A Prospective, Randomized Trial for the Comparison of 19-G and 22-G Endobronchial Ultrasound-Guided Transbronchial Aspiration Needles; Introducing a Novel End Point of Sample Weight Corrected for Blood Content

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Abstract

The demand for tissue has increased in lung cancer through personalized medicine. Recently, larger endobronchial ultrasound needles have become available for transbronchial lymph node biopsy. We compared the new 19-gauge (G) needle with 22-G needles regarding tissue quality, feasibility, safety, and performance in a prospective manner. Significantly more tissue and tumor cells per slide were obtained with a 19-G needle.

Background: The use of 22- or 21-gauge (G) endobronchial ultrasound (EBUS) needles are recommended for lung cancer diagnosis and staging. Performance of detailed molecular workup and programmed death ligand 1 (PD-L1) staining in lung cancer patients increases the demand for tissue. The aim of this prospective, randomized two-center trial was to compare 19-G and 22-G EBUS needles regarding tissue quality, diagnostic yield, feasibility, safety, performance, and blood content. **Patients and Methods:** Patients with a computed tomography scan indicative of lung cancer with mediastinal or hilar lymph node metastases were prospectively enrolled and randomized for the use of either a 19-G or a 22-G EBUS needle. A blood content score from 0 to 2 was applied. Samples were weighed, tumor cells were counted per slide, and complications and final diagnoses were documented. **Results:** We enrolled 107 patients (53 [49.5%] in the 19-G group/54 [50.5%] in the 22-G group) and samples were weighed immediately after performing EBUS. Samples obtained with a 19-G needle contained significantly more tissue ($P = .0119$). Non–small-cell lung cancer-infiltrated EBUS samples contained significantly more tumor cells when sampled with a 19-G needle ($P = .0312$). The diagnostic yield was equally adequate in both groups. Four moderate EBUS-related bleedings occurred (2 per group), hemostasis was rapidly achieved in all cases. Further complications did not occur. **Conclusion:** Endobronchial ultrasound-guided transbronchial needle aspirations with a 19-G needle contain significantly

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more tissue and tumor cells per slide with a safety profile similar to 22-G needles. Further research is needed to investigate the relevance of this finding in terms of molecular analyses and PD-L1 staining.

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Introduction

Lung cancer is the second most commonly diagnosed cancer for men and women and the most frequent cause of cancer-related death worldwide.[1] Endobronchial ultrasound (EBUS)-guided transbronchial needle aspiration (TBNA) is a well established method for lung cancer diagnosis and staging.[2-5] Current guidelines recommend at least 3 EBUS-TBNA samples from each enlarged lymph node with a 22-gauge (G) or 21-G needle to achieve diagnostic accuracy of up to 96%,[6-9] and 4 passes if additional molecular workup for epidermal growth factor receptor, Kirsten rat sarcoma viral oncogene homolog and/or anaplastic lymphoma kinase mutations is intended.[10] Although EBUS-TBNA samples are much smaller than surgical lymph node biopsies, enough material for complete and thorough evaluation is provided in most cases.[11-15] Although the diagnostic yield of EBUS-TBNAs is almost optimal with 90% to 95% using 22-G needles, recent developments in personalized medicine, particularly in pretreatment lung cancer management, require larger amounts of tissue for thorough molecular and other workup such as programmed death ligand 1 (PD-L1) staining in addition to traditional pathology testing. EBUS samples obtained using a 22-G and even with a 21-G needle are sometimes not sufficient for these extensive molecular analyses and PD-L1 staining.[10,16] The manufacturer, Olympus, has addressed this problem and recently developed a larger EBUS-TBNA needle. The 19-G Vizishot FLEX EBUS needle (Olympus) has the same outer diameter as a 22-G EBUS needle but a larger inner diameter. In addition the needle is composed of a more flexible material (nitinol) than the 22-G EBUS needle.

The existing comparative data of 19-G needles compared with smaller-bore 22-G needles have failed to show a difference in the diagnostic yield and ability to obtain tissue cores.[17,18] However, this might have been limited because of relatively small sample sizes and variable methods to assess tissue quality. We hypothesized that the 19-G needle would yield more tissue, without increasing complications compared with 22-G needles. The aim of this prospective, randomized two-center study was to compare 19-G and 22-G EBUS needles regarding specimen tissue quality and procedural safety. To improve the assessment of tissue quality, we sought to introduce a novel end point of tissue weight adjusted for blood content.

