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Frequency of complications and risk factors associated with computed tomography guided core needle lung biopsies

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BACKGROUND: Although transthoracic needle biopsy (TTNB) is an effective method for diagnosis of lung tumors, it has some complications. It is crucial to know the frequency and severity of the complications of TTNB and its risk factors in order to avoid them.

OBJECTIVES: Evaluate the complications and risk factors of computed tomography guided core needle lung biopsies (CT-CNLB).

DESIGN: Prospective evaluation of complications.

SETTING: Single center in Turkey.

PATIENTS AND METHODS: For CT-CNLBs performed between October 2017 and March 2018, the complications of biopsies were noted and classified as major and minor based on guidelines of the Society of Interventional Radiology.

MAIN OUTCOME MEASURES: The complications and risk factors for complications were evaluated.

SAMPLE SIZE: 123 adult patients.

RESULTS: The most common complications were pulmonary hemorrhage (30.9%) and pneumothorax (22%). Increased overall pulmonary hemorrhage was observed with underlying emphysema (P=.022), non-peripheral location of the lesion (P<.001), increased needle pathway (P<.001), fissure penetration (P=.011), increased number of pleura penetrations (P=.024), prolonged needle time across pleura (P=.037), and decreased lesion size (P=.033). The pneumothorax rate increased with non-peripheral location of the lesion (P<.007), fissure penetration (P=.021), prolonged needle time across the pleura (P= .013), and decreased lesion size (P=.002). In the logistic regression analyses for he two most common complications, the only risk factor for both alveolar hemorrhage and pneumothorax was a non-peripheral location of the lesion (P<.001, OR=14.7, 95% CI=3.9–55.4 for alveolar hemorrhage) and (P=.001, OR=156.2, 95% CI =7.34–3324.7 for pneumothorax).

CONCLUSION: Most common complications of CT-CNLB were pneumothorax and pulmonary alveolar hemorrhage with a 5.7% major complication rate. Choosing the shortest possible trans-pulmonary needle pathway minimizes the risk of complications.

LIMITATIONS: Limited number of patients, absence of rare complications as death, air embolism, and needle tract seeding.

CONFLICT OF INTEREST: None.

The leading cause of death in patients with cancer diagnosis is lung cancer.[1] Due to the increase in the usage and availability of imaging methods, especially computed tomography (CT), the number of CT detected lung lesions has increased. Even if patients with incidental lung nodules or tumors have no symptoms, histopathological analysis is needed to obtain a specific diagnosis. Bronchoscopy guided transbronchial biopsy is the first line choice for centrally located lung lesions; it has with a diagnostic accuracy of 60%.[2] Thoracoscopic biopsy and open biopsy are two other methods used for lung biopsies; however, both are more invasive than other types of methods and both require the use of anesthesia. Transthoracic needle biopsy (TTNB) is a minimally invasive procedure which is preferred for peripherally located lung lesions or if other techniques have failed.[3] CT is the common choice of imaging guidance for TTNB. The decision to use an aspiration needle or a core biopsy needle primarily depends upon the characteristics and location of the lesion.[4] Although TTNB is an effective method for diagnosis, it has complications, such as hemoptysis, alveolar hemorrhage, and pneumothorax.[3,5] While these complications are usually self-resolving, in more severe cases, hospitalization and some interventional procedures may be needed.[6,7] Thus, it is crucial to know the frequency and severity of the complications of TTNB and its risk factors in order to properly manage or avoid them. This prospective study aimed to identify the complications related to and the risk factors associated with CT-guided core needle lung biopsies (CT- CNLB).

PATIENTS AND METHODS

Patients who underwent CT-CNLBs at Ondokuz Mayis Medical Faculty, Samsun, Turkey between October 2017 and March 2018 were included in the study. Patients were selected from the biopsy procedures performed upon clinical indications. Exclusion criteria were pulmonary arterial hypertension, pneumonectomy of contralateral lung, bullous disease of adjacent lung to lesions, significant coagulopathy, and serious chronic obstructive pulmonary disease. Aspirin and clopidogrel were withheld for 5 days, and 1 day before the biopsy heparin was withheld. Prior to the procedure coagulation parameters (activated partial thromboplastin time [aPTT], prothrombin time [PT], international normalized ratio [INR]) and complete blood count were obtained. The biopsy procedure was performed if the PT was >60%, and the aPTT was ≤1.5 times the normal limit, platelet count (PLT) was >50 000/mm^3. This prospective study was approved by the institutional ethical committee (Protocol Number: B.30.2.ODM.0.20.08/1333-1780).

