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CT-guided transthoracic lung biopsy: Complications and success in yielding a specific diagnosis

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Abstract

Aim: To present risk factors for common complications of CT-guided transthoracic lung biopsy and to analyzing the diagnostic success of the procedure in terms of specific diagnostic rates.

Materials and Methods: 461 consecutive procedures retrospectively enrolled. Patient, lesion and technical variables are scrutinized in terms of complications and their severity. Pathology results were evaluated for diagnostic specificity.

Results: 27% total complications with 17% alveolar hemorrhage, 7% pneumothorax and 3% developed both. $\leq$ 15 mm size and $\geq$ 20 mm distance from pleura significantly increases the risk of both PTX and AH. Perilesional emphysema is a predisposing factor of both severe PTX and extended bleeding. Lateral decubitus position increases the likelihood of pneumothorax. Patients with a needle angle of less than 90$\pm$15° had an approximate 2-fold increase risk of PTX (P = 0.034). Semi-solid lesions carry a risk of significant bleeding. The accuracy was 96.9% with a specific malignant diagnosis rate of 83% and a specific benign diagnosis rate of 52%.

Conclusion: Perilesional emphysema is risk factor of severe complications. Semi-solid lesions are prone to severe bleeding. Lateral decubitus position and low needle angle are important as preventable predisposing factors of PTX. Although the diagnostic yield is satisfactory, the specific benign diagnosis rates are still below expectations and that larger needle biopsies are more beneficial in this regard.

Introduction

Most lung lesions requiring biopsy cannot be reached by bronchoscopy. Percutaneous CT-guided transthoracic lung biopsy (TTLB) is widely used due to its practicability, safety and patient comfort. In including its primary malignancies and metastasis, lung is one of the most common malignancies bearing organs. Another reason for the high number of biopsy referrals is the diagnostic limitations of chest CT, especially in some benign diseases. It has become a part of the daily routine of interventional radiology departments. Alveolar hemorrhage (AH) and pneumothorax (PTX) are the most common complications. Although many of these are mild and self-limiting, they at least reduce the comfort of this minimally invasive technique by prolonging the hospital stay or requiring chest tube drainage, which can sometimes interrupt the procedure [1]. There have been many studies on the complications of TTLB. Conflicting results on predisposing factors make the subject still of interest. The aim of this study is to identify the patient, lesion and technique-related factors of CT-guided TTLB leading to AH and PTX and to present the success rates in terms of tissue-specific diagnosis.

Materials and Methods

Four hundreds and sixty-one consecutive patients underwent CT guided TTLB procedure in our hospital were retrospectively enrolled. The number of patients was well above the minimum expected to have 80% power with 5% type 1 error to achieve effect size (Cohen'd) of 0.5 in a non-directional analysis. Written informed consents were obtained for all patients before the procedure. The study was approved by our hospital institutional review board (Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee, Approval no: 709). All biopsies were performed with 18G coaxial true-cut semi-automatic core-biopsy needle by a 20-year experienced interventional radiologist. Patients with uncorrectable coag-

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ulopathy (platelet level \50,000 K/UL and an international normalized ratio 1.5) were not included. Sampling adequacy was determined by the operator. Non-complicated patients, mild pneumothoraxes and alveolar hemorrhages were discharged 6 hours after the procedure with control chest radiography. Symptomatic pneumothoraxes or alveolar hemorrhages were hospitalized.

Lesion location, size, density and radiologic appearance were included in lesion related variables. The maximum long axis was measured in size. Mean density of lesion and perilesional parenchyma calculated by using automatic ROI. Location was classified according to lobe (apical, upper, middle, lower lobe). The lesions were classified as solid, semisolid (subsolid or ground glass), cavitary (central necrosis and emphysema) and consolidation in terms of radiologic appearances. Biopsy position, needle path length, needle to pleural angle, needle passes were included in technical variables. Angle was measured between needle trajectory route to relevant pleural surface and needle path length was taken from pleural surface to the lesion margin. Malignant and benign biopsy results were accepted as positive and negative respectively. True positive and true negative diagnoses were confirmed either by surgical results or imaging follow-ups. Re-biopsies were not included in the study. Cytologic results of the biopsies were further evaluated for diagnostic specificity.