Patients and Methods

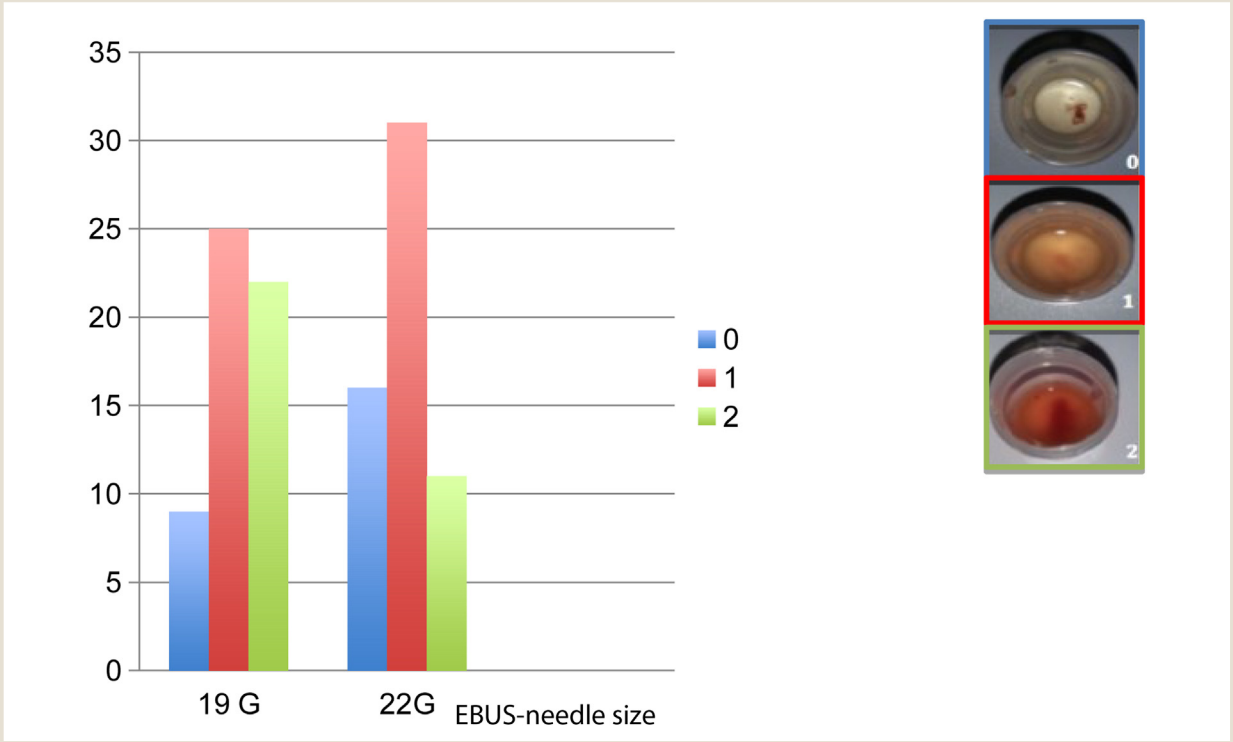
In this study we prospectively collected data from consecutive patients with a clinical indication for a diagnostic EBUS procedure between April 2016 and October 2017 at 2 academic centers. Participating institutions were the Department of Interventional Pneumology (University Hospital Essen, Germany) and the Division of Pulmonology, University Hospital Zurich (Zurich, Switzerland). We included patients suspected to have lung cancer with mediastinal and/or hilar lymph node metastases on the basis of enlarged lymph nodes measuring at least 10 mm. Exclusion criteria included pregnancy, age younger than 18 years, standard exclusions for EBUS-TBNA (coagulopathy, international normalized ratio >1.5, clinical instability), and inability to give informed consent.

The study was approved by the ethics committees of the University Duisburg-Essen, Germany (approval 16-6799-BO) and the University Zurich, Switzerland (approval 2016-00968) and registered at ClinicalTrials.gov (NCT02813603). Written informed consent was obtained before sampling from each patient who participated in the study.

Endobronchial Ultrasound TBNA

A rigid scope with jet ventilation or a laryngeal tube were used to access the airway. EBUS was performed using flexible bronchoscopy with an EBUS bronchoscope (model BF-UC180F; Olympus, Tokyo, Japan) connected to an ultrasound scanner (EU-ME1 or EU-ME2, Olympus). Either the 19-G (NA-U402SX-4019; Olympus) or the 22-G (NA-201SX-4022; Olympus) needles were used by experienced attending interventional pulmonologists. Additional suction was not applied. Simple randomization to the 19-G or 22-G group was performed using a randomization list (Microsoft Excel 2013) in the bronchoscopy suite before the procedure. Patients underwent lymph node biopsy with the use of either a 19-G or a 22-G needle. Patients and pathologists were blinded for the needle size. The lymph node biopsy procedure was standardized as follows: all patients received a complete mediastinal and hilar lymph node staging via EBUS, sampling all lymph nodes larger than 5 mm. The lymph node with the highest probability for malignant infiltration on the basis of size and sonographic appearance was sampled with 3 to 5 passes.[6,19,20] Each pass consisted of 10 to 15 needle thrusts. Samples were considered adequate if cytological analysis identified lymphocytes or if a definitive diagnosis could be established. In this study rapid on-site evaluation (ROSE) was omitted. EBUS-TBNA samples were expelled from the needle into a vessel of 5 mL 4% buffered formalin using the internal stylet in accordance with recent guideline recommendations[21] and were subsequently sent for cytopathological evaluation. Immunohistochemistry (IHC) was performed for lung cancer subtyping if required. Blood content of each sample was evaluated using a semiquantitative score from 0 to 2 (0 = no visible blood, 1 = light red shading, 2 = red shading; Figure 1). Each lymph node sample was weighed on a pathology slide using a precision balance (Sartorius BP61, Goettingen, Germany) and divided by the number of passes. Each lymph node size was recorded on the basis of the computed tomography (CT) scan image and confirmed via EBUS image. Complications and final diagnoses were documented. The final diagnosis was established on the basis of cytological and

