Ultrasound Guided Sure Cut Needle Biopsy of Peripheral Lung and Mediastinal lesions for more than 2.0cm size: Efficacy, Safety and Feasibility- as an out-patient procedure in 179 Patients

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ABSTRACT

Objective: To evaluate the efficacy, safety and feasibility of Ultrasound guided Sure-Cut Needle biopsy for peripheral lung and mediastinal nodules, as an out-patient procedure.

Study Design: A Prospective Interventional study.

Place and Duration: At Pulmonology-OPD, Gulab Devi Teaching Hospital Lahore from 1st October, 2016 to 28th February, 2019.

Methodology: Peripheral lung, mediastinal or pleural lesions measuring greater than 2.0cm by ultrasound, abutting the visceral pleura were biopsied with Sure-Cut needle, gauge-16 under real-time ultrasonography with 3.5--5.5 MHZ machine in out-patient department. Adequacy of procedure was confirmed after receiving the histopathology report. All complications encountered during or after procedure were recorded.

Results: Out of 179 procedures, 98.32% samples were adequate and among them 63.63% cases were malignant while 36.37%patients were with non-malignant etiology. The biopsy-induced complications observed were biopsy site pain (10.05%) and mild ooze at puncture site in 6.70% patients. No life threatening complication or table-death encountered.

Conclusion: Ultrasound guided biopsy of peripheral lung and mediastinal lesions, greater than 2.0cm, has an excellent efficacy, safety and feasibility when performed as an out-patient-procedure.

Keywords: Peripheral lung lesion, Mediastinal lesion, Pleural lesion, Biopsy, Out- door procedure, Sure-Cut-needle biopsy, Efficacy, Complications, Safety

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INTRODUCTION

Peripheral lung nodules abutting the visceral pleura and mediastinal lesions are common owing to increasing cigarette smoking, industrialization and environmental pollution and majority are found malignant[1]. Such lesions are not reachable by bronchoscopy[2]. All patients do not produce sputum, while in expectorating patients, sputum examination gives limited diagnostic yield[3]. Mediastinal pathologies are investigated by surgical methods like mediastinoscopy and open operative procedure. Tissue sampling and histopathology is considered the gold standard for definitive diagnosis. Per-cutaneous Sure-cut Needle Biopsy is an important and useful tool, capable of investigating such pathologies and is considered next to imaging[4,5]. The procedure is conventionally performed under Computerized Tomographic scan (CT-scan) guidance as an in-door procedure because of the documented complications like pneumothorax and hemoptysis which can be life threatening and may require active intensive care /surgical management to prevent fatalities[6,7]. In addition, patient has to remain away from home or work-place and also affords finances for hospital stay in addition to the cost of biopsy procedure.

A CT-guided procedure requires a dedicated CT-scan department along with the services of a qualified and experienced radiologist. Being a high cost project, the facility of CT-scan is not frequently available in resource limited populations**.** A CT-guided procedure has the additional disadvantage of involving ionizing radiations, having mutagenic effects[8]. Furthermore, CT-scan department is often over-loaded and usually long appointments are faced, resulting delayed investigation and worsening of disease. Similarly, patient has to wait for a long time for surgical biopsy due to over-busy schedule of thoracic surgeon. The delay in diagnosis, irrespective of the reason, may lead to further progression of disease, resulting in disease dissemination and poor prognosis[9].

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On the other hand, ultrasound guidance can be obtained very easily. No Hi-fi machinery is needed. The only requirement is an ultrasound machine whose cost is negligible as compared to a CT-department. Mediastinal and peripheral lung lesions can be approached safely, using trans-thoracic per-cutaneous ultrasound by an experienced pulmonologist or radiologist in OPD, eliminating the need of hospitalization. Ultrasound guided procedure is very cost effective, costing only a few thousand PKR which is far economical than a CT-guided procedure, amounting to many thousands. In this way, by using this modality, not only the time, rather cost of the procedure can be reduced for the patient. If these cases are handled in OPD, obviously, the work load on a busy CT-scan department and in-door beds is reduced.

Modern literature states that Ultrasound (US) guided lung biopsy is safe and gives an attractive diagnostic yield. Hussain et al reported that in-door biopsy procedure is safe and gives good diagnostic yield if performed by a pulmonologist[10]. Ultrasound is not frankly being used in pulmonology due to lack of understanding and inadequate training, but awareness is increasing gradually over the time. Previously US-guidance was limited to pleural aspiration or thoracic drain insertion but it has been tried successfully for the sampling of chest wall, pleural, pulmonary and mediastinal lesions[11-13]. As US-guidance is readily available, cost effective, free from radiation hazards. We conducted this study with an objective to evaluate the efficacy, safety and feasibility of Ultrasound guided Sure-Cut Needle biopsy for peripheral lung and mediastinal nodules, as an out-patient procedure.

