Multidetector CT Evaluation of Neoplastic Lung Lesions with Image Guided Transthoracic Tissue Sampling.

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Abstract:

Background and Purpose: To study the efficacy of Multidetector CT in the evaluation of various types of neoplastic lung lesions and correlating these findings with CT guided biopsy of the suspected lesion.

Materials and Methods: After an initial clinical assessment, 44 patients who were suspected of having neoplastic lung lesions on chest radiogram and clinically were subjected to CECT and later CT guided biopsy was done using GE brightspeed elite 16 slice CT scanner.

Results: Of the 44 patients, 68.2 were males and 31.8 % were females. Mean age of presentation 59 yrs. 95.4 % (n = 42) lesions were malignant and 4.5 % (n = 2) lesions were benign. Adenocarcinoma was the commonest 43.1% (n = 19), followed by Squamous cell carcinoma, 31.8% (n = 14), Small cell carcinoma,9% (n = 4), Large cell carcinoma,2.2% (n = 1), Mesenchymaltumors 4.5% (n = 2) and undifferentiated carcinomas 4.5% (n = 2). The benign lesions turned out as abscess. CT guided biopsy lead to development of pneumothorax in 9% (n = 4) of cases. Sensitivity of CT in diagnosing malignant lung lesions was 100% with a positive predictive value of 94.5%.

Conclusions:Multi Detector Computed Tomography has a high positive predictive value suggestive of great diagnostic accuracy in the evaluation of Bronchogenic Carcinoma. It is ofimmense value in delineating lobar and segmental involvement of tumor there by aiding in surgical resection. There is significant correlation with the MDCT diagnosis of Bronchogenic carcinoma with that of Histopathology with a P value of 0.03.

I. INTRODUCTION:

Bronchogenic carcinoma is a leading cause of death worldwide. Although the underlying etiology for this malignancy is thought to be multifactorial, cigarette smoking is the most important causative factor responsible for at least 85% cancer deaths worldwide. Patients with bronchogenic carcinomahave a poor prognosis with an overall 5year survival rate of 10-15%. The incidence of lung cancer has seen a steady rise in incidence over the past few years especially in developing countries like India. In our study an attempt has been made to evaluate the accuracy of MDCT in diagnosing neoplastic lung lesions correlating with Histopathological findings.

II MATERIALS AND METHODS:

This is a prospective cross-sectional study to evaluate the role of MDCT in diagnosing neoplastic lesions of lung in 44 patients referred to the Department of Radiodiagnosis and Imaging, PES Institute of medical sciences, Kuppam for CECT thorax between October 2013 to September 2015. All male and female patients of all age groups ,referred with clinical and plain radiogram diagnosis of Lung mass were imaged.

Selection of patients:

Patients who were clinically and radiographically diagnosed with lung mass were subjected for MDCT examination. The lesions were characterised on the basis of Morphology, Location, Extent, Enhancement pattern etc, and these radiological findings were correlated clinically and histopathologically. Patients with contraindications to iodinated contrast, Pregnant women, Patients with severe respiratory distress who are unable to co-operate and Patients with history of chest trauma and prior thoracic surgery were excluded from the study.

All the MDCT scans were performed at our institute on the GE Bright speed Elite 16 slice CT Scanner. Patients were kept nil orally 4 hours prior to the CT scan. Risks of contrast administration were explained to the patient and consent was obtained prior to the contrast study.

Routine antero-posterior and lateral topograms of the chest was initially taken in all patients in the supine position with the breath held. Axial sections of 5 mm thickness were taken from the thoracic inlet to adrenals. CT parameters used were 120 kV, mAS- 80 to 160. In all cases plain scan was followed by intravenous contrast scan in suspended inspiration. For contrast enhancement 70-80 ml of 300mg/ml non-ionic iodinated contrast was injected using pressure injector at the rate of 3-4ml/s. Sections were taken after an initial delay of 35 seconds in the late arterial phase. Post study retro reconstructions were done at 0.625 mm section thickness. Sagittal and coronal reconstructions were made wherever necessary. Thescans were reviewed on a direct display console at multiple window settings. The Pre and Post contrast images were viewed and analyzed.

