Comparison of Ultrasonography with Computed Tomography in Diagnosis and Staging of Lung Cancer

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ABSTRACT

Background

Ultrasound (US) can aid in lung cancer diagnosis and staging in peripheral-based lesions by demonstrating chest wall invasion, aiding as a guide to biopsy, and detecting supraclavicular lymph nodes which are often missed by computed tomography (CT).

Objective

This study is to compare the ultrasound with computed tomography in the diagnosis and staging of lung cancer.

Method

This was an observational prospective study conducted from October 2020 to April 2023 in patients with or suspected lung cancer sent for imaging assessment to the Department of Radiology and Imaging. Out of 306 patients who underwent computed tomography scan, a total of 234 patients with proven lung cancer were subjected to ultrasound of the chest, liver, bilateral adrenal, and supraclavicular regions for the evaluation of lung mass, pleural effusion, and metastasis in lung, adrenal, and supraclavicular lymph nodes. Diagnostic values of ultrasound to detect peripheral lung lesions, chest wall invasion, pleural effusion, liver and adrenal metastasis, and supraclavicular lymph nodes were compared with contrast-enhanced computed tomography scans. Ultrasound's performance was evaluated against computed tomography scans as the gold standard, using the chi-square test, z-test, and area under the curve for comparison ($p < 0.05$ for significance).

Result

The majority of patients (53.8%, n=126) were aged 61-75, with 53% being male and 89% smokers. Ultrasound was superior in detecting pleural effusion (sensitivity 80.3%, NPV 92.2%, AUC 0.860) and supraclavicular lymph nodes (sensitivity 72.2%, NPV 91.6%, AUC 0.817).

Conclusion

In resource-constrained settings like Nepal, where advanced imaging may be limited, integrating ultrasound with contrast-enhanced computed tomography significantly improves lung cancer diagnosis. This non-radiation approach is particularly beneficial for peripheral lesions, patients with renal function impairment and aiding effective staging of lung cancer.

KEY WORDS

Computed tomography, Lung cancer, Role, Ultrasound

INTRODUCTION

Over the past century, there has been a dramatic shift in the prevalence and impact of lung cancer. Once regarded as a rare cause of death, it has now become the most common cause of mortality worldwide.[1] In 2018 alone, lung cancer accounted for a staggering 40% of all cancer-related deaths.[2] Lung cancer is increasingly being recognized in Nepal and is most common malignancy in Nepal.[3] Lung cancer is also the leading cause of cancer related death in Nepal.[4] Shockingly, approximately 85% of lung cancer cases are detected at an inoperable stage, when treatment options are limited.[5] There are many diagnostic modalities available worldwide for the evaluation of suspected lung cancer, with radiography being the most basic and initial imaging modality. The least invasive method available for diagnosis and staging of the cancer is recommended.[6-8]

The imaging modality of choice for diagnosis and staging of lung cancer is contrast-enhanced chest CT.[8] However, it does have certain limitations, including irradiation, less reliability in assessing mediastinal and chest wall invasion, limited availability in certain geographic regions, and higher cost. In consideration of these limitations, ultrasonography (USG) is the next alternative imaging modality.[9] It has been widely used by emergency/ intensive care physicians for the evaluation of pleural fluid collection, pneumothorax, and various lung parenchymal diseases.[10-14] Literature is available demonstrating superior detection of chest wall invasion by USG over CT scan, which can help in staging lung cancer. Also, sonography-guided thoracocentesis is very easy, less time-consuming, cost-effective, and without risk of radiation as compared to CT.[11] Thoracocentesis can also help in the diagnosis as well as the staging of lung cancer.[15-17] Even, though some studies have shown a superior yield of USG-guided biopsy over CT-guided biopsy of lung lesions, the reason could be a real-time assessment of the lesion with sonography.[12,18] Importantly, USG can also play a crucial role in detecting metastatic lymph nodes in the supraclavicular region, which may be missed by CT scans. This enables clinicians to obtain tissue samples for cytology and histopathology evaluation, aiding in the diagnosis and staging process.[19,20]

METHODS

This was a prospective, observational analytical study carried out in the Department of Radiology and Imaging in Tribhuvan University Teaching Hospital, Institute of Medicine. The study was carried out from October 2020 to April 2023 in total 306 patients.

