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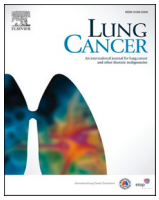

Endobronchial ultrasound in diagnosing and staging of lung cancer by Acquire 22G TBNB versus regular 22G TBNA needles: A randomized clinical trial

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ABSTRACT

Objectives: Endobronchial ultrasound guided transbronchial needle aspiration (EBUS-TBNA) has an important role in the diagnosis and staging of lung cancer. Evaluation of programmed death ligand 1 (PD-L1) expression and molecular profiling has become standard of care but cytological samples frequently contain insufficient tumor cells. The 22G Acquire needle with Franseen needle tip was developed to perform transbronchial needle biopsy (TBNB) with improved tissue specimens. This study evaluated if the 22G Acquire TBNB needle results in enhanced PD-L1 suitability rate compared to the regular Expect 22G TBNA needle.

Methods: in this multi-center randomized clinical trial (Netherlands Trial Register NL7701), patients with suspected (N)SCLC and an indication for mediastinal/hilar staging or lung tumor diagnosis were recruited in five university and general hospitals in the Netherlands, Poland, Italy and Czech Republic. Patients were randomized (1:1) between the two needles. Two blinded reference pathologists evaluated the samples. The primary outcome was PD-L1 suitability rate in patients with a final diagnosis of lung cancer. In case no malignancy was diagnosed, the reference standard was surgical verification or 6 month follow-up.

Results: 154 patients were randomized (n = 76 Acquire TBNB; n = 78 Expect TBNA) of which 92.9% (n = 143) had a final malignant diagnosis. Suitability for PD-L1 analysis was 80.0% (n = 56/70; 95 %CI 0.68–0.94) with the Acquire needle and 76.7% (n = 56/73; 95 %CI 0.65–0.85) with the Expect needle (p = 0.633). Acquire TBNB needle specimens provided more frequent superior quality (65.3% (95 %CI 0.57–0.73) vs 49.4% (95 %CI 0.41–0.57, p = 0.005) and contained more tissue cores (72.0% (95 %CI 0.60-0.81) vs 41.0% (95 %CI 0.31–0.54, p < 0.01). There were no statistically significant differences in tissue adequacy, suitability for molecular analysis and sensitivity for malignancy and N2/N3 disease.

Conclusion: The 22G Acquire TBNB needle procured improved quality tissue specimens compared to the Expect TBNA needle but this did not result in an improved the suitability rate for PD-L1 analysis.

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1. Introduction

Endosonography (endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) and endoscopic ultrasound fine-needle aspiration (EUS-(B-)FNA) from the esophagus) allows minimally invasive tissue verification of intrathoracic lymph nodes and lung tumors.

Personalized treatment, including immunotherapies against programmed death ligand 1 (PD-L1) and its receptor PD-1, has become standard of care [1]. Adequate molecular profiling and immunohistochemical staining of cytological samples is therefore a crucial in patients with advanced lung cancer. To date, insufficient tumor cells and lack of preserved tissue architecture of cytological samples can limit the success rate of PD-L1 analysis and molecular profiling.

Potential factors that impact cytology sample quality, includes size and type of the biopsy needle. Recently a biopsy needle with a "Franseen" tip (Acquire Needle, Boston Scientific, Marlborough, Massachusetts, USA) was introduced with the aim to obtain improved specimens with histological core tissue (transbronchial needle biopsy (TBNB)).

We hypothesized that the Acquire 22G TBNB needle yields improved tissue samples with more core tissue, resulting in a higher suitability rate for PD-L1 assessment.

2. Materials and methods

This randomized clinical trial was conducted from November 2019 to August 2022 in five centers in the Netherlands (Amsterdam University Medical Centers and Leiden University Medical Center), Italy (Fondazione Policlinico Universitario Agostino Gemelli, Rome), Poland (Pulmonary Hospital Zakopane) and Czech Republic (General University Hospital Prague). All patients provided written informed consent before the procedure. The trial is registered at the Netherlands Trial Register (NL7701). An extensive description of the study protocol has been published [2].

