Chapter-6

Unveiling Lung Cancer: Understanding, diagnosis, Treatment, and Future Frontiers

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Abstract

Lung cancer remains one of the leading causes of cancer-related mortality worldwide, necessitating a comprehensive understanding of its etiology, diagnosis, treatment, and emerging therapeutic frontiers. This abstract aims to elucidate the complexities of lung cancer, focusing on its underlying genetic and environmental factors, advancements in diagnostic techniques, and evolving treatment modalities. The pathogenesis of lung cancer is intricately linked to genetic mutations, such as those in the EGFR, ALK, and KRAS genes, alongside environmental triggers like smoking and air pollution. Diagnostic innovations, including liquid biopsies and advanced imaging techniques, have significantly improved early detection, facilitating timely and targeted interventions.

Treatment paradigms have shifted from conventional chemotherapy to precision medicine approaches, including targeted therapies and immunotherapy, which offer tailored treatment based on specific genetic alterations and tumor characteristics. These novel therapies have demonstrated improved survival rates and quality of life for patients, particularly in advanced stages of the

disease. Despite these advancements, challenges such as drug resistance and the need for personalized treatment strategies persist.

Future research is directed towards overcoming these hurdles through the development of next-generation therapeutics, exploration of combination therapies, and the integration of artificial intelligence in diagnostic and treatment planning. As our understanding of lung cancer deepens, the integration of cutting-edge science with clinical practice promises to enhance outcomes and pave the way for more effective management of this formidable disease.

Keywords: Lung Cancer, Therapeutics, Symptoms, Haemoptysis

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1. INTRODUCTION

Lung Cancer

Epidemiology

Globally, Lung cancer is one of the most commonly reported cancer with incidence of 2.2 million and 1.8 million deaths in 2020. Lung cancer rates vary between the countries with turkey having highest cancer rate in males and Hungary for females as seen in figure 1 (1). 59% of total lung cancer cases occur in Asia. In 2018 lung cancer was the third most common cause of death in India with 64000 lung cancer related death(2). NCRI 2022 provided incidence of lung cancer with 1, 03, 371 new cases of lung cancer in India. Incidence is more common among the males with a cumulative risk of 1 in 67 males(3). Lung cancer is the leading cancer among males of India (if mouth and tongue are calculated separately). In males, Among, various age groups lung cancer incidence is 11% among 40-64 year and 13.1 % among 65 and above year(3).

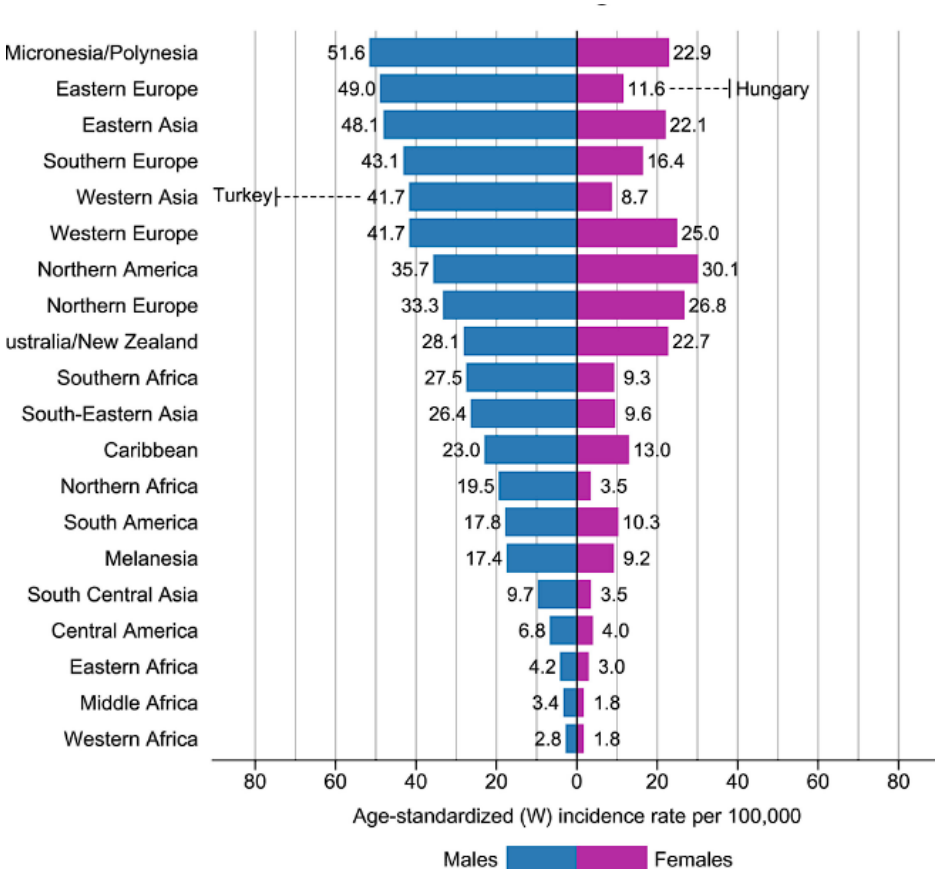


Figure 1 Reproduced from globocon 2020 Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021 May;71(3):209-249. doi: 10.3322/caac.21660

2. CLINICOPATHOLOGY

To understand the clinical features of lung cancer. We will first asses the risk factors for development of lung cancer.