Statistical analysis

SPSS version 28 was used for statistical analysis. The proportion of uncomplicated patients and patients with AH or PTX and their subgroups with severe complications were studied in terms of risk analysis of patient, lesion and technique-related variables. Chi-square test or Fisher's exact test, where appreciate, were used for categorical variables. In normally distributed variables, Student's t-Test, One-Way-ANOVA and Levene test were used to compare measurements between the groups (uncomplicated vs AH or PTX) and the sub-groups (uncomplicated, mild vs severe). Descriptive analyses were presented using means and standard deviations for normally distributed continuous variables and proportions for categorical variables. Multivariate logistic regression test was carried out for independent variables with p value of < 0.1 in univariate tests. Statistical significance of multivariate analysis was accepted as $p<0.05$.

Results

461 biopsies were involved, 32% (n: 148) were female and 68% (n: 313) were male with mean age of 61±12 years (range, 23-91). Mean lesion size was 2.6 cm (±1.5 SD, min-max: 0.5-8). The overall complication rate was 27% (n: 126). Alveolar hemorrhage developed in %17 (n: 79), pneumothorax in 7% (n: 34) and in 3% (n: 13) both occurred simultaneously. In 33 procedures, the first attempt failed and at least 1 additional needle incision needed and in 8 cases fissure passed. The necessity of chest tube intervention (CTI) is accepted as severe PTX. In 15 patients with progressive pneumothorax or respiratory distress chest tube drainage needed. Hemothorax developed in 3/3 patients with segmental bleeding, haemoptysis occurred in 6 of 19 patients with subsegmental bleeding; all were self-limiting and did not require further intervention (Figure 1). The remaining 70 cases of bleeding were needle tract or perilesional AH. Air embolism was suspected in 2

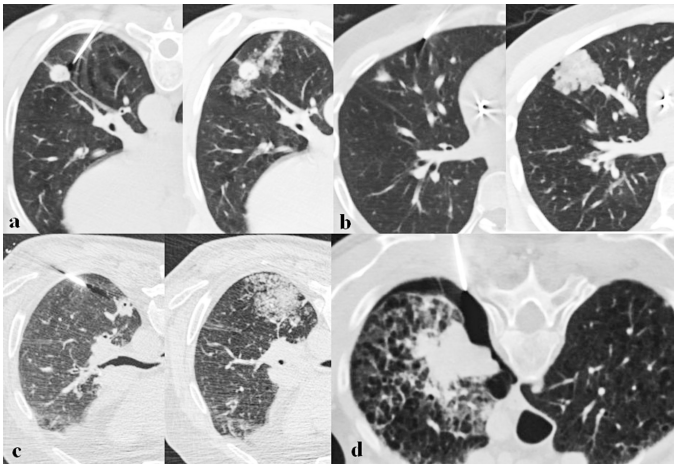

Figure 1. TTNB complications examples, CT images during procedure and after needle removal are shown. (a) Needle tract alveolar haemorrhage, (b) subsegmental bleeding, (c) segmental bleeding. (d) PTX during needle insertion, we would also like to draw attention to the narrow needle pleural angle in this case.

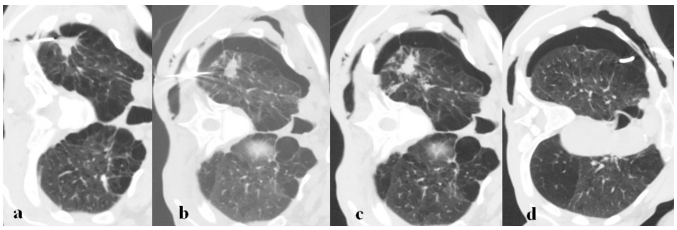

Figure 2. In lateral decubitus position, prominent emphysematous parenchyma is seen at lung window settings, (a) right after needle insertion, (b) PTX developed during procedure and (c) rapid progression and soft tissue emphysema can also be seen after needle removal, (d) inserted chest tube tip is seen.