<u>III CT GUIDED BIOPSY:</u>

After localization of mass lesion by NECT and CECT, patients were subjected to CT guided FNAC and Biopsy. The criteria of patient selection for FNAC were as follows:

- $\hfill\square$ Patient who were cooperative and were able to hold breath for a short while.
- □ Patients who had no bleeding tendency or coagulopathy, pulmonary hypertension or
- AV malformation in the suspected lesion.

Relevant investigations such as BT, CT, PT with INR were done to exclude coagulopathy.

Patients were counselled regarding the procedure and complications, written consent for invasive procedure taken in all cases. Surface sterilization at the puncture site done with povidine iodine solution. The pathway of the needle was anaesthetized by local anaesthetic infiltration and skin and subcutaneous tissue. Trajectory of the needle was planned as per the location of the mass as depicted by CT scan images using radio-opaque needle stripes. The shortest possible pathway was chosen. After the patient was made to lie in required position, i e supine, prone or lateral decubitus, the Biopsy needle was inserted. The needle was advanced to the level of the pleura without piercing it, and the needle position and angle were verified with a short segment CT. Next,

the needle was advanced in one motion through the pleura to the prescribed depth into the lung in suspended respiration following which the patient was instructed to breathe normally.

The needle position inside the lesion was confirmed by taking intermittent thin slice andmaking positional adjustment of the needle accordingly. Cooks Co-axial cutting edge 18Gneedles were used for all cases. By fully pressing plunger, cutting cannula is fired and tissue sample is captured within specimen notch.

After the biopsy was complete, a short spiral CT was performed to evaluate for complications including pneumothorax, hemothorax, and soft tissue hematoma. A check radiogram of chest was taken after 4 hrs to look for a pneumothorax. All the patients were instructed to seek medical advice if he or she developed dyspnea, breathlessness or hemoptysis.

IV RESULTS:

Of the 44 patients, the age at presentation ranged from 26 year to 80 years. The mean age was 59 years and the maximum numbers of patients affected belonged to the age group of 51 to 60 years. In this study Males were 68.2% (n = 30) and females 31.8%, (n = 14). 73% were smokers (n = 32) with a Smoker: Non-smoker ratio of 2.6:1. Out of 44 cases, chest radiograph findings favouring malignant lesions was seen in only 28 (63.6%) cases. In rest of the 16 (36.3%) cases chest radiograph showed findings like consolidation, collapse, pleural effusion, hilar lymphadenopathy etc. CECT findings, 52.2% lesions were peripherally located out of which 64% turned out to as Adenocarcinoma, 45.4% were centrally located, Out of which 50% turned out as Squamous cell carcinoma on HPE. The average size of the lesions was 6.2 cms, 25% of cases had multiple lesions. 46% of squamous cell carcinoma had spiculated margins (n = 7) and another 46% had irregular margins (n = 7). Among adenocarcinoma 42 % had smooth margins, (n = 8), 36% had spiculated margins. 23% of SqCC showed cavitations, calcifications were seen in 20.4% (n = 9), out of which 6 cases turned-out as SqCC, 2 were Adenocarcinoma and 1 case was mesenchymal tumor. 50% SqCC and 22.7% of Adenocarcinoma had necrosis. Contrast enhancement which was moderate (> 15 HU) and heterogenous was seen in 98% of the lesions.72% showed nodal involvement. Collapse was seen in 19 cases, air bronchogram in 6 lesions , lymphangitis

carcinomatosa in 7 cases, pleural effusion in 23 cases. Mediastinal invasion were seen in 17 cases and Chest wall invasion in 8 cases. Commenest organ metastasized was opposite lung(11 cases) followed by liver(10 cases) and bone (10 cases). Final CECT diagnosis was Adenocarcinoma 43.1%, Squamous cell carcinoma 38.6% followed by Small cell carcinoma 6.8%. All 44 underwent CT guided Biopsy, 4 patients developed pneumothorax. Final HPE diagnosis was SqCC 14 cases, Adenocarcinoma 19 cases , small cell 4 cases and 2 cases which were diagnosed as malignant on CECT turned out as abscess. Senstivity of CECT in diagnosing malignant lesions was 100% and Positive predictive value of 95.5%.