The primary outcome was to assess if the 22G Acquire TBNB needle results in an enhanced PD-L1 suitability rate of lymph node and/or tumor aspirates obtained by EBUS/EUS-B in patients with a final diagnosis of lung cancer compared to the 22G Expect TBNA needle. Cellblocks were considered suitable for PD-L1 if more than 100 vital tumor cells were present in a single cellblock slide. Secondary endpoints include the following:

- Suitability for molecular analysis (>1000 tumor cells present in the cellblocks and glass slides combined)
- Sample adequacy (presence of lymphocytes, tumor cells or other pathogenic characteristics)
- Diagnostic sensitivity for malignancy (proportion of patients with malignancy diagnosed by EBUS/EUS-B, relative to the total number of patients with a final malignant diagnosis determined by the reference standard)
- Diagnostic sensitivity for N2/N3 disease (proportion of patients that had N2/N3 disease diagnosed by EBUS/EUS-B, relative to the total number of patients with a final diagnosis of N2/N3 disease as determined by the reference standard)
- Diagnostic sensitivity for malignancy in the subset of patients with a sampled centrally located lung tumor (proportion of patients with malignancy diagnosed by EBUS/EUS-B, relative to the total number of patients with a final diagnosis of malignancy)
- Sample quality using Mair's objective scoring system (score 0–2 for the following five domains: [1] amount of cellular material, [3] tissue architecture preservation, [3] degree of cellular degeneration, [4] degree of cellular trauma and [5] background of blood; total score 0–10)
- Sample bloodiness (retrieved from the Mair's bloodiness score 0–2)
- Complication rate
- Endoscopist satisfaction score (range 1–10)
- Presence and cumulative length tissue core

Although not defined as a secondary endpoint in the study protocol, during the study course we decided to additionally assess the impact of ROSE (rapid on site evaluation) on study outcomes.

Patient with (suspected) lung cancer requiring EBUS-TBNA and/or EUS-B-FNA for mediastinal/hilar staging or lung tumor sampling, were eligible for study participation. Patients needing mediastinal restaging after neoadjuvant therapy, those with contraindications for EBUS/EUS-B (e.g., severe respiratory insufficiency), non-correctable coagulation or inability to provide informed consent were excluded from study participation.

Patients were randomized 1:1 between the 22G Acquire TBNB needle or the 22G TBNA Expect needle (both Boston Scientific, Marlborough, Massachusetts, USA) using web-based block randomization. Stratification by participating center ensured equal-sized groups for each hospital.

Procedures were performed by experienced endoscopists with a linear ultrasound bronchoscope. Patients received either deep (propofol) or conscious sedation (midazolam with or without fentanyl). In case no malignancy or N2/N3 disease was diagnosed, surgical verification or 6-month clinical/radiological follow-up served as reference standard.

Aspirates were handled as per institutional practice. ROSE was optional and present in two centers (Amsterdam and Rome). Smears of needle aspirates were prepared when ROSE was available. All cellblock specimens were reviewed by two independent reference pathologists, who were blinded to needle randomization but provided with clinical information. The reference pathologists evaluated the samples for PD-L1 suitability, molecular analysis, adequacy, sample quality using Mair's score and presence with cumulative length of tissue core. Discrepancies between reference pathologists were resolved through a consensus review meeting.

Based on the local success rates of PD-L1 assessment and published literature, a 22% difference in PD-L1 suitability rates between the regular 22G TBNA needle (64%) and the Acquire 22G TBNB needle (86%) was anticipated (3–5). Factoring in an estimated 5% drop-out rate and expecting that 80% of included patients has a final diagnosis of lung cancer, 158 patient are needed to show this 22% difference with alpha = 0.05 and power = 0.80. An intention-to-treat analysis was applied.

