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Accuracy of Fine Needle Aspiration (FNA) in Comparison to Tru-Cut Biopsy in Diagnosis of Bronchogenic Carcinoma

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Summary

Bronchogenic carcinoma is one of the leading causes of death worldwide. Histopathological investigations using tru-cut or FNA reveal the tumor subtype of the bronchogenic carcinoma which is needed for treatment planning. We aimed to evaluate the diagnostic accuracy of fine-needle aspiration (FNA) technique as compared with the tru-cut technique in the diagnosis of bronchogenic carcinoma. We conducted a cross-sectional study at the Radiology unit in Al-Sader Medical City in Al-Najaf province during the period (January 2019 to January 2020), included 100 Iraqi patients with bronchogenic carcinoma aged 40-90 years. Tru-cut tissue biopsy and FNA samples were collected from all cases and then sent for two different laboratories for subtyping . Our study revealed that definite FNA/ Tru-cut matching was seen in (81%) of cases, with a sensitivity of 96.34%, specificity of 100. %, and a diagnostic accuracy of 96.7%. In conclusion, fine needle aspiration technique is safe diagnostic procedure with considerable sensitivity, specificity and diagnostic accuracy, with minimal subsequent complications, and can be trusted for diagnosis of bronchogenic carcinoma subtypes.

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1 INTRODUCTION

Lung cancer also called (bronchogenic carcinoma) is one of the most frequently. It is the leading cause of cancer related mortality in the world. The two main types are small-cell lung carcinoma (SCLC) and non-small-cell lung carcinoma (NSCLC). Worldwide Lung cancer is associated with high incidence of morbidity and mortality . It is the leading cause of cancer related mortality in the world with 5-year survival rate 17% after diagnosis. Actually, poor prognosis occurred in many patients, owing to being diagnosed at a late stage (1-6). In Iraq and according to the Iraqi cancer registry 2018, lung cancer occupied the second from top ten cancers in Iraq (2123) new cases were recorded 8.4 % of the total population). It is classified as the first famous cancer in male (1573) cases with percentage 13.9 %) and the fifth famous type of cancer in female (550 case 3.9 %) (7). There are many risk factors have a role in the etiology of lung cancer including Tobacco where approximately 85% of cases of lung cancer are directly associated with smoking (5). Exposure to radon gas, exposure to asbestos, Air Pollution, Genetic factors, Race and Ethnicity , older Age , Family history, diet contributes as the risk for approximately 30% of all cancers, Infection such as human papilloma virus , human cytomegalovirus (CMV) (8), measles virus (9) and Chlamydia pneumonia (10). Different diagnostic tests, procedures and techniques are available for diagnosis of lung cancer include imaging (11) , Sputum Cytology (12). Tissue Sample (biopsy), Needle Biopsy or Needle Aspiration (13). Transthoracic tru-cut tissue biopsy (14).Mediastinoscopy (15) , Thoracoscopy (16) and Bronchoscopy in addition to Laboratory Tests of Biopsy Samples like immunohistochemical and Molecular Tests (17-19) . Fine-needle aspiration (FNA) and Tru-cut biopsy are parts from several interventional procedures that needed to reach the final diagnosis (20, 21). Indication of FNA and / or Tru-cut biopsy include patients need starting chemotherapy and/or radiotherapy or a noncancerous lesion is strongly suspected, or patients need confirmation of cancer before surgery or if metastasis is a high likelihood (22). The major limitation of these interventions is the possibility of pneumothorax especially when parenchyma lies in the path of the needle (10%–35% overall). In addition, bleeding (5%), pain and death (0.15%) are other complications (20,23). The contraindications of these

interventions include limited pulmonary reserve, (20). However, accuracy of a diagnostic test is crucial in treatment planning and outcomes.

2 | PATIENTS AND METHODS

This was a cross sectional prospective study of 100 patients presented with suspected LC lesion (discovered previously by CT-scan examination), and referred for radiology department to do tru-cut biopsy. This study conducted in the radiology department in Al-Saddir medical city /Al-Najaf / Iraq during the period from January 2019 to January 2020.

The study involved patients presented with a suspicious lung mass while exclusion criteria involve all patients with contraindications to biopsy (such as patients with bleeding tendencies, severely dyspneic patients, severely ill patients) and patients with diagnosis other than bronchogenic carcinoma (such as lymphoma, metastasis, etc..).