Patients sent to the Department of Radiology for diagnosis and imaging of suspected lung carcinoma were included in the study. Patients already on treatment for lung carcinoma and those not willing to undergo USG and not giving consent for the study were excluded.

The study was started after receiving the approval letter from the institutional review committee, the Institute of Medicine (IOM) with an approval number of 95 (6-11) E2 077/078. This study was done in those stable participants who were referred to the Department of Radiology, Tribhuvan University Teaching Hospital (TUTH) for evaluation of suspected lung cancer. No extra cost was taken from the participants. No vulnerable members of the population were included in the research. Informed written consent was taken from the patients meeting the inclusion criteria.

CT images and other available imaging studies of the patient were evaluated initially. The person performing the ultrasound was blinded with CT findings and other imaging findings. Then, detailed thoracic sonography was performed to look for any chest wall lesion, pleural lesion/ fluid collection, and peripheral lung lesions. If any lesion was visualized, characterization of the lesion was done, and loco-regional spread (including chest wall/ diaphragmatic infiltration in case of peripheral lung lesion). Depending upon the patient's build and the depth of the lesion, both low-frequency convex probes and high-frequency linear transducers were used to assess the lesion. Then, supraclavicular lymph node status was assessed with the high-frequency linear transducer. After that ultrasound assessment of the upper abdomen was done for any lesions in the liver, adrenals, kidney, and upper abdominal lymph nodes using a convex transducer. Any lymph nodes or focal lesions thus visualized were noted and assessed for the feasibility of FNA/ Biopsy.

After assessment of all the lesions, if the pleural fluid was visualized, thoracocentesis was done with a 20-21 G needle and sent for cytology. If an extrathoracic suspicious lymph node or focal lesion was seen, then the safest lesion based on its size and relation to adjacent structures, including vessels, was approached for ultrasound-guided trucut biopsy with 18 G needle. Semiautomatic trucut biopsy instrument with coaxial introducer was used. If trucut biopsy was not feasible, then fine needle aspiration with a 22 G needle was done from the lesion. If extrathoracic lesions and pleural fluid were not seen, then the peripheral-based lung lesion was targeted under ultrasound guidance for trucut biopsy. Any visualized peripheral lung lesion with a size greater than 1 cm was targeted for biopsy. If the size was less than 1 cm, only FNA was performed. Central lung lesion was targeted for trucut biopsy if visualized through the window of a peripheral collapsed lung (Image. 1, 2 and 3).

All the samples thus obtained were sent for cytology/ histopathology evaluation. The reports were followed up. To avoid the possibility of bias due to the observer trying to prove USG as a better modality, the observer performing USG was blinded to the CT scan report. Although USG had no safety concerns for the participant, necessary precautions were taken to perform the thoracocentesis, biopsy/FNAC.

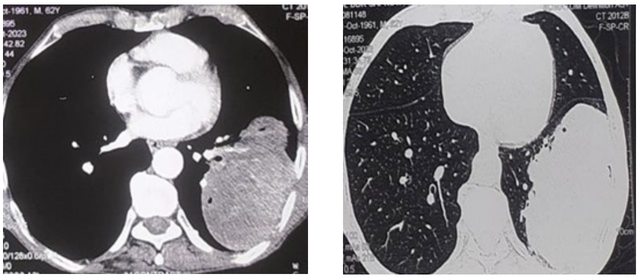

Image 1a & b. Contrast Chest CT in mediastinal and lung window show a large enhancing peripheral left lung mass.

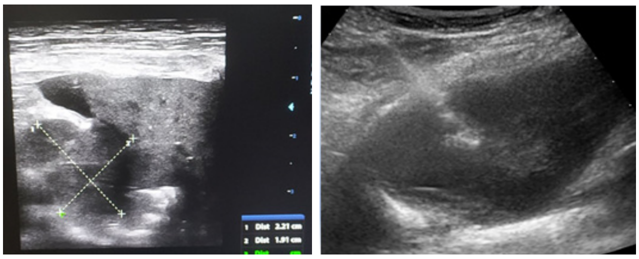

Image 2a & b. Ultrasound image in a different patient shows a central lung mass with adjacent collapsed lung and minimal pleural effusion (2A). Image 2B shows Needle biopsy of the peripheral lung mass in Ultrasound.

