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Evaluation of risk factors of diagnostic failure in fine needle biopsy in pulmonary nodules; conventional computed tomography versus computed tomography flouroscopy

Mehmet Kolu[1], Ismail Okan Yildirim[2]

[1]Harran University Faculty of Medicine, Department of Radiology, Sanliurfa, Turkey
[2]Inonu University Faculty of Medicine, Department of Radiology, Malatya, Turkey

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Abstract

Aim of this study was to determine the risk factors of diagnostic failure of o fine needle aspiration biopsy (FNAB) procedures under the guidance of conventional computed tomography (CCT) and CT fluoroscopy (CTF) comparing their diagnostic performance by single operator in pulmonary lesions. Total of 241 patients underwent FNAB procedure (123 CCT guided and 118 CTF-guided). All pulmonary nodules were classified by size (≤10 mm, 11-20 mm, 21-30 mm and >30 mm) and diagnostic yield was calculated according to the lesion size. Independent risk factors for diagnostic performance of CCT and CTF-guided FNAB were determined using multivariate logistic regression analysis. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of CCT-guided FNAB were 88.2%, 100%, 100%, 70%, and 90.7%, respectively. For CTF-guided FNAB were 91.4%, 100%, 100%, 79.4%, and 93.5%, respectively. In multivariate logistic regression analysis, small lesions (OR 1,096; 95% CI, 1.045-1.148 p<0.001) and lesions without pleural contact (OR 1.661; 95% CI, 1.414-1,951 p<0.001) were found to be significant independent risk factors for CCT-guided FNAB procedure. No independent risk factor was determined for CTF-guided FNAB. Small nodule size and lack of contact with pleura are independent risk factors associated with diagnostic failure and may decrease diagnostic accuracy of CCT Guided FNAB. However, real-time imaging capability of CT fluoroscopy increases diagnostic accuracy in difficult pulmonary nodules.

Keywords: Computed tomography fluoroscopy, conventional computed tomography, fine needle aspiration biopsy, Pulmonary Nodule

Introduction

Management of suspicious pulmonary lesions requires imaging guided biopsy in many clinical senarious. Bronchoscopic biopsy works commonly in central lesions visible through airways [1]. Percutaneous approach has been done under ultrasonography (US) or computed tomography (CT) guidance. Only pleura based or neighbouring lesions are sampled undersonography which has the ability of real time, quick and radiation-free guidance [2]. CT has been preferred in the rest of lesions offering high diagnostic rates. CT presents advantages including high spatial resolution and low complication rates in experienced hands [3]. Conventional CT (CCT) can not provide real time assesment during needle insertion; this disadvantage brings diffulty in deep lesions, oblique accesses, movements related respiration which leads long procedure period and radiation exposure for patients. Computed tomography floroscopy (CTF) as a newer technique, has been used for last two decades which supplies reconstructed CT images rapidly [4]. From this perspective, availability of real-time imaging during access to the target lesion, lower number of pleural passages and improved respiratory motion compensation in small nodules has increased the importance of CTF guided needle biopsy [5-9]. Besides this radiation exposure during CTF is an apparent hazard for both patients and particulary scattered radiation to the interventional radiologist in comparison with conventional fluoroscopy and CCT [10].

In the past, discrete studies have been held regarding CCT [5-9], or CTF guided lung biopsy [11,12] which gave promising results on the diagnostic yield and safety. There were only a few ones which put forth a comparison between CCT and CTF [3,9].

In this study CCT and CTF guided lung biopsy techniques were evaluated within a large and consecutive selected cohort of patients done by the same interventional radiology (IR) team. Authors aimed to directly compare the diagnostic performance and complication rates of these two techniques retrospectively.

Material and Methods

Patients

This retrospective study was approved by the institutional Review

***Coresponding Author:** Mehmet Kolu, Harran University Faculty of Medicine, Department of Radiology, Sanliurfa, Turkey
E-mail: drrdylg@gmail.com

Board of our institution. A written informed consent was obtained from each patient.

