases. The complication rate was very low (2%), in the form of a minor complication with spontaneous resolution of the pneumothorax type. Such results were possible thanks to close collaboration between clinicians, pathologists, and radiologists in order to optimize the workflow of a “molecular priority” biopsy as recommended by Aisner et al[13].

One of the criteria for inclusion in our study was the osteolytic nature of bone lesions on CT images, i.e., the calcified bone structure was replaced by soft attenuation tissue, with or without rupture of the cortical bone. This presentation at CT allowed for the following:

1/ Using a simple coaxial technique protocol of biopsy without specific tools that are required to biopsy suspected osteoblastic metastasis on the bone.

2/ Using a selected needle-length of the sample (13, 23, 33 mm) adapted to the size of the target lesion. As bone biopsies are at lower risk for complications than intrathoracic biopsies [8-10], we used larger diameter needles (16G) to optimize the quantity and quality of tissue samples. In our study, 66% of the samples (33 biopsies) were obtained with 16G needles and 34% (17 biopsies) with 18G needles.

3/ Specifying to the pathologist that the sample should not be decalcified before analysis. The absence of decalcification and subsequent absence of degradation of nucleic acids and antigens explains the excellent yield of histopathological and molecular analyses [3].

Indeed, the histopathological yield of bone biopsies in the literature varies according to the series, depending on the osteoblastic or osteolytic nature of the targeted lesion. The yield of histopathology in cases of lytic lesions biopsies was 71% in the study by Jelinek et al. [14] (bone tumors) and 85% in the study by Fraser-Hill et al. [15]. For osteoblastic lesions, the yield varies between 69 and 82% [15, 16]. The study by Vieillard et al. [6] evaluated the yield of percutaneous bone biopsies for vertebral and peripheral bone tumors. The efficacy was higher for lytic lesions (87%; 64/73) than for osteoblastic lesions (66%; 2/3) but with no significant difference between these subgroups due to small figures. The lower diagnostic yield of osteoblastic lesions is due to the difficulty in identifying the tiny spinal cord areas within bone fragments containing a few groups of neoplastic cells [6].

When the amount of calcified bone tissue is small, it is not necessary to perform a decalcification step, which deteriorates membrane antigens and nucleic acids [17]. The study by VanderLaan et al. [5] evaluated the success rate of *EGFR/KRAS* mutations and *ALK* rearrangements by comparing surgical specimens of all types (pulmonary / lymph node / bone / pleural and cerebral) vs. percutaneous biopsy vs. bronchoalveolar lavage in non-small cell lung cancers. Failure rates for *EGFR* molecular testing were higher in percutaneous biopsy if the biopsy sample was bone: 40% (4/10) compared to 0% (0/13) ($p=0.024$) in surgical resection. Bone samples were of all types, lytic and condensing, with decalcification of tumor tissue before sample preparation correlating with a higher failure rate for genotypic research: 60% (3/5) vs. 5.5% (1/18) ($p=0.021$) for *EGFR* with similar rates for *ALK* (44% vs. 0%) and *KRAS* (22% vs. 0%).

It is well known that pre analytical steps including decalcification by acid or heavy metal fixatives can be responsible for DNA degradation [18], high molecular testing failure rates having been reported in the past from bone specimens [19]. However, several recommendations have been proposed to maximize molecular testing from bone samples [13,20] such as 1; investigating for potential molecular testing when a bone specimen is received in the setting of lung cancer 2; performing a manual dissection of the bony component if possible 3; including the different samples in different formalin-fixed, paraffin-embedded blocks 4; avoiding decalcification as much as possible 5; using alternatively ethylene diamine tetraacetic acid (EDTA) solution, which seems less detrimental for molecular testing than strong acid decalcification [21, 22, 23, 24] ; 6; mentioning the occurrence of decalcification and the type of solution used in the pathological report.