Data were collected using statement of questioner for each patient included general demographic data, age, gender, history of smoking, occupation, history of TB, history of the present illness (cough, hemoptysis, dyspnea) supported by Ct-scan report mentioning suspicious lung mass to be malignant.

Specimens were collected according to the standard methods . After localizing the exact position by CT-scan exam or under ultrasound exam the measurement of the site and the angle of the entry of the needle (coaxial tru-cut gauge 20×150 mm), path of the needle and the distance between the skin and the lesion on the CT-scan monitor or ultrasound screen. Choosing site of the shortest distance to the mass with less lung tissue in the path of the needle by labeling the site of entry, the patient position was supine, prone or lateral according to the location of the lesion, the skin surface was cleaned with povidone-iodine, and then true cut biopsy needle was introduced through small skin incision approach localizing the exact position by CT-scan or ultrasound machine. Following the placement of the needle, CT-scan slice was taken to ascertain whether the tip was within the mass, the biopsy was obtained by firing of the needle within the mass by three to four trial and the tissue gained will be kept in solution of formalin 10% container and sent for histopathological study then taking specimens for FNA is done by passing the FNA needle (gauge 22× 3.5 inch) through the same path and follow the same steps to make sure that the sample from the mass, then performing up to 10 to-and-fro needle movements per

pass to obtain the mass lesion, the aspirate from the needle will be put on slides kept within alcohol container and sent for cytology in different lab. If the patient is not developed a complication immediately (hemorrhage or pneumothorax). The patient will be kept under observation for 2 hours to be sure of not developing this complication lately. The results of tru-cut histopathology considered as the final diagnosis. Reports of cytology with malignant cells and Presence of highly suspicious tumor cells was used to describe the samples as positive findings. Smears with no malignant tumor cells or only a small quantity of cells with nuclear atypia were regarded as negative findings. The classification of positive samples was conducted according to the 2015 WHO classification criteria of lung cancer. All the cases were diagnosed by two different labs and two experienced pathologists.

Statistical analyses were performed using IBM SPSS software version 21.0 for windows. Inc. Quantitative data were expressed as number and percentage, while continuous numerical data were presented as Mean ± SEM. Chi-square ($\chi 2$), Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value and diagnostic accuracy were also applied for categorical data. In all tests, $P \leq 0.05$was considered statistically significant.

3 | RESULTS

The present study involved 100 as total patients that are included as bronchogenic carcinoma cases. Their age group ranged between (40-90) years including 70 males and 30 females. Highest frequency of bronchogenic carcinoma reported in the age groups (61-70) and (71- 80) , (46%) and (25%) respectively, on the other hand, Results revealed that highest frequency of lung cancer recorded for 31:64 (48.4%) of squamous cell carcinoma, and 15:35 (42.9%) of adenocarcinoma cases that were related to the patients of 61-70 years age group, followed by cases of the 71-80 age group that include 9:35 (25.7%) of adenocarcinoma cases, 15:64(23.4%) of squamous cell carcinoma and 1:1 case of small cell carcinoma, (Table 1). The majority of bronchogenic carcinoma cases , (70%) were males with a mean age of 67.54 female cases had a mean age of 63.70. The male to female ratio was 2.3:1. (Table 2). Results revealed 47 cases (67.14%) of squamous cell carcinoma subtype, and adenocarcinoma subtype that comprise 23

cases (32.86 %) of bronchogenic carcinoma cases were from males population, while 17 cases (56.7%) of squamous cell carcinoma subtype, adenocarcinoma subtype that comprise 12 cases (40 %), and only one small cell carcinoma case (3.3%) were related to females population (Table 3). However, the results were not significant , p >0.05. The majority of bronchogenic carcinoma cases (82 %) had positive history of smoking, of them (68.3%) with squamous cell carcinoma subtype, and (31.7%) with adenocarcinoma subtype, (P. value < 0.05, significant) (Table 4). Among the studied group, 60 cases (60%) of urban and 40% of rural residence, of them 66.7% and 60%, respectively, had squamous cell carcinoma followed by adenocarcinoma subtype that comprise (40%) and (31.7%) from rural and urban areas respectively, while one small cell carcinoma case only (1.6%) was from urban population However, the result is not significant , p > 0.05. The histopathological results of Tru-cut biopsy of study samples showed that 64 (64%) were squamous cell carcinoma, 35 (35%) cases were adenocarcinoma and only one case (1%) was small cell carcinoma. While no diagnosis was seen for large cell carcinoma in this study(Table 5).