Figure 1 Blood Content in 22-Gauge (G) and 19-G Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) Samples. The Blood Content After Endobronchial Ultrasound-Guided Needle Sampling With 19-G and 22-G Needles Is Shown (Left). Right Panel: A Color Scale Was Used to Quantify the Blood Content (0 = No Visible Blood, 1 = Light Red Shading, 2 = Red Shading, 0 = No Visible Blood, 1 = Light Red Shading, 2 = Red Shading)



histopathological results, surgery (mediastinoscopy, video-assisted thoracoscopic surgery or thoracotomy), or clinical follow-up via chest CT scan.

Cytopathological Processing and Cell Amount

Endobronchial ultrasound samples were processed with a ThinPrep processor (ThinPrep 2000; Hologic, Wiesbaden, Germany) and stained with the Papanicolaou method according to standard procedures. Alternatively, alcohol-fixed direct smears were stained with the Papanicolaou method. Solid components were manually sealed with either agarose gel or using the plasma-thrombin method for cell block preparation. The cell block was then stored in 4% buffered formaldehyde for 12 hours. Further embedding was performed in a paraffin block, which was used to prepare 2- to 3-μm slides. Afterward, the slides were dried at 50°C for 2 hours. The first slide was stained with hematoxylin and eosin (H&E). IHC preparation of additional slides were performed as needed.[22] Tumor cells from each H&E slide were manually counted. At each site 1 pathologist was responsible for the slide preparation to achieve comparable conditions.