Assessment of Risk Factors

US general's report of 1964 was first to report smoking to be linked to lung cancer. Now, it is proved beyond any doubt that smoking doesn't only have a causal link to lung cancer and death but is also related to adverse effects on outcomes of patient.(4) Cigarette smoking is responsible for has 90% lung cancer among men and 70 -80 % among women (5). Moreover, 30% of all cancer deaths have smoking as their primary causal factor.(4) Epidemiology of other 15-25% of lung cancer that develops in absence of smoking is less developed. Environment pollutants like indoor radon, air pollution, asbestos, nickel arsenic, chromium, cadmium, silica and diesel.(6)

Radon is a radioactive gas produced as natural decay of uranium-238. Its indoor concentration depends on the uranium content of rocks on the earth's crest beneath the dwellings. It decays by emitting alpha particles into short lived polonium 218 and polonium 214.Indoor radon is the most common (almost 50%) source of the natural radiation to which humans are exposed. (6) In India radon exposure is found to higher in mud houses because of emaciation of ground surface and poor ventilation. Radon exposure ranges from 68.7.0 Bq/m3 in kapakkam district of kerala or 76.25 Bq/m3 in Malwa Punjab to 20.9 Bq/m3 in Chennai city(7).In a sweedish study it was found that among never-smokers residential radon exposure can excess relative risk of 10% of every 100 bq/m3(8).

Other risk factors for development of lung cancer includes indoor air pollution mainly from burning of wood or coal, violation of oils, second hand smoke(passive smoking)(9). Environment and occupational toxins like asbestos, radon, arsenic, chromium, and organic dust increases risk of lung cancer in smokers as compared with nonsmokers.(10)

Clinical Features of Lung Cancer

Lung cancer presents with cough, haemoptysis, shortness of breath, loss of weight, fatigue, chest pain. A population bases case control trial with 247 patients found symptoms like cough , haemoptysis, loss of weight, loss of appetite, dyspnoea, chest pain was associated with lung cancer. Out of above, mentioned symptoms only haemoptysis has positive predictive value of more than 25. Haemoptysis with cough had lower chances of harbouring lung cancer when compared with haemoptysis alone. Cough is the most common symptoms seen with lung cancer with range of 40-65% of cases. Dyspnoea is rarely an isolated symptom noted in lung cancer. (11) On general physical examination. Clubbing of finger is associated with lung cancer, seen in around 4-6 % of cases.

Superior sulcus cancers termed as Pancoast tumors presents with shoulder and arm pain, Horner's syndrome, atrophy of intrinsic hand muscles. This is often called "Pancoast -Tobias syndrome". Hoarseness of voice, stridor and facial oedema can also be seen.

Blood test may show abnormalities like thrombocytosis, seen in 14% cases in one study. It has a positive predictive value of 1.6%. Thrombocytosis in patient with respiratory symptoms should alarm a physician about differential of lung cancer in their list.(11)

Approach to a Case with Lung Cancer

History taking and physical examination can suspect a diagnosis of lung cancer. The first investigation performed in work up is a chest X ray. It is low cost. Low risk, easy available investigation even at a peripheral centre. Lung tumors may be centrally or peripherally located. Central lesion may present with enlargement of mediastinal . bronchial obstruction may present as partial or complete atelectasis or consolidation. A peripheral lesion seen as nodules with spiculated margins figure 2. Adenocarcinoma in situ can also been as an area of chronic air space disease. (12)

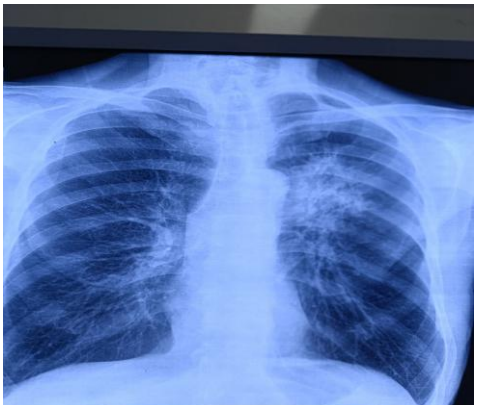


Figure 2: showing chest X ray with a lesion in left lung middle zone with spiculated margins.

Chest x ray can also show rib erosion and it is considered as sign of malignant sign(12). Abnormal Chest x ray warrant urgent referral. Sensitivity of chest x ray is 75.4% and negative predictive value of 99% suits its role as a first line investigation in areas with low prevalence.(13)

Cornerstone in imaging diagnosis of lung caner is computed tomography scan (CT scan). It used to identify the tumor site along with stage the disease. A CT scan on entire thorax along with upper abdomen till adrenals is recommended. A spiral Ct with slice thickness of 5 mm or less is modality of choice. Contrast enhancement is required as it helps in increasing detection rate of mediastinal lymph nodes and adrenals metastasis. Lung nodule characterisation can be equally with a non-contrast CT as with contrast enhanced (14).

Lung tumors can vary on CT scan from solitary pulmonary nodule to amorphous calcification. Various pathological subtypes have different presentation on CT imaging.

Adenocarcinoma: It is usually peripheral located tumor with <4 cm diameter which lacks cavitation. It can also present as localised ground glass opacity

which grows slowly (doubling time >1 year) or rapidly growing solid mass (doubling time >1 year).