METHODOLOGY

This Prospective Interventional study was conducted at the out-patient department of Gulab Devi Teaching Hospital, Lahore, a tertiary care center, from 1st October 2016 to 28th February, 2019. The study included 179 consecutive patients with peripheral lung, mediastinal or pleural based nodules more than 2.0cm in diameter, not diagnosed by bronchoscopy and sputum cytology. Only those peripheral lung nodules, abutting the visceral pleura were selected. While those less than 2.0cm in size, unfit for procedure and cases with aerated lung interposed between visceral pleura and lung were excluded. The exact size of the nodule was confirmed by thoracic ultrasonography. The patients were declared unfit for the procedure, due to platelet count <100,000/ml, APTT or PT ratio >1.4, patients with FEV1 <35% of predicted, absence of a safe path way to the lesion, non-cooperative patients and those having central pulmonary nodule.

Procedure: After fulfilling the indications and ruling out risk factors, a written informed consent was obtained, complete case history, investigations, Chest X-ray and pertinent images of CT were reviewed by interventionist. A disease-localizing ultrasound scan was performed by Sonovista-fx (Siemens) machine, using 3.5–5.5MHz convex transducer and the entry point was marked. Sure-Cut Needle no.16 was used for tissue sampling. The transducer was placed in the intercostal space, parallel to the rib, with firm contact with the skin, and the needle was advanced to the lesion during suspended respiration, under real-time visualization. Any damage to the blood vessel, in needle pathway, was eliminated by using Color Doppler Ultrasound. Samples were collected in a jar containing 10% formalin solution, while sample for Acid Fast Bacillus culture were collected in normal saline for further examination. A post procedure scan was done for any sign of pneumothorax or hemorrhage. All patients were subjected to an expiratory Chest X-ray PA view, one hour after the procedure, to monitor the complications. Puncture site pain was evaluated by verbal pain intensity scale, those experienced pain were managed with oral analgesia. Physical and hemodynamic status was recorded at the conclusion of the procedure. Patients were sent home after examining the satisfactory check X-ray and were advised to report immediately to our emergency department or to make a telephonic contact, in case of any abnormality like difficult breathing, rapid heart rate, biopsy site bleeding or blood in sputum. The time from skin cleaning to dressing was noted for each procedure.

Data collection: The biopsy success was determined on receiving the histopathology report. The reports not representing the lesions were regarded as inadequate while those showing successful sampling were considered as adequate. A record of the expected complications, like biopsy site pain, bleeding, hemoptysis, pneumothorax, surgical emphysema, vasovagal shock, air-embolism and mortality if any, were entered in the pre-formed proforma. The patients were followed properly and true positive, false positive, true negative and false negative cases were isolated. The results were tabulated and conclusions were drawn by statistical analysis.

Data Analysis: SPSS-16 software package was utilized for statistical evaluation. Quantitative data was expressed by mean and $\pm$ standard deviation. Categorical data was presented as percentage or frequency. Sensitivity, Specificity, Positive predictive value (PPV), Negative predictive value (NPV) and diagnostic accuracy were calculated. Specific disease characterization was computed. Fisher exact test was used for comparison. A p-value < 0.05 was considered significant.

RESULTS

A total 179 biopsies performed among them 122 (68.15%) patients had lung lesions, 47 (26.25%) mediastinal while 10 (5.58%) were with pleural pathologies. The age range was 14 to 70 years and majority of the patients belonged to the age group of 42 to 60 years. Mean age of the participants was 33.4 years and SD $\pm$ 11.3. Male patients were 71.50% (n=128) with Male: Female ratio of 2.5:1. The commonest symptoms in study population were chest pain (n=144, 80.44%), cough (n=137, 76.53%), fever (n=123, 68.71%), hemoptysis (n=21, 11.73%) and shortness of breath (n=76, 42.45%). After procedure, three samples (1.67%) were declared inadequate while 98.32% samples (n=176) were found adequate. The nodule size ranged from 2 to 3.5 cm with mean 2.7cm. Skin preparation to dressing time ranged from 9–16 minutes with an average of 10.4

minutes. Histopathology results revealed 112 patients (63.63%) with malignant and 64 cases (36.37%) with non-malignant etiology. Biopsy Success Rate was 98.32%.