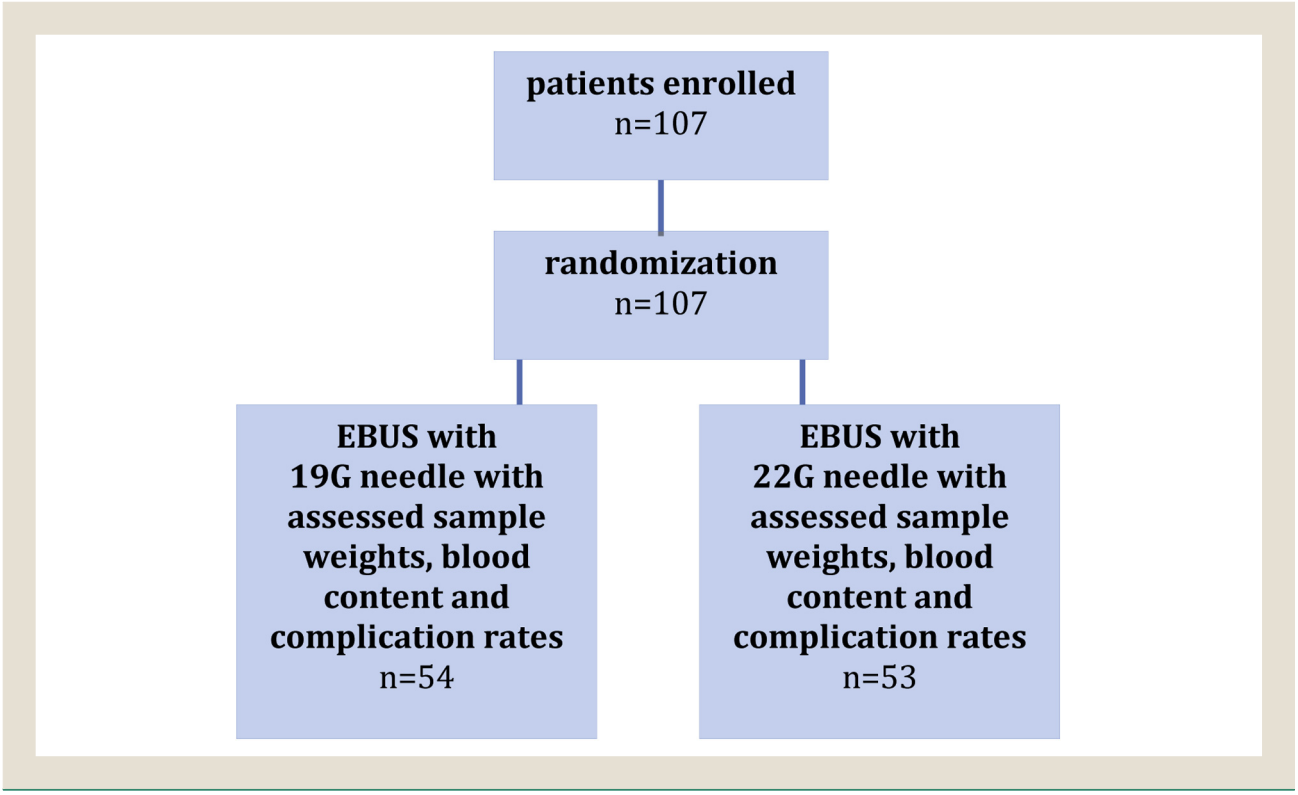
Outcomes

To address the necessity of more tissue for molecular workup, we chose the sample quality assessed according to tissue weight and corrected for blood content as the primary end point of our study. Secondary end points included tumor cell count, diagnostic yield, and procedure-related complications, as reported in previous comparative trials. Complications were assessed in the immediate procedural period. Severe complications were defined as bleeding requiring intervention such as insertion of a bronchial blocker or an endoscopic Watanabe Spigot, postprocedural infection that required the use of antibiotics, or pneumothorax that required the insertion of a chest tube and/or prolonged hospitalization. Moderate complications were defined as bleeding requiring bronchial wedging and/or the application of xylometazoline to achieve vasoconstriction, or pneumothorax that did not require a chest tube.

Statistical Analysis

A power of 80% to detect the effect size of 0.59 SDs using two-sample t test with two-sided α of 0.05 was applied for the sample size calculation to compare 19-G and 22-G groups. Diagnostic sensitivity and specificity for 19-G and 22-G needles were calculated according to standard formulas. Patient demographic and other characteristics were summarized using descriptive statistics. Normal distribution of sample weights and non–small-cell lung cancer (NSCLC)-infiltrated lymph node samples per group were evaluated using the Kolmogorov–Smirnov test with a P value $> .15$ indicating normality. Log10 transformation was conducted to achieve normal distribution. Log10 transformed sample weight and tumor cell amount of NSCLC-infiltrated lymph node samples were compared between the 19-G and 22-G groups using a two-sample t test. The association between blood content and needle size was assessed using the χ^2 test. The analysis of variance model was used to study the

Figure 2 Consolidated Standards of Reporting Trials Flow Diagram. The Number of Patients Enrolled and the Number of Sample Weights and Tumor Cell Counts of Non–Small-Cell Lung Cancer Infiltrated Endobronchial Ultrasound (EBUS) Samples Assessed Are Shown



Abbreviation: G = gauge.

association between log10 transformed sample weight and blood content. To study the association between log10 transformed sample weight and needle size the analysis of covariance (ANCOVA) model was used, controlling the confounding factor of blood content assessed using the previously mentioned blood content score.

Results

A total of 107 patients (54 [50.5%] in the 22-G group and 53 [49.5%] in the 19-G group) were enrolled between April 2016 and October 2017 (Figure 2). An average of 3 needle passes was performed per lymph node in each group. Average lymph node size and patient demographic characteristics were similar in both groups (Table 1).

Sample Weights and Blood Content

The samples of all 107 (53 [49.5%] in the 19-G group, 54 [50.5%] in the 22-G group) patients were weighed. Sample weights were divided by the total amount of passes per lymph node station and averaged 10.2 mg in the 22-G group and 20.0 mg in the 19-G group. Because the sample weight per pass for both needle sizes was not normally distributed ($P < .01$), a log10 transformation was performed using the Kolmogorov–Smirnov test and normal distribution was achieved. The log10 transformed sample weights were compared between 19-G and 22-G EBUS needles using a two-sample t test. After normalization, the sample weight per needle pass was significantly larger when sampled with a 19-G EBUS needle ($P = .0016$; Table 2, Figure 3).

Larger needle size was associated with significantly higher blood content ($P = .029$). Samples acquired using 19-G needles contained more blood; a blood content score of 2 was present in 22 patients (41.51%) of 19-G samples compared with 10 patients (18.52%) in the 22-G group (Figure 1, Table 3, sections A and B). After controlling for blood content using the ANCOVA model, the sample weight obtained with 19-G needles was significantly higher in the 19-G group compared with the 22-G group ($P = .0119$; Table 3, sections B and C, Figure 3).

Diagnoses Established Using EBUS-TBNA

Histopathological EBUS-TBNA results were diagnostic in 93 patients (86.9%). Three of 53 patients (5.7%) in the 19-G group and 2 of 54 patients (3.7%) in the 22-G group had a tumor-infiltrated lymph node in a higher N position than the lymph node sampled

Table 1 Patient Characteristics

Needle Size	22-Gauge	19-Gauge
Total cases	54	53
Age (y), mean (± SD)	66 (±9)	67 (±10)
Sex		
Male	38 (70.4%)	31 (58.5%)
Female	16 (29.6%)	22 (41.5%)
Study Lymph Node Diameter (± SD), mm	25.0 (±11.7)	24.6 (±12.6)

Table 2 Log10 Transformed Sample Weights Comparing 19-Gauge and 22-Gauge Samples

Needle Size	Patient n	Variable	Mean	SD	*P*
19-Gauge	54	Sample weight per needle pass	0.0200	0.0222	.0016 (log10 transformed)
		Sample weight log10	−1.899	0.424	
22-Gauge	53	Sample weight per needle pass	0.0102	0.0093	
		Sample weight log10	−2.154	0.388	

Log10 transformed sample weights were compared between 19-gauge and 22-gauge samples using a 2-sample *t* test. Sample weights per pass were larger when a 19-gauge endobronchial ultrasound-guided transbronchial needle aspiration needle was used.

and analyzed within the study and were transferred to palliative treatment without re-evaluating the study lymph node. Seven patients (2 patients [3.7%] in the 22-G group, 5 patients [9.4%] in the 19-G group) did not attend their planned follow-up imaging appointments. Two patients (3.8%) in the 19-G group refused mediastinoscopy. Assuming conservatively that all patients who were lost to follow-up had false negative results the sensitivities would have been 78.26% in the 19-G group and 88.57% in the 22-G group, respectively. Assuming that all patients who were lost to follow-up indeed had benign diagnoses of the study lymph node the sensitivity would have accounted for 100% in both groups. Overall the diagnostic yield was comparable in both groups.