3. Results

The study included 158 patients who were randomly assigned to undergo EBUS/EUS-B using either the 22G Acquire TBNB needle (n = 78) or the 22G Expect TBNA needle (n = 80). Four patients were excluded since no punctures or endosonographic procedure was performed after randomization (Fig. 1), leaving 154 patients for final analysis (n = 76 Acquire TBNB needle, n = 78 Expect TBNA needle). Patient demographics and diagnoses were well-balanced across both groups (Table 1). In 143 (92.9%) patients a final malignant diagnosis was established.

During the procedures, lymph node stations 7 and 2–4 were most often sampled and centrally located lung tumors were sampled in 59 patients (38.3%). No statistical difference was found in the number of sampled lymph nodes between both groups. ROSE was present in a minority of cases (38.0%) and equally present in both groups. The average number of needle passes was 5.5, which was consistent between the groups.

Blinded cytopathological review showed that samples obtained with the Acquire TBNB needle were considered suitable for PD-L1 analysis in 80.0% of cases compared to 76.7% with the Expect TBNA needle (p = 0.633, Table 2). The suitability for molecular analysis was similar for both needles (68.6% vs 68.5%, p = 0.992). Acquire TBNB samples were considered adequate in 92.0% of cases compared to 87.2% with the Expect TBNA needle (p = 0.330).

The overall sensitivity for malignancy was 94.3% for the Acquire

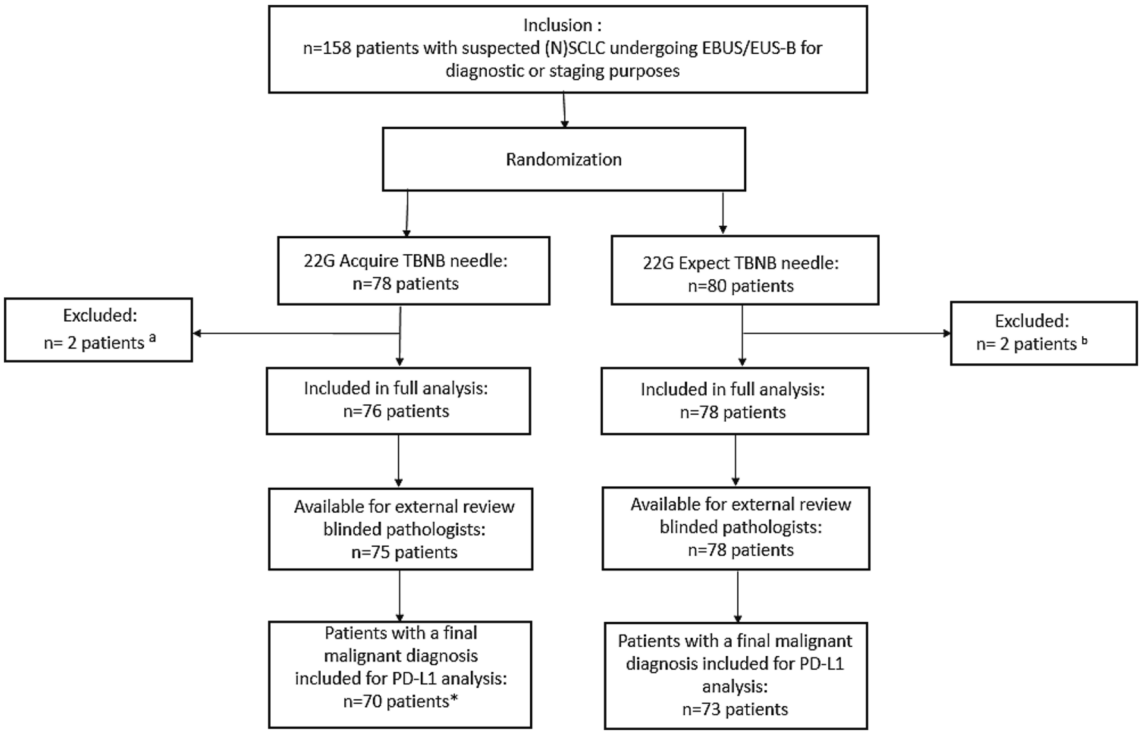

Fig. 1. Study flow diagram [a] In the Acquire TBNB arm two patients were excluded since no punctures were performed during the procedure [b] In the Expect TBNA arm two patients were excluded since in one patient no procedure was performed and in the other patient no punctures were performed during the procedure. * In the Acquire TBNB arm, PD-L1 analysis was performed in 69 patients with a final malignant diagnosis and 1 patient with no conclusive diagnosis who was considered false-negative for malignancy.