The patients were divided into two groups as patients undergoing CCT-guided and CTF-guided fine needle aspiration biopsy (FNAB). There were 123 patients (93 males, 30 females) underwent CCT-guided FNAB (mean age: 64.68±11.43 years) and 118 patients (91 males, 27 females) underwent CTF-guided FNAB (mean age: 64.51±10.71 years).

FNAB Technique

Patients whom had normal platelet count and activated thromboplastin time within the last one week underwent the procedure. Acetylsalicylic acid, clopidogrel, and warfarin were discontinued one week before the procedure. Patients who required continuous anticoagulation received IV heparin instead of warfarin, and patients who received acetylsalicylic acid or clopidogrel were switched to subcutaneous low molecular-weight heparin injections.

All FNAB procedures were performed by the same IR team consisted of two interventional radiologist which had 10 years (İOY) and 3 years (MK) experience. The patients were placed in prone, supine or lateral position depending on the localization of the lesion. The entry site for biopsy was chosen to reach perpendicularly to the lesion, through the aerated lung tissue for the shortest distance, avoiding bullous and emphysematous regions, inter-lobar fissures, and visible bronchi (Figure 1). None of the patients received sedatives. After sterilization of the entry site, 5-10 cc of prilocaine 2% solution was administered subcutaneously. All biopsy procedures were performed using 19-gauge outer coaxial guide needle that was 10 or 15 cm long and a 22-gauge inner Chiba aspiration needle that was 15 or 20 cm long (Argon, USA) and using coaxial technique. Specimens were immediately placed on slides. If present, tissue fragments were collected from the slide or the syringe, immersed in 10% formalin solution for the cell blocks, and sent to the cytologist. Since an on-site cytopathologist was not routinely available, decisions for additional sampling were based on visual inspection of the adequacy of the specimen by the operator.

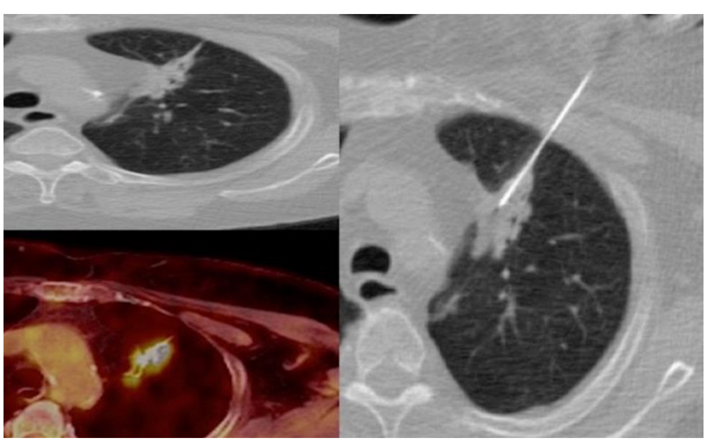

Figure 1. During the biopsy, it was avoided to injure important structures such as bronchioles with a needle (black circle)

In CCT (Aquillion 64 MDCT, Toshiba, Japan)-guided FNAB procedure, scout film was obtained using radio-opaque grid to mark the chest wall and the appropriate site of entrance to the lesion was determined over the acquired images. Technical parameters during CCT-guided biopsy were 120mAs, 100 kV, and slice thickness of 5 mm.

In CTF-guided FNAB procedure (256 MDCT Somatom, Siemens, Germany), localization was determined by using the CTF gantry lights and the grid on the patient's skin. Fluoroscopic images were visualized on a split screen displaying three images showing center of the lesion and sections 5-mm superior and inferior to the center of the lesion. Fluoroscopic images were then acquired with short intervals and the target lesion was reached. CT parameters during fluoroscopic biopsy procedure were as follows: scanning speed of 0.75 sec per rotation (360°), 120-kV tube voltage, 30-mA current and 5-mm collimation.