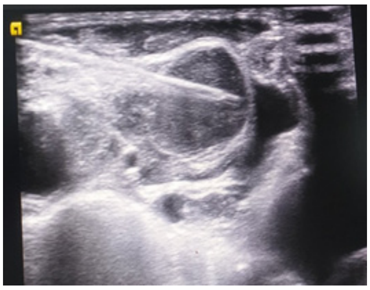

Image 3. Ultrasound image shows needle biopsy of the supraclavicular node.

Regular monitoring and supervision were done periodically by the principal investigator to ensure the quality control of the study. Data was collected in a preformed proforma and entered into an Excel spreadsheet. IBM SPSS Statistics 25 package was used for data analysis.

Categorical variables are presented as percentages and numerical variables are presented as mean and median. The sensitivity, specificity, and accuracy of ultrasound were calculated by using a CT scan as the gold standard. Chi-square and z-tests were used and the area under the curve was obtained to compare ultrasound and CT findings. $p < 0.05$ was taken as significant.

RESULTS

Out of a total of 306 patients, 72 cases were excluded from the study (25 did not provide consent for the study, 32 were lost to follow-up, seven cases were inflammatory/ infective pathology in histopathology and eight were under treatment for lung cancer). A total of 234 patients with histologically proven diagnoses of lung cancer were analyzed in this study and had both contrast-enhanced CT images and ultrasound.

The median age of the included patients was 68 years. Most of the patients were in the age group of 61-75 years (126, 53.8%) (Figure 1). About 46.6% (n=109) of the study population were female. A total of 89.3% (n=209) of patients gave a history of smoking. Cough with expectoration, weight loss, loss of appetite, and dyspnea were the most common presenting symptoms among various other clinical presentations (Table 1).

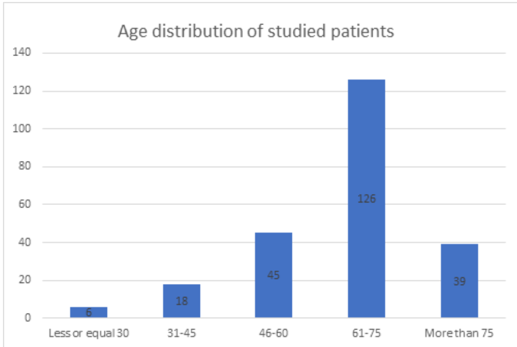

Figure 3. Age distribution of the studied patients.

Table 1. Clinical Characteristics of the studied patients.

Characteristics	Number (n=234)	Percentage (%)
Cough with expectoration	114	48.7
Weight loss	108	46.2
Loss of appetite	98	41.9
Dyspnea	75	32.1
Hemoptysis	26	11.1
Chest pain	37	15.8
Fever	11	4.7

CT Characteristics of Tumors

The mean longest diameter of the lesion, measured through chest CT, was 5.6 ± 3.5 cm. The tumor site was comparable in both lungs, with bilateral lesions observed in only 5 (2.1%) patients. A significant proportion (n=72, 30.8%) displayed a lobulated margin, all lesions exhibited contrast enhancement (Table 2 for specific tumor locations and margin characteristics).

Histopathological Evaluation of Tumor

Squamous cell carcinoma was found to be the most common (78, 33.4%) followed by adenocarcinoma (55, 23.5%) and small-cell carcinoma (27, 11.5%) with Spindle cell tumor and Lymphoma being the least common types (3, 1.3% each) (Table 3).

CT versus USG Characteristics in Lung Cancer

Among 234 cases with lung carcinoma, ultrasound was able to detect a primary tumor in 40.2% (n=94) cases. Ultrasound demonstrated significantly superior efficiency in pleural effusion detection compared to CT ($P < 0.001$). CT outperformed ultrasound in detecting lymphadenopathy, particularly in peri-bronchial, hilar,

Table 2. CT Findings / Tumor Characteristics

Tumor Location	Number (n=234)	Percentage (%)
None	18	7.7
Both Lungs	5	2.1
Endobronchial	1	0.4
Left Hilar	27	11.5
Left Lower Lobe	22	9.4
Left Lung	1	0.4
Left Upper Lobe	43	18.4
Right Hilar	24	10.3
Right Lower Lobe	54	23.1
Right Lung	5	2.1
Right Middle and Lower Lobe	1	0.4
Right Middle Lobe	4	1.7
Right Upper and Middle Lobe	1	0.4
Right Upper Lobe	28	12.0
Tumor Margin		
Characteristics	**Number(n=234)**	**Percentage (%)**
None	18	7.7
Ill-defined	18	7.7
Irregular	71	30.3
Lobulated	72	30.8
Smooth	16	6.8
Spiculated	39	16.7