The FNA biopsy results were seen in 92 samples out of 100 (92%), with malignant cells, including 35 patients (35%) were diagnosed as adenocarcinoma, 56 patients (56%) were diagnosed as squamous cell carcinoma, one case of small cell carcinoma that comprise 1% of the total cases, 8 cases showed non-malignant tumor cells, (Table 6). The matching between FNA and tru-cut biopsy were significant at $p \leq 0.05$, with a sensitivity of 96.34%, specificity of 100. %, Positive Predictive Value of 100%. %, Negative Predictive Value of 70.89 % and diagnostic accuracy of 96.7%. Results were revealed that definite FNA/ Tru-cut matching (Positive matching) was seen among 81 cases (81%), while the negative matching (non-diagnostic) were recorded for 19 cases (19%) included in our study (Figure 1). Definite diagnosis was recorded for 29 cases (35.8%) samples of adenocarcinoma cases, 51 cases (62.96%) of squamous cell carcinoma and single case of small cell carcinoma (1.24%). No matching of Tru cut/ FNA were recorded for 6:19 cases (31.6%) of adenocarcinoma cases, 5:19 cases (26.3%) of squamous cell carcinoma and 8:19 (42.1%) of non-malignant cases. (Table 7). This study revealed that 8:100 (8%) patients were developed mild pneumothorax after biopsy collection, 2 of them needed hospitalization for 24-48 hours with chest tube insertion.

Table 1. Bronchogenic carcinoma subtypes according to the age groups

Age groups	No. of cases	Adenocarcinoma	squamous cell carcinoma	Small cell carcinoma
40-50	14	5 (14.3%)	9 (14.1%)	0 (0%)
51-60	11	5 (14.3%)	6(9.4%)	0 (0%)
61-70	46	15 (42.9%)	31(48.4%)	0 (0%)
71-80	25	9 (25.7%)	15(23.4%)	1(100%)
90-81	4	1 (2.8%)	3(4.7%)	0 (0%)
Total	100	35	64	1 (1.0%)

Table 2. The mean ages for the gender of study samples

Gender	No. of cases	Age Mean ± SEM
Males	70	67.54 ± 1.16
Females	30	63.70 ± 2.11
Total	100	66.39 ± 1.04

Table 3. Distribution of bronchogenic carcinoma subtypes according to gender

Bronchogenic carcinoma Type	No. of cases	Male	Female
Adenocarcinoma	35.0	23 (32.86%)	12 (40%)
squamous cell carcinoma	64.0	47 (67.14%)	17 (56.7%)
Small cell carcinoma	1.0	0.0	1 (3.3%)
Total	100.0	70	30
P. value > 0.05, not significant			

Table 4. The correlation of bronchogenic carcinoma with smoking history

Bronchogenic carcinoma Type	No. of cases	Smoking +ve	Smoking -ve
Adenocarcinoma	35.0	26 (31.7%)	9 (50%)
squamous cell carcinoma	64.0	56 (68.3%)	8 (44.4%)
Small cell carcinoma	1.0	0 (0%)	1 (5.5%)
Total	100.0	82	18

Table 5. Distribution of bronchogenic carcinoma cases according to demographic distribution.

Bronchogenic carcinoma Subtypes	No. of cases	Rural	Urban
Adenocarcinoma	35.0	16 (40%)	19 (31.7%)
Squamous cell carcinoma	64.0	24 (60%)	40 (66.7%)
Small cell carcinoma	1.0	0 (0%)	1 (1.6%)
Total	100.0	40	60

Table 6. Tru-cut and FNA diagnostic positivity of bronchogenic carcinoma subtypes presented by number and percentage.

Bronchogenic carcinoma Subtypes	Tru-cut	FNA
	No. of cases (%)	No. of cases (%)
Adenocarcinoma	35 (35%)	35 (35%)
squamous cell carcinoma	64 (64%)	56 (56%)
Small cell carcinoma	1 (1%)	1 (1%)
Non malignant	0 (0%)	8 (8%)
Total	100	100