Procedures

Informed consent was obtained from all patients before the biopsy. All the biopsies were performed under the guidance of a 4-slice helical CT Asteion (Toshiba, Tokyo, Japan). The patient position (supine, prone, or lateral position) and the biopsy pathway were decided with the help of a previous thorax CT scan before the procedure. The shortest parenchymal needle pathway from the pleura was preferred, and large vessels, bullae, and fissures were avoided if possible. All the patients were scanned using a routine thorax CT protocol (slice thickness 2.5 mm, 120 kV, 150–180 mAs without injecting a contrast agent). The maximum diameter of the lesion was noted in the lung window settings. The center of the lesion was marked with a radiopaque marker on the skin of the patients using CT landmarks. Skin disinfection and local anesthesia with injection of 2% lidocaine subcutaneously were applied before the needle insertion. Eighteen-gauge automated core needle biopsy system with a 2-cm throw length (Geotek; Medical Technologies, Ankara, Turkey) was used for all the procedures. The patients were told to hold their breath while the clinician inserted the needle. The needle position was checked several times. The procedure was continued if the lesion was on the path of the needle. If not, the path of the needle or the puncture site was changed. When the needle tip reached the lesion, the biopsy was performed. After removing the needle, the patient was told to lie on the needle entry side for reducing the pneumothorax risk. CT images were acquired immediately after the biopsy to uncover any complications. A posteroanterior (PA) chest X-ray (PA CXR) was performed on all the patients 1 hour and 4 hours after the biopsy. Patients with asymptomatic pneumothorax or alveolar hemorrhage were observed for 24 hours, and they were discharged if they were still asymptomatic. A chest tube was inserted in patients with respiratory distress or dyspnea having pneumothorax. An additional thorax CT or CXR was performed in patients with complications, if needed.

Data analysis

The patients' position, distance from the pleura to the lesion edge on the needle path, number of punctures through the pleura, and the length of time after the needle insertion to end of the procedure were noted. Lesions were classified into three categories based on their morphology: solid, subsolid, and cavitary. Lesion was defined as a cavitary lesion when an air-filled area was detected within the lung lesion on the pre-biopsy CT scans. When the centrilobular or panlobular emphysema, bullae, or blebs were detected on CT, em-

physema was diagnosed. Post-procedure CTs and follow-up PA CXR were prospectively evaluated for complications, commonly pneumothorax and pulmonary hemorrhage. If pneumothorax was detected, the largest distance of retraction of the pulmonary surface was measured. Pulmonary hemorrhage was identified as new ground-glass opacity on post-biopsy. The severity of pulmonary hemorrhage was classified into the following grades: Grade 0 as no hemorrhage; Grade 1 as a needle tract hemorrhage <2cm in width; Grade 2 as a hemorrhage >2cm in width but sublobar; and Grade 3 as a lobar hemorrhage or greater as derived from the classification used by Tai et al.[8] Hemoptysis limited to the sputum was considered as mild, and otherwise as abundant. Any intervention to manage the complications and additional complications were also noted. Pathological results were classified as malignant, benign, or nondiagnostic.

Table 1. Characteristics of lesions and biopsy procedures.

Lesion diameter (mm)[a]	40 (10-134)
Morphology[b]	
Solid	104 (84.6)
Subsolid	5 (4.1)
Cavitary	14 (11.4)
Lesion density (HU)[a]	38 (–385-103)
Lobar location[b]	
Right upper	37 (30,1)
Right middle	4 (3.3)
Right lower	23 (18.7)
Left upper	28 (22.8)
Left lower	31 (25.2)
Lesion location[b]	
Peripheral	53 (43.1)
Central	70 (56.9)
Length of needle pathway (mm)[a]	10 (0-60)
Underlying parenchyma[a]	
Normal	96 (78)
Emphysema	27 (22)
Lesion histopathology[b]	
Malignant	78 (63.4)
Benign	20 (16.3)
Nondiagnostic	25 (20.3)
Patient position during biopsy[b]	
Prone	79 (64.2)
Supine	32 (26)
Lateral	12 (9.8)
Fissure penetration[b]	6 (4.9)
Number of pleura penetration[b]	
1 time	106 (86.2)
2 times	11(8.9)
3 times	5 (4.1)
4 times	1 (0.8)
Time of needle across the pleura (min)[a]	**3 (1-13)**

[a]Data are median (minimum-maximum), [b]Data are n (%).