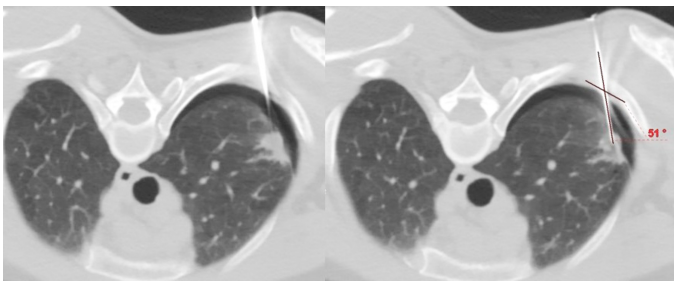

Figure 3. TTNB CT image of upper lobe and peripherally located lesion. The biopsy was performed in prone position and the needle was inserted medial to the scapula at an acute angle to the pleura due to superposition. Mild PTX developed when the needle was inside. Needle-to-pleural measurement is also shown.

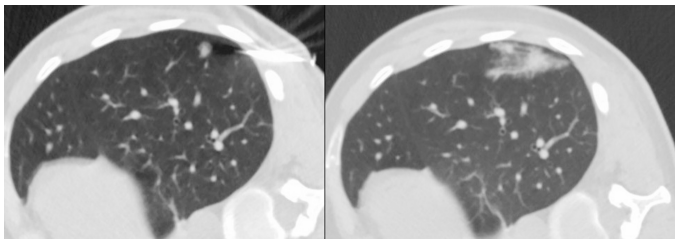

Figure 4. Biopsy of a small and semi-solid lesion. (a) CT image during needle insertion. (b) In control image after needle removal, needle tract alveolar haemorrhage is seen.

Table 1. Patient, Lesion And Techniqual Features & Complications.

Patient age; (y)	
Mean±SD (min-max)	61±12 (23-91)
Patient; n (%)	461
Female	148 (32%)
Male	313 (68%)
Biopsy position; n (%)	
Supine	196 (42%)
Prone	244 (53%)
Lateral	21 (5%)
Lesion size (cm)	
Mean±SD (min-max)	2.6±1.5 (0.5-8)
Lesion lobar location; n (%)	
Apical	11 (2%)
Upper	239 (52%)
Middle	24 (5%)
Lower	187 (41%)
Lesion radiologic appearance; n (%)	
Solid	320 (69%)
Semisolid	78 (17%)
Cavitary	32 (7%)
Consolidation	31 (7%)
Pleural insicion; (n)	
1 pleural incision	420 (91%)
2 or more pleural incisions	33 (7%)
Fissure pass	8 (2%)
Complications; n (%)	126 (27%)
Alveolar Hemorrage; n (%)	79 (17%)
Perilesional or Needle tract AH (minor)	70 (15%)
Sub-segmental AH	19 (7%)
Segmental AH	3 (3%)
Pneumothorax; n (%)	34 (7%)
Minor PTX	19 (4%)
PTX with chest tube insertion	15 (3%)
Both AH&PTX	13 (3%)

patients with short-term neurological disturbances shortly after the procedure, but their brain CTs and DWIs were normal and the symptoms resolved spontaneously. Table 1 summarizes the patient, lesion and procedure related features and complications.

The size, needle path length and needle track emphysema were in common predisposing factors of PTX and AH. Lesions $\leq$ 15 mm in diameter had significantly increased rate of pneumothorax (OR, 2.106; 95% CI 1.225–3.621; P: 0.007, $\chi 2$) and bleeding (OR, 3.847; 95% CI 2.687–5.509; P$<$ 0.001, $\chi 2$). It should also be noted that small lesions have a higher risk of bleeding than PTX. PTX and AH rates were also significantly increased where needle path distance exceeded 20 mm. OR was 3.162 (95% CI 1.675–5.969; P$<$ 0.001, $\chi 2$) for PTX and 2.918 (95% CI 1.812–4.699; P$<$ 0.001, $\chi 2$) for AH. We found that the likelihood of developing PTX was more than AH in distant lesions. Perilesional emphysema was the only independent risk factor of both severe pneumothorax and extended bleeding. The mean needle tract parenchymal density was significantly lower in CTI patients, than in those with mild pneumothoraxes or uncomplicated patients (HU: -857 vs -755 vs -724, respectively, P:0.004, ANOVA) (Figure 2). Perilesional emphysema also significantly increases the rate of either minor or extensive bleeding (P: 0.018, ANOVA).