TBNB needle and 98.6% for the Expect TBNA needle ($p = 0.157$, Table 3). The diagnostic sensitivity for N2/N3 disease was 93.0% for the Acquire needle compared to 97.6% for the Expect needle ($p = 0.329$). The diagnostic sensitivity for malignancy in the subgroup of centrally located lung tumors was 100% for the Acquire needle and 93.1% for the Expect needle ($p = 0.143$). No significance in complication rates was found between both arms (8.0% vs 5.1%, $p = 0.472$). The endoscopist satisfaction score was similar for both arms (6.5 vs 6.0, $p = 0.185$).

Samples obtained with the Acquire needle were more frequent scored with superior diagnostic ease (Mair's score 7–10; 72% vs 41%, $p < 0.01$), while samples obtained with the Expect needle were more frequent scored with poor diagnostic ease (Mair's score 0–2; 3% vs 10%, $p = 0.026$). There was no significant difference in sample bloodiness (Table 4). Tissue cores were significantly more frequent present in Acquire TBNB samples (72.0% vs 41.0%, $p < 0.01$), and the cumulative length of tissue cores was similar (7.48 mm vs 6.48 mm, $p = 0.515$).

The impact of ROSE was evaluated in 59 patients, with no significant improvement in sample adequacy (84.5% vs 91.6%, $p = 0.175$) or sensitivity for malignancy (100% vs 94.4%, $p = 0.081$, Table 5). However, when considering both needle types together, the presence of ROSE was associated with a significant lower suitability rate for PD-L1 (64.2% vs 86.6%, $p = 0.02$) and molecular analysis (56.6% vs 76.4%, $p = 0.018$). No significant difference in the mean number of needle passes was found when ROSE was present (6.1 vs 5.2, $p = 0.103$).

4. Discussion/Conclusion

This is the first randomized trial comparing the 22G Acquire TBNB and Expect TBNA needles for sampling intrathoracic lymph nodes and lung tumors in patients with (suspected) lung cancer. The Acquire TBNB needle provided improved tissue specimens with more frequent tissue cores, but did not result in the expected superiority for PD-L1 analysis.

The study was conducted in response to the lack of consensus on the optimal EBUS biopsy needle and limited data to support specific recommendations. Two previous studies retrospectively evaluated the performance of the Acquire TBNB needle during EBUS procedures in lung cancer patients [6,7]. Balwan et al evaluated the EBUS Acquire TBNB needle in 100 patients and reported a diagnostic yield of 97% [7]. The second study evaluated the use of Acquire TBNB and conventional TBNA needles during EBUS procedures within the same 66 patients [6]. Although no higher diagnostic yield for malignancy was found between the TBNB and TBNA needles, a higher suitability for molecular testing (86% vs 48%) and next generation sequencing adequacy (76% vs 47%) was found with the Acquire needle.

It is supportive to our findings that these retrospective studies reported similar findings concerning the diagnostic performance and suitability for molecular analysis of the Acquire TBNB needle [6,7]. However, one retrospective study reported a significant improvement in the suitability for molecular analysis which was not found in our dataset [6]. This is mainly the result of the fact that the Expect TBNA needle performed much better in the present study. The reason for this is unclear, but the randomized design and blinded pathology evaluation might have excluded bias that could have played a role in the retrospective analysis.