Squamous Cell Carcinoma: Contrary to adenocarcinoma squamous presents with centrally located mass with > 4 cm diameter with cavitation seen in figure 3. They can cause collapse of segment or lobe of lung.

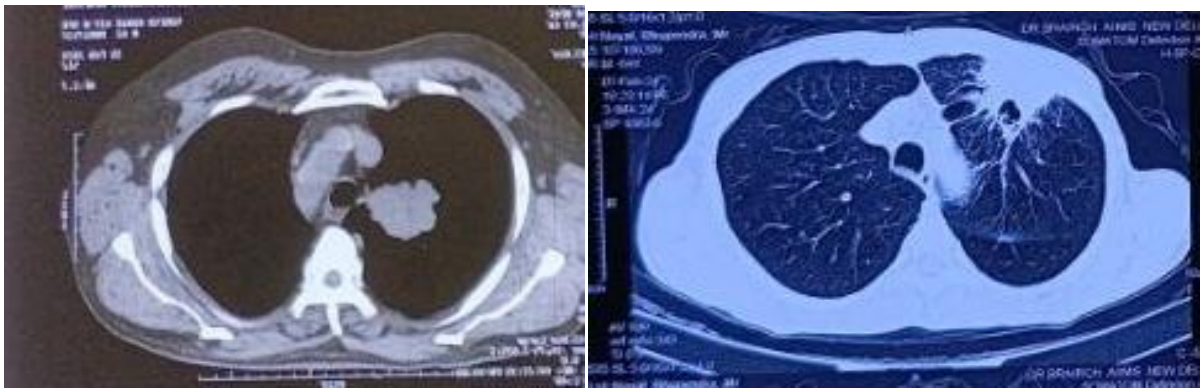


Figure 3: Showing Left Side a Central Localate Lesion with Solid Component and Slight Necrosis Present at Centre and Image on Right Showing A Peripheral Lesion with Spiculated Margins.

Bronchoalveolar Carcinoma: It can present in 3 ways – commonly as solitary pulmonary nodule, diffuse multicentric disease, localised area of pulmonary consolidation. Bubbles like area of low attenuation mass within are characteristic of it. Lymphadenopathy is fairly uncommon.

Small Cell Carcinoma: It presents often with bulky hilar and mediastinal lymph nodes masses .In almost half of cases a non-contiguous hilar solid parenchymal mass is also identified.

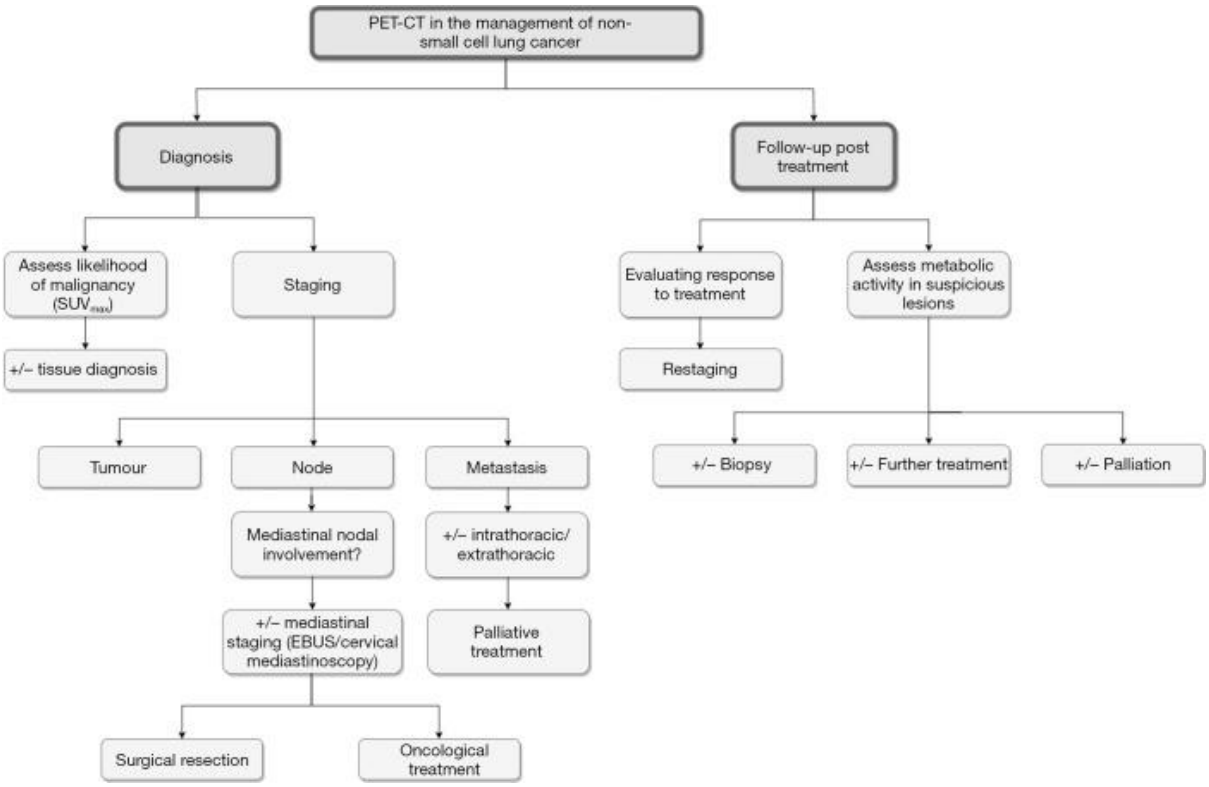
Large Cell Carcinoma: They are rapidly growing mass with tendency of excavation. They often metastasise early with to hilar of mediastinal lymph nodes (12)