After specimen acquisition control CT was obtained for all complications. Needle was discharced in the end of process, after management of complications. After procedure the patient was placed in puncture-site-down position and were administered oxygen 2 L/sec via nasal cannula and the patients were closely monitored with heart rate, respiratory rate, blood pressure, and oxygen saturation monitorization. Control chest x-ray was obtained after three hours.

Lesion Characterization

Maximal diameters were measured in all pulmonary lesions. In addition, the lesions were grouped according to their sizes (≤10 mm, 11-20 mm, 21-30 mm and >30 mm). The distance between pleura - lesion and the distance between skin - lesion were recorded. The position of the patient during the puncture, lung lobe in which the lesion was located, the relation of the lesion with pleura, and the number of pleural passes were recorded in two groups.

Evaluation of Diagnostic Yield

Biopsy results were classified malignant, benign or non-diagnostic. Non-diagnostic result meant inadequate cells and small number of atypical cells determined by a cytologist. Malignant nodule was diagnosed after examination of the surgical specimen, nodules showing enlargement and showing shrinkage after initiation of chemotherapy, and nodules in patients with new metastatic foci were considered in final diagnosis. Benign nodul was diagnosed if examination of the surgical specimen showed benign findings, nodule size decreased even if anticancer therapy was not administered; nodule size remained unchanged for at least 12 months. Positive and negative biopsy results were classified as true-positive, false-positive, true-negative or false-negative depending on malignant or benign test results in the final diagnosis. Specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of FNAB procedure in diagnosing malignancy were calculated.

Statiystical analysis

Patient characteristics such as age and gender, and lesion characteristics such as lesion size and localization in the lung were compared for the two methods. Procedure-related features included distance pleura-lesion and skin-lesion, and the number of pleura passage.The risk factors for diagnostic failure were separately calculated for CCT-guided and CFT-guided FNAB procedures. In order to determine independent risk factors for diagnostic failure, the results in all lesions were grouped as diagnostic success (true-positive, true-negative results) and diagnostic failure (non-diagnostic, false-positive and false-negative). Numeric values of diagnostic success and diagnostic failure for CCT and CTF were evaluated in univariate analysis using student's t test. Fisher's exact test was used to analyze categorical variables. Multivariate logistic regression analysis was performed to determine independent risk factors for variables that showed significant difference. The category with the lowest risk associated with diagnostic failure as indicated by the univariate analysis was used as the reference. An odds ratio (OR) >1.00 indicated high probability of diagnostic failure. A p value less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS 15 software (SPSS Inc., Chicago, IL, USA).

Assessment of Complications

Patients with pneumothorax detected on chest CT obtained shortly after the procedure was either followed or air aspirated via coaxial needle. If pneumothorax improved on 3th hour control CT or patient was sypmtomathic, the chest tube was placed. Patients who developed hemoptysis within 3 hours after the procedure, had followed up 24 hours with laboratuary tests and clinical signs. Management of patients were done according to continuity of symtoms and control CT findings.

Results

Baseline properties fort he CCT and CTF groupd were presented in Table 1. Mean age of two groups ± standard deviation (SD) and distrubition of gender were similiar in both grops ($p>0.05$). The data of lesion characterization and procedure details were listed in Table 1. The number of lesions in subgroups in terms of lesion sizes were not statistically different in two groups ($p>0.05$). When positions of patient during the procedure compared, pron and supin positions were the same in each group however lateral position was selected once in only CTF group. Target lesion details including pleura-lesion length, skin-lesion length, pleural contact status, localization of lobe, procedure positioning and number of pleural passages did not significantly differ between the groups ($p>0.05$) (Table 1).