As an exploratory endpoint, the effects of ROSE was evaluated. In this study ROSE was present in two centers and the centers without ROSE served as reference. Although a strong significance was found between the presence of ROSE and a reduced PD-L1 suitability, differences between centers, including cellblock preparation and fixation, might have played a role. In our experience, Acquire needle aspirates were less suitable for ROSE due to presence of core tissue. Therefore, we recommend to store tissue first in the cellblock as core tissue is probably be at the distal end of the needle tip, and put subsequent tissue on a glass slide.

Previous studies have assessed the impact of ROSE on diagnostic yield [8], but limited data is available on its effects on PD-L1 and molecular analysis. Livi et al conducted a randomized trial involving 136 patients and found no significant difference in diagnostic yield,

Table 1
Patient and procedure characteristics.

	Overall	Acquire TBNB needle	Expect TBNA needle	p-value
Number of patients	154	76	78	
Male gender	98 (63.6%)	52 (68.4%)	46 (59.0%)	0.182
Mean age (SD)	67.8 (9.0)	68.3 (8.6)	67.3 (9.5)	0.839
Centrally located tumor sampled	59 (38.3%)	30 (39.5%)	29 (37.2%)	0.770
Lymph nodes sampled per patient				
0	13 (8.4%)	5 (6.6%)	8 (10.3%)	0.412
1	59 (38.1%)	33 (43.4%)	26 (33.3%)	0.198
2	63 (40.6%)	27 (35.5%)	36 (46.2%)	0.180
3	19 (12.3%)	11 (14.5%)	8 (10.3%)	0.426
Lymph node location	90 (58.1%)	44 (57.9%)	46 (59.0%)	0.969
Station 2–4	92 (59.4%)	48 (63.2%)	44 (56.4%)	0.286
Station 7	47 (30.3%)	25 (32.9%)	22 (28.2%)	0.492
Station 10–11	5.5 (2.2)	5.3 (1.8)	5.6 (2.4)	0.352
Mean number of needle passes (SD)	59 (38.3%)	30 (39.5%)	29 (37.2%)	0.900
Rose present				
Final diagnosis of EBUS/EUS-B sampled structures				
NSCLC	102 (65.8%)	51 (67.1%)	51 (65.4%)	0.821
N2/N3 disease	84 (54.5%)	43 (56.6%)	41 (52.3%)	0.284
SCLC	28 (18.1%)	12 (15.8%)	16 (20.5%)	0.447
Pulmonary metastases	13 (8.4%)	7 (9.2%)	6 (7.7%)	0.735
Benign	10 (6.5%)	5 (6.6%)	5 (6.4%)	0.966
Unknown*	1 (0.6%)	1 (1.3%)	0	

Data are number (percentage), unless indicated otherwise.
*EBUS not conclusive and patient lost to follow-up.

Table 2
Evaluation of the samples by two blinded reference pathologists.

	Acquire TBNB needle	Expect TBNA needle	p-value
Suitability for PD-L1 analysis (>100 tumor cells in cellblock specimen)*	80.0% (56/70; 0.68–0.94)	76.7% (56/73; 0.65–0.85)	0.633
Suitability for molecular analysis (>1000 tumor cells)*	68.6% (48/70; 0.56–0.79)	68.5% (50/73; 0.56–0.79)	0.992
Sample adequacy			
Adequate	92.0% (69/75; 0.83–0.97)	87.2% (68/78; 0.77–0.93)	0.330
Indeterminate	5.3% (3/75; 0.02–0.14)	3.8% (3/78; 0.01–0.12)	0.660
Not adequate	2.7% (2/75; 0.05–0.11)	9.0% (7/78; 0.04–0.18)	0.097

Data are presented as percentage (number; 95% CI).
* Calculation of suitability for PD-L1 evaluation and molecular analyses were based on the samples of 143 patients with a final malignant diagnosis including one patient in the Acquire arm with no conclusive final who was considered false-negative for malignancy.

Table 3
Clinical outcomes.