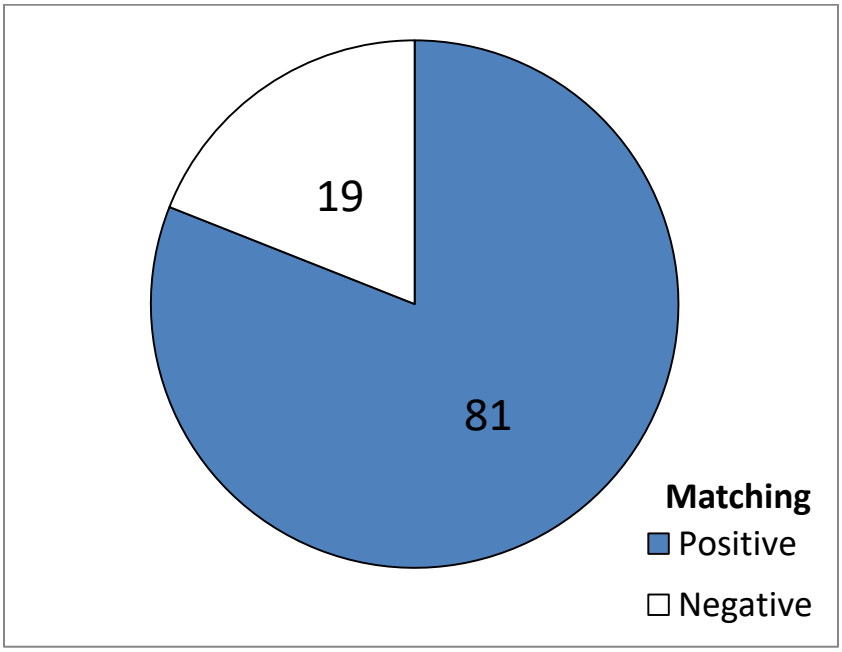

Figure 1. Total FNA/ Tru-cut positivity matching of bronchogenic carcinoma cases

Table 7. Frequency of FNA /Tru-cut diagnostic positivity matching according to bronchogenic carcinoma subtypes

Bronchogenic carcinoma subtypes	No. of cases	FNA/Tru-cut Matching %	
		Positive matching	Negative matching
Adenocarcinoma	35	29 (35.8%)	6 (31.6%)
squamous cell carcinoma	56	51 (62.96%)	5 (26.3%)
Small cell carcinoma	1	1 (1.24%)	0 (0%)
Non malignant	8	0 (0%)	8 (42.1%)
Total	100	81	19

4 | DISCUSSION

Bronchogenic carcinoma is one of the most frequently diagnosed cancers and is the most common cause of cancer-related death worldwide (1,2). Treatment options have expanded considerably in recent years, and now include surgery, radiation therapy, chemotherapy, targeted therapy, and immunotherapy (24). Fine-needle aspiration (FNA) and Tru-cut biopsy are parts of several diagnostic procedures that needed to reach the final diagnosis. Our study was planned to evaluate the results of FNA (ultrasound guided and CT guided) in diagnosis of bronchogenic carcinoma in comparison to Tru-cut biopsy and to assess the accuracy, sensitivity, specificity, PPV and NPV of FNA in the diagnosis of bronchogenic carcinoma lesions.

Results of this study showed that the highest frequency of bronchogenic carcinoma cases within age group (61-70) and (71- 80) than other groups, with a percentage of (46%) and (25%) respectively.

According to the distribution of bronchogenic carcinoma subtypes in patients related to the same age group. Iraqi cancer registry 2018 also mentioned that the highest incidence was among the age group ≥ 70 years, and the incidence increased with the age (7). According to data published by the National Cancer Institute, the median age of diagnosis of bronchogenic carcinoma in the United States is 70 years, and the median age of death is 72 years (25-27). Our results came in agreement with other reports; Alberg et al., were mentioned that the most common age at diagnosis is 70 years (28) (116). Sidoun et al. from Libya, were also mentioned that the peak age of incidence was 65–67 years (29). Highest age incidence is seen in the 7th decade of life which came in agreement with the findings Provencio et al., 2019, who mentioned that the mean age of bronchogenic carcinoma patients was 64.0 years (30). In this study, the incidence of bronchogenic carcinoma is more common in males compared to females (ratio= 2.3:1), with ages mean ± SEM of 66.39 ± 1.04. This result was may be partly attributed to the low incidence of smoking in women in this study. The result of this study according to the subtypes of bronchogenic carcinoma showed higher incidence of squamous cell carcinoma in both female and male population. Our results in agreement with the findings of annual report of Iraqi cancer registry that squamous cell carcinoma is the top pattern in