V DISCUSSION:

Lung cancer has been the most common cancer in the world for several decades. There are estimated to be 1.8 million new cases in 2012 (12.9% of the total), 58% of which occurred in the less developed regions. The disease remains as the most common cancer in menworldwide (1.2 million, 16.7% of the total).

In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all ancer related deaths in both sexes, it is the commonest cancer and cause of cancer related mortality in men, with the highest reported incidences from Mizoram in both males and females57 (Age adjusted rate 28.3 and 28.7 per 100,000 population in males and females, respectively)2. of Population Based Cancer Registries: 2009-2011. Indian Council of Medical Research; 2013.

In this study the age group of patients ranged from 26-80 years with a mean age of 59 yrs. Most of the cases were in 51 - 60 (36.3%), followed by 61-70 yrs. (27.2%) and 71-80(18.1%). We had only one case (2.2%) below the age of 30 years and 2 patients (4.4%) below 41 years. Krishnamurthy et al .in their study found the mean age of presentation as 55 yrs.

With the increasing incidence of cigarette smoking amongst female and the fact that Never-smokers are also at a high risk of developing lung cancer, the gap between male and female is becoming narrower. So far, our results in this regard are comparable with most of Indian workers.

Cough is the most common presenting complaint among patients in our study (84 .0%) followed by loss of weight(68.1%) and dyspnoea (46.1%). This is in agreement with study by Arora VK et al .Quamrul et al concluded I their study that, cough is the most common symptom (89%), followed by chest pain (62.7%).D Dehera and Balamugesh in their review cited that cough was commonest symptom with most Indian studies reporting range 40-94%, chest pain 16-66.7%, Dyspnea 24-59%, hemoptysis 8-60%, fever 22-68% and Hoarseness of voice 9-33%.

SQUAMOUS CELL CARCINOMA:

In our present study 42% of the cases were squamous cell carcinoma with 80.9% of the squamous cell carcinoma presenting as central mass. Cavitation was found in 19% of cases. All the cavities were thick walled and eccentric, the size of the masses with cavitation were more than 4 cm and were peripherally located. 3 lesions with chest wall invasion were found in the upper lobes, one in right upper lobe and two in left upper lobe, however typical pancoast tumour with all features of pancoast syndrome was not found in any case . In the present study all the cases shows homogenous/heterogeneous enhancement more than 15 HU. Cavitated mass shows enhancement of the wall of the cavities. The contrast enhanced scans are particularly useful in evaluation of mediastinal lymphadenopathy which is not a usual feature of squamous cell carcinoma. In the study of Byrd, et al 18 squamous cell carcinoma presented as hilar or peripheral mass. Peripheral mass was seen in 24% of 263 patients studied. Cavitation was found in 6.8% of peripheral mass majority of them were larger than 4.0 cm. The wall of these cavities was eccentric and thick walled

ADENOCARCINOMA:

Edward F. Patz Jr (13,18) in his review article stated Adenocarcinoma accounts for 25 to 30% of NSCLC and is the most common type. Adenocarcinoma typically presents as a small (often <4 cm), peripheral, round or oval, smoothly marginated, solitary pulmonary nodule. Occasionally, a more central location or spiculation and irregular margins are noted. Some lesions distort surrounding vessels (corona radiata) or cause retraction of the

adjacent pleura ("pleuroparenchymal tail"), eccentric or amorphous calcification has been reported in up to 6% of cases at CT with peripheral adenocarcinoma, lymphadenopathy is seen in 18% and 2% of hilar and mediastinal lymph nodes, respectively. Central lesions, however, have hilar nodal metastases in 40% of cases, and mediastinal lymph node metastases in 27% of cases. Bronchioloalveolar cell carcinoma (BAC) may present with solitary or multiple lesions. Pseudocavitation, the presence of small focal low-attenuation regions within or surrounding the periphery of the nodule and air bronchograms, is more

commonly associated with these tumors than other cell type.