Complication severity was stratified as major or minor according to the Quality Improvement Guidelines for Percutaneous Biopsy of the Society of Interventional Radiology. Major complications were those that resulted in admission to a hospital for therapy for outpatient procedure, an unexpected increase in the care level, prolongation of hospitalization, persistent adverse sequelae, or death. Minor complications were complications requiring a hospital stay overnight for observation or nominal therapy with no sequelae.[9]

Statistical analysis

SPSS 21.0 for Windows was used for statistical analyses. Data were presented as frequency (%), and as mean (standard deviation) or median (min-max). To analyze the normal distribution assumption of the quantitative outcomes, the Shapiro–Wilk test was used. The *t*-test and Mann–Whitney test were used to analyze normal and non-normal data, respectively. The frequencies were compared using the Pearson chi-square, continuity correction chi-square, and the Fisher exact test. The significant factors in the univariate analyses were used as variables in logistic regression analyses to describe risk factors for the two major complications. Odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated. A *P* value less than .05 was considered statistically significant.

RESULTS

CT-CNLBs in 123 patients (101 males [82.1%] and 22 females [17.9%]) were included in the study. The mean patient age was 66 (10.5) years (min: 37 years, max: 95 years). Seventeen patients (13.8%) were regularly taking either an antiplatelet or anticoagulant, which was ceased prior to the procedures (**Table 1**). Non-diagnostic results were obtained in 25 patients (20.3%). Of the remaining 98 patients (79.7%), 78 (63.4%) had

positive results for malignancy, and 20 (16.3%) had benign results.

Of the total sample population, 57 patients (46.3%) had at least one complication; 7 (5.7%) had major complications, while 50 (40.7%) had minor complications (**Table 2**). The most common complications were pulmonary hemorrhage (30.9%) and pneumothorax (22%). A Grade 1 pulmonary hemorrhage was detected in 21 patients (17%), Grade 2 in 14 patients (11.4%), and Grade 3 in 3 patients (2.4%); all were self-limited with no need for therapy. Mild hemoptysis occurred in only 4 patients (3.3%). Pneumothorax was seen in 27 patients (22%), 7 of which (5.7%) required chest tube drainage. In 26 patients (21.1%), pneumothorax was detected by CT immediately after biopsy. (No newly diagnosed pneumothorax was detected in the control PA-CXR. One patient (0.8%) applied to emergency service with severe pneumothorax a week after the lung biopsy, which was not detected in the post-biopsy CT nor the control PA-CXR. Increased overall pulmonary hemorrhage was observed with underlying emphysema (*P*=.022), non-peripheral location of the lesion (*P*<.001), increased needle pathway (*P*<.001), fissure penetration (*P*=.011), increased number of pleura penetration (*P*=.024), prolonged needle time across pleura (*P*=.037), and decreased lesion size (*P*=.033; Table 3). The rate of pneumothorax increased with a non-peripheral location of the lesion (*P*<.007), fissure penetration (*P*=.021), prolonged needle time across pleura (*P*=.013), and decreased lesion size (*P*=.002; **Table 3**). No statistically significant difference was observed in pneumothorax rate with the prolonged needle pathway (*P*=.473). In the logistic regression analyses, the only risk factor for having either a pulmonary hemorrhage or a pneumothorax was a non-peripheral location of the lesion (*P*<.001, OR=14.7, 95% CI=3.9-55.4 for alveolar hemorrhage) and (*P*=.001, OR=156.2, 95% CI=7.34-3324.7 for pneumothorax). No statistically significant difference was observed in patients having hemoptysis for all modifiable and non-modifiable variables.