The most frequently established diagnosis was NSCLC. NSCLC was diagnosed in 67 (62.6%) of 107 patients. In 43 NSCLC patients (23 patients [53.5%] in the 19-G group, 20 patients [46.5%] in the 22-G group) the study lymph node was tumor-infiltrated. The diagnoses of the other patients were: small-cell lung cancer (SCLC; 15 patients [14.0%]), lymphoma (3 patients [2.8%]), metastasized breast cancer (2 patients [1.9%]), metastasized melanoma (2 patients [1.9%]), metastasized hypopharyngeal carcinoma (1 patient [0.9%]), metastasized pancreatic cancer (1 patient [0.9%]), metastasized sarcoma (1 patient [0.9%]), metastasized renal carcinoma (1 patient [0.9%]), sarcoidosis (2 patients [1.9%]), other benign diseases (11 patients [10.3%]), 1 remained unknown because the patient refused further diagnostic tests.

Amount of Tumor Cells Per Sample in NSCLC-Infiltrated Lymph Nodes

Tumor cells were counted in 37 (86.0%) of 43 EBUS-TBNA samples of NSCLC-infiltrated lymph nodes (20 in the 19-G

Figure 3 Cytopathological Endobronchial Ultrasound-Guided Transbronchial Needle Aspiration (EBUS-TBNA) Slides of 22-Gauge (G) and 19-G EBUS-TBNA Samples. Core Biopsies From Cell Blocks of EBUS-TBNA Samples of Lymph Nodes Containing Adenocarcinoma Tissue. (A and C) Two Adenocarcinomas of the Lung; (B) Metastatic Colon Carcinoma; (D) Metastatic Breast Carcinoma, Sampled With (A and B) 22-G or (C and D) 19-G Needle. The Tissue Cores From the 19-G Needle EBUS-TBNA Samples Are Bigger and Show Less Fragmentation. Hematoxylin and Eosin Stain; Magnification of All Microphotographs ×100

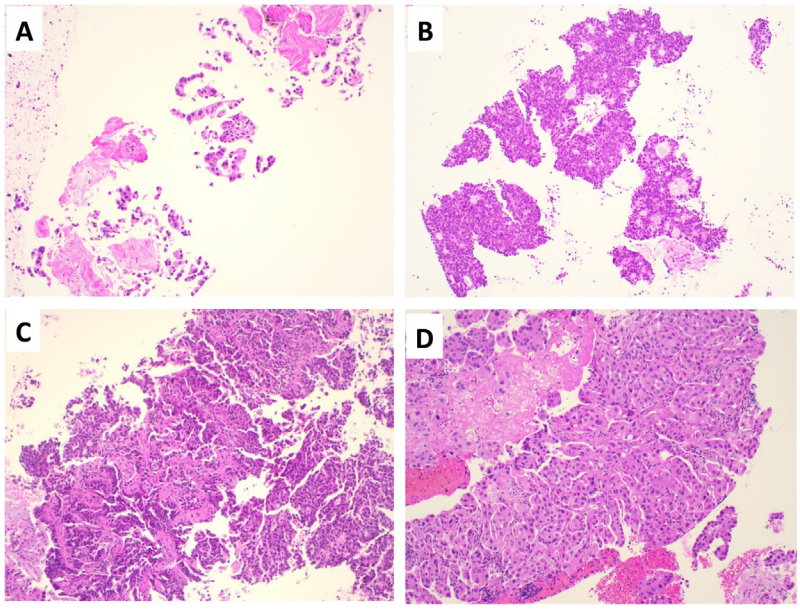


Table 3 Association Between Blood Content and Needle Size

A. χ^2 Test: The Needle Size Is Significantly Associated With Increased Blood Content. Using 19-Gauge EBUS-TBNA Needles the Percentage of Blood Content Score of 2 Is Increased (41.51% vs. 18.52%) Compared With Using 22-Gauge EBUS-TBNA Needles

	Blood Content			
Needle Size	0	1	2	*P*
19-Gauge, n (%)	8 (15.09)	23 (43.40)	22 (41.51)	.029
22-Gauge, n (%)	14 (25.93)	30 (55.55)	10 (18.52)	

B. ANOVA Model Was Used to Study the Association Between Log10 Transformed Sample Weight and Blood Content. The Sample Weight Per Needle Pass Was Significantly Associated With Increased Blood Content. Larger Sample Weight Is Associated With a Higher in-Blood Content Score