N. Hollings, P. Shaw(2,4,5) in their review article stated Adenocarcinoma represents 31% of all lung cancers, including bronchoalveolar carcinoma. Adenocarcinomas are typically peripherally located and showed cavitation.

In the present study we have found that that adenocarcinomas account for 43.1% (19 cases)of all bronchogenic carcinoma. Most of these lesions presented as peripherally located. Average size of lesions was 4.6 cm with irregular margins or spiculated margins and homogeneous enhancement on post contrast study. Necrosis was present in only 9 cases.

SMALL CELL CARCINOMA:

In our present study we have found that all small cell carcinoma accounted for 6.8% (3) cases, all of whom were male smokers aged 40-70 years. All three cases presented as hilar or perihilar mass with bulky hilar and mediastinal lymphadenopathy which caused infiltration of mediastinal structures such as aorta, pericardium, pulmonary veins and pulmonary arteries. Superior vena cava involvement with thrombosis was noted in one cases Byrd RB et al 30 found in his study 76% of small cell carcinoma presented as hilar or perihilar mass. Bronchial obstruction (29%) and mediastinal widening 12. 28% is the most common presenting feature. Peripheral mass account for 29% of cases of which 36% of cases associated hilar or perihilar mass was found.

Edward F. Patz Jr in his review article in stated that the primary lesion may be small or not even visible on radiograph studies, but early extrathoracic metastases are common and even present prior to the development of pulmonary symptoms. Liver, bone marrow, adrenal glands, and brain are frequent sites of metastatic disease.

LARGE CELL CARCINOMA:

In our study we have found that 2.2 % large cell carcinoma (1 case.) which was 6.3 cm in diameter. The lesion was peripherally located causing invasion of chest wall and hilar lymphadenopathy. Cavitation was not found in any of the cases. Contrast study revealed homogenous enhancement of the whole mass. The lesion was associated with pleural thickening and ipsilateral pleural effusion

Sanjeet Kumar Mandal et al found the incidence of large cell carcinoma as 3.3%, mostly associated with smoking, peripherally located and 40% cases showed associated pleural effusion.

In a study Byrd RB et al stated that large cell carcinoma presents as a peripheral mass which are mostly more than 4 cm. Hilar lymphadenopathy was present in 32% of cases. Pleural effusion was associated with 2% of cases.

N. Hollings, P. Shaw in their review article stated that Large cell carcinoma represents 9% of all lung cancers. It is diagnosed histologically after exclusion of adenocarcinomatous or squamous differentiation . It may grow extremely rapidly to a large size but metastasizes early to the mediastinum and brain with invasion of chest wall

UNCLASSIFIED NSCLC:

In present study, 2 cases (4.5) has been diagnosed as undifferentiated NSCC. One was centrally located and the other peripheral. Both of them were large sized measuring 6.3 cms and 8.1 cms. Centrally located lesion showed cavitation with mediastinal lymphadenopathy. One of them showed associated peural effusion of them were central. No evidence of metastasis noted in either of the cases.

Rawat et al, Shetty CM, Krishna murthy et al in their studies reported incidence of undifferentiated NSCC as 8.3%, 9.8% and 2.3% respectively

MESENCHYMAL TUMORS:

Primary mesenchymal tumors of lung are uncommon tumors that resemble their counterparts in soft tissue. The incidence of these tumors are very low accounting for less than 3% The spectrum of malignant tumors displaying a mixed epithelial/ mesenchymal growth pattern is rather narrow when these tumors occur primarily in the lung. The two most often encountered neoplasms showing features of epithelial and mesenchymal differentiation are carcinosarcomas and pulmonary blastomas. The sarcomas constitute to a major proportion of mesenchymal tumors.