Table 1. Characteristics of Patients and Lesion

Characteristics	CCT (n= 123)	CTF (n=118)
Sex		
Male	93	91
Female	30	27
Age $_{\text{Mean} \pm \text{SD}}$	64.68 ±11.43	64.51±10.71
Lesion Size $_{\text{Mean} \pm \text{SD}}$		
≤ 10 mm	n=12 9.25 ± 0.62	n=12 9.11 ± 0.54
11-20 mm	n= 24 16. 79± 2.53	n=28 16.29± 2.12
21-30 mm	n=30 25.93±3,04	n=37 25.67±2.32
>30 mm	n=57 49.83±13.33	n=41 48.26± 14.25
All	33.40 ±18.26	29.89±16.94
Pleura-Lesion Leght (mm) $_{\text{Mean} \pm \text{SD}}$	15.39±14.73	13.63±12.45
Skin- Lesion Leght (mm) $_{\text{Mean} \pm \text{SD}}$	56.70±19.45	52.68±15.46
Contact with pleura (Yes/ No)	39/74	35/83
Lobe		
Upper /Middle / Lower	40 / 33/ 50	39 /21 /58
Procedure Positioning (Prone/ Spine /lateral)	63 / 38/ 22	61 /38 /19
Pleural passes (1/2/3)	99 /18/ 6	111 /5 /0

Diagnostic Performance

Final diagnosis was malignancy in a total of 167 patients (CCT=85; CTF=82), and of these patients, 79 (CCT=35; CTF=44) were diagnosed with malignancy in the examination of surgical specimen, 20 (CCT=12, CTF=8) had a previous diagnosis of malignancy in addition to histologic findings suspected for malignancy, 68 (CCT=38; CTF=30) post procedural clinical course was consistent with an obvious malignant process (showed increased lesion size or shrinkage after chemotherapy and were found to have new metastatic foci).

Final diagnosis was benign in a total of 50 patients (CCT=23; CTF=27), and of these patients, 7 (CCT=3; CTF=4) were diagnosed with benign in the examination of surgical specimen, 40 (CCT=18; CTF=22) had consistent histologic findings and showed decrease in lesion size after conservative therapy and had matched culture results, and 3 (CCT=2; CTF=1) ,for at least 12 months, showed no change in the lesion size. The numbers of non-diagnostic results were24 (CCT=15; CTF=9).

Of all the 17 false-negative biopsy specimens, inflammation was reported 8 in CCT group and 7 in CTF group showed reactive epithelial cells and 2 had benign bronchial cells. Of these patients, 13 underwent additional biopsy procedure (n=5, FNAB; n=8, core biopsy), and 4 of them were operated. The final diagnosis were yield respectively (n=7, adenocarcinoma; n=5, squamous cell carcinoma; n=3, metastasis; n=1, lymphoma, n=1 mesothelioma).

Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of CCT-guided FNAB in the diagnosis of malignancy were 88.2%, 100%, 100%, 70%, and 90.7% respectively. Sensitivity, specificity, PPV, NPV, and diagnostic accuracy of CTF-guided FNAB in the diagnosis of malignancy were 91.4%, 100%, 100%, 79.4%, and 93.5% respectively. Diagnostic yields of CCT- and CTF guided FNAB procedures according to lesion size were presented in Table 2 and 3.

Table 2. Diagnostic Yields According to Conventional CT FNAB

			Size of Pulmoner Nodules		
Lesion Size	**True-positive**	**True-negative**	**False-positive**	**False-negative**	**Nondiyagnostic**
≤ 10 mm	3	1	0	2	6
11-20 mm	11	6	0	3	4
21-30 mm	17	8	0	2	3
>30 mm	44	8	0	3	2
All	75	23	0	10	15
	Sensitivity%	**Sensitivity%**	**PPV %**	**PPV %**	**Accuracy %**
≤ 10 mm	60	100	100	33.3	66.6
11-20 mm	78.5	100	100	66	85
21-30 mm	89.4	100	100	80	92.5
>30 mm	94.5	100	100	72.7	94.5
All	88.2	100	100	70	90.7