Patient position and needle angle are technical variables that have a significant impact on PTX development. Biopsies performed in lateral decubitus position were significantly more likely to result in pneumothorax than those in the supine and prone position (P: 0.012, $\chi 2$) Patients with a needle angle of less than 90±15° were found to have an approximate 2-fold increased risk of PTX (OR, 2; 95% CI 1.028–3.893; P = 0.034, $\chi 2$) (Figure 3). The incidence of alveolar hemorrhage was relatively higher in semi-solid lesions compared to others; consolidations, cavitary and solid lesions (RR, 3.404; 95% CI 2.358–4.916; P $<$ 0.001, $\chi 2$) (Figure 4). Mean lesion density was 10.9(±8.57) HU in hemorrhagic and 29.11(±19.47) HU in non-hemorrhagic cases (P $<$ 0.001, t-test). Although at the limits of statistical significance, semi-solid lesions predispose severe bleeding risk (RR: 2.047, 95% CI 0.992–4.225; P: 0.051, $\chi 2$). The risk factors associated with pneumothorax and alveolar haemorrhage were shown in Table 2.

77% (n: 354) of the biopsy results were malignant, 23% (n: 107) were benign. The final diagnosis was confirmed by follow-up imaging in 75% (n: 250) and by surgery in 25% (n: 82). The results could not be validated due to missing follow-up in 28% (n: 129). Of the 332 confirmed results, 99% (259/261) were true malignant and 89% (63/71) were true benign diagnoses. 2 malignant biopsy results proved to be benign (follow-up) and 8 benign results proved to be malignant. The accuracy was 96.9% with 97% sensitivity, 96.9% specificity, 99.2% PPV and 88.7% NPV. Among confirmed results, the overall true specific tissue diagnosis rate was 77% (n: 254/332); for benign lesions, the true specific diagnosis rate was 52% (n: 37/71) and for malignant lesions, the true specific diagnosis rate was 83% (217/261). Diagnostic analyses and pathology results were listed in Table 3.

Discussion

Non-interventional pneumothorax, perilesional or needle tract hemorrhage and transient hemoptysis are frequent and mild complications that are not life-threatening but can compromise the safety of the method and comfort of

Table 2. Multivariate Analysis Results.

Variables	No-complication	PTX	P'	AH	P"
Sex, F/M	32%-68%	28%-72%	0.554	35%-65%	0.550
Age (mean, yrs)	61	64	0.087	64	0.149
Location (%)					
Apical	2.7%	2.1%		1.3%	
Upper	52.8%	53.2%	0.998	46.8%	0.465
Middle	5.4%	6.4%		3.8%	
Lower	39.1%	38.3%		48.1%	
Biopsy position					
Supine	44%	30%	*0.012	44%	0.634
Prone	52%	57%		54%	
Lateral-decubitus	4%	13%		1%	
Lesion type					
Semisolid + GG	11%	19%		41%	
Solid	75%	60%	0.088	51%	*<0.001
Consolidation	8%	4%		4%	
Cavitary	6%	17%		4%	
Lesion Size			*0.007		*<0.001
≤15 mm	19%	36%	OR: 2.106	60%	OR: 3.847
>15 mm	81%	64%	(95%CI: 1.225-3.621)	40%	(95%CI: 2.687-5.509)
Pleural Distance			*<0.001		*<0.001
≤ 20 mm	64%	36%	OR: 3.162	38%	OR: 2.918
> 20 mm	36%	64%	(95%CI: 1.675-5.969)	62%	(95%CI: 1.812-4.699)
Needle Angle			*0.034		
≤ 75°	63%	79%	OR: 2	63%	1
> 75°	37%	21%	(95%CI: 1.028-3.893)	37%	
Lesion density					*<0.001
(Mean HU±SD)	29.11 (±19.47)	24.06 (±18.92)	0.070	10.9 (±8.57)	(95%CI: 6.518- 19.92)
Needle Tract Parenchyma Density					
(Mean HU±SD)	724 (±24.404)	755(±26.427)	0.170	767(±17.225)	*0.003
Severity	Minor PTX / PTX+CTI			Minor AH / Segmental+Subsegmental AH	
Needle Tract Parenchyma Density			*0.002		*0.006
(mean HU)	755/857		(95%CI: -103.109; -40.870)		
Semisolid Structure	17.4%-20%		0.479	31.4%-54.5%	*0.051 OR: 2.047 (95% CI 0.992–4.225)

PTX: pneumothorax, P': p value of PTX, AH: alveolar haemorrhage, P'': p value for AH. HU: Hounsfield unit. GG: ground-glass. * Statistical significancy: p<0.05.

patient. The reported overall complication rate of TTLB varies between 23% and 38.8% [2]. The majority of our 27% of complicated patients were self-limiting PTX and AH. Our 7% PTX, 17% pulmonary hemorrhage and 3% CTI are in line with previously reported rates, which range from 15.4% to 40.2% for PTX, 3.6% to 73.5% for AH and 1.5% to 15% for CTI using 18G and smaller biopsy needles [3-5].