Radiological features include, large sized lesions usually more than 7 cms, which are smoothly marginated, showing no calcifications or necrosis. Necrosis can be seen in a minority of patients. Usually shows chestwall/mediastinal invasion. These lesions show homogenous/heterogenous enhancement. Identification of intratumoral vascularity is a sure sign of mesenchymal tumors.

In our study, we encountered 2 mesenchymal tumors. Both the lesions were large sized, one measured 21cms and the other 18.5 cms, The smaller lesion had smooth and lobulated countour, no calcifications/necrosis. Post contrast it showed intralesional vascularity which is pathognomic of mesenchymal tumors. The larger lesion was ill-defined as it occupied entire left lung causing chest wall and mediastinal invasion and showed heterogenous enhancement. These findings were in concordance with other studies done by Minerva Chir, Marcel Koenigkam-Santos and Lee HJ et al.

BENIGN TUMORS:

Two lesions which were diagnosed as malignant lesions on CT, turned out to be benignlesions.

A 47 year old male patient with h/o cough, hemoptysis and chest pain was reffered for chest xray. He was a smoker for 10 years. Chest radiogram revealed well defined irregular focal opacity in right upper zone, with features of pneumonic consolidation. Patient presented after 10 days of antibiotic treatment, no resolution of the lesion was noted on follow up chest radiogram. CECT was performed, which revealed, an irregular lesion measuring 6.3 cms and was peripherally located. The lesion showed central necrosis with enhancing peripheral solid component and was not associated any lymphnodal enlargement .It was diagnosed as squamous cell carcinoma. FNAC revealed it to be an abscess. Patient was started on appropriate antibiotic medication which completely resolved on follow up radiogram done after 20 days.

Other case was a 60 year old diabetic female, who presented with c/o coughand chest pain.Chest X-ray revealed a well-defined opacity in right upper zone, CECT revealed a well-defined smoothly marginated mass lesion measuring 4.6 cms, located peripherally Central necrosis and peripheral enhancing component. No satellite nodules seen. A cavitating adenocarcinoma was our probable diagnosis. FNAC demonstrated inflammatory infiltrates .It was finally diagnosed as abscess. Christopher et al studied 80 patients with suspected lung abscess, and concluded80% had thick walled, 67% of lesions were round, 45% had smooth margins and 75% had cavity.

	Positive		Negative		Total	
	No. of Pts	%	No. of Pts	%	No. of Pts	%
CT Scan	44	100	0	0	44	100
FNAC/HPE	42	95.4	2	4.5	44	100

ACCURACY OF CT IN DISTINGUISHING BENIGN FROM MALIGNANT LESIONS

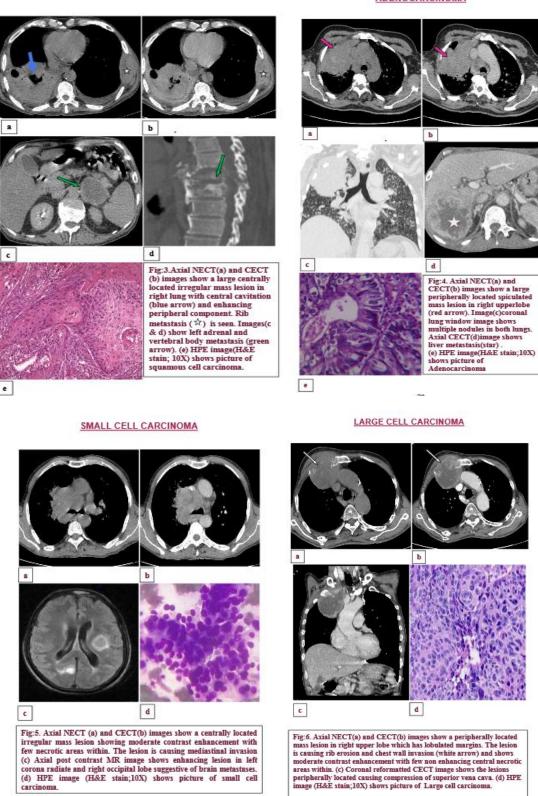
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COMPARISON OF CT SCAN AND CT GUIDED FNAC/HPE DIAGNOSIS

