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A Randomized Clinical Trial of Flex 19G Needles versus 22G Needles for Endobronchial Ultrasonography in Suspected Lung Cancer

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Keywords
EBUS-TBNA · Flexible 19G needles · Lung cancer · Lymph node · Next-generation sequencing · Randomized trial

Abstract
Background: A flexible 19-gauge (Flex 19G) needle has been developed for endobronchial ultrasonography. ***Objectives:*** We aimed to evaluate quantitative and qualitative specimen characteristics of Flex 19G in a randomized controlled setting for patients with suspected lung cancer. ***Methods:*** We undertook a single-center, randomized, controlled trial. A computer-generated randomization assigned all enrolled patients 1:1 to undergo endobronchial ultrasonography using a Flex 19G or a 22-gauge (22G) needle for lymph node tissue sampling. Pathologists were blinded to the group assignment. The primary end point was histological tissue core procurement. The secondary end points were diagnostic yield, specimen bloodiness and overall quality, tissue surface area and performance for next-generation sequencing (NGS), and procedure-related complications. ***Results:*** Between June 2016 and February 2017, we randomly allocated a total of 78 patients: 39 patients to Flex 19G and 39 patients to 22G. No superiority in tissue core procurement was observed for Flex 19G compared to 22G (67 vs. 72%, $p = 0.81$). No significant difference was observed in diagnostic yield and overall specimen quality, but transbronchial needle aspiration specimens by Flex 19G were bloodier and had a larger tissue surface area. NGS was successful for clinically relevant genes in 96% and for all 26 genes tested in 81% of the samples. There was no difference in clinically relevant complications. ***Conclusions:*** No superiority is observed for Flex 19G in histological tissue core procurement rate. The Flex 19G needle could be considered when a larger tissue surface is of special interest.

Introduction

Conventional transbronchial needle aspiration (TBNA) has long been an integral part of the diagnostic algorithm for the evaluation of suspected lung cancer [1, 2]. A conventional 19-gauge (19G) Wang needle may procure histological samples, resulting in a higher sensitivity compared to a conventional 22-gauge (22G) needle

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[3–5]. The major limitations were the lack of flexibility for the 19G needle and the lack of real-time visual guidance for the conventional TBNA needle, making sampling of some lymph node stations difficult.

In the last decade, endobronchial ultrasound-controlled (EBUS)-TBNA with the use of a 22G needle has become an established practice to obtain a histopathological specimen in patients with advanced stage lung cancer [6]. Tissue sampling can be performed with needle capillary sampling or needle aspiration, and a (minimum) number of 4 passes to obtain sufficient tissue for genomic testing has been determined [6–8]. The ability to procure sufficiently adequate histological tissue core samples using the 22G needle with an inner diameter of 0.41 mm remains a concern. Recent advances in needle development resulted in a flexible 19G (Flex 19 G) needle with an inner diameter of 0.69 mm. In a preclinical swine model of granulomatous lymphadenopathy, the Flex 19G and 22G EBUS-TBNA needles had a similar diagnostic yield, but the Flex 19G needle samples were larger [9].

The inner diameter of the Flex 19G needle for EBUS-TBNA is considered a key determinant for the tissue biopsy quantity. In particular, predictive genetic alteration testing is relevant as the molecular complexity of lung cancer is evolving [10]. Targeted PCR-based sequencing can be performed on >80% of the routine EBUS-TBNA specimens, but only a limited number of studies did evaluate next-generation sequencing (NGS) assays performed on fine needle aspirations [11–14].

Given the frequent use of 22G needles for molecular diagnostics and the recent technical advancements in Flex 19G needle technology and NGS assays, we designed a randomized trial to compare quantitative and qualitative characteristics of specimen obtained by endobronchial ultrasonography-guided needle aspiration biopsy with either a Flex 19G or a 22G needle in patients with suspected lung cancer.