Patients with non-peripheral lesions (*P*<.001), alveolar hemorrhage (*P*<.001), and hemoptysis (*P*<.001) showed a statistically significant increased rate of major complications. With the increased grade of hemorrhage, the major complication rate was increased (chi-square, *P*<.001). Lesion size was smaller (*P*=.001) and density (*P*=.016) was lower in patients with major complications, while procedure time (*P*=.001) was longer.

Table 2. Severity classification and frequencies of complications.

Complications	Frequency (%)
Complications	57 (46.3)
Major	7 (5.7)
Minor	50 (40.7)
Pneumothorax	27 (22)
Alveolar hemorrhage	38 (30.9)
Grade 1	20(16.3)
Grade 2	14 (11.4)
Grade 3	3 (2.4)
Other complications	
Hemoptysis	4 (3.3)
Chest pain	6 (4.9)
Dyspnea	5 (4.1)

Data are n (%).

DISCUSSION

This study showed that CT-CNLB has an overall complication rate of 46.3% with a 5.7% major complication rate. Most common complications were pneumothorax (22%) and pulmonary alveolar hemorrhage (30.9%). The only identifiable risk factor for alveolar hemorrhage and pneumothorax was a non-peripheral location of the lesion. With an increased needle pathway, the alveolar hemorrhage rate was increased. Nevertheless, the rate of pneumothorax did not show a significant difference. Smaller lesion size, fissure penetration, and prolonged needle time across pleura also increased the rate of both complications. Patients with emphysema had a greater alveolar hemorrhage rate.

Previous studies have also shown that pneumothorax and pulmonary hemorrhage were the most frequent complications of CT-guided lung biopsies.[3,5,6,9-11] Rare major complications such as hemothorax, needle tract seeding, air embolism, and death were not seen in our study. The frequency of pulmonary hemorrhage ranged from 4-58% and the frequency of hemoptysis ranged from 4-20% in the literature.[3,9,11,12] In the current study, the alveolar hemorrhage rate was 30.9%, and the hemoptysis rate was 3.3%, which are within the expected range. All of the alveolar hemorrhage and the hemoptysis were self-limited with no need for therapy as in previous studies.[3,5] Variation in the definition and the grading of alveolar hemorrhages could be an explanation for the wide range in the frequency of alveolar hemorrhage. As an example, Elshafee et al graded alveolar hemorrhages below 1 cm in the needle tract as Grade 0, because it often occurred based on their prior experience, and was not considered a complication.[5] They reported the complication rate of alveolar

Table 3. Univariate analysis of nonmodifiable and modifiable parameters associated with complications.