Table 3. Diagnostic Yields According to CT Fluoroscopy FNAB

			Size of Pulmoner Nodules		
Lesion Size	**True-positive**	**True-negative**	**False-positive**	**False-negative**	**Nondiyagnostic**
≤ 10 mm	7	2	0	1	2
11-20 mm	14	8	0	2	4
21-30 mm	23	9	0	3	2
>30 mm	31	8	0	1	1
All	75	27	0	7	9
	Sensitivity%	**Sensitivity%**	**PPV %**	**PPV %**	**Accuracy %**
≤ 10 mm	87.5	100	100	66.6	90
11-20 mm	87.5	100	100	80	91.6
21-30 mm	88.4	100	100	75	91.4
>30 mm	96.8	100	100	88.8	97.5
All	91.4	100	100	79.4	93.5

Risk Factors Associated With Diagnostic Failure

There were 75 true-positive and 23 true-negative results in diagnostic success subgroup (n=98) and there were 10 false-negative and 15 non-diagnostic results in the diagnostic failure subgroup in the overall CCT-guided FNAB group

There were 75 true-positive and 27 true-negative results in the diagnostic success subgroup (n=102) and there were 7 false-negative and 9 non-diagnostic results in the diagnostic failure subgroup in the overall CTF-guided FNAB group.

In univariate analysis, small nodule size, distance of the lesion to pleura, number of pleural passages, and lack of pleural contact were significant risk factors for diagnostic failure in CCT-guided FNAB procedure. In multivariate logistic regression analysis, small lesion size (OR: 1.096, 95% CI:1.045-1.148, $p<0.001$) and lack of pleural contact (OR:1.661, 95%CI:1.414-1.951, $p<0.001$) appeared as significant independent risk factors. For CTF-guided FNAB procedure, only distance of the lesion to the pleura was found to be a significant risk factor in univariate analysis; however, this parameter did not appear as a significant independent risk factor in multivariate logistic regression analysis (OR:0.956, 95%CI:0.917-0.995, $p<0.001$). Age, gender, skin-lesion distance, lobar localization, position of the patient during the procedure did not significantly differ between diagnostic success and diagnostic failure groups in both groups ($p>0.05$).

Complications

Among 123 CCT-guided FNAB patients, 28 (% 22.7) of them revealed pneumothorax on chest CT obtained immediately after the procedure and manual air aspiration through coaxial needle was done in 5 of patients, while 9 (%7.3) of them required chest tube placement. In 118 CTF-guided FNAB cohort, 17 (%14) of them revealed pneumothorax. For treatment 8 of them was aspirated manually, chest tube was placed in 4 patients (%2.5) in this group. Hemopthysis developed in a total of 9 (CCT=6, CTF=3) patients, none of them need treatment. Air embolus was not detected in any of patients.

Discussion

This study provides a direct comparison of diagnostic yield and safety of CCT to CTF guided lung biopsies using cases performed by the same IR team. CTF gained better over all diagnostic performances than CCT guided FNAB. Sensitivity and diagnostic accuracy of CCT were 88.2% and 90.7% while sensitivity and diagnostic accuracy of CTF were 91.4% and 93.5% respectively.

Diagnostic performances of CCT showed improvement in relation with sizes but they did not affected in CTF. In smaller than 10 mm lesions CTF revealed remarkable higher diagnostic values of sensitivity and diagnostic accuracy (87.5%, 90%) against CTT group (60%, 66.6%) (table 2-3). Small nodule size and lack of contact with pleura were independent risk factors associated with diagnostic failure in CCT guided FNAB group while CTF technique did not affected from any of these.