Patients and Methods

Study Design and Participants

We conducted a randomized controlled trial at the University Hospitals KU Leuven, Leuven, Belgium. All patients 18 years and older, with suspected non-small cell lung cancer identified on computed tomography, and referred for a targeted EBUS-TBNA investigation to obtain intrathoracic lymph nodal tissue from one nodal station for pathological diagnosis, subtyping, and genotyping of lung cancer were eligible for participation in this study. Consecutive patients with suspected advanced-stage (i.e., stage IVA or stage IVB) lung cancer were enrolled from June 2016 to February 2017. All patients provided written informed consent. The Institutional Review Board of the University Hospitals KU Leuven approved the study (B32220162793). The trial has been registered with Clinicaltrials.gov: NCT02906280.

Randomization and Masking

A computer randomly assigned patients 1:1 to either a ViziShot Flex 19G needle (NA-U402SX-4019; Olympus Respiratory America, Redmond, WA, USA) or ViziShot 22G needle (NA-201SX-4021; Olympus). The pathologists remained blinded to the randomization result and needle type used.

Procedures

Endobronchial Endosonography Procedure

All procedures were performed using a linear array echoendoscope (Olympus BF-UC180F or Fujinon EB-530US) under moderate sedation. A standard operating bronchoscopy protocol regarding the sampling technique and the number of needle passes was applied in every patient.

The first 2 needle passes were performed without suction, but by moving the needle back-and-forth 10 times in multiple directions while the stylet is partially retracted, after which the needle was withdrawn, and the material was expressed using the stylet into a container with cytorich red solution (Hologic, Marlborough, MA, USA). This sampling technique allows a smooth extraction of lymph node tissue material without the need for suction, and is called transbronchial needle capillary sampling. Thereafter, 4 needle passes were performed according to a TBNA technique: after puncturing the lymph node, the stylet is completely removed and continuous suction is applied using a 10-mL syringe. while manipulating the needle back-and-forth 10 times in multiple directions within the lymph node. Then the suction is closed, the needle is retracted, and finally the TBNA needle is rinsed releasing the specimen into a second container with cytorich red solution. Per patient, one container with the specimens of 2 times transbronchial needle capillary sampling (TBNCS) and one container with the specimens of 4 times TBNA were submitted to the Pathology lab. Clinical complications, such as bleeding, desaturation <90%, intolerance leading to premature procedure termination, or any need for hospitalization, were reported.

Preparation and Processing of Tissue Specimens in the Laboratory

The material received in the Pathology lab was prepared following standard procedures. After centrifugation, the supernatant was discarded. Two droplets of material were placed in a vial containing Preservcyt (Hologic) to be processed in a Thinprep 5000 processor (Hologic). The rest of the material was embedded in Agar and paraffin-embedded overnight. As such, one Papanicolaou-stained monolayer and one 5-µm-thick hematoxylin and eosin (H&E)-stained slide from the cell block were available for the diagnosis.

Evaluation of the Specimens by the Pathologist

Diagnostic samples were classified as either malignant or benign (normal lymphoid tissue or granulomatous inflammation) after cytopathological examination. Immunocytochemistry was added to subtype the malignant cases. When there was inadequate material (defined as having a predominance of blood or bronchial epithelial cells) to make a diagnosis by cytopathological examina-