	Pneumothorax			Pulmonary hemorrhage			Hemoptysis		
	No	**Yes**	***P* value**	**No**	**Yes**	***P* value**	**No**	**Yes**	***P* value**
Age (years)[a]	65.6 (10.8)	67.7 (9.3)	.361[1]	66.3 (10.3)	65.4 (11.2)	.673[1]	66.2 (10.4)	60.2 (14)	.267[1]
Lesion diameter (mm)[b]	45 (14-134)	36 (10-80)	**.002[2]**	45 (10-134)	36 (17-82)	**.033[2]**	40 (10-134)	26.5 (20-58)	.154[2]
Density (HU)[b]	38.9 (–385-103)	35.4 (–316-50)	.057[2]	38.2 (–385-103)	36.4 (–22-58)	.320[2]	38.2 (10-134)	26.1 (20-41)	.075[2]
Length of needle pathway (mm)[b]	3 (0-60)	28(0-53)	.473[2]	0 (0-53)	27.5 (0-6-)	**<.001[2]**	13.78	33.75	.432[2]
Number of pleura penetration[b]	1 (1-3)	1 (1-4)	.318[2]	1 (1-4)	1 (1-3)	**.024[2]**	1 (1-4)	1 (1-1)	.419[2]
Time of needle across the pleura (min)[b]	3 (1-12)	4 (2-13)	**.013[2]**	3 (1-13)	4 (1-12)	**.037[2]**	3 (1-13)	5.5 (1-8)	.406[2]
Gender			.257[3]			.169[3]			1.0[3]
Male	81 (84.4)	20 (74.1)		73 (85.9)	28 (73.7)		97 (81.5)	4 (100)	
Female	15 (15.6)	7 (25.9)		12 (14.1)	10 (26.3)		22 (18.5)	0 (0)	
Morphology			.753[4]			.841[4]			.685[4]
Solid	80 (83.3)	24 (88.9)		71 (83.5)	33 (86.8)		100 (84.0)	4 (100)	
Subsolid	4 (4.2)	1 (3.7)		4 (4.7)	1 (2.6)		5 (4.2)	0 (0)	
Cavitary	12 (12.5)	2 (7.4)		10 (11.8)	4 (10.5)		14 (11.8)	0 (0)	
Lesion location			**.007[5]**			**<.001[5]**			.133[2]
Peripheral	48 (50)	5 (18.5)		50 (58.8)	3 (7.9)		53 (44.5)	0 (0)	
Central	48 (50)	22 (81.5)		35 (41.2)	35 (92.1)		66 (55.5)	4 (100)	
Lung parenchyma			.176[5]			**.022[5]**			.575[2]
Normal	78 (81.3)	18 (66.7)		61 (71.8)	35 (92.1)		92 (77.3)	4 (100)	
Emphysema	18 (18.8)	9 (33.3)		24 (28.2)	3 (7.9)		27 (22.7)	0 (0)	
Lobar location			.347[4]			.95[4]			.59[4]
Right upper	30 (31.3)	7 (25.9)		25 (29.4)	12 (31.6)		37 (31.1)	0 (0)	
Right middle	2 (2.1)	2 (7.4)		3 (3.5)	1 (2.6)		4 (3.4)	0 (0)	
Right lower	17 (17.7)	6 (22.2)		17 (20)	6 (15.8)		22 (18.5)	1 (25)	
Left upper	20 (20.8)	8 (29.6)		18 (21.2)	10 (26.3)		26 (21.8)	2 (50)	
Left lower	27 (28.1)	4 (14.8)		22 (25.9)	9 (23.7)		30 (25.2)	1 (25)	
Lesion histopathology			.119[4]			.269[4]			.146[4]
Malignant	65 (67.7)	13 (48.1)		50 (58.8)	28 (73.7)		76 (63.9)	2 (50)	
Benign	15 (15.6)	5 (18.5)		15 (17.6)	5 (13.2)		18 (15.1)	2 (50)	

Data are [a]mean (standard deviation) or [b]median (minimum-maximum), or n (%).

[1]*t* test, [2]Fischer's exact test, [3]Man-Whitney U test, [4]Pearson's chi square test, [5]Continuity-corrected chi-square test

Table 3 (cont.). Univariate analysis of nonmodifiable and modifiable parameters associated with complications

	Pneumothorax			Pulmonary hemorrhage			Hemoptysis		
	No	**Yes**	***P* value**	**No**	**Yes**	***P* value**	**No**	**Yes**	***P* value**
Nondiagnostic	16 (16.6)	9 (33.3)		20 (23.5)	5 (13.2)		25 (21)	0 (0)	
Patient position			.249[4]			.525[4]			.485[4]
Prone	60 (62.5)	19 (70.4)		53 (62.4)	26 (68.4)		77 (64.7)	2 (50)	
Supine	28 (29.2)	4 (14.8)		22 (25.9)	10 (26.3)		30 (25.2)	2 (50)	
Lateral	8 (8.3)	4 (14.8)		10 (11.8)	2 (5.3)		12 (10.1)	0 (0)	
Fissure penetration			.02[2]			.0112			1.0[2]
Positive	94 (97.9)	23 (85.2)		1 (1.2)	5 (13.2)		6 (5)	0 (0)	
Negative	2 (2.1)	4 (14.8)		84 (98.8)	33 (86.8)		113 (95)	4 (100)	

Data are [a]mean (standard deviation) or [b]median (minimum-maximum), or n (%).

[1]*t* test, [2]Fischer's exact test, [3]Man-Whitney U test, [4]Pearson's chi square test, [5]Continuity-corrected chi-square test

hemorrhage as 22%, which was a lower rate compared to our study.