Small lesion size, increased pleural distance and perilesional emphysema were in common risk factors of PTX and AH. The difficulty in targeting small lesions requires more needle adjustment for correct positioning. On the other hand, distance from the pleural surface is directly increases the amount of tissue penetration. Both conditions increase the likelihood of parenchymal injury and are therefore predictable but mostly inevitable causes of PTX and AH. A maximum lesion size of >15 mm and a needle tract length of > 20 mm can be associated with increased risk of both PTX and AH. Although most studies agree that small lesion size and pleural distance are the key risk factors, reported thresholds often vary, probably depending on operator experience [3, 6-10]. J. Takeshita et al. reported 3.08 increased risk of PTX requiring drainage for the lesion of 15 mm or greater in dept [4]. Khan et al. notified needle path length of >4 cm for significantly increased rates of both PTX and perifocal hemorrhage [11]. Sabatino et al. reported that the ORs for the development of PTX, AH and clinically significant PTX increased by

Table 3. Biopsy results.

	N (%)
Total No	461
Malignant	354 (77%)
Bening	107 (23%)
Confirmed results	332 (72%)
By surgery	82 (25%)
By follow-up	250 (75%)
Lack confirmation	129 (28%)
Within Confirmed results	
Malignant	261 (78%)
Bening	71 (22%)
Non-diagnostic	0
True malign	259 (99%)
True benign	63 (89%)
False positive	2 (0.8%)
False negative	8 (3%)
Confirmed malignant results (n)	
Primary involvement	
Specific Diagnosis	217 (83%)
Adenocarcinoma	101
Squamous cell carcinoma	41
Small cell ca.	8
Neuroendocrine Tumour	7
Large cell carcinoma	3
Lymphoma	4
Solitary fibrous tumour	3
Langerhans cell histiocytosis	2
Non-specific Diagnosis	23
NSCC	22
Undifferentiated	1
Metastasis	69
Target organ specified	48
Target organ non-specified	21
Bening disease	
Specific Bening Diagnosis	37 (52%)
Anthracosis	4
Sarcoidosis	1
Tuberculosis	8
Schwannoma	2
Fungal infection	3
Hamartoma	3
Granuloma	4
Vasculitis	2
Organising pneumonia	8
Interstitial pneumonia	1
GVHD	1
Non-specific Bening Diagnosis	34
Inflammation	22
Fibrosis	5
Necrosis	4
Haemorrhage	3

5.2%, 7.7% and 4.6% for each millimeter increase in distance from pleural surface respectively [7].

Perilesional emphysema was associated with severe PTX, but it was not connected with mild PTX. Additionally, the likelihood of both mild and severe bleeding was significantly increased by perilesional emphysema. Loss of elasticity in emphysematous parenchyma impairs the self-limiting role of alveolar collapse against needle-induced perforation, which may lead to the development of severe PTX rather than mild air leakage. Additionally impaired mechanical tamponade effect in emphysema may also be the reason of increased AH rates. Our results are consistent with the literature with subtle differences. Saad et al. included emphysema in risk factors of severe complications without sub-specification whereas Lee and Tai et al associated perilesional emphysema with only major bleeding [12-14]. In contrast, Otto et al did not include emphysema among the complications of TTLB [10].