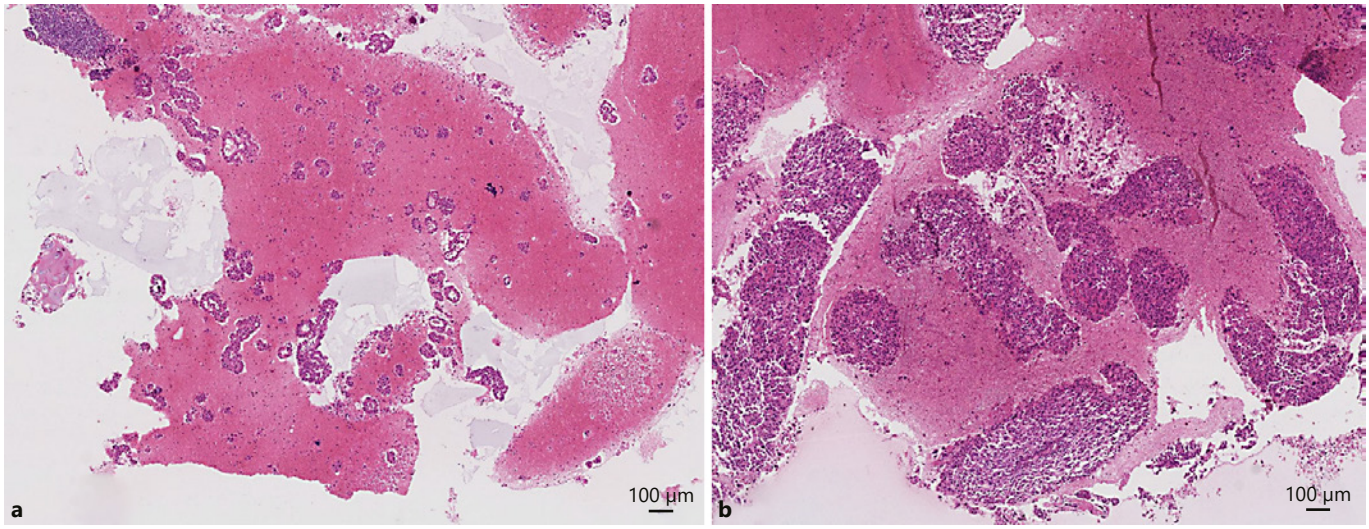

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Fig. 1. H&E-stained slide to evaluate tissue core procurement. **a** H&E-stained slide from a TBNCS by Flex 19G needle showing no tissue core present with the diagnosis lung adenocarcinoma. **b** H&E-stained slide from a TBNA by 22G needle showing tissue core present with the diagnosis lung adenocarcinoma.

tion of the monolayer and H&E-stained slide, the sample was classified as "non-diagnostic."

The 5-µm-thick H&E-stained slide from the cell block was evaluated for the presence of a tissue core, defined as a continuous string of tissue (Fig. 1). A standard operating protocol for further tissue and tumor surface area analysis was applied in every patient (see online suppl. e-Appendix 1; for all online suppl. material, see www.karger.com/doi/10.1159/000489473).

The quality of the sample was evaluated using both a bloodiness score and an objective Mair's scoring system. Specimen bloodiness was categorized based on the percentage of blood in the microscopic field: mild (i.e., <33%), moderate (i.e., 33–66%), and severe (i.e., >66%). The Mair's scoring was based on 5 objective criteria, and the cumulative total score was categorized into unsuitable or "poor" for diagnosis (total score 0–2), adequate or "good" for diagnosis (total score 3–6), and "superior" for diagnosis (total score 7–10) [15, 16].

Genomic Sample Analysis from the Selected Cell Block

In malignant cases, the pathologist reviewed both cell block sections and selected one block from which 12 consecutive 4-µm-thick sections were prepared, the first and last of which to be stained with H&E and evaluated for the presence and amount of tumor cells. The proportion of tumor cells was estimated semi-quantitatively, and the representative tumor-rich area was marked on the H&E slide. Samples were rejected if the proportion of tumor cells by visual estimation was <10%. For all samples with at least 10% tumor cellularity, a standard operating protocol for DNA extraction, quantitation, and sequencing for hotspot mutations was followed (see online suppl. e-Appendix 2).

