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# SHIFTING PARADIGMS IN MANAGEMENT OF LUNG CANCER

**Lt Col. Dr. Virender Suhag*[1] and Lt Col. Dr. Manu Chopra[2]**

[1]MD DNB Radiation Oncology, Professor Radiation Oncology, Department of Radiation Oncology, Army Hospital (R&R), Delhi, India.

[2]MD DNB Pulmonary Medicine, Classified Specialist, Department of Pulmonology, Army Hospital (R&R), Delhi, India.

***Corresponding Author: Dr. Lt Col. Virender Suhag**

MD DNB Radiation Oncology, Professor Radiation Oncology, Department of Radiation Oncology, Army Hospital (R&R), Delhi, India.

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## INTRODUCTION

Lung cancer is the most common cancer worldwide and is the leading cause of cancer-related mortality and morbidity in both men and women. In 2012, approximately 1.8 million new cases of Ca lung were diagnosed, accounting for 13% of the global cancer burden and 19 per cent of cancer related deaths. In 2016, the number has risen further and an estimated 224,390 new cases of lung cancer will be diagnosed.[1] In India, lung cancer constitutes 6.9 per cent of all new cancer cases and 9.3 per cent of all cancer related deaths in both sexes. The overall 5-year survival rate of lung cancer is dismal with approximately 15 per cent in developed countries and 5 per cent in developing countries.[2]

Traditionally, lung cancer treatment was decided based on histological subtyping into small cell lung cancer (SCLC) and non small cell lung cancer (NSCLC). NSCLC is again subdivided into adenocarcinoma, squamous cell carcinoma and large cell carcinoma. With the changing smoking habits, adenocarcinoma has surpassed squamous cell carcinoma. There is also increasing incidence of lung cancer in females and non smokers. The histological classification is now stretching to molecular classification. Newer molecular targets and driver mutations have been identified which play a major role in pathogenesis that can be addressed with therapeutic interventions. These advancements have led to the development of more individualized treatment modalities, the so called era of "personalized medicine".[3]

The etiopathogenesis of Ca lung is multifactorial, involving exogenous exposures, genetic variations and an accumulation of somatic genetic events. The epidemiological, geographical and histopathological scenario of lung cancer has witnessed considerable change in the past two decades and so has the management. Pharmacologic agents that target protein products of oncogenes in tumors are playing an increasing clinical role in the treatment of cancer and targeted therapy is playing a vital role in the management of lung cancer. Historically, the mainstay of treatment was lobectomy for resectable lung cancer and chemoradiation for advanced disease. Minimally invasive local treatment modalities including dose-intensified conformal radiation therapy, stereotactic ablative radiotherapy and thermal ablation methods such as radiofrequency ablation and microwave ablation are emerging as promising treatment options in the treatment of early stage lung cancer.[4,5]

Recent advancement in molecular biology techniques has enabled the clinicians to understand the molecular basis of the disease, and the concept of targeted therapy has gained popularity. Clinically relevant molecular subsets are being identified which are governed by driver mutations in genes crucial for cell proliferation and survival. The most frequently mutated genes in lung cancer are TP53 (53.6%), KRAS (16.1%), STK11 (9.8%), EGFR (7.2%), KEAP1 (6.6%) and NFE2L2 (4.5%). This molecular subtyping would enable practice of personalized medicine which is based on the concept of giving "right medicine for the right patient at the right time". Adequacy of tumour tissue for molecular profiling is an important issue and even more relevant in lung cancer where the tissue yield is limited by small core biopsies. Judicious use of immunohistochemistry and conservation of samples for molecular testing would be helpful. Cell free circulating tumour DNA is also emerging as a useful tool in these situations and can be used for mutation testing and therapeutic monitoring.[2,6]

Epidermal growth factor receptor (EGFR) mutation positive NSCLC is emerging as an important subtype of lung cancer comprising 10% to 15% of non-squamous tumours. This subtype is more common in women than men and is less associated with smoking. Erlotinib, gefitinib, and afatinib are all active agents in these patients, and demonstrate an increased tumour response rate and prolonged progression-free survival. EGFR

mutation should be done in patients of adenocarcinoma lung particularly non-smoker females with Stage III and IV disease.[7-9] Similarly Crizotinib is a novel targeted anticancer agent that appears to be a favorable treatment option for patients with locally advanced or metastatic NSCLC that is anaplastic lymphoma kinase (ALK-positive), with low toxicity, predominantly restricted to the gastro-intestinal and visual systems, and generally self-limiting or easily managed. However, resistance to these agents continue to pose a challenge.[10,11]