males (7,31). However, the result differences were not significant at p <0.05 . There is disparity in the incidence of lung cancer between both genders (32). In Iraq, also bronchogenic carcinoma represented the 2nd order in top ten neoplastic diseases after breast cancer comprising 2579 with a percentage of 8.19% from the total neoplastic cases (31.502), with gender distribution as 1830 patients (13.44%) from male population (total 13612), and 749 patients (4.19%) from female population (total 17.890). Bronchogenic carcinoma was also the second in top ten cancers after breast cancer, and 3rd according to the distribution of incidence rate (7.81%:100,000), after breast and prostate cancers (17.6% and 8.27% respectively) in the population of Al-Najaf province, Iraq, in the year 2018 only (7,31). The majority of study patients (82:100) were smokers, and results revealed 56:82 (68.3%) of patients with squamous cell carcinoma subtype, and 26:82 (31.7%) of cases with adenocarcinoma subtype were from smokers. Cigarette smoking is strongly associated with bronchogenic carcinoma ($p < 0.05$). This indicates a statistically significant correlation between smoking as a risk factor with all types of bronchogenic carcinoma. This came in agreement with global concept of all published reports about relation of smoking with bronchogenic carcinoma. One of the most important causes of bronchogenic carcinoma, accounting for about 85% of cases, is cigarette smoking, the risk of bronchogenic carcinoma increases with exposure to cigarette smoking. Other well-known risk factors include air pollution, different types of smoking (marijuana smoking, exposure to cigar smoke and second-hand cigarette smoke). The bronchogenic carcinoma risk also associated with electronic nicotine delivery pipes (e.g., e-cigarettes) remains to be mentioned. The risk of cancer decreases after stopping smoking, but it will not returns to baseline. About 15 - 20% of people who develop bronchogenic carcinoma have no smoking history or have smoked minimally (33). These cases are usually caused by either a combination of genetic factors and exposure to carcinogens (radon gas, asbestos, second-hand smoke), or other forms of air pollutions (34-36). Demographic distribution revealed that bronchogenic carcinoma was recorded in 60 cases (60%) of urban resident patients, while 40 cases (40%) were from rural areas (most of them from Al-Najaf.province, and nearby governorates). Results revealed that (66.7%), and (60%) of Squamous cell carcinoma cases were related to urban and rural areas respectively, followed by

bronchogenic cancer of adenocarcinoma subtype that comprise 16:40 (40%) and 19:60 (31.7%) from rural and urban areas respectively, while one small cell carcinoma case only (1.6%) was from urban demographic population. The result is not significant at $p < .05$ according to the distribution of different bronchogenic carcinoma between urban and rural areas of the Al-Najaf province. However, there is no accurate statistics data about the exact number of the demographic distribution of population in the province, so no way to find any statistic differences of this parameter. Globally, outdoor air pollutants, more precisely chemical substances released from the burning of fossil fuels, increase the risk of bronchogenic carcinoma (116). Tiny particles (PM2.5) and sulfate gas aerosols, which may be released in traffic exhaust fumes, are associated with a slightly-increased risk of developing lung cancer (28,37). Outdoor air pollution has been estimated to be a cause of 1–2% of bronchogenic carcinoma (28). Established evidence supports an increased risk of lung CA from indoor air pollution in relation to the burning of wood, charcoal, dung for cooking and/or heating (38). Women who are exposed to indoor coal smoke have roughly double the risk, and many of the by-products of burning biomass are known or suspected carcinogens (39). This risk affects about 2.4 billion people worldwide (38) , and it is believed to result in 1.5% of bronchogenic carcinoma deaths (39).

In this study, tru-cut histopathological results of bronchogenic carcinoma patients showed that the most common subtype was squamous cell carcinoma that comprise 64 patients (64%), followed by adenocarcinoma including 35 patients (35%), Our results were came in agreement with the study done in our same center (radiological department in Al Sadder teaching hospital), in 2016 by Shaimaa A. Kadhum , who mentioned that the squamous cell carcinoma was the commonest bronchogenic carcinoma subtype (74%), followed by adenocarcinoma that comprised 18.5% (40) . In this study Squamous cell carcinoma is the most frequent histological type (56%) followed by adenocarcinoma (35%). These results were came in agreement with that mentioned by Alamoudi et al, 2010 that Squamous cell carcinoma was the most common cell type (51.8%) (41). While Zhu et al., 2018 in other study included 150 cases, mentioned that out of 96 malignant cases, Adenocarcinoma comprise the majority of bronchogenic carcinoma subtypes 64 (66.7%) followed by Squamous cell carcinoma 10 (10.4%) and Small cell carcinoma