Outcomes

The primary end point was the acquisition rate to procure a tissue core on the cell block preparation. A tissue core was defined as a continuous string of material as observed on the microscopic examination of the cell block (Fig. 1). Secondary end points were the tissue surface area (or surface area of diagnostic tissue objectively quantified after automatic scanning of the section; see online suppl. e-Fig. 2.B.1.), the quality of the sample evaluated using a Mair's objective scoring system, the specimen's bloodiness categorized based on the percentage of blood in the microscopic field, and the diagnostic yield. Additionally, tumor surface area (see online suppl. e-Fig. 2.B.2.), tumor cellularity, the quantity of DNA extracted, and the success rate of NGS based on a panel of 26 genes were evaluated for the cancer specimen. Finally, the complications related to the needle type used were recorded.

Statistical Analysis

For the primary end point, a 2-tailed sample size calculation was performed with a type I error rate set at 0.05 to obtain 90% power for detecting a tissue core in 90 and 60%, or a difference of 30%, between 19G and 22G needles, respectively. A sample size of 39 patients was required.

Quantitative variables are summarized as mean (and SD) or median (and interquartile range) for Gaussian or skewed distribution, respectively. Comparisons were performed with the Student *t* test or Mann-Whitney test for skewed distributions. χ^2 or Fisher's exact test were used for comparisons of qualitative variables as appropriate. All tests were two-sided, and statistical significance was determined as p value <0.05. All of the statistical analyses were performed with a statistical software package, GraphPad Prism version 5.0 for Mac, GraphPad Software, San Diego, CA, USA.

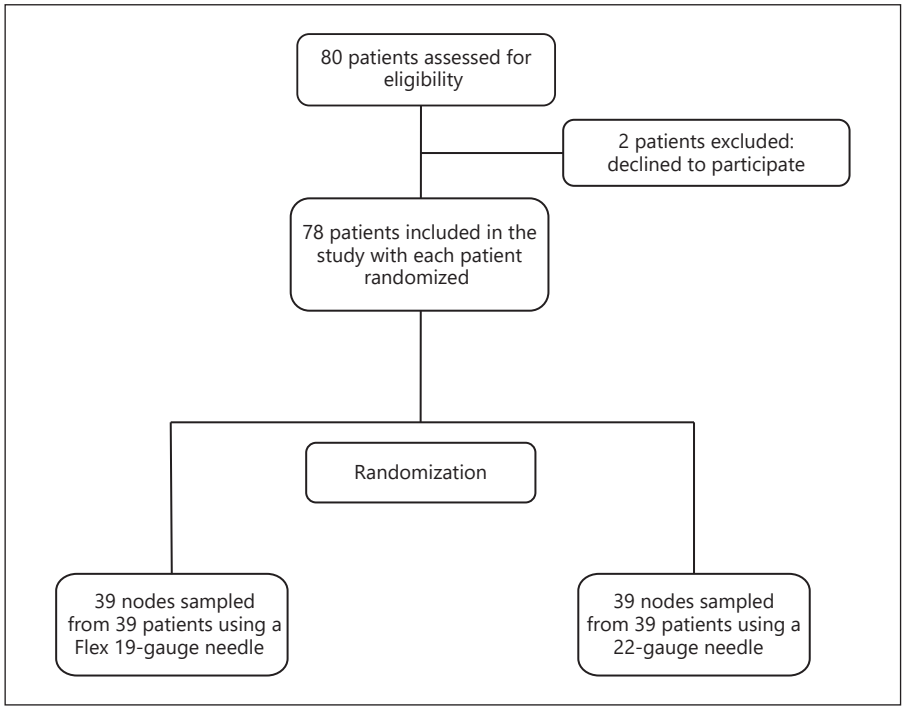

Fig. 2. Study flow chart of enrolled patients with suspected lung cancer and an indication for nodal tissue diagnosis by endobronchial ultrasonography.

Table 1. Patient and lesion characteristics

	19-gauge needle (n = 39)	22-gauge needle (n = 39)
Male gender, n (%)	29 (74)	24 (62)
Mean age ± SD, years	67±10	63±10
T location (right), n (%)	22 (56)	18 (46)
LN location, n (%)		
Station 2–4	16	22
Station 7	15	6
Station 10–11	8	11
Median LN size, mm (IQR)[a]	18 (15–29)	18 (15–25)
Diagnosis on specimen		
Lung cancer	30	34
Benign	7	2
Other neoplasia	2*	3**

n, number per variable; T, primary tumor; LN, lymph node; IQR, interquartile range.