	Acquire TBNB needle	Expect TBNA needle	p-value
Diagnostic sensitivity for malignancy [a]	94.3% (66/70; 0.85–0.98)	98.6% (72/73; 0.91–1.0)	0.157
Diagnostic sensitivity for N2/N3 disease [b]	93.0% (40/43; 0.80–0.98)	97.6% (40/41; 0.86–1.0)	0.329
Diagnostic sensitivity for malignancy in central lung tumors [c]	100% (30/30; 0.86–1.0)	93.1% (27/29; 0.76–0.99)	0.143
Overall complication rate	8.0% (6/75; 0.03–0.17)	5.1% (4/78; 0.02–0.13)	0.472
Procedure related hemorrhage	4.0% (3/75; 0.01–0.12)	0	0.076
Mean procedure duration (SD)	22.9 (8.3)	24.0 (10.0)	0.122
Mean Endoscopist satisfaction score (SD) [d]	6.5 (2.1)	6.0 (2.0)	0.185

Data are presented as percentage (number; 95% CI) unless specified otherwise.
[a] one patient with a non-conclusive EBUS and lost to follow-up in the Acquire arm was considered false-negative for malignancy. Sensitivity for malignancy was defined as the proportion of patients that had malignancy diagnosed by EBUS/EUS-B, relative to the total number of patients with a final diagnosis of malignancy as determined by the reference standard.
[b] defined as the proportion of patients that had N2/N3 disease diagnosed by EBUS/EUS-B, relative to the total number of patients with a final diagnosis of N2/N3 disease as determined by the reference standard.
[c] defined as proportion of patients that had malignancy diagnosed with EBUS/EUS-B, relative to the total number of patients with a final diagnosis of malignancy.
[d] Endoscopist satisfaction score could range from 1 to 10.

Table 4
Qualitative specimen outcomes based on the evaluation of the two blinded reference pathologists.

	Scoring	Acquire TBNB needle	Expect TBNA needle	p-value
Bloodiness				
Large amount- diagnosis compromised	0	7.3% (11/150; 0.04–0.13)	9.6% (15/156; 0.06–0.16)	0.474
Moderate amount- diagnosis possible	1	59.3% (89/150; 0.51–0.67)	59.0% (92/156; 0.51–1.67)	0.949
Minimal amount- diagnosis easy	2	33.3% (50/100; 0.26–0.42)	31.4% (49/156; 0.24–0.39)	0.719
Mair's total score				
Diagnostic ease "poor"	0–2	3.3% (5/150; 0.01–0.08)	9.6% (15/156; 0.06–0.16)	0.026
Diagnostic ease "good"	3–6	31.3% (47/150; 0.24–0.39)	41.0% (64/156; 0.33–0.49)	0.078
Diagnostic ease "superior"	7–10	65.3% (98/150; 0.57–0.73)	49.4% (77/156; 0.41–0.57)	0.005
Presence of tissue core	n/a	72.0% (54/72; 0.60–0.81)	42.1% (32/76; 0.31–0.54)	<0.01
Cumulative length tissue core (mean in mm, SD)	n/a	7.48 (4.93)	6.48 (6.13)	0.515

Data are presented as percentage (number; 95 %CI) unless otherwise specified. Scores were calculated based on the evaluation of the samples from 153 patients by two separate reference pathologists resulting in a total of 306 evaluations.

Table 5
Impact of ROSE on study outcomes.

	Overall			Acquire TBNB needle			Expect TBNA needle		
	ROSE	No ROSE	p-value	ROSE	No ROSE	p-value	ROSE	No ROSE	p-value
Suitability for PD-L1 analysis[a]	64.2% (34/53)	86.6% (78/90)	0.02	69.2% (18/26)	86.4% (38/44)	0.083	59.3% (16/27)	86.9% (40/46)	0.007
Sensitivity for malignancy[b]	100% (53/53)	94.4% (85/90)	0.081	100% (26/26)	90.1% (40/44)	0.113	100% (27/27)	98.0% (45/46)	0.440
Suitability for molecular analysis[c]	56.6% (30/53)	76.4% (68/90)	0.018	57.7% (15/26)	75.0% (33/44)	0.132	55.6% (15/27)	76.1% (35/46)	0.068
Sample adequacy[d]	86.2% (50/58)	91.6% (87/95)	0.292	86.2% (25/29)	95.7% (44/46)	0.142	86.2% (25/29)	87.8% (43/49)	0.843
Mean number of needle passes (SD)	6.1 (2.6)	5.2 (1.8)	0.103	5.7(2.0)	5.2 (1.8)	0.310	6.4 (3.0)	5.2 (1.8)	0.124