The rate of pneumothorax varied in previous studies from between 12-45% and 2-15% of cases required a chest tube replacement.[9,13-15] In our study, a 22% rate of pneumothorax with a 5.7% rate of chest tube replacement was identified. In previous studies, factors increasing the risk of pneumothorax included a smaller lesion size, underlying emphysema, an increased depth of lesion, multiple pleural passes, and fissure punctures. On the other hand increased patient age, patient position, increased time of needle across the pleura, needle entry angle and needle indwelling time had differing results between studies.[4,13-18] Smaller lesion size (<2-3 cm), a higher number of pleural passes, smaller needle entry angle (<75°) and an increased transpulmonary needle-path length were the most frequently reported risk factors for pulmonary hemorrhage.[3,8,12,17,19,20] In the current study, a non-peripheral location of the lesion, smaller lesion size, fissure penetration, and prolonged needle time across the pleura increased the rate of both complications. Soylu et al reported that patient position, gender, and age were not related to the pulmonary hemorrhage rate, which supports our results.[12]

A non-peripheral location of the lesion was the only identified significant risk factor for alveolar hemorrhage and pneumothorax in the logistic regression analyses, which may be explained by the small number of patients. With the increase in the needle pathway, the risk of alveolar hemorrhage increased. This could be explained by the fact that it is difficult to accurately target the lesion if the needle path is longer. Also, the risk of damaging the pulmonary vessels increases with an increased distance of the lung parenchyma crossed by the biopsy needle. So, chances of lung parenchymal damage will be increased if the length of the needle pathway is increased.[9,21-24] The pneumothorax rate increased in non-peripheral lesions once the aerated lung was violated. However, no further increase in pneumothorax rate with increasing needle pathway was observed. There is still conflict about the correlation of pneumothorax rate and length of intrapulmonary path in the literature. Some studies claim that an increase in intrapulmonary path is associated with a higher pneumothorax rate;[15,20,25] whereas other studies showed no significant relationship.[17,18] Choosing the shortest transpulmonary needle pathway may reduce the risk of both pneumothorax and alveolar hemorrhage.[15,17, 26]

Surprisingly, there was no relationship between pneumothorax and emphysema of the underlying lung, in contrast to reports.[11,13,15, 27] The only explanation for this could be the limited number of patients with emphysema in this study, which may have obscured the expected increased risk of pneumothorax. An increased overall pulmonary hemorrhage was observed with underlying emphysema. Because of the lack of effective tamponade by adjacent tissue in emphysematous lung, the hemorrhage rate increased.[28]

In the current study, one patient returned to the emergency service with severe pneumothorax after a week. The complication had not been detected in the post-biopsy CT nor in the control PA-CXR. After chest

tube insertion, the patient was hospitalized for 7 days and discharged without any sequela. We suggest that an additional CXR be obtained at 1 h and 4 h after biopsy in outpatients because studies have shown that a delayed detection of pneumothorax is possible and may require chest tube insertion.[29] However, pneumothorax rarely occurs after 4 h into the follow-up period.[13,30,31] In previous studies, a commonly accepted risk factor for delayed pneumothorax was an upper lobe location of the lesion.[13] In our case, pneumothorax, which actually existed, could not be detected by CXR and may have caused the diagnosis to be delayed, or as in some of the reported cases, a delayed pneumothorax occurred.[13,16]

Patients with smaller non-peripheral, lower density lesions and prolonged puncture time showed a statistically significant increased rate of major complications. With the increased grade of hemorrhage, the major complication rate was also increased. Elshafee et al demonstrated that underlying emphysema, lesion depth from the pleura, and fissure puncture were independent risk factors for major complications.[5] A meta-analysis of core biopsies by Heerink et al found no significant risk factors for overall complications or for major complications.[11]

There are some limitations to this study. First, the limited number of patients made it difficult to obtain statistically significant results, especially in the regression analyses. Lastly, we could not determine the rate of rare complications, such as death, air embolism, and needle tract seeding, which could be explained by two factors: the sample size was not large enough to detect these rare complications and no long-term follow-up was made.

In conclusion, CT-CNLB has an overall complication rate of 46.3% with a 5.7% major complication rate. The most common complications are pneumothorax and pulmonary alveolar hemorrhage. The only identifiable risk factor for alveolar hemorrhage and pneumothorax was a non-peripheral location of the lesion. With an increased needle pathway, the alveolar hemorrhage rate increased. Choosing the shortest possible transpulmonary needle pathway minimizes the risk of complications.

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