Many factors including lesion characteristics, biopsy method and variations in the biopsy needles affect the outcomes of a biopsy procedure. Using cytological assessments in FNAB samples, most studies have reported a diagnostic accuracy in a wide range from 67 to 98% [11-16]. Although variation in diagnostic performance of biopsy procedures has been considered to be associated with lesion characteristics and biopsy method, no particular assessment has been made on the effects of operator experience while evaluating diagnostic performance of biopsy procedures. That said, operator experience is indeed supposed to affect diagnostic accuracy and complication rates in FNAB procedure. All studies cited in the current manuscript that evaluated diagnostic accuracy and complication rates in FNAB procedure have used multiple operators and there are a limited number of studies in the literature in this regard. We consider that CCT and CTF-guided FNAB procedures performed by a single operator would be more valuable in evaluating respective efficacy of the two methods.

From this point of view, the present study determined nodule size and lack of contact with pleura as significant independent risk factors in CCT-guided biopsy performed by the operator after diagnostic failure; however, no significant risk factor was determined for CTF-guided biopsy procedure. The fact that the risk factors of nodule size and contact of the lesion with pleura in CCT-guided procedure did not appear as a risk factor for CTF-guided procedure suggests that CTF-guided biopsy procedure may be less operator-dependent compared with CCT-guided biopsy procedure. The level of diagnostic performance achieved in the study by Choi et al. using CCT-guided biopsy procedure could only be reached in the present study in CTF-guided biopsy procedure arm and the authors think that their results could be attributed to the level of operator experience [17]. In that, although CCT FNAB technique has been standardized, we suggest that the procedure may be operator-dependent particularly in small-sized nodules.

In a prospective study by Kim et al. sensitivity was 95.3% and accuracy was 96.7%, for CCT-guided and was 97.8% and 98.4% CTF-guided FNAB procedures [9]. In a similar study conducted by Prosch et al. sensitivity was reported to be 95.5% and 95.9%, and accuracy was reported to be 96.7% and 95.5% for CCT-guided and CTF-guided biopsy procedures [15]. Heck et al. reported sensitivity of 95% and 98%, and diagnostic accuracy of 93% and 95% for CCT-guided and CTF-guided cutting needle biopsy procedures, respectively [3]. No remarkable difference was found in overall sensitivity and diagnostic accuracy results of CCT and CTF-guided biopsy procedures in this study. The present study also did not find significant difference in sensitivity and diagnostic accuracy between CCT-(88.2%, and 90.7%), versus CTF-guided (91.4% and 93.5%) procedures in all lesions.

Some studies that compared diagnostic performances in large and small nodules have reported diagnostic accuracy ranging from 96% to 66% for CCT-guided FNAB procedure in large nodules, and diagnostic accuracy was reported to be lower with decreasing lesion size [18-20]. On the other hand, Choi et al. reported high diagnostic performance in a study (which was the largest study to our knowledge ever conducted using CCT-guided FNAB procedure in lesions ≤10 mm in size) with a sensitivity of 89.2%, specificity of 100%, and accuracy of 93.4% for malignancy [17]. When all lesions were evaluated according to their sizes (11-20mm, 21-30 mm and >30 mm), CCT-guided FNAB procedures in lesions ≤10 mm yielded low sensitivity (60%) and diagnostic accuracy (66.6%). The number of failed nodules was also higher among nodules ≤10 mm (non-diagnostic=6, false-negative=2). Sensitivity and diagnostic accuracy for CTF guided FNAB procedure in the same nodule size were 87.5% and 90%, and there was a significant improvement in diagnostic performance in lesions ≤10 mm when compared with the results of CCT-guided FNAB. Yamagami et al. reported sensitivity of 86.6% and diagnostic accuracy of 92% in CTF-guided FNAB procedures performed in pulmonary nodules ≤10 mm, and their results are similar to those obtained for CTF-guided FNAB procedure in this study [5]. On the other hand, diagnostic performances of CCT- and CTF-guided FNAB procedures in lesions measuring 21-30 mm and >30 mm were high in the both groups (Tables 2 and 3).