[a] On chest CT.

* One malignant pleural mesothelioma and one non-Hodgkin's lymphoma; ** one metastatic ovary cancer, one metastatic prostate cancer, and one diffuse large B-cell lymphoma.

Results

We randomly assigned 78 patients with suspected lung cancer to undergo endobronchial ultrasonography with either a Flex 19G (n = 39) or a 22G (n = 39) needle tissue sampling (Fig. 2). Patient demographics and tumor characteristics were well-balanced for all major clinical characteristics and are presented in Table 1. The final diagnosis was malignancy in 69 patients (lung adenocarcinoma, n = 36; squamous cell lung carcinoma, n = 9; small cell lung cancer, n = 17; non-small cell lung cancer not otherwise specified, n = 1; large-cell neuroendocrine carcinoma, n = 1; lymphoma, n = 2; metastasis of extrathoracic carcinoma, n = 2; malignant pleural mesothelioma, n = 1) and a benign condition in the remaining 9 patients (reactive lymphadenopathy, n = 8; sarcoidosis, n = 1). None of the samples obtained by EBUS-TBNA were non-diagnostic, while for TBNCS 10% of all 19G and 5% of all 22G samples yielded inadequate material for diagnosis. There was no difference in the number of needle passes (2 plus 4 needle passes in all patients) or in procedural complications (no clinical complication directly related to the procedure was recorded) between the Flex 19G and the 22G cohorts.

Primary and secondary quantitative specimen outcome measures are reported in Table 2. In all patients, we

Table 2. Quantitative specimen outcomes

	19-gauge needle (n = 39)	22-gauge needle (n = 39)	p value
Tissue core present on cell block, n (%)	26 (67)	28 (72)	0.81
Median tissue surface area, mm^2 (IQR)	6.0 (3.7–11.7)	4.6 (1.9–10.3)	0.15

n, number per variable; IQR, interquartile range.

Table 3. Qualitative specimen outcomes

Outcome measure	Scoring	19-gauge needle (n = 39)	22-gauge needle (n = 39)	p value
Bloodiness on TBNA, n				0.004
Severe	>66%	14	3	
Moderate	33–66%	22	29	
Mild	<33%	3	7	
Bloodiness on TBNCS, n				0.42
Severe	>66%	12	8	
Moderate	33–66%	16	15	
Mild	<33%	11	16	
Mair's background blood on TBNA				0.057
Large amount – diagnosis compromised	0	2	2	
Moderate amount – diagnosis possible	1	30	21	
Minimal amount – diagnosis easy	2	7	16	
Mair's background blood on TBNCS				0.13
Large amount – diagnosis compromised	0	8	5	
Moderate amount – diagnosis possible	1	22	19	
Minimal amount – diagnosis easy	2	9	15	
Mair's total score on TBNA				0.73
Diagnostic ease "poor"	0–2	1	0	
Diagnostic ease "good"	3–6	2	3	
Diagnostic ease "superior"	7–10	36	36	
Mair's total score on TBNCS				0.78
Diagnostic ease "poor"	0–2	7	8	
Diagnostic ease "good"	3–6	7	3	
Diagnostic ease "superior"	7–10	25	28	

n, number per variable; TBNA, transbronchial needle aspiration; TBNCS, transbronchial needle capillary sampling.

were able to procure at least 1 cell block. A tissue core was present in a similar proportion of patients randomized to the Flex 19G and the 22G needle (67 vs. 72%, p = 0.81). There was a trend towards larger tissue surface area on the cell block for specimens obtained with Flex 19G compared to 22G (6.0 vs. 4.6 mm^2, p = 0.15). Qualitative specimen outcome measures are reported in Table 3. Severe bloodiness was observed significantly more in TBNA specimens randomized to Flex 19G than to 22G (36 vs. 8%, p = 0.0035), which was not observed in TBNCS specimens. The bloodier specimens procured using Flex 19G did not impede the diagnostic assessment as evaluated by Mair's background blood criterion, which also takes into account a qualitative description for diagnostic ease. The