The biopsy position of supine, prone or lateral decubitus is determined regarding lesion location to provide the shortest and easiest route. In our study, lateral decubitus position was associated with increased PTX risk. Conflicting results present as to patient position and complications. In the study of Wang et al. and meta-analysis of Chan et al. lateral decubitus position included among the risk factors for PTX [3, 15]. Takeshita et al. related supine biopsy position with severe PTX [4]. In contrast, Kaplan et al. and Chui et al. found no significant impact of patient position on overall risk of complications [5, 8]. Some studies suggested biopsy site down positioning as a protective option to reduce PTX and CTI incidences [16-18]. We think that the pathophysiological explanation for the protective role of the puncture site down position and the predisposing role of the lateral decubitus position in the development of PTX is similar. The lung parenchyma under the dependent side could not expand as in the non-dependent side due to weight bearing, as seen in dependent atelectasis on routine imaging. The smaller body surface area in the lateral decubitus position compared to the supine and prone positions creates more pressure on the dependent side, which further hinders its expansion. As a result, a greater volume of air may enter the contralateral lung and be the reason for the increased incidence of PTX in the lateral decubitus position.

Needle trajectory angle has a significant influence on PTX rates, which is of particular importance as a modifiable and preventable parameter, however we believe that it has not been properly emphasized. PTX rates were lower in patients with a needle to pleura angle of $90\pm15^\circ$ compared to narrow angles. Ko. et al. mentioned the risk of PTX with needle angle of $< 80^\circ$ [19]. Saji et al were also one of the first that declared needle trajectory deviation from the right angle of the pleural surface as a predictor of PTX [20]. Uzun et al. stated $\leq 45^\circ$ as threshold, whereas Mir et al. generalized that a narrow angle increases the risk [21, 22]. However, among published studies conflicting results are also present. Kituyama et al. found no impact of needle angle on PTX incidences [23]. In different, Chui et al. associated a narrow needle pleural angle with bleeding [5].

The incidence of post-biopsy bleeding was higher than that of PTX. No intervention was required for any bleeding, regardless of severity. The incidence of segmental and sub-

segmental bleeding in semisolid lesions was significantly higher than the others (P: 0.051). Thus, it is clear that semi-solid, low-density lesions carry risk of more extensive bleeding during biopsy. It is difficult to make a rational explanation of the underlying mechanism. The loose structure of semi-solid lesions may not provide a sufficient tamponade effect on adjacent parenchyma compared to solid lesions, or vasculature in loose connective tissue may be more prone to injury. Tai et al. in their paper also emphasized the severe bleeding risk in semi-solid lesions [14].

The reported overall accuracy rate of CT guided cutting needle biopsy is range from 92.9% to 98.5% [1, 4, 15, 24-25]. Kim et al. reported 10.6% false negative ratio among non-specific benign biopsy results with 18G core needle [26]. Oint et al. published 68% NPV and 9% false positive result with 17% specific benign diagnosis rate [27]. H. Chen et al. stated 87% (289/322) non-specific malign diagnosis rate (NSCLC) [24]. In comparison with larger needle biopsy results; Ocak et al. reported 97% cancer-specific malignant diagnosis and 71% specific benign diagnosis with 6% false-negative result with 14G biopsy needle [28]. Beslic et al. study with a 14G core needle, cancer specific diagnosis ratio of malignant results was stated as 82% [29]. Heyer et al. published 100% PPV and 88% NPV with a 16G biopsy needle, without scrutinizing the results in terms of diagnostic specificity [30]. Based on the published reports, biopsies performed with larger needles appear to be more beneficial than those with smaller needles in terms of tissue-specific diagnosis.

The retrospective design of the study was the main limitation. We also had to exclude a large number of patients due to lack of follow-up. The absence of serious or rare complications supports the safety of the procedure. However, we weren't able to analyze the variables in this regard. The small cohort size and single operator make the results less generalizable.

Conclusion

Small size, distant location from pleura and the presence of perilesional emphysema constitutes well-established, but usually uncorrectable risk factors of both PTX and AH. The presence of emphysematous parenchyma in the needle tract increases the risk of PTX requiring chest tube insertion, while the low-density semisolid lesions are more prone to bleeding and may result in more extended bleeding than anticipated. We believe it is important to highlight the association of lateral decubitus position and low needle angle with the risk of PTX as technical variables that can be avoided. We believe that despite the high diagnostic success of the procedure, the specific diagnosis rates are below expectations, especially in benign diseases. A comparison of the results of studies using larger needles suggests that biopsies using larger needles are more beneficial in this respect.

Ethical approval

Ethical approval was received for this study from Istanbul Medipol University Non-Interventional Clinical Research Ethics Committee (Approval number: 709).

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