Due to the infrequent availability of PET-CTs in our PACS system at the time of bone biopsy, it was not possible to assess the correlation between the lytic nature of a bone lesion at CT chosen as a target and the hypermetabolic activity at PET-CT. This correlation was performed by Wei Guo et al. [25] in 51 patients with a strong suspicion of metastatic lung cancer and bone lesions. Biopsies confirmed the metastatic nature of bone lesions in 96.1% of cases (49/51 patients) after the first biopsy while a second sampling was needed in two patients. Forty-seven out of 51 lesions showed lung cancer metastases. *EGFR* molecular testing was performed in 23 cases, 7 of which were positive (31.4%). *ALK* rearrangements tested positive in 31.6% of cases (6/19 patients). The results of the study by Wei Guo et al. [25] are comparable to those of the present study regarding the pathological efficiency of biopsies. We therefore question the interest of PET-CT to target the bone lesion in a lung cancer context, regarding its cost and low availability [26].

In the context of recent diagnosis or progression of lung cancer with secondary bone metastases, the question of the choice of the lesion to biopsy, either the primary lung tumor or a secondary lytic bone lesion, arises. For many clinicians, a biopsy of a bone lesion is not desirable because of the decalcification process that degrades the quality of the samples [17]. The study by Ferretti et al. performed in 2013 [26] included CT-guided lung biopsies. Confirmation of lung cancer was obtained in 80 to 95% of cases, with successful molecular biology tests in nearly 95% of cases for *EGFR* and *KRAS* and 100% for *ALK*. The cancer cell count on the samples was approximately 42%. The results of the present study are similar and demonstrate the importance of osteolytic bone sampling in the specific context of bronchopulmonary cancers.

The benefit/risk ratio is an important issue for the choice of any invasive procedure. All of the published studies in the literature on percutaneous bone biopsies show extremely low complication rates [6, 13, 18, 27-30], including Monfardini's retrospective study [31], which included 308 percutaneous bone metastases and reported complications in 3.5% (11/308), all considered minor. This result is consistent with our study, which found only one minor complication (2%), a limited pneumothorax. In contrast, CT-guided lung biopsies have a substantially higher complication rate as recently confirmed in the multicenter retrospective analysis by Fontaine-Delaruelle et al. [32], who showed complications in 34% of cases (pneumothorax and hemoptysis), including 6% that were severe complications (drained pneumothorax, hemoptysis or hemothorax).

Conclusion

CT-guided biopsy of lytic bone lesions occurring in a context of diagnosis or progression of lung cancer is a simple, safe and cost-effective procedure for pathological diagnosis and

molecular biology analysis. The excellent yield of lytic bone biopsies associated with a low complication rate should encourage biopsies of lytic bone lesions if present and accessible instead of lung targets. In addition, these biopsies can be performed with the same material as soft tissue biopsies.

'Declarations of interest: none'.

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Figure 1: CT-guided biopsy of focal osteolysis of right transverse process extended to the pedicle.

Figure 2. Flowchart of the study.

Table 1. Patients' characteristics

*Qualitative variables are expressed as n (%), and quantitative variables are expressed as the median (interquartile 25-75%).