In 64 non-malignant cases, 39.06% (n=25) had Caseation necrosis, 21.87% (n=14) Acute inflammation, 15.62% (n=10) Interstitial Lung Disease, 10.93% (n=7) Chronic inflammation, 6.25% (n=4) Mucormycosis, 4.68% (n=3) Non-caseation granulomata and 1.56% (n=1) had Hamartoma. Frequencies of non-malignant pathologies divulged that caseation necrosis (39.06%) is the most common finding among non-malignant nodules in our study population. Except 07 cases of non-specific chronic inflammation, all benign reports were assigned specific etiology. That is why specific disease characterization for non-malignant issues is 89.0% (Figure-1).

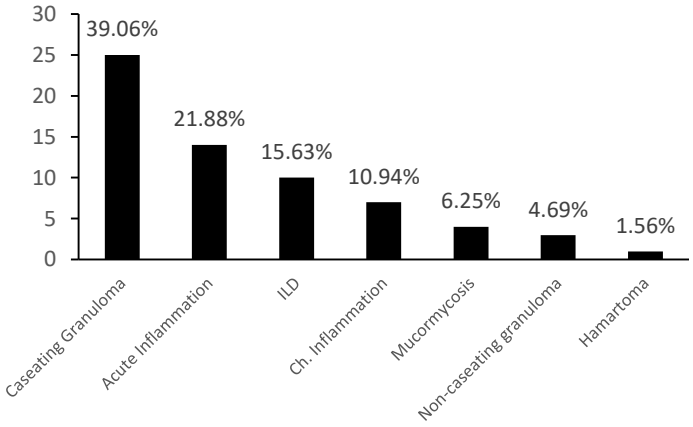

Figure-1: Frequency of non-malignant disorders (n=64)

Of 112 malignant reports, 53.57% (n=60) were non-small cell carcinoma, 14.28 % (n=16) small cell carcinoma, 8.92% (n=10) lymphoma, 8.92% (n=10) malignant cells and 14.28 % (n=16) with miscellaneous malignant pathology as shown in Figure-2.

Among miscellaneous malignant pathologies, majority (n=60) were non-small cell lung cancers followed by squamous cell carcinoma (41.66%, n=25), adenocarcinoma (36.66%, n=22) and only 1.66% cases (n=1) were Alveolar cell carcinoma. Among 10 cases of lymphoma, 30.0% (n=03) were Lymphoblastic lymphoma, 50.0% (n=05) Hodgkin's lymphoma, 20.0% (n=02) non-Hodgkin's lymphoma, and 14.28% patients (n=16) with miscellaneous malignant etiology (Table-I).

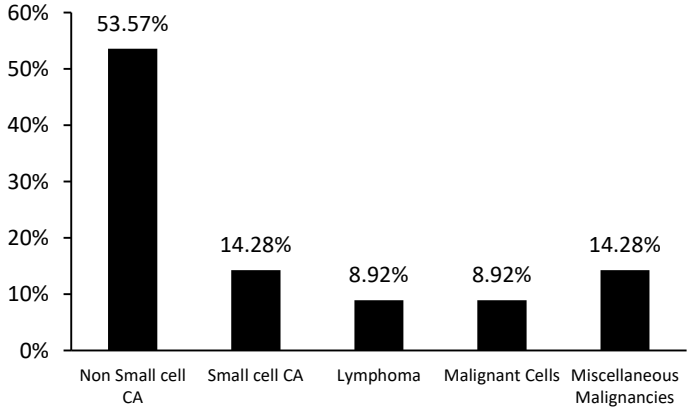

Figure-2: Frequency of Malignant Etiologies in 112 patients

Among of 47 mediastinal biopsies performed, 97.87% (n=46) biopsies were performed from anterior mediastinum and among all, majority (42.55%, n=20) were benign lesions on histopathology. Among 46 anterior mediastinal nodules, commonest finding (39.13%, n=18) was caseation necrosis, followed by lymphoblastic lymphoma (8.69%, n=04) and only 2.17% (n=01) were having malignant teratoma (Table-I).

Table-I: Frequency of miscellaneous malignant disorders (n=16).

Etiology	Observed Cases	Frequency
Ewing Sarcoma	05	31.25%
Malignant Thymoma	03	18.75%
Malignant Mesothelioma	02	12.50%
Metastatic Synovial Sarcoma	02	12.50%
Carcinoid Tumor	02	12.5%
Malignant Teratoma	01	6.25%
Malignant Spindle Cell Tumor	01	6.25%

The frequency of observed complications during procedure were given in Table-II. Which shows commonest was mild biopsy site pain (10.05%), followed by mild blood ooze at puncture site in 6.70% cases.