Blood Content	Sample Weight log10 Mean	SE	
0	−2.253	0.086	.0021
1	−2.041	0.055	
2	−1.851	0.071	

C. The Association Between Log10 Transformed Sample Weight and the Needle Size Controlling the Confounding Factor of Blood Content Was Calculated Using the ANOVA Model. While Controlling the Effect of Blood Content, the Sample Weight Per Needle Pass Was Significantly Larger Using 19-Gauge Than 22-Gauge

Needle Size	Sample Weight log10 Estimated Mean		
19-Gauge	−1.946	0.057	.0119
22-Gauge	−2.148	0.056	

Abbreviations: ANOVA = analysis of variance; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; SE = standard error.

group [54.0%], 17 in the 22-G group [46.0%]). In 6 cases (14.0%) cell blocks were not available for cell counting (3 per group). The average tumor cell count per slide was significantly higher in the 19-G NSCLC-infiltrated lymph nodes group ($P = .0312$; Figure 4).

Complications

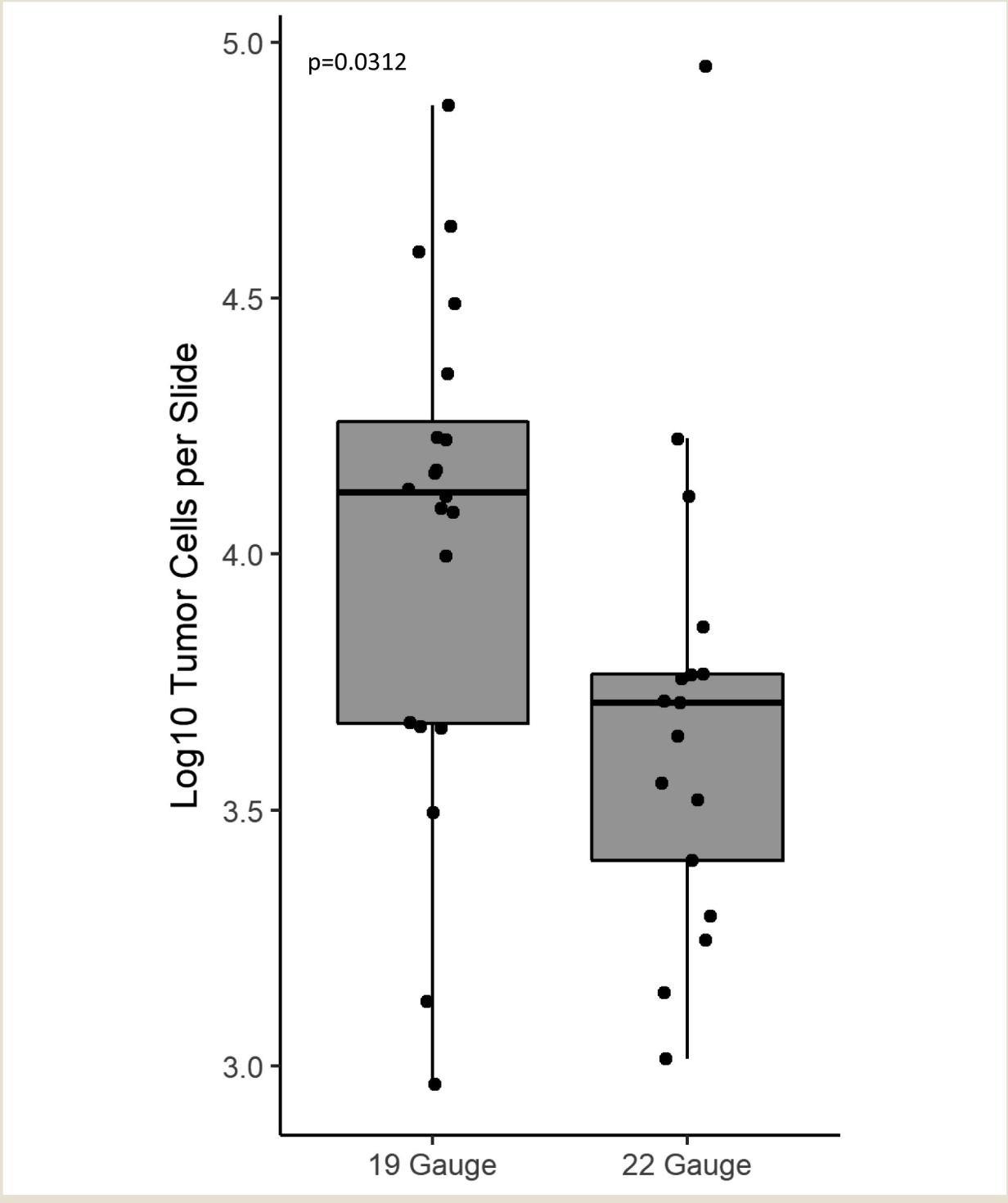
Four moderate bleeding events occurred, 2 (3.8%) in the 19-G group and 2 (3.7%) in the 22-G group. Hemostasis was achieved after xylometazoline application through the working channel of the bronchoscope. Further complications did not occur.