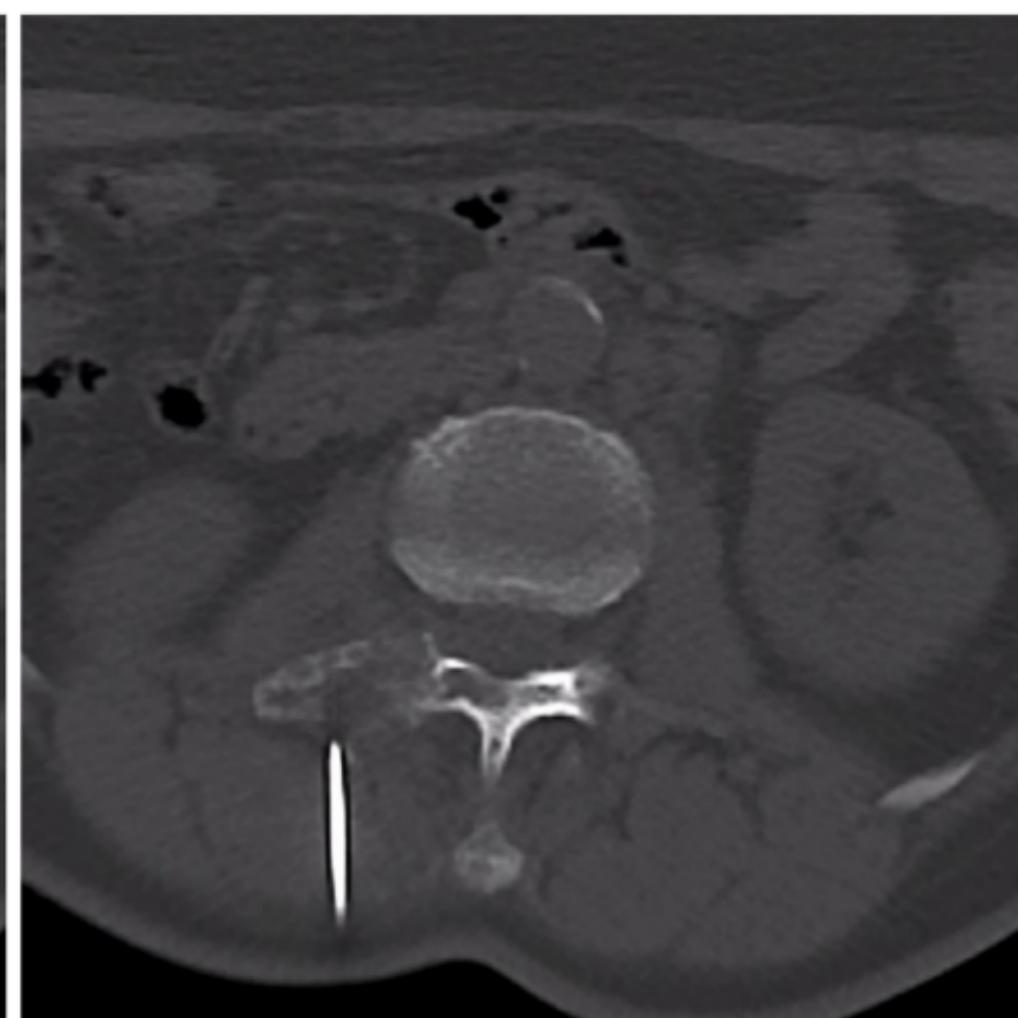
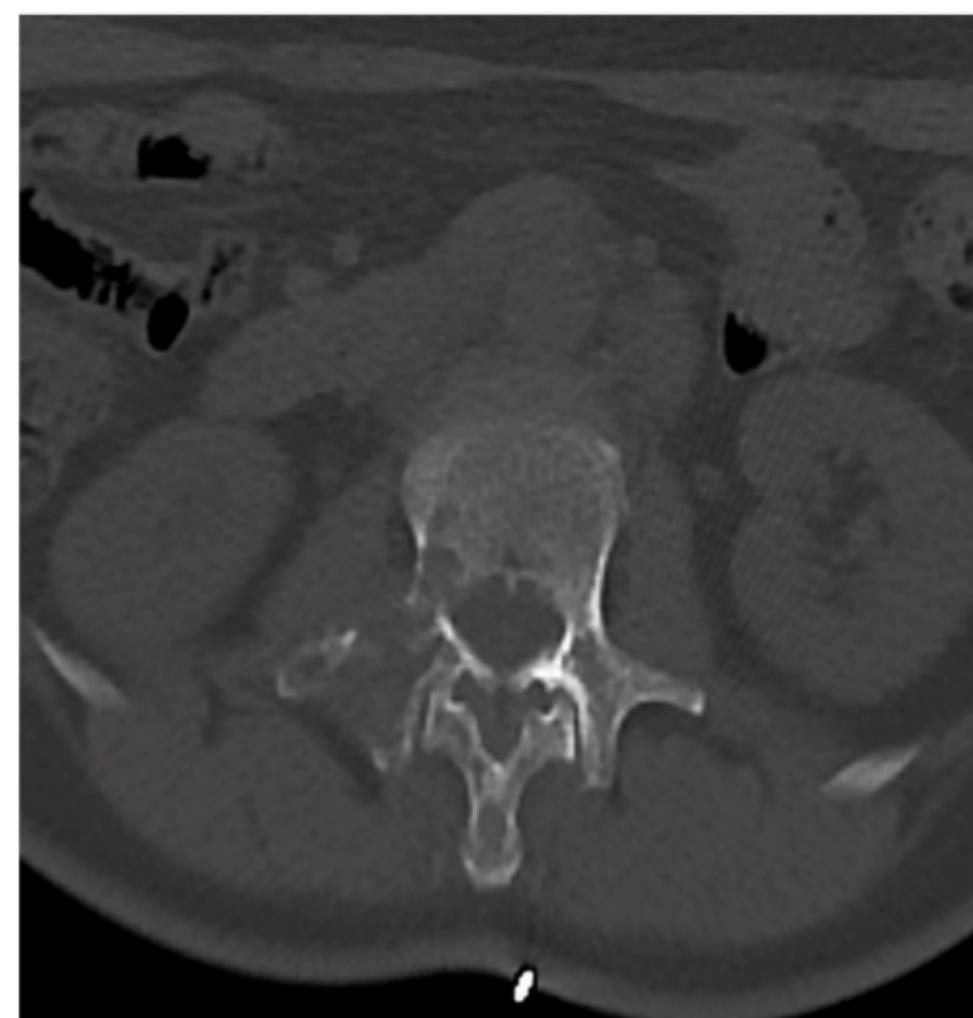
CT, computed tomography-guided percutaneous bone biopsies; NSCLC, non-small cell lung cancer