Table-II: Frequency of complications after procedure. (n=179)

Complications in 179 cases	No. of cases	Frequency
Biopsy site pain	18	10.05 %
Biopse site bleeding (only a few drops)	12	6.70 %
Haemoptysis	00	0.00 %
Pulmonary hemorrhage	00	0.00%
Pneumothorax	00	0.00%
Vaso-vagal Shock.	00	0.00%
Air-embolism	00	0.00%
Mortality	00	0.00%
Tumor seeding along biopsy track	00	0.00%
Biopsy site Hematoma formation	00	0.00%
Scar mark	00	0.00%

Statistically, all benign and malignant cases were true-positive. No false positive or false negative case was found. Sensitivity, Specificity and Diagnostic accuracy was 100% each for defining benign and malignant pathologies with 95% Confidence intervals 96.76-100%, 94.40-100% and 97.93-100%respectively. PPV and NPV were 100% each. Specific disease characterization for benign etiology was 89.0 % and 91.08% for malignancy with overall rate 90.04%. By applying Fisher exact test for comparing Specific Disease Characterization between malignant and benign issues, p-value is 0.014 which is significant at 0.05.

DISCUSSION

The current study was conducted to evaluate the efficacy, safety and feasibility of Ultrasound guided biopsy of peripheral lung and mediastinal lesions on Out Patient Basis. Our study revealed biopsy success rate 98.32% in OPD. Khosla et al displayed 92.1%,

khan and colleague reported 88.3% success of procedure in their studies on in-door patients, using ultrasound guidance[14,15]. On the other hand, the diagnostic yield of CT-guided procedures reported by Basti et al were 83.94% [16], by Galluzzo et al. (87.0%) [17], Tian et al (96.1%)[18] and Heerink et al (58.96%)[19]. The current study displayed rather superior diagnostic yield to all above mentioned reports.

The superior diagnostic efficacy to CT-guided-procedure can be explained by the fact that ultrasonography is superior to CT, in differentiating solid from necrotic areas. We took biopsy selectively from non-necrotic part of the lesion, under real-time visualization, that is why our diagnostic yield is superior to several CT guided studies[17-20]. The diagnostic yield for mediastinal pathologies was 100% in our study with 95.64% specific disease characterization. Tuberculosis was rapidly diagnosed by caseation necrosis in 42.55% cases before the arrival of AFB-culture report, enabling the earlier diagnosis of TB. The histopathology results and later course of management would have been same even with CT guided procedure or even in indoor patient. The only difference is in getting the biopsy done early, using ultrasound guidance, without hospitalization, low expenditure. Patient remains at home or at his work-place and does his routine business. No issue of bed availability for biopsy procedure. No burden on hospital, no burden of cost of hospitalization on the patient.

In this study, benign and malignant disorders were differentiated with a sensitivity and specificity of 100%. While Jeon et al[11] showed a sensitivity of 90.0% for malignant and 67% for benign pathologies. The current study showed that this modality provided such adequate tissue material that not only malignant etiology was identified, rather small cell and non-small cell carcinoma were classified. Even Adenocarcinoma, Alveolar cell carcinoma, Squamous cell carcinoma and Lymphoma of different grades were diagnosed. This modality plays an important role in disease staging and starting early treatment, without any delay for further work-up. The efficacy of having high diagnostic yield (98.32%), precise disease diagnosis and classification of different pathologies, makes this procedure as a reliable alternative to CT-guided or open surgical biopsy procedure, bearing tremendous efficacy.

As far as safety is concerned, our study demonstrated only minor biopsy site pain in10.05% case (n=18) and a few drops-bleeding at puncture site in 6.70% cases which is lower than all national and international studies, on in-patients[15-20]. The most commonly reported complication in literature is pneumothorax which varies between 6.5%--69.0 % for pulmonary lesions. Heerink et al [20] reported pneumothorax in 34.0% cases. A recent meta-analysis[19] of 8133 cases, revealed pneumothorax in 25.3% case for which thoracic drain was placed in 5.6% cases. Similarly, another study reported a pneumothorax rate of 12–45%, requiring chest tube placement in 2–15%[19] Wiener et al[21] analyzed CT-guided lung biopsy results of two North American databases, containing 15,865 procedures and reported pneumothorax in 15.0 % cases while 6.6 % cases required chest drain insertion. We did not find even a single case of pneumothorax in our study, showing excellent safety.