Solitary Pulmonary Nodules (SPN): CT scan when used for population bases screening were found to detect lot many nodules as compared with chest X ray. However, very few out of them are malignant. A single mass, well or poorly defined, of size 3 cm or less. Size, radiological characteristics and doubling time are important factors that predict behaviour of the SPN. A triangular or polygonal shaped, located near the fissure, smooth borders with popcorn calcifications indicated a benign nature. A subsolid morphology with spiculation and pleural retraction, bronchial abnormality, vascular convergence sign indicates malignant behavior (15).

Ground Glass Opacities: It refers to an area of increased attenuation with preserved bronchial and vascular markings. They can be pure ground glass, part solid or mixed GGN. A part solid GGN has highest malignant potential. A change in size of GGO or development of solid component also indicated malignant transformation. 2016 Asian consensus guidelines on GOO recommend a solitary Pure GGO <5mm requires no follow up. Larger >=5 mm requires annual follow up for at least 3 years.(16)

Part solid <8 mm requires follow up CT on 3,12,24 month and annual follow up thereafter. Larger part solid >= 8mm or with solid component > 6mm requires a biopsy or Pet CT as additional staging option (16).

Role of PET scan: 18-FDG PET (positron emission tomography) is now considered to be standard of care in staging work up of lung cancer. Combined with CT, PET-CT combines both anatomical and metabolic data to yield a better result when compared with CT or PET alone. Sensitivity and specificity of PET-CT for malignant pulmonary lesion is 94.2% and 83.3% respectively (14).



Reproduced from Volpi S, Ali JM, and Tasker A, Peryt A, Aresu G, Coonar AS. The role of positron emission tomography in the diagnosis, staging and response assessment of non-small cell lung cancer. Ann Transl Med. 2018 Mar;6(5):95. doi: 10.21037/atm.2018.01.25

For primary lesion PET can help characterise SPN to benign or malignant with a diagnostic accuracy of 93.5%. SUV values are generally higher for malignancy except for the bronchoalveolar carcinoma and adenocarcinoma in situ (17).

PET-Ct has greater accuracy than CT alone for nodal staging of lung cancer. It has been reported to have an accuracy of 90% with sensitivity and specificity of 85% and 92% respectively. However small nodes of size 10-15 mm diameter are less likely to be detected on PET imaging (18). PET Ct can now used as tool of mediastinal staging, as a negative mediastinum on pet can be proceed with surgery without invasive staging of mediastinum (figure 4).

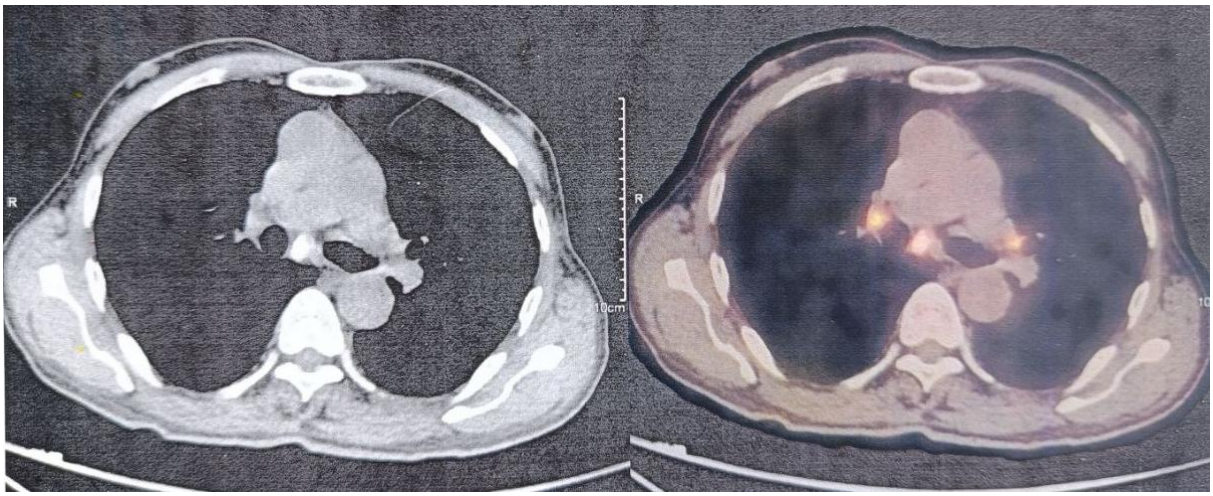


Figure 4: Shows Mediastinal Lymph Nodal Enlargement Seen on Ct Image on left which is FDG Avid as seen in the Image on Right.