Table 2. Biopsy characteristics Qualitative variables are expressed as n (%), and quantitative variables are expressed as the median (IQR 25-75%)

Table 3: Histological and molecular biology results

Figure 1: CT-guided biopsy of focal osteolysis of right transverse process extended to the pedicle.

Figure 2. Flowchart of the study.



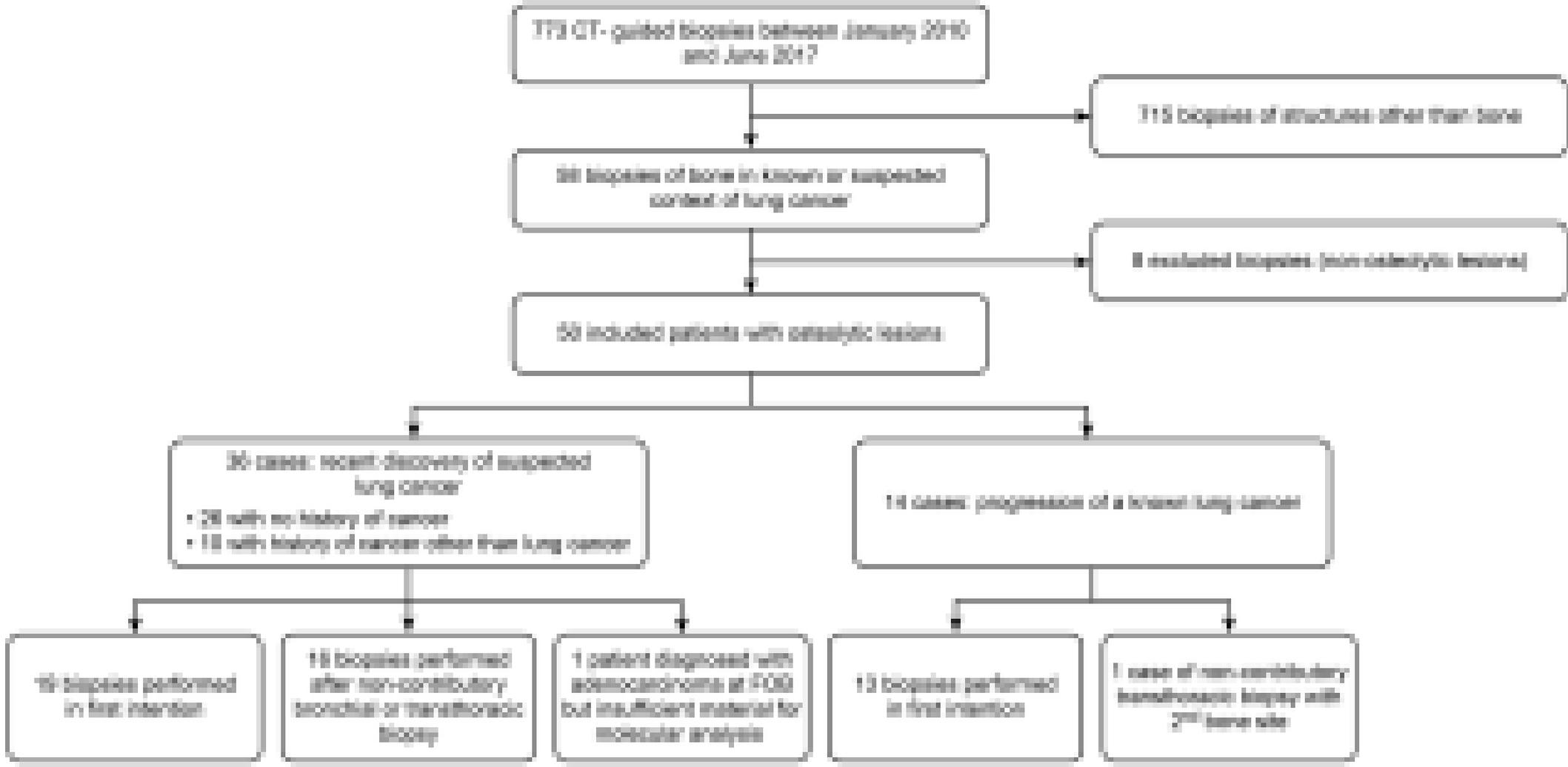


Table 1. Patient characteristics

Patient characteristics	N = 50
Age (years)	65 [62-73]
History of cancer	24 (48%)
Nonsmokers	9 (18%)
Former/current smokers	38 (76%)
Unknown	3 (6%)
Number of packs/year	28 [40-50]
Prior cancer	
Lung cancer	14 (58%)
Adenocarcinoma	8 (33%)
NSCLC	3 (13%)
Squamous cell carcinoma	2 (8%)
Carcinoid tumor	1 (4%)
Other cancer	9 (42%)
Initial molecular biology in patients with adenocarcinoma of the lung (mutations)	N = 10
No	8 (80%)
EGFR 19 21	1 (10%)
ALK	1 (10%)
Indication of CT-guided percutaneous bone biopsies	N = 50
Initial evaluation of suspected lung cancer	35 (70%)
Progression of lung cancer	14 (28%)
Molecular biology testing	1 (2%)
Initial extra osseous biopsy failure's causes	N = 18
Tissue without cancer	10 (56%)
Uncertain pathology	3 (17%)
Uncertain adenocarcinoma histology	2 (11%)
No molecular biology	2 (11%)
Uncertain squamous cell carcinoma histology	1 (5%)