Discussion

Endobronchial ultrasound-guided TBNA has been shown to provide a high diagnostic yield and few post procedural complications.[3,4,22] However, with the advent of personalized therapy the collection of more tissue material for molecular and other workup in addition to traditional pathology testing is essential, including next-generation sequencing analysis and PD-L1 staining to evaluate the therapeutic option of immunotherapy. Several studies have shown, that although the diagnostic yield of EBUS-TBNA samples is nearly optimal with 22-G and 21-G needles, the obtained material is not always sufficient for extensive molecular workup and PD-L1 staining.[10,16,23]

In this prospective, randomized two-center trial we provide a prospective comparison of EBUS-TBNA biopsy with 19-G versus 22-G needles. This trial was designed to test the tissue quality of the EBUS sample, which was significantly improved using the 19-G needle, even after correction for blood content (Table 3). The introduction of the 19-G needle has raised concerns about increased blood content. In our comparison of the 2 needle sizes we used a semiquantitative blood content score when comparing the EBUS sample weights. We found that 19-G needle samples showed significantly more blood content as shown in Figure 1. This finding is consistent with that of previous studies, including 2 smaller trials that compared 19-G and 22-G EBUS needles, suggesting increased blood content for larger needles.[7,17,18] In the study by Nakajima et al, who compared 22-G and 21-G needles, increased blood content was also documented.[7] In that study the authors described if a sample contained more or less blood using the 21-G needle or the 22-G needle without mentioning the exact amount or using a score.[7] Of note, in the study by Nakajima et al, 2 needle sizes were used on the same lymph node; in this trial only a single needle was used per patient, making direct comparison of the blood content more difficult. Saji et al also compared 21-G and 22-G EBUS-TBNAs. They used the width of the sample as a parameter of tissue quality and reported not to have assessed the weight of the sample because of differences in blood content.[24] They did not report any differences between the sample widths of specimens obtained with a 21-G or a 22-G needle, however, a single dimension is probably not sufficient to assess the size of a sample. In a recently published retrospective trial comparing 22-G and 19-G EBUS-TBNA samples, the volume of the EBUS-TBNA samples was assessed. To overcome the blood content effect, the tissue samples were placed on filter paper.[25] The authors conclude that volumes of 19-G EBUS samples were larger, however, the retrospective nature of the report did not allow sample size calculation and only 45 patients were studied. Also, one could argue that through putting the sample on filter paper, cells would get lost, and it would be hard to control how many tumor cells are actually lost and not be counted for the secondary end point of tumor cell

Figure 4 Tumor Cell Count in Non–Small-Cell Lung Cancer-Infiltrated Endobronchial Ultrasound Samples Is Significantly Higher When Sampled Using a 19-Gauge (G) Needle. Thirty-Seven Samples (20 in the 19-G Group; 17 in the 22-G Group) Were Included in the Analysis. Normality Was Achieved After Log10 Transformation. A Significant *P* Value (.0312) Was Achieved Using a 2-Sided Two-Sample *t* Test. The Box Plots Show the Log10-Transformed Tumor Cell Counts for the 19-G and 22-G Groups



content. A recent randomized trial to compare 19-G and 22-G needles in a smaller cohort used tissue core procurement as a primary end point, and tissue surface area as a secondary end point, bloodiness of samples was assessed using a microscope.[17] The authors did not report significant differences between the groups regarding tissue core procurement or tissue surface area, however,

they reported that significantly bloodier samples were obtained with a 19-G needle. Chaddha et al prospectively compared 27 patients sampled with a 19-G and a 22-G needle using diagnostic yield as a primary end point and assessed the bloodiness of samples in the ROSE slide. Significant differences between the 2 groups regarding diagnostic yield were not reported; the authors reported significantly higher blood content in the ROSE slide of 19-G samples.[18] Our results are consistent with the 2 previously mentioned trials, showing similar diagnostic yield and larger blood amount in 19-G samples. Because of the high diagnostic yield for EBUS exceeding 90%, it is not surprising that no differences were detected. A problem with both studies was the relatively small size. In our current study, we have overcome some of the methodological problems of comparing tissue quality, and introduced a novel end point of tissue weight corrected for blood content, which is clinically more meaningful with regard to molecular analyses.

We believe that the assessment of blood content using the mentioned semiquantitative score is more adequate than other methods to assess the blood content of samples. However, we are aware that it is technically not feasible to document the exact amount of blood in milliliters, because the sample is either collected in a vessel prefilled with formalin or on a slide. The prospective nature of our trial with a sample size calculation is a strength, showing a significantly higher blood content in 19-G EBUS-TBNA samples and also a significantly higher tissue amount per sample in the 19-G group after correction for blood content.