that comprise 3 (3.1%) (42). In this study, FNA positive cytological results of bronchogenic carcinoma patients were seen in 92 samples out of 100 (92%), with malignant cells, including 35 patients (35%) diagnosed as adenocarcinoma, 56 patients (56%) were diagnosed as squamous cell carcinoma, one case of small cell carcinoma that comprise 1% of the total cases, and 8 cases showed non-malignant tumor cells. Furthermore, FNA was confidently diagnosed in 81 cases (81%), while the non-diagnostic cases were recorded for 19 cases (19%) included in our study. Confidently diagnosis was recorded for 29:35 were adenocarcinoma cases, 51:56 of squamous cell carcinoma and single case only of small cell carcinoma. Non diagnostic cases (no matching of Tru cut/ FNA) was recorded for 6:35 cases of adenocarcinoma, 5:56 cases of squamous cell carcinoma and 8 patients of non-malignant cases. These results were significant at $p \leq 0.05$, with a sensitivity of 96.34%, specificity of 100. %, Positive Predictive Value of 100%. %, Negative Predictive Value of 70.89 % and diagnostic accuracy of 96.7%. These results came in agreement with the findings of Sidoun et al., who mentioned that diagnostic accuracy was 96.96% (43). Other reports were mentioned that the diagnostic accuracy of CT-guided FNA for malignant lung tumors up to 97%, depending on factors such as the size and depth of the lesion as well as the number of needle paths (44,45). Several factors can influence the diagnostic yield of FNA biopsy, such as needle size (46), length of the needle path, and lesion size (47-49). Imaging-guided tissue sampling is relatively safe and accurate (50). The main end results of imaging-guided fine needle samplings may be governed by adverse events, accuracy, histology, and diagnostic yield (51). There are several factors that affect the outcome of this technique such as lesion location and pathological characteristics (52,53). FNA is less invasive than an open biopsy of the lung, one through an incision into the chest. In a study done by Sangha et. al., 2016, they were found that FNA was successful in retrieving a sample sufficient to adequately diagnosis bronchogenic carcinoma in 91 percent of people on which the procedure was performed (54). In other study done by Chen et al., 2020, FNA also contributed to 10.3% of molecular analyses as a complementary tissue source, potentially reducing patient inconvenience and morbidity associated with repeated lung needle biopsy (55). It's important to note, however, that this procedure may be not possible for all tumors, and may not be an option for tumors at some locations in the lungs (54,55).

In this study, 8/100 patients were developed mild pneumothorax after tru-cut biopsy collection, 2 of them needed hospitalization for 24 hours with chest tube insertion. This is one of the complications that necessities using FNA instead of Tru-cut due to its low risk of pneumothorax. No cases of hemorrhage and no air embolism cases were seen in this study. Beşir et al. also mentioned that out of 102 cases using CT-guided Tru-Cut biopsy, a pneumothorax rate was 15.7% and a chest tube placement rate of 8.8% (56). However, the reported incidence of pneumothorax is highly variable, most likely the result of multiple factors such as differences in patient population, procedural technique, operator experience, and methods of detection (chest radiograph or CT) (57). Emphysema, older age, smoking, intrapulmonary location, deeper location, presence of cavitary and irregular contour lesions, and smaller needle-pleural angles were the most important factors related to the occurrence of complications (58-60). With coaxial biopsy systems, multiple fine-needle aspirates and core biopsy specimens can be obtained through an introducer needle, which remains within the lung parenchyma for a variable time. This time between pleural puncture and needle removal has been called as “dwell time”. Investigators have shown that the incidence of pneumothorax is higher when performed with CT rather than fluoroscopic guidance because of the longer procedure duration and the fact that biopsy of smaller lesions is often performed under CT guidance. Smaller size and greater depth of lesions have been shown to correlate with an increase in pneumothorax frequency due to longer “dwell time” (57).

5 | CONCLUSIONS

Fine-needle aspiration biopsy is a reliable diagnostic tool for bronchogenic carcinoma cases with matching sensitivity of 96.34%, specificity of 100. %, Positive Predictive Value of 100. %, Negative Predictive Value of 70.89% and diagnostic accuracy of 96.71%, and can be trust especially in critical cases in whom tru-cut biopsy carry high risk of complications. However, further studies are suggested for better evaluation

Ethical Issue:

All ethical issues were approved by the author, in accordance with Ethical Principles of Declaration of Helsinki of the world Medical Association, 2013, for research involving human subjects

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