Table 4. Subgroup analysis of cancer specimen outcomes

Outcome measure	19-gauge needle (n = 31)*	22-gauge needle (n = 36)*	p value
Cell block selected for NGS, n/N (%)			0.57
TBNA cell block	24/31 (77)	26/36 (72)	
TBNCS cell block	6/31 (20)	9/36 (25)	
None selected	1/31 (3)	1/36 (3)	
Presence of tissue core (yes), n/N (%)	21/31 (68)	25/36 (69)	1.00
Median tissue surface area, mm^2 (IQR)	5.94 (2.54–10.52)	4.01 (2.01–8.60)	0.26
Tumor cellularity, % QNC			0.64
<10%	2	0	
11–50%	10	14	
51–100%	19	22	
Median tumor surface area, mm^2 (IQR)	4.91 (2.08–9.31)	2.35 (1.21–6.35)	0.09
Median amount of DNA extracted, ng (IQR)	1,150 (673–1,880)	818 (428–1,473)	0.09
NGS testing successful (yes), n/N (%)	29/31 (94)	35/36 (97)	0.59

NGS, next-generation sequencing; N, total number; n, number per variable; TBNA, transbronchial needle aspiration; TBNCS, transbronchial needle capillary sampling; IQR, interquartile range; QNC, quantitative nucleated cellularity.

* One lymphoma case excluded.

present study proved the efficacy of both needle types in obtaining qualitatively superior material with a Mair's score between 7 and 10, enabling tumor diagnosis and additional molecular testing.

A total of 67 cell block specimens from patients with newly diagnosed malignancy (with the exception of lymphoma, n = 2) were evaluated for routine clinical NGS testing of hotspot mutations across 26 genes. Outcome measures of these cancer specimens are depicted in Table 4. The cell block selected for DNA extraction and NGS testing turned out to be the TBNA specimen in the majority of patients. A tissue core was reported present in almost 70% of the specimens for both needle types. There was no significant difference in tumor cellularity between Flex 19G and 22G specimens. Both the tumor surface area measured and the amount of DNA extracted from the selected cell block were larger (p = 0.09) for the Flex 19G compared to the 22G specimen, with a median tumor surface area of 4.91 versus 2.35 mm^2 and median DNA extracted of 1,150 versus 818 ng, respectively.

In 3 out of 67 (4%) patients, clinical NGS testing was either not attempted due to inadequate tumor cellularity (n = 2) or failed due to abundant necrosis (n = 1), and was therefore unsuccessful. In 64 out of 67 (96%) patients, we completed clinical NGS testing in whom targeted sequencing of all clinical potentially actionable variants (EGFR, BRAF, METex14, ERBB2) was successful. All non-squamous non-small cell lung cancer samples also successfully underwent concurrent ALK and ROS1 testing. In 10 out of 64 (15.5%) patients the predetermined coverage of 1,000-fold was not reached for some amplicons/specific codons of the library pool. As these genes were not clinically relevant we did not attempt a resequencing with a higher DNA library input. Overall, we were able to report on successful NGS testing with complete library pool reached for all 26 genes in 54 out of 67 (81%) patients.

Discussion

This study is the first randomized clinical trial to compare Flex 19G and 22G needles for sampling intrathoracic lymph nodes by linear endosonography. We did not observe the anticipated superiority in procuring a tissue core in the cell block preparation for a Flex 19G needle compared to a 22G needle. A tissue core was found in 67 and 72% of the samples obtained with Flex 19G and 22G needles, respectively. Per patient, 2 cell blocks (1 from TBNCS and 1 from TBNA) with corresponding H&E-stained slides were prepared, and for each slide the tissue surface area was analyzed using software for tissue analysis. Considering the H&E slide with the largest tissue surface area per patient, we observed a trend (p = 0.15) towards a larger tissue surface area of 6.0 versus 4.6 mm^2 for Flex 19G compared to 22G, respectively. This might

be of interest as more tumor tissue leftover could be archived, which enables additional testing when further predictive biomarker testing becomes available in the future.