This level of safety was achieved, because we selected patients having peripheral nodules abutting the visceral pleura, without any aerated lung interposed between the chest wall and the nodule. As no aerated lung tissue was punctured during procedure, no question of pneumothorax, hemoptysis, pulmonary hemorrhage, surgical emphysema or air-embolism. The literature shows 18% rate of pulmonary hemorrhage[20,21] but we did not encounter any type of hemorrhage. Biopsy site bleeding and hematoma were eliminated by frank use of Color Doppler ultrasound during procedure. The blood vessels in the needle path were rightly identified and spared. Furthermore, flexibility of availability of multi-planer approach by ultrasound guidance provided additional safety and more accuracy, by which needle path was modified accordingly, to avoid injury to blood vessels. Systemic air embolism is a rare complication with reported rate of 3.8% which may be over-looked[21,22]. We did not find any case of air-embolism in our study. Similarly, mortality is documented internationally due to systemic air-embolism, pneumothorax and hemoptysis but no fatality encountered in this study.

As far as modality specific safety is concerned, in contrary to CT, no ionizing radiations were used in the procedure, no question of mutagenic effects that is why its use in young children, pregnancy and those within child bearing age is safe[23]. Furthermore, an iodinated contrast is essentially used during a CT-guided procedure, which may cause nausea, vomiting, restlessness, tachycardia and allergic reactions. Additionally, it is contraindicated for patients with known hypersensitivity or having compromised renal functions. Such patient cannot be subjected to CT-guided procedure, while no such disadvantage is found with ultrasound guided method, adding further safety to the technique[24].

A CT-guidance requires a full-fledged radiology department along with the services of a qualified radiologist but availability is a genuine issue in resource limited populations while ultrasonography is very cost effective, easily available and guided procedures can be done by a pulmonologist. Furthermore, a CT-guided procedure is not well tolerated by patient because of being a tiring procedure. Patient has to tolerate the inconvenience of breath-holding, again and again for longer periods during disease localizing scan, multiple repeated check-scans and biopsy taking. On the other hand, during an ultrasound guided procedure, patient holds his breath for a shorter time which is usually in seconds, that is why this procedure is well tolerated by the patient. Similarly the side effects of intravenous iodinated contrast are avoided. A CT-scan department is usually over-burdened, very long appointments are given for CT-guided biopsy. Patient is hospitalized for the procedure, occupies a bed and requires the services of medical and para-medical staff. Patient remains away from home or work place and has to afford a lot of finances just for hospitalization, in addition to the cost of biopsy procedure. Patient and his family feel disturbed at hospital.

On the other hand, no such issue is found with our procedure. Patient is biopsied in OPD without any wastage of time, long appointment or bed availability. There is no hospitalization, no question of the cost of hospitalization. No fear of radiation or

unpleasant exposure to contrast. Patient remains at home/work places, does normal routine activity and diagnosis is made early, that is why ultrasound guided biopsy as an OPD-procedure is well liked and tolerated by patients, indicating maximum feasibility.

Our study results may find applications in resource-limited populations where availability of CT-guidance is a genuine issue. Similarly, in settings, where CT-departments are over-busy, ultrasound guidance can be utilized as a problem solving tool. We feel, a CT-guided procedure should be reserved for specialized jobs like smaller and central nodules or those peripheral nodules where aerated lung is interposed between the lesion and the chest wall or if the ultrasound is technically limited or discrepant with clinical findings. This step will not only lessen the burden on the patient as well as on the hospital, rather the burdened radiologists will take a breath of peace and cases getting long appointments will be able to have early services of the radiologist.

It is clear from above discussion that ultrasound guided thoracic biopsy has shown superior diagnostic efficacy as compared to several CT-guided studies, excellent safety and significant feasibility in this study.

We have no hesitation to comment that ultrasound guided biopsy of peripheral lung and mediastinal lesions, performed in out-patient department is cost effective, portable, safer, faster and reliable, providing high diagnostic yield, low complication rate and as accurate as CT-guided biopsy

CONCLUSION

Ultrasound guided biopsy of peripheral lung and mediastinal lesions, more than 2.0cm in size, shows good diagnostic efficacy, excellent safety and significant feasibility, when performed as an out-patient-procedure.

Limitations: The main limitation of our study is that it is the out-come of 179 patients, by extending the study with more number of patients, the authenticity of the study can further be increased. We suggest that thoracic ultrasonography should be made part of the curriculum for pulmonology training in the country, which has already been done internationally, this step will develop good understanding and skill, regarding the role of ultrasound in pulmonary medicine[25].

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AUTHOR'S CONTRIBUTION

Qureshi AR: Conceived idea, Designed research study, Ultrasonography, Biopsy Procedure, Manuscript writing, Critical revision and approval for publication, Agreement to be accountable for the accuracy and integrity of work.

Irfan M: Data collection, Critical revision, Data drafting, Study supervision, Manuscript revision, Final approval for publication, Agreement to be accountable for the accuracy and integrity of work, Correspondence.

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