40% of patients OF NSCLC (Non-small cell lung cancer) presents as metastatic disease. PET CT is useful in diagnosing adrenal metastasis with a PPV of 95%. Bone metastasis can also be diagnosed as 'hot spots' within in the bone. PET CT is superior to bone scintigraphy for their detection with specificity of 98%. PETCT is inferior to MRI brain for diagnosis of Brain metastasis.

Pathology of Lung Cancer: Lung cancer is classified into 2 major subgroups non small cell carcinoma (NSCLC) and small cell lung carcinoma(SCLC).
Non small cell carcinoma is further subclassified broadly into

1. Adenocarcinoma
2. Squamous Cell Carcinoma
3. Large Cell Carcinoma

IN 2015 WHO has updated the classification further with introduction of IHC (immunohistochemistry) for accurate identification and classification of

lung cancer subtype(12) . Genetic testing and thereby, molecular pathology continues to evolve in the lung cancer and hence WHO 2021 came with recent update in Lung cancer classification with major features 1) broader emphasis on genetic testing 2) classification for small diagnostic samples 3) part lepidic non-invasive mucinous adenocarcinoma 4) prognostic significance of spread through airspaces (STAS) 5) Lymphoepithelial carcinoma to be reclassified as squamous cell carcinoma .(19)

1. **Adenocarcinoma:** It is most common type of lung cancer in the west accounting for 60% of NSCLC. It arises from lung epithelium and has glandular differentiation or mucin production. It presents as peripherally occurring mass with central fibrosis which leads to pleural puckering.. On IHC they show pneumocytic marker like Napsin A and TTF-1. (20)If diagnosed solely on the basis of IHC a diagnosis of NSCLC favouring adenocarcinoma is reported(19). Adenocarcinoma can be further divided in to various subtypes with different prognosis they include
   a. **Preinvasive or Minimally Invasive Adenocarcinoma:** Previously called bronchoalveolar carcinoma or alveolar cell carcinoma. They are usually <= 3 cm size tumor with shows characteristic lepidic growth. Lepidic (Greek Lepis- scaly) pattern of growth refer to cell proliferating along the surface of intact alveolar wall. They are seen as ground glass opacity on the radiograms and if excised and good prognosis.

      If invasive component is found it is usually <= 5 mm and such is called minimally invasive Adenocarcinoma.

   b. **Invasive Adenocarcinoma:** They are subdividing on the basis of the predominant pattern of growth like lepidic, acinar, papillary, micropapillary and solid pattern. Solid and micropapillary are associated with poor prognosis. They are graded as below

Grade 1 (well differentiated)	Lepidic predominant with no or <20% high grade pattern
Grade 2 (moderately differentiated)	Acinar or papillary predominant with no <20% high grade pattern
Grade 3 (poorly differentiated)	Any tumor with >= 20% high grade pattern

Table 1 Adapted from WHO classification of Tumors, Thoracic Tumours, and Fifth Edition. Cooper WA, Bubendorf L, Kadota K et al. Tumours of the lung. Page 71, IARC, 2021(21)

c. **Other Variants:** It includes mucinous adenocarcinoma, enteric type adenocarcinoma and foetal adenocarcinoma.

2. **Squamous Cell Carcinoma (SCC):** SCC is 20% of lung cancer. They are more frequent in Asian population owing to smoking behaviour. Keratin pearls, intercellular bridges and nested growth pattern are characteristic of SCC. It can be further divide into keratinising, none keratinising and basaloid type. Basaloid type has poor prognosis and is resistant to chemotherapy (20).on IHC p40, Ck5/6 P63 will represent squamous differentiation.

3. **Large Cell Carcinoma:** They are characterised by large tumor cell polygonal shape with pleomorphic and vesicular nuclei. Ther lack morphological differentiation and IHC markers. Hence on biopsy are classified as NSCLC NOS (Not otherwise specified). Other type of NSCLC includes Giant cell, spindle cell and pleomorphic cell carcinoma.

   2021 Update: Lung adenocarcinoma identified oncogenic driver mutations that include EGFR, ALK, ROS, and ERBB2. The incidence of the mutation in East Asia and US is given below in the table Table 2 adapted from.(19)

Gene Altered	East Asia (%)	USA/Europe (%)
EGFR	40–59	5–19.4
ALK	3–7	3–6
ROS1	1–3	1–2
ERRB2	2–3	2–3
RET	1–2.2	1–2
BRAF V600E	0.5–1	2–3
Met ex14	2	3
NTRK1/2/3	<1	0.23
KRAS	7.4–11	20–30
NRAS	0.4	1.2
MAP2K1	<2	0.7
TP53	36	42
STK11	4.4	11
KEAP1	5	15
PIK3CA	4	2
CTNNB1	4.4	2.5
PTEN	4.8	2
NF1	3	1.9
TSC ½	<2	0.7
FGFR1/2	NA	0.7

Diagnosis and Work Up: Diagnosis of lung cancer, Non small cell type, requires a biopsy which can be fine needle aspiration biopsy of lung mass/ lymph node regional or non regional or core needle biopsy of the lung mass. Core needle biopsy of the lung mass is often done with image guidance than can be ultrasound fluoroscopy or CT. In cases of pleural effusion associated with lung cancer, cytology of pleural fluid can be sending for cytology. Differentiation is between NSCLC vs SCLC is prime importance as management of them is very different from each other.(22) Bronchoscopy can allow diagnosis of central tumors with a sensitivity of 88% for central tumors and 78% for peripheral tumors (23). Bronchoscopy can also be clubbed with endobronchial ultrasound to identify the regional lymph nodes and biopsy them at the same time. (24)

After confirmation of histological diagnosis staging of lung cancer will include a CT chest, PET scan < MRI brain for accurate staging tumor (T) and Metastasis (M) criteria. Staging of lung cancer according to AJCC 8th edition is described in the Figure.