OF NEOPLASTIC LESIONS OF LUNG.					
NATURE OF LESION BASED ON FINAL DIAGNOSIS	DISEASE	CT Scan	CT Guided FNAC/BIOPSYDiagnosi s		
	Squamous Cell Carcinoma	17	14		
	Adenocarcinoma	19	19		
	Large cell carcinoma	1	1		
Malignant	Small cell carcinoma	3	4		
	Unclassified (non small cell)	0	2		
	Mesenchymal	2	2		
	Metastasis	2	0		
Benign	Abscess	0	2		
	TOTAL	44	44		

VI : CONCLUSION

Multi Detector Computed Tomography has a high positive predictive value suggestive of great diagnostic accuracy in the evaluation of Bronchogenic Carcinoma. MDCT is of immense value in delineating lobar and segmental involvement of tumor there by aiding in surgical resection. There is significant correlation with the MDCT diagnosis of Bronchogenic carcinoma with that of histopathology.



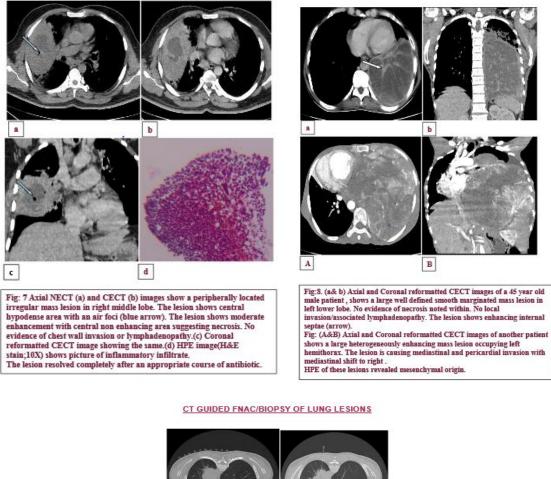
SQUAMOUS CELL CARCINOMA

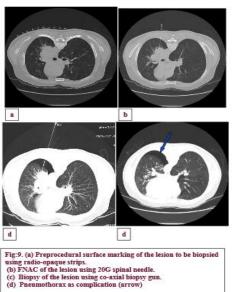
ADENOCARCINOMA

carcinoma.

LUNG ABSCESS

MESENCHYMAL TUMORS





VII: REFERENCES

1. Robert AS, Thomas J G. Epidemiology Of Lung Cancer ,RadiolClinN.Am May 2003; Vol 38, Issue 3

2. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM; Estimates of worldwideburden of cancer in 2008: GLOBOCAN 2008.Int J Cancer 2010; 127:2893-917.

3. Moore MA, Ariyaratne Y, Badar F, Bhurgri Y, Datta K, Mathew A, et al Cancer epidemiology in South Asia-past, present and future. Asian Pac J Cancer Prev2010.

4. Global burden of disease 2004 update.

5. Swati Khurana; Lungcancer.South Asia Network for Chronic Disease;http://sancd.org/ uploads/pdf/ lung-cancer-fact-sheet.pdf.

6. GLOBOCON 2012.

7. RamnathTakiar, Deenu Nadayil, A Nandakumar; Projections of Number of Cancer Cases in India (2010-2020) by Cancer Groups. Asian Pacific J Cancer Prev, 11, 1045-1049.

8. Das CJ, Ashu S, Sima M. Thoracic Application of Multi-detector CT.Indian J Chest Disease Allied Sci2007; 49: 29-36

9. Milroy R. Staging Of Lung Cancer, Chest2008; Vol 133, Issue 3.

10. Li T, Kung H-J, Mack PC, Gandara DR. Genotyping and 35.genomic profiling of nonsmall-cell lung cancer: implications for current and future therapies. J Clin Onco 12013; 31:1039-49.