Table 3. Type of carcinoma from HPE diagnosis using CT

Tumor Type	Number (n=234)	Percentage (%)
Squamous cell carcinoma	78	33.4
Adenocarcinoma	55	23.5
Small-Cell carcinoma	27	11.5
Non-small cell	12	5.1
Carcinoid	8	3.4
Spindle cell tumor	3	1.3
Lymphoma	3	1.3
Poorly differentiated	5	2.1
Other tumors	13	5.6
Metastatic carcinoma	25	10.7
Malignant pleural effusion	5	2.1
Total	234	100

mediastinal, and subcarinal regions, except for the cervical and supraclavicular regions, where ultrasound exhibited superior and statistically significant performance [Table 4].

While ultrasound exhibited lower sensitivity for detecting chest wall invasion and distant metastasis, it maintained a high specificity of 96.5% for both. Ultrasound is notably sensitive and specific in identifying pleural effusion and supraclavicular lymphadenopathy, surpassing CT scans, as evident from the higher Area under the Curve values (Table 5).

Table 4. CT vs USG for detection rate on Tumor characteristics (n=234)

Characteristics	CT	USG	p-value*
Pleural effusion detected	66 (28.2)	67 (28.6)	0.920
Hilar lymphadenopathy	102 (43.6)	-	
Peribronchial lymphadenopathy	53 (22.6)	-	
Supraclavicular lymphadenopathy	54 (23.1)	55 (23.5)	0.920
Mediastinal lymphadenopathy	157 (67.1)	-	
Sub-carinal lymphadenopathy	114 (48.7)	-	
Adjacent consolidation	-	36 (15.4)	
Chest wall invasion	33 (14.1)	16 (6.8)	0.009
Distant metastasis	64 (27.4)	34 (14.5)	0.0006
Other cervical lymphadenopathy	-	4 (1.7)	

*Calculated using z-test for comparison of proportions.

Table 5. Diagnostic evaluation of Ultrasound compared to CT for detection of Chest wall invasion, distant metastasis, pleural effusion, and supraclavicular lymphadenopathy.

Characteristics	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Area under curve (95%CI)
Chest wall invasion	27.3	96.5	56.3	89.0	0.619 (0.503-0.735)
Distant metastasis	45.3	96.5	82.9	82.4	0.709 (0.625-0.793)
Pleural effusion	80.3	91.7	79.1	92.2	0.860 (0.799-0.921)
Supraclavicular lymph node	72.2	91.1	70.9	91.6	0.817 (0.742-0.892)

DISCUSSION

In our research, a predominant occurrence of lung cancer was observed among individuals aged 61-75 years, constituting 53.8% of the cases. Interestingly, the prevalence of lung cancer was notably higher in males when compared to females, contradicting the findings of Fultz et al. and Hoosein et al.[21,22] This aligns with the results from studies by Hafez et al. and van Overhagen et al., where lung cancer was more frequently observed in males (approximately 80%) than in females (approximately 20%).[15,19] A comprehensive investigation into cancer distribution in Nepal, conducted by Neupane et al. also confirmed that lung cancer ranked as the most common cancer in males and the third most common in females.[23]

In our study, a significant 89.3% of lung cancer patients had a documented history of smoking, a well-established risk factor for the development of lung cancer. This finding aligns with the research by Hafez et al. reporting that 73.6% of lung cancer cases had a history of smoking.[15]

Our study further revealed that the most prevalent presenting symptoms of lung cancer included cough with expectoration (114, 48.7%), weight loss (108, 46.2%), loss of appetite (98, 41.9%), and dyspnea (75, 32.1%). Hafez et al. also reported cough as the most common presenting symptom of lung cancer followed by chest pain, dyspnoea, hemoptysis, fever, and hoarseness of voice.[15]

Despite the availability of numerous advanced diagnostic modalities, chest X-ray (CXR) continues to serve as the initial investigation for evaluating suspected lung cancer, offering a sensitivity ranging between 77% to 80%. Subsequently, contrast-enhanced CT scans (CECT) are employed to provide a comprehensive staging assessment.[19,20] In our study, CECT was the primary imaging modality chosen for staging purposes. Notably, the mean longest diameter of the lesions, as ascertained through chest CT, measured at 5.6 ± 3.5 cm. It is worth noting that a study conducted by Hafez et al. also reported the mean diameter of masses in CT scans, which averaged 6.39±3.79 cm.[15] The variance in the mean tumor size might be attributed to the small sample size within Hafez et al. study. The involvement of bilateral lungs was present in only 5 (2.1%) patients in our study.