Figure 5: reproduced from Lababede O, Meziane MA. The Eighth Edition of TNM Staging of Lung Cancer: Reference Chart and Diagrams Oncologist 2018 Jul;23 (7):844-848. doi: 10.1634/theoncologist.2017-0659.

Primary Tumor (1)	
Category	**Definition**
Tx	Tumor that is Proven Histopathologically (Malignant Cells in Bronchopulmonary Secretions/Washings) but Cannot be Assessed or is not Demonstrable Radiologically or Bronchoscopically.
T0	No Evidence of Primary Tumor.
Ts	Carcinoma in Situ: Squamous cell carcinoma in situ. Adenocarcinoma in situ (pure lepidic pattern and ≤3 cm in greatest dimension).
T1	Size: ≤ 3 cm. Airway Location: in or Distal to the Lobar Bronchus. Local Invasion: none (Surrounded by Lung or Visceral Pleura). Subdivisions: T1mi: Minimally invasive adenocarcinoma (pure lepidic pattern, ≤ 3 cm in greatest dimension and ≤ 5 mm invasion)-Tla (size ≤1 cm)-T1b (1 cm < size ≤2 cm)-T1c (2 cm < size≤3 cm).
T2	Any of the Following Characteristics: Size: > 3 cm but ≤5 cm. Airway Location: Invasion of the main bronchus (regardless the distance to the carina) or presence of atelectasis or obstructive. Pneumonitis that extends to hilar region (whether it is involving part or the entire lung).

	Local Invasion: Visceral Pleura (PL1 or PL.2). Subdivisions: T2a (3 cm ≤ size ≤4 cm or cannot be Determined) and T2b (4 cm < size ≤ 55 cm).
T3	Any of the Following Characteristics: Size: > 5 cm but ≤ 7 cm. Local Invasion: Direct Invasion of Chest Wall (Including Superior sulcus Tumors), Parietal Pleura (PL3), Phrenic Nerve, or Parietal Pericardium. Separate Tumor Nodule(s) in the same Lobe of the Primary Tumor.
T4	Any of the Following Characteristics: Size >7 cm. Airway Location: Invasion of the Carina or Trachea Local Invasion: Diaphragm, Mediastinum, Heart, Great Vessels, Recurrent Laryngeal Nerve, Esophagus or Vertebral Body. Separate Tumor Nodule(s) in an Ipsilateral Different Lobe of the Primary Tumor.
Lymph Nodes (N)	
Descriptor	**Definition**
Nx	Regional Lymph Nodes cannot be Evaluated.
N0	No Regional Lymph Nodes Involvement.
N1	Involvement of Ipsilateral Peribronchial and/or Ipsilateral Hilar Lymph Nodes (Includes Direct Extension to Intrapulmonary Nodes).
N2	Involvement of the Ipsilateral Mediastinal and/or Subcarinal Lymph Nodes.
N3	Involvement of any of the following lymph node groups: Contra lateral meditational, contra lateral Hilar, Ipsilateral or Contralateral Scalene, or Supraclavicular Nodes.
Distant Metastasis (M)	
M0	No Distant Metastasis.
M1	Presence of Distant Metastasis. Subdivisions: Mla (Separate Tumor Nodule(s) in a Contralateral Lobe to that of the Primary Tumor or tumors with Pleural or Pericardial Nodules or Malignant Effusion); M1b (Single Extrathoracic Metastasis); MIc (Multiple Extrathoracic Metastases to One or more Organs).
Note: Tumor's size is determined by the greatest dimension of the lesion. "The Uncommon Superficial Spreading Tumor With Invasive Component Limited to Bronchial Wall is Classified as Tla Regardless of Size or Extent to Main Bronchus.	

Nodal (N) Stage: The nodal stations of lung cancer are classified broadly in to three groups. N1 hilar or intra pulmonary nodes (nodal station 10-14), N2 is ipsilateral mediastinal lymph node(nodal station 2-4 and 7-9) of ipsilateral side and subcarinal lymph node , N3 is contralateral mediastinal(station 2-4),

contralateral hilar and bilateral supraclavicular and scalene group of lymph nodes(station 1)(25). The figure below represents nodal station in lung cancer