The number of tumor cells obtained using EBUS-TBNA biopsy is another marker of tissue quality, and was a secondary end point in this study. We show that tumor cell counts per slide in NSCLC-infiltrated EBUS samples are significantly higher if sampled with a 19-G needle (Figure 4). In this study only 43 lymph nodes (40.2%) were infiltrated with NSCLC; tumor cells were counted in 37 patients (86%), and these results should be validated in studies with a higher amount of samples. The groups of other tumor entities such as SCLC were too small for reliable comparisons. However, because of the larger tissue amounts sampled with the 19-G needle and higher tumor cell counts in the NSCLC-infiltrated samples and a previously reported significant correlation between EBUS sample weights and DNA content it is very likely that SCLC tumor cell counts would also be significantly higher if sampled with a 19-G needle compared with a 22-G needle.[21] Tumor cell counts per biopsy might be influenced by several factors: the biology of the tumor, the pattern of lymph node infiltration by tumor cells, and the angle at which the EBUS-TBNA needle is inserted into the lymph node. One of the limitations of this study was that a single needle size was used for each patient. Because cellularity of tumors can vary between patients, the differences between the tumor cell counts might have been even more significant if needles of both sizes were used in the same lymph node in every patient; this might be considered in future studies. We still believe, that with the calculated sample size and overall similar lymph node sizes in both groups, the results would have been very similar if 2 needles would have been used per lymph node.

We recently published that there is a significant correlation between tissue weight of EBUS-TBNA samples and genomic DNA (gDNA) concentration.[23] Although not proven with further molecular or sequencing workup in this study, we assume that a larger sample with significantly more gDNA will in turn yield a greater amount of tumor gDNA. Tumor gDNA yield is essential for the performance of next-generation sequencing, which is increasingly demanded for personalized therapy and usually requires higher amounts (> 40 ng) of DNA than is needed for polymerase chain reaction-based diagnostic tests. The effect of additional nodal tissue weight obtained using the 19-G needle on the ability to enable comprehensive molecular analyses and PD-L1 staining should be further investigated. There are multiple factors that might increase the adequacy and utility of EBUS biopsies. In particular, ROSE was associated with increased adequacy for diagnostic and molecular analyses.[26-28] In this study, ROSE was omitted because the entire sample was weighed in the formalin vessel. The effect of ROSE on the reported findings should be investigated in further studies.

Regarding the safety profile, we found that the use of the 19-G needle is as safe as the use of the 22-G needle. There were no severe complications in either group. All procedure-related complications were related to bleeding from the biopsy site. We observed 4 cases of moderate bleeding, which were distributed equally between groups. Two patients experienced moderate bleeding (1 per group), both of which had received therapeutic anticoagulation until the evening before the intervention and therefore had an increased bleeding risk. Overall the bleeding risk with both needles is minimal and not increased with use of a larger needle size.

Limitations

Several limitations in this study need to be acknowledged. Although we were successful in showing a significantly larger tissue weight in the 19-G group when corrected for blood content, the comparison of secondary end points was limited by the sample size in some of the groups such as SCLC. Additionally, the overall complication rate of EBUS-TBNA is known to be low, and larger cohorts will be necessary to assess rates of rare, severe complications.[29-31] However, we do not anticipate significant differences in complication rates on the basis of our results and those of previous retrospective studies on 19-G EBUS-TBNA needles with smaller patient cohorts, which reported similar complication rates and diagnostic yields.[25,32,33] Last, the comparative evaluation of EBUS samples for molecular testing extends beyond the scope of this trial. Although we clearly showed that 19-G needles can yield more tissue and tumor cells and have previously shown a significant correlation between EBUS-TBNA weight and DNA concentration, we are unable to correlate this with the adequacy for various molecular tests in this study. The absolute tissue amount required to fulfill all current and future diagnostic tests likely varies significantly between institutions, and depends largely on the extent and type of tests performed. One could argue that acquisition of more cores with a smaller needle (22-G) would lead to the same tissue amount, however, because of high costs of procedural times ($10-$60 per minute) and busy clinical schedules, it would be beneficial to reduce procedural durations even minimally.[34]

Conclusion

The EBUS-TBNA samples obtained using a 19-G needle contain significantly more tissue and tumor cells than samples obtained using a 22-G needle. The diagnostic yields were similar. Complications with the use of the 19-G EBUS needle were rare, and similar to those of the 22-G needles. Further research is needed to

investigate the relevance of these findings in the context of molecular workup of patients.

Clinical Practice Points

- Personalized medicine has led to an increasing demand for tissue in lung cancer patients. EBUS-TBNA is well established for lung cancer diagnosis and staging. Current guidelines recommend either a 22-G or a 21-G needle. The manufacturer, Olympus, recently introduced a 19-G needle with the same outer but a larger inner diameter than the previously most commonly used 22-G needles. To date, there are no prospective studies that have shown the benefit of the 19-G needle.
- We prospectively compared the 22-G and 19-G needles in 107 patients regarding the tissue quality. We introduced a novel end point of tissue quality reflected by the sample weight corrected for blood content. Secondary end points were diagnostic yield, feasibility, safety, and tumor cell content per slide. We could show, that samples obtained with a 19-G needle provide significantly more tissue after correction for the blood content, and in NSCLC patients the tumor cell count per slide was significantly higher with the use of a 19-G needle compared with a 22-G needle.
- Providing more tissue and more tumor cells can facilitate multiple molecular tests such as next-generation sequencing and additional staining such as PD-L1 staining.

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Disclosure

The authors have stated that they have no conflicts of interest.

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