Trans-thoracic US has become a valuable diagnostic tool for chest physicians with its various advantages including bedside availability, absence of radiation, and guided interventions (aspiration/ biopsy of fluid/ solid lesions).[9,10] Chest ultrasound which was previously used mainly for diagnosis of chest wall and pleural diseases, has been used in diagnosing peripheral lung and mediastinal lesions as well.[11]

In our study, squamous cell carcinoma emerged as the predominant histological subtype, constituting approximately 33.4% of cases, followed by adenocarcinoma 23.5% as the second most common subtype. These findings align with similar research by Rawat et al. reporting squamous cell carcinoma in 44.8% of cases, and Shetty et al. where it was found in 44.4% of cases.[24,25]

In lung cancer, supraclavicular lymph nodes (N3 stage in TNM staging) are frequently involved lymph nodes group with a prevalence of up to 24% in NSCLC patients and 31% in SCLC patients.[6] Our study found that ultrasound had a slightly higher detection rate of supraclavicular lymph nodes than a CT scan (p < 0.001) which shows ultrasound being slightly more effective in detecting supraclavicular lymph node metastasis compared to CT scan. Similar to our study, Hafez et al. and van Overhagen et al. reported that the US has higher sensitivity in detecting supraclavicular LN than CT-scan.[15,19] In addition, Ikezoe et al. found out that ultrasound examination has high sensitivity (100% vs 72%) and specificity (95.06% vs 93.83%) for primary supraclavicular lymph node metastasis in lung cancer compared to the CT scan.[14] Similarly, van Overhagen et al. and Abu-Youssef et al. found out that the US yields higher sensitivity in detecting supraclavicular LN than clinical examination.[19,26] Supraclavicular lymph node involvement was more common in those with mediastinal invasion thus recommending for sonographic evaluation for supraclavicular lymph node in patients with mediastinal invasion.[27,28] Kumaran et al. found significant supraclavicular lymph nodes involvement in lung cancer and yielded 45.5% of malignancy after FNAC. The result of FNAC avoided more invasive procedures in 42.6% of patients.[29]

In lung cancer, malignant pleural effusion is recognized as an indicator of advanced disease, poor prognosis, and poor survival; and also upstages the cancer to stage four.[26,30] We found that the US has higher but non-significant detection rate for pleural effusion as compared to CT, (28.6% vs 28.2%, p=0.920). Similar to our study, Hafez et al. and Abu-Youssef et al. found out thoracic US has a higher but non-significant detection rate of pleural effusion compared to CT scans.[15,26]

In our study, an ultrasound assessment of the upper abdomen was done for any lesion in the liver, adrenals, kidney, and upper abdominal lymph nodes to look for extra-thoracic metastasis of lung cancer. We found that CT has a significantly higher detection rate of distant metastasis as compared to the US (27.4% vs 14.5%, p < 0.001). Contrast CT of the chest and upper abdomen with adrenals and positron emission tomography/CT should be included to rule out extrathoracic metastasis in the staging of lung cancer in patients considered for surgical resection.[5] However, abdominal US can be used as an initial screening tool for extra-thoracic metastasis in the liver and adrenal gland in resource-poor settings.

Various studies reported that the thoracic US has significantly better sensitivity and specificity of the rate of the chest wall and pleural invasion in lung cancer compared to chest CT scans.[9,21,32] On the contrary our study found a higher detection rate of chest wall invasion in CT compared to the US (14.1% vs 6.8%, p=0.009). It could be due to overestimation of chest wall invasion in CT scans. Minimally invasive modalities of ultrasonography; endoscopic ultrasound-fine needle aspiration (EUS-FNA) and/or endobronchial ultrasound-transbronchial needle aspiration (EBUS-TBNA) are recommended for staging of the mediastinal lymph nodes.[16]

The study was not correlated with surgical findings which could be the reason for the underestimation of chest wall invasion in ultrasound.