During CCT-guided FNAB procedure, the authors of the present manuscript have encountered several challenges in small-sized nodules (≤10 mm, 11-20 mm) such as subpleural location of the nodule, lack of direct route due to masking scapula and rib, and lesion mobility with respiration in lesions closely located to the diaphragm. We used tangential approach in some patients, which require advanced experience. Even though the lesions were reached despite the mentioned difficulties, the operator had to reposition the needle during aspiration . We consider that such circumstances have decreased our diagnostic performance in small-sized nodules.

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We, however, felt more comfortable in easily accessing the target lesion intermittently using real time imaging in small nodules in the guidance of CTF. Sufficient amount of specimen could be obtained safely particularly from lesions located adjacent to the aorta (Figure 2). On the other hand, high doses of radiation are the most significant disadvantages for the patient, as well as for the operator, in CTF-guided FNAB procedure [9,15,21]. Lack of a significant difference between diagnostic performances of the two methods in lesions >20 mm and high radiation exposure in CTF-guided biopsy are reasons for the preference of CCT-guided procedure by the operator in large nodules.

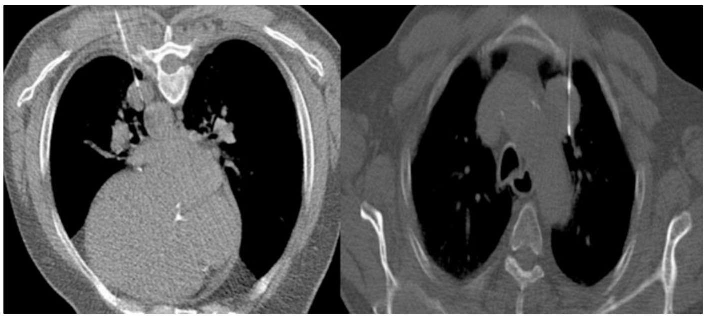

Figure 2. Safe insertion of biopsy needles into lesions adjacent to the aorta

Percentages of complications after these two tecniques were acceptable. We have documented pneumothorax in 22.7% of CCT and in 14 % of CTF groups which did not have significant difference ($p<0.05$) those were closer to percentages in Kim et al's study; 27.1% as for CTT versus 11.1% for CTF. Difference complication rates among techniques were attributed to lower number of pleural passes in CCT than CTF previously [9].

Pneumothorax rates of both procedure was fewer than previous studies such as Heck et al (%38 for CCT and %26 for CTF) that may be related smaller size of needles we used [3]. The percentages of cases that required chest tube placement was 7.3% in CCT and 2.5% CTF group which did not have significant difference. From another study with %16 pneumothorax [6] and %18 pneumothorax [11] with a rate of chest tube placement 7 % were documented in CTF studies. The number of patients which presented hemopthysis were 6 among CCT and 3 among CTF both were limited clinically in our study.

The limitations of the study were being retrospective manner, unavailability of an on-site pathologist to evaluate adequacy of the specimen during FNAB procedure and small number of pulmonary nodules measuring ≤10 mm. Because of CTF biopsies were done during more recent years as a more experienced period for IR team, patient selection bias was present. Prospective and randomized patient selection should avoid this bias.

Conclusion

In conclusion, we found better overall diagnostic performances and post procedurel complications in CTF than CCT guided FNAB technique. For smaller lesions, CTF revealed marked higher diagnostic performances than CCT. In addition small nodule size and lack of contact with pleura are independent risk factors associated with diagnostic failure and may decrease diagnostic accuracy of CCT guide FNAB. Real-time imaging capability of CTF increases diagnostic accuracy in difficult pulmonary nodules. In other words small sized or difficult (no contact with pleura/far from pleura) lesions should be candidates for CTF guided biopsy in order to yield high diagnostic performance and safety despite higher radiation rates.

Conflict of interests

We declare that we have no conflict of interest.

Financial Disclosure

This study received no financial support.

Ethical approval

This retrospective study was approved by the institutional Review Board of our institution.

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