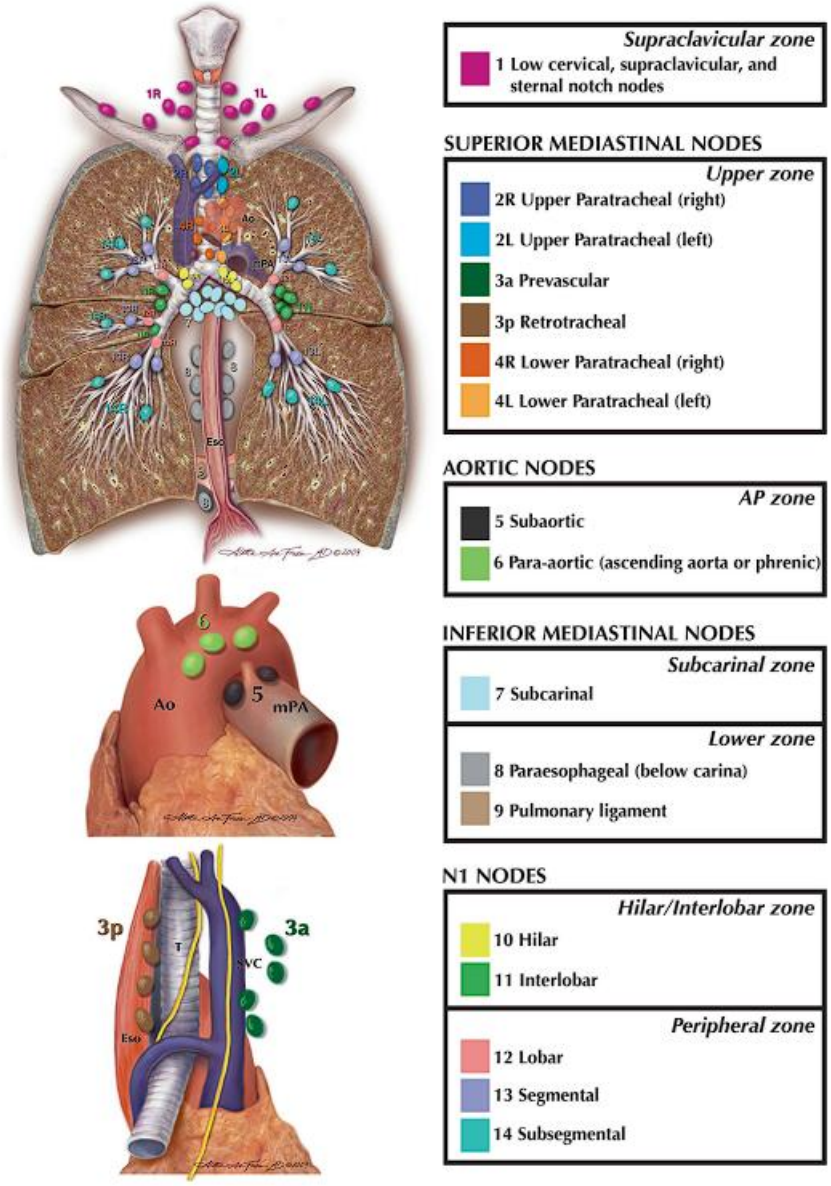


Figure 6: Reproduced from International Association for the Study of Lung Cancer Lymph Node Map (From Rusch et al.15 Copyright © 2008 Aletta Ann Frazier, MD)

Though PET -CT or diffusion weighted MRI can diagnose presence of mediastinal lymph node and their likely involvement. Invasive mediastinal staging is still done to confirm the nodal involvement.

Endoscopic bronchial Ultrasonography (EBUS) with fine needle aspiration is most widely used method of mediastinal staging in the current era. It allows evaluation of 2R,2L,3P4R,4L and station 7 lymph node. EBSU is

unlikely in evaluating Station 5,6,8,9,10 lymph nodes. Station 8 and 9 can be evaluated through oesophagus.(26)

Mediastinoscopy is done through cervical incision allows evaluation of superior and middle mediastinum. This can evaluate station 2R,2L, 4R, 4L, 7, 8R, 8L10R, 10L.

Chamberlain's procedure was initially developed as a technique to biopsy bronchogenic carcinoma reaching the anterior mediastinum. It involved incision in left 2nd intercoastal space removing the 2nd coastal cartilage. On right side lymph nodes along trachea and SVC can be evaluated and left side hilar Ap window lymph nodes can be evaluated. (27)

Video assisted mediastinoscopic lymphadenectomy and transcervical mediastinal lymphadenectomy are newer techniques for mediastinal lymph node evaluation. (26)

3. MANAGEMENT OF LUNG CANCER (NSCLC)

Multimodal approach involving surgery, systemic therapy and radiation are intrinsic in management of NSCLC. Staging of lung cancer as per AJCC 8th edition is depicted in the table below

Table 3: Staging of Non Small Cell Lung Cancer Reproduced from AJCC 8th Edition.

Stage	T	N	M
Occult carcinoma	TX	N0	M0
0	Tis	N0	M0
IA1	T1mi	N0	M0
	T1a	N0	M0
IA2	T1b	N0	M0
IA3	T1c	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIB	T1a, b, c	N1	M0
	T2a, b	N0	M0
	T3	N0	M0
IIIA	T1a, b, c	N2	M0
	T2a, b	N2	M0
	T3	N1	M0
	T4	N0	M0

	T4	N1	M0
IIIB	T1a, b, c	N3	M0
	T2a, b	N3	M0
	T3	N2	M0
	T4	N2	M0
IIIC	T3	N3	M0
	T4	N3	M0
IVA	Any T	Any N	M1a
	Any T	Any N	M1b
IVB	Any T	Any N	M1c

Surgical resection is curative in stage I,II. Adjuvant platinum provided absolute benefit of 5 year of overall survival of 5.4%. Hence recommended Patients with large tumors T3 or above or N2 nodes or above will benefit from preoperative systemic therapy (26) . Non surgical candidates will require chemoradiation with or without immunotherapy. We will discuss management of NSCLC stage wise.