CONCLUSION

Thoracic US had a significantly higher detection rate of malignant pleural effusion, and a significant detection rate of supraclavicular lymph node metastasis in lung cancer compared to chest CT-scan. Therefore, in a resource-poor setting, the use of thoracic and neck US evaluation and thoracic US-guided biopsy plays a significant role in the diagnostic workup and staging of lung cancer.

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REFERENCES

1. Didkowska J, Wojciechowska U, Mańczuk M, Łobaszewski J. Lung cancer epidemiology: contemporary and future challenges worldwide. *Ann Transl Med.* 2016 Apr;4(8):150. doi: 10.21037/atm.2016.03.11. PMID: 27195268; PMCID: PMC4860480.

2. World Health Organization [Internet]. 2018 [cited 2019 Sep 12]. Cancer. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer

3. Report P. Population Based Cancer Registry in Nepal Cancer Registry Principal Investigator / Co- Investigators. 2018. - Google Search [Internet]. [cited 2024 Jan 27].

4. Poudel KK, Huang Z, Neupane PR, Steel R, Poudel JK. Hospital-Based Cancer Incidence in Nepal from 2010 to 2013. *Nepal J Epidemiol*. 2017 Mar 31;7(1):659-65.

5. Liam CK, Andarini S, Lee P, Ho JCM, Chau NQ, Tscheikuna J. Lung cancer staging now and in the future. *Respirology (Carlton, Vic)*. 2015 May;20(4):526-34.

6. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2013 May;143(5 Suppl):e142S-e165S.

7. Silvestri GA, Gonzalez A V, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest.* 2013 May;143(5 Suppl):e211S-e250S.

8. Maconachie R, Mercer T, Navani N, McVeigh G. Lung cancer: diagnosis and management: summary of updated NICE guidance. West D, Aslam S, Campbell L, Walters-Davies R, McIver A, Borg E, et al., editors. *BMJ*. 2019;364.

9. Chira R, Chira A, Mircea P. Transthoracic Ultrasonography: Advantages and Limitations in the Assessment of Lung Cancer. In 2017.

10. Raheja R, Brahmavar M, Joshi D, Raman D. Application of Lung Ultrasound in Critical Care Setting: A Review. *Cureus.* 2019 Jul 25;11(7):e5233-e5233.

11. Sartori S, Tombesi P. Emerging roles for transthoracic ultrasonography in pleuropulmonary pathology. *World J Radiol.* 2010 Feb 28;2(2):83-90. doi: 10.4329/wjr.v2.i2.83. PMID: 21160921; PMCID: PMC2998926.

12. Sheth S, Hamper UM, Stanley DB, Wheeler JH, Smith PA. US guidance for thoracic biopsy: a valuable alternative to CT. *Radiology.* 1999 Mar;210(3):721-6.

13. Ikezoe J, Morimoto S, Arisawa J, Takashima S, Kozuka T, Nakahara K. Percutaneous biopsy of thoracic lesions: value of sonography for needle guidance. *AJR Am J Roentgenol.* 1990 Jun;154(6):1181-5. doi: 10.2214/ajr.154.6.2110724. PMID: 2110724.

14. Ikezoe J, Sone S, Higashihara T, Morimoto S, Arisawa J, Kuriyama K. Sonographically guided needle biopsy for diagnosis of thoracic lesions. AJR Am J Roentgenol. 1984 Aug;143(2):229-34. doi: 10.2214/ajr.143.2.229. PMID: 6611048.

15. Hafez MR, Sobh ES, Elsawy SB, Abo-Elkheir OI. The usefulness of thoracic ultrasonography in diagnosis and staging of bronchogenic carcinoma. *Ultrasound.* 2017 Nov;25(4):200-12.

16. Lim W, Ridge CA, Nicholson AG, Mirsadraee S. The 8th lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg*. 2018 Aug;8(7):709-718. doi: 10.21037/qims.2018.08.02. PMID: 30211037; PMCID: PMC6127520.

17. UyBico SJ, Wu CC, Suh RD, Le NH, Brown K, Krishnam MS. Lung cancer staging essentials: the new TNM staging system and potential imaging pitfalls. Radiographics. 2010 Sep;30(5):1163-81. doi: 10.1148/rg.305095166. PMID: 20833843.