Data are presented as the percentage (number) unless specified otherwise.
[a] Samples were considered suitable for PD-L1 analysis if more than 100 tumor cells were present in a single cellblock slide in patients with a final diagnosis of lung cancer.
[b] Defined as the proportion of patients that had N2/N3 disease diagnosed by EBUS/EUS-B, relative to the total number of patients with a final diagnosis of N2/N3 disease as determined by the reference standard.
[c] Samples were considered suitable for molecular analysis if more than 1000 tumor cells were present in cellblocks and glass slides comibed.
[d] Samples scored with indeterminate adequacy by the two reference pathologists were considered inadequate.

molecular analysis, and PD-L1 testing between the presence or absence of ROSE [9]. However, their study prepared glass slides independently of the ROSE evaluation. In contrast, in the present study, the preparation of glass slides was optional, and all material was used for cellblock processing in the absence of ROSE. This may have contributed to the remarkable finding that ROSE negatively impacted the suitability rate for PD-L1 and molecular analysis. Our results suggest that comparative studies are needed to evaluate the effects of ROSE on PD-L1 suitability.

Some limitations of this study should be acknowledged. The performance of the Expect TBNA needle, exceeded expectations, which is reflected by the fact that we anticipated a PD-L1 suitability rate of 64%, which turned out to be 76.7%. As a consequence, this study lacked power to show a statistically significant difference. However, the identified (non-significant) 3.3% difference between needles is clinically probably irrelevant. Secondly, the PD-L1 suitability and molecular analysis was based on an estimate of the two reference pathologists but not based on a specific tumor count. To improve the generalizability of our findings, a consensus meeting was conducted to discuss discrepant cases and the reference pathologists agreed on all cases.

Strengths of this study include the randomized multi-center study design, including university and general hospitals, that contribute to the generalizability of this study. Additionally, for an objective evaluation of the samples, two external pathologists, blinded for needle allocation, evaluated all the samples in an uniform manner.

In conclusion, this randomized clinical trial found no significant difference in suitability for PD-L1 or molecular analysis between the Acquire TBNB and Expect TBNA needle, despite that the Acquire TBNB needle obtained improved quality tissue specimens with more tissue cores.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Statement of Ethics

This study protocol was reviewed and approved by the Medical Ethical Committee Amsterdam UMC, approval number 2019_117. Patients provided written informed consent prior to study participation.

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Author contributions

TK contributed to the design of the work, data collection and analysis, writing of the manuscript and gave final approval to the manuscript. JCK contributed to the design of the work, data analysis and gave final approval to the manuscript. JvdT contributed to the design of the work, data analysis and gave final approval to the manuscript. DC contributed to the design of the work, data analysis and gave final approval to the manuscript. AZ contributed to the data collection and gave final approval to the manuscript. MG contributed to the data collection and gave final approval to the manuscript. MKN contributed to the data collection and gave final approval to the manuscript. BH contributed to the data collection and gave final approval to the manuscript. RT contributed to the data collection, critically revised the manuscript and gave final approval to the manuscript. ZS contributed to the data collection and gave final approval to the manuscript. JV contributed to the data collection and gave final approval to the manuscript. DAK contributed to the design of the work and critically revised the manuscript and gave final approval to the manuscript. PIB contributed to the design of the work and critically revised the manuscript and gave final approval to the manuscript. JTA contributed to the design of the work, data analysis, critically revised the manuscript and gave final approval to the manuscript.

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