Stage 1 and Stage 2: Stage 1 included patient with tumor size <4 cm without obvious lymph nodal involvement. Patient firs for surgery are then assessed for if they can tolerate pneumonectomy or bilobectomy or lobectomy. (28)

Lung sparing anatomic resection including sleeve resection are preferred over pneumonectomy. Segmentectomy or wedge resection are done only if the patient is not fit for lobectomy or peripheral tumors <2 cm size with very low risk features. Segmentectomy should achieve negative margins. If the patient is not fit for any of the surgical procedure stereotactic ablative radiotherapy (SABR) is an option for tumor less than 5 cm size(29).

Adjuvant systemic therapy is indicated in the people with stage II and above. cisplatin based chemotherapy is preferred includes cisplatin75mg/m2 day 1 and pemetrexed 500 mg/m2 day 1 for 21 days cycles for 4 cycles for non-squamous histology and for squamous histology cisplatin and gemcitabine (1250mg/m2) or docetaxel(75mg/m2) is recommended.(30)

All patients above stage 1 b and above can be considered for neoadjuvant systemic therapy followed by surgical resection.

Minimal invasive thoracic surgery including (VATS(video assisted thoracic surgery, uniportal lung resections) are equivalent to routine open resection with decreased pain , blood loss, number of days in hospital and aids better recovery

Lymph node dissection in patients who had already underwent invasive mediastinal staging and found to N0, N1 disease. Systematic mediastinal lymph node sampling is equivalent to complete mediastinal lymph node dissection (ACOSOGZ0030). Systematic mediastinal lymph node sampling includes evaluation of station 2R,4R,7,8,9 for right side tumors and Station 4L,5,6,7,8,9 for left side tumors. A minimum of 3 N2 station have to be sampled (31).

Stage 3: Preoperative systemic therapy is indicated in the selected patients who can undergo surgical resection. T3 and T4 with local extension of the disease can be resected enblock with negative margins. For patient with N2 disease found while performing resection. Planned resection should be completed. If N2 node is found preoperatively neoadjuvant systemic therapy is given and surgical resection of primary mediastinal lymph node dissection should be considered if appropriate response (30).

Neoadjuvant systemic therapy includes chemotherapy and immune check point inhibitor/ targeted therapy. All patients should undergo test for PDl-1, EGFR, ALK rearrangements. Nivolumab/pembrolizumab with platinum doublet therapy is recommended in the patients with Resectable NSCLC. Importantly, neoadjuvant should not be used to induce resectability and patient deemed unresectable should undergo chemoradiation. (31)

Role of Chemoradiation

Concurrent or sequential chemoradiation can be offered. Concurrent regimens are preferred and are recommended for all histologies. Cisplatin based doublet regimen or weekly paclitaxel with carboplatin is recommended. Radiation is given at dose of 60-70 gy with 2 gy/fraction. Preoperative Rt can also be given but surgery post radiation is associated with higher complications and require experience surgical techniques for the same.(30)

Consolidation immunotherapy with durvalumab can be given to patient who had no disease progression after definitive concurrent chemoradiation

Metastatic NSCLC

Advanced or metastatic lung cancer should undergo testing for all the biomarkers below and targeted therapy should be directed as indicated. The table given below mentions the agents that can be used against specific targets. If progression is seen with these agents platinum based systemic therapy can be utilised. Non responsive patients may require best supportive care and symptoms palliation like palliative RT, Laser therapy, photodynamic therapy or embolization for haemoptysis SVC obstruction may require external Beam RT.

SVC stenting, endobronchial obstruction may require laser, or photodynamic therapy bronchial stenting ,Recurrent pleural effusion indwelling pleural catheters(32) .

Table 4: Adapted from NCCN Version 2.2024 and Update 2020: Management of Non-Small Cell Lung Cancer Alexander M, Kim S, Cheng H et al

Target Muations	Targeted Therapy
EGFR exon 19 deletion or exon 21 L858R mutation positive NSCL	Osimertinib, Erlotinib, Afantinb, Gefitinib
EGFR S768I, L861Q, and/or G719X mutation positive NSCL	Afantinib Preferred
EGFR exon 20 insertion mutation positive NSCL	Amivantamab
ALK rearrangement positive NSCL	Alectinib, Brigantinib
ROS1 rearrangement positive NSCL	Entrectinib,Crizotinib, Repotrectinib
BRAF V600E mutation positive NSCL	Dabrafeninb + Tarmetinib
NTRK1/2/3 gene fusion positive NSCL	Larotrectinib
METex14 skipping mutation positive NSCL	Capamatinib, Tepotinib
RET rearrangement positive NSCL	Selpercatinib,Praseltinib
ERBB2 (HER2) mutation positive NSCL	Fam Trastuzumab Deruxtecan
PDL1 ≥1% and negative for actionable molecular biomarkers above NSCL	Pembrolizumab, Atezolizumab, Nivolumab

4. CONCLUSION

Non-small cell lung cancer is one the most common cancer in India and world. Reduction of risk factors with early diagnosis and accurate staging provides key to management. Multimodal therapy with use of Targeted agents has paved a new landscape for management in resectable, unresectable and metastatic disease.

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