18. Sconfienza LM, Mauri G, Grossi F, Truini M, Serafini G, Sardanelli F, et al. Pleural and peripheral lung lesions: comparison of US- and CT-guided biopsy. *Radiology.* 2013 Mar;266(3):930-5. doi: 10.1148/radiol.12112077. Epub 2012 Nov 30. PMID: 23204543.

19. Overhagen H, Brakel K, Heijenbrok M, Kasteren J, Moosdijk C, Roldaan A, et al. Metastases in Supraclavicular Lymph Nodes in Lung Cancer: Assessment with Palpation, US, and CT1. *Radiology*. 2004 Jul 1;232:75-80.

20. López F, Rodrigo JP, Silver CE, Haigentz Jr M, Bishop JA, Strojan P, et al. Cervical lymph node metastases from remote primary tumor sites. Head & Neck. 2015/12/29 ed. 2016 Apr;38 Suppl 1(Suppl 1):E2374-85.

21. Fultz P, Feins R, Strang J, Wandtke J, Johnstone D, Watson T, et al. Detection and Diagnosis of Nonpalpable Supraclavicular Lymph Nodes in Lung Cancer at CT and US1. *Radiology.* 2002 Jan 1;222:245-51.

22. Hoosein MM, Barnes D, Khan AN, Peake MD, Bennett J, Purnell D, et al. The importance of ultrasound in staging and gaining a pathological diagnosis in patients with lung cancer-a two year single centre experience. *Thorax*. 2011 May;66(5):414-7.

23. Neupane PR, Poudel KK, Huang ZB, Steel R, Poudel JK. Distribution of Cancer by Sex and Site in Nepal. Asian Pac J Cancer Prev. 2017 Jun 25;18(6):1611-1615. doi: 10.22034/APJCP.2017.18.6.1611. PMID: 28670003; PMCID: PMC6373810.

24. Rawat J, Sindhwani G, Gaur D, Dua R, Saini S. Clinico-pathological profile of lung cancer in Uttarakhand. *Lung India*. 2009 Jul;26(3):74-6. doi: 10.4103/0970-2113.53229. PMID: 20442840; PMCID: PMC2862510.

25. Shetty CM, Lakhkar BN, Gangadhar VSS, Ramachandran NR. Changing pattern of bronchogenic carcinoma: A statistical variation or a reality? *Indian J Radiol Imaging*. 2005 Apr;15(2):233-8.

26. Abu-Youssef HA, Kamel KM, Selim S, Gamal El-Deen SM. Study of the added value of transthoracic ultrasound in staging of lung cancer. *Egypt J Chest Dis Tuberc*. 2014 Oct 1;63(4):1025–34.

27. Kendirlinan R, Ozkan G, Bayram M, Bakan ND, Tutar M, Gür A, et al. Ultrasound guided fine-needle aspiration biopsy of metastases in nonpalpable supraclavicular lymph nodes in lung cancer patients. Multidiscip Respir Med. 2011 Aug 31;6(4):220-5. doi: 10.1186/2049-6958-6-4-220. PMID: 22958429; PMCID: PMC3463075.

28. Fultz PJ, Harrow AR, Elvey SP, Feins RH, Strang JG, Wandtke JC, et al. Sonographically guided biopsy of supraclavicular lymph nodes: a simple alternative to lung biopsy and other more invasive procedures. *AJR Am J Roentgenol.* 2003 May;180(5):1403-9. doi: 10.2214/ajr.180.5.1801403. PMID: 12704059.

29. Kumaran M, Benamore RE, Vaidhyanath R, Muller S, Richards CJ, Peake MD, et al. Ultrasound guided cytological aspiration of supraclavicular lymph nodes in patients with suspected lung cancer. *Thorax*. 2005 Mar 1;60(3):229 LP – 233.

30. Gayen S. Malignant Pleural Effusion: Presentation, Diagnosis, and Management. *Am J Med.* 2022 Oct;135(10):1188-1192. doi: 10.1016/j.amjmed.2022.04.017. Epub 2022 May 14. PMID: 35576996.

31. Sugama Y, Tamaki S, Kitamura S, Kira S. Ultrasonographic Evaluation of Pleural and Chest Wall Invasion of Lung Cancer. *Chest*. 1988;93(2):275-9.

32. Bandi V, Lunn W, Ernst A, Eberhardt R, Hoffmann H, Herth FJF. Ultrasound vs. CT in detecting chest wall invasion by tumor: a prospective study. *Chest*. 2008 Apr;133(4):881-6.