*Qualitative variables were expressed as n (%) and quantitative variables as the median (interquartile 25%-75%).

CT, computed tomography-guided percutaneous bone biopsies; NSCLC, non-small cell lung cancer

Table 2. Biopsy characteristics

Biopsy characteristics	N =50
Size of lesions (mm)	
Maximum diameter	40 [29-55]
Minimum diameter	22 [17-31]
Mean diameter	33 [23-42]
Distance from skin (mm)	27 [20-36]
Distance from pleura if thoracic biopsy (mm)	0 [0-6]
Number of samples	3 [2-3]
Needle size	
16 G	33 (66%)
18 G	17 (34%)
Location	
Ribs	28 (56%)
Pelvis	8 (16%)
Sternum	6 (12%)
Arm	5 (10%)
Vertebra	3 (6%)

Qualitative variables were expressed as n (%) and quantitative variables as the median (IQR 25%-75%)

Table 3. Histological and molecular biology results

Results	Number (%)
Histological subtype	
Pulmonary adenocarcinoma	31 (62)
Non-small cell carcinoma	6 (12)
Squamous cell carcinoma	5 (10)
Small cell carcinoma	2 (4)
Lung atypical carcinoid	1 (2)
Other cancer metastasis	3 (6)
Non-tumoral	2 (4)
Molecular biology performed	
No	13 (26)
Insufficient material	2 (4)
Yes	35 (70)
No genomic alteration	14 (40)
KRAS/NRAS mutation	11 (31)
EGFR exon 19-21 mutation	5 (14)
EGFR T790M mutation	1 (3)
ALK rearrangement	2 (6)
MET amplification or exon 14 mutation	2 (6)