11. Stella GM, Luisetti M, Pozzi E, Comoglio PM. Oncogenes in 17.non-small-cell lung cancer: emerging connections and novel therapeutic dynamics. Lancet Respir Med 2013; 1: 251-61

12. HiraLal et al CT-Guided Percutaneous Biopsy of Intrathoracic Lesions Korean J Radiol2012 : 13(2),210.

13. Noronha V, Dikshit R, Raut N, Joshi A, Pramesh CS, George 15.K, et al. Epidemiology of lung cancer in India: focus on the differences between non-smokers and smokers: a single-centre experience. Indian J Cancer 2012; 49 : 74-81

14. Wakelee HA, Chang ET, Gomez SL, Keegan TH, Feskanich 12.D, Clarke CA, et al. Lung cancer incidence in never smokers. J ClinOncol 2007; 25 : 472-8

15. ICMR, Development of an Atlas of Cancer in India, A project of national Cancer Registry Programme. 2012.

16. Minna JD, Higgins GA, Glatstein EJ; Cancer of the Lung. Cancer principles and practice Multidetector CT Evaluation of Neoplastic Lung Lesions with Image Guided Transthoracic Tissue Sampling.of oncology.2nd Ed: DeVita VT. Philadelphia: JB Lippincott Co., 1985, 507-597.

17. Bhattacharyya Sujit Kumar et al; Clinico-pathological profile of lung cancer in a tertiary medical centre in India: Analysis of 266 cases; Journal of Dentistry and Oral Hygiene March 2011. 3 (3), 30-33.

18. Byrd RB, et al: The roentgenographic appearance of squamous cell carcinoma of thebronchus. Mayo Clinproc 43: 327-332, 1968

19. Heitzman ER: Bronchogenic carcinoma; radiologic-pathologic correlations. SeminRoentgenol 165: 174, 1977.

20. Swensen S.J. et al pulmonary nodules: C.T Evaluation of Enhancement of lodinated contrast Material. Radiology 194: 393-398; 1995.

21. Shankar PS: Bronchogenic Carcinoma. Ind. J. Chest Dis. 1967; 9:161-4.

22. Jindal SK and Behera D; Clinical Spectrum of primal lung cancer-review of Chandigarh experience of 10 years. Lung India 2012; 8(2): 94-98.

23. Rigler LG: An overview of cancer of lung. Semin Rowntgenol 12: 161-164, 1977.

24. Malhotra V, Malik R, Beohar PC, Gondal R,Khanna SK, Narayanan PS. Tumours of the lung : Histomorphological study. Indian J Chest Dis Allied Sci1986; 28: 28-40.

25. Sujit Kumar et al; Clinico-pathological profile of lung cancer in a tertiary medical centre in India: Analysis of 266 cases; Journal of Dentistry and Oral Hygiene March 2011. 3 (3), 30-33.

26. Mondal SK, Nag D, Das R, Mandal PK, Biswas PK, Osta M Computed tomogram guided fine needle aspiration cytology of lung mass with histological correlation: A study in Eastern India.South Asian J Cancer 2013.2(1):14-18.

27. Mimi Gangopadhyay, Indranil Chakrabarty, Nilanjana Ghosh, AmitaGiri; Computed Tomography Guided Fine Needle Aspiration Cytology of Mass Lesions of Lung. Indian Journal of Medical and Pediatric Oncology2011Oct –Dec; 32(4) 192-196.

28. William E B,Clyde A. Helms Fundamentals of Diagnostic Radiology, Third Edition; Lippincott Williams & Wilkins, 2006, p444.

29. Byrd RB, Miller WE, Carr DT, Payne WS, Woolner LB: The roentgenographic appearance of small cell carcinoma of the bronchus. Mayo Clin Proc 43:337-341.

30. Basu BK and Ghosh T; A study of brochogenic carcinoma;Ind.J.Chest1971; 13:1-9.

31. Sanjeet Kumar Mandal et al Asian Pac J Cancer Prev, 14 (12), Asian Pacific Journal of Cancer Prevention, Vol 14, 2013; 7277-7281