Our study shows that TBNA specimens were significantly bloodier when procured by a Flex 19G needle compared to a 22G needle, without impeding the diagnostic assessment in most patients because of the presence of diagnostic tissue. Our study did not report any adverse events associated with its use, which is similar to recent reports on a safe and good diagnostic ability of the Flex 19G needle [17, 18]. Applying Mair's objective parameters, neither needle type produced diagnostically superior material (qualitatively better and therefore more easily interpretable), while both needle types obtained a total Mair's score of 7–10 in the vast majority of patients.

Recent NGS platforms have facilitated multigene mutational profiling using small amounts of DNA (nanograms). The requirement of only small amounts of DNA makes the NGS technology attractive for and applicable to TBNA specimens in the clinical laboratory. Our study focused on clinical specimens obtained by a fixed bronchoscopic sampling protocol and analyzed them following a DNA extraction protocol from a selected cell block that did not undergo earlier DNA extraction. The majority of specimens underwent successful targeted sequencing for clinically relevant genes, and 81% underwent successful NGS testing with a complete library pool reached for all 26 genes.

The strengths of this study are its prospective randomized design, the blinding of the pathologist, and the usage of a standard operating bronchoscopy and pathology protocol. Some limitations of the study should be acknowledged. First, the study was performed at a single institution, and the procedure was performed without rapid on-site evaluation which may be beneficial in judging the quantity of available malignant cells when testing for molecular markers is planned [6–8]. Second, our work has been a first attempt to quantify the performance of a new needle type, ViziShot Flex 19G, within a clinical setting of suspected lung cancer. The study hypothesis for the primary end point was based on an endoscopic ultrasonography trial on a different type of organ tissue, i.e., solid pancreatic mass, which could be responsible for the difference in tissue core procurement rates [19]. Third, specimen quantity and quality analyses were applicable to all specimens included, but cell block analysis of specimens sent for reflex NGS testing was performed on cancer specimens with different histological subtypes and should ideally be evaluated in a larger data set of a specific lung cancer subtype. Fourth, it was not our purpose to compare TBNCS and TBNA in terms of sample adequacy, diagnosis, and quality. Finally, we excluded patients with a high clinical suspicion of lymphoma and mesothelioma, which should be evaluated accordingly using the 19G needle.

In conclusion, the current study suggests that a Flex 19G needle enables tissue sampling irrespective of the location of the mediastinal or hilar lymph node. We did not observe superiority of a Flex 19G needle compared to a 22G needle in tissue core procurement and sample adequacy for diagnostic yield, with the drawback of more bloody samples for TBNA by a Flex 19G needle. We believe that the choice between Flex 19G and 22G could be based on the need for a larger tissue and tumor surface area on the cell block preparation. The results of this study further enhance the feasibility and utility of NGS-based testing methods to perform multigene mutational tumor profiling on needle aspiration specimens.

Statement of Ethics

All patients provided written informed consent. The institutional review board of the University Hospitals KU Leuven, Leuven, Belgium, approved the study (B32220162793).

Disclosure Statement

There was no funding source for this study.

Author Contributions

C.D. is the guarantor of this paper and takes responsibility for the literature search, study design, data collection, data analysis and interpretation, and manuscript writing. S.V.d.B., B.W., and E.V. contributed to the data collection, data analysis and interpretation, and manuscript revision. J.Y. and D.T. contributed to the data collection and manuscript revision. E.W., J.V., and K.N. contributed to the manuscript revision. All authors had access to the data and final manuscript for approval prior to submission.

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