Interventional pulmonology is a rapidly expanding field offering less invasive diagnostic, therapeutic and palliative procedures for a wide spectrum of lung cancer cases. Various techniques, including standard bronchoscopy, transthoracic needle aspiration and mediastinoscopy, are used for diagnosis and staging of lung cancer. Currently available techniques for the initial diagnosis of lung cancer include electromagnetic navigation bronchoscopy with computed tomography mapping and sample collection, endobronchial ultrasound (EBUS) using radial or convex probe tips, and the combination of the two approaches. EBUS is performed with a specially design flexible bronchoscope and allows safe and accurate sampling of intrathoracic structures through the airway wall under direct visualization. EBUS with transbronchial needle aspiration (EBUS-TBNA) is highly specific and sensitive for the examination of mediastinal lymph nodes. EBUS-TBNA and mediastinoscopy achieve similar results for the mediastinal staging of lung cancer and the former can replace mediastinoscopy in patients with potentially resectable non-small cell lung cancer.[12,13]

Interventional pulmonologists can also be trained to perform ultrasound guided thoracentesis, closed-needle pleural biopsy and medical thoracoscopy to help in the diagnosis of different pleural pathologies. Airway stenting and ablative techniques such as laser, electrocautery, cryosurgery and microdebrider techniques are example of resources that can be used by interventional pulmonologists for therapeutic purposes. A number of effective therapies for the management of malignant pleural disease have been studied in recent years, including chemical pleurodesis and tunnelled pleural catheters, greatly adding to our understanding of which therapy to use in which patient. Specialized anaesthetic support and appropriately trained endoscopy staff are essential, allowing a multimodality approach to meet the high complexity of these cases.[14,15]

Computed tomography (CT) and positron emission tomography (PET) using fluorodeoxyglucose (FDG) play an important role in the diagnosis and staging of lung cancer. PET-CT has revolutionized the management of Ca lung by more accurate initial workup of primary and metastatic disease, response assessment and early detection of recurrence during follow-up. FDG-PET allows differentiation between malignant and benign lesions based on differences in glucose metabolism between normal and cancer tissues. FDG-PET is more accurate than CT for the diagnosis and staging of NSCLC. CT provides excellent morphologic information but has significant limitations in differentiating between benign and malignant lesions either in an organ or in lymph nodes. FDG-PET is highly accurate in the detection of mediastinal lymph node metastases as well as extrathoracic metastases. FDG-PET accurately differentiate recurrent cancer from benign inflammatory process in patients with clinically suspected recurrence. PET CT can also help take guided biopsies from most representative tissue and also assist in radiation treatment planning.[16,17]

Over the past 10 years, considerable progress in radiation delivery techniques has been made by the development of highly sophisticated linear accelerators compatible with 3 dimensional conformal radiotherapy (3DCRT), intensity modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT); leading to high-precision radiotherapy and dose escalation to improve local control and thus probability of overall survival.[18] Accurate delineation of critical organs and pretreatment analysis of toxicity-predicting factors allow for better protection of normal intrathoracic tissues such as lung, heart and esophagus with a significant reduction in the incidence of radiation esophagitis and pneumonitis. Concurrent administration of cytotoxic drugs like paclitaxel, carboplatin and cisplatin along with radiotherapy further enhance this effect though at the cost of added toxicities. The respective benefits of either induction or consolidation full-dose chemotherapy before or after concurrent chemoradiotherapy have shown encouraging results. Stereotactic body radiotherapy (SBRT) has emerged as a novel radiation modality with significant applications in the inoperable and in early-stage lung cancer population. SBRT is noninvasive, convenient, fast and economically attractive; it achieves results similar to surgery for early or metastatic lung cancer patients who are older, debilitated and with comorbidities.[19,20]

The standard of care for unresectable lung cancer is a combination of chemotherapy and external-beam radiation. Selected patients, especially those with predominantly endobronchial tumor, may benefit from endobronchial brachytherapy, either alone or as a boost to external-beam radiation therapy. The ideal patients for curative endobronchial radiation alone are those with occult carcinomas of the lung confined to bronchus or trachea. Endobronchial brachytherapy with curative intent is indicated in early-stage patients who are medically inoperable because of decreased pulmonary function, advanced age, or refusal of surgery. Endobronchial brachytherapy can be used as adjuvant treatment after surgical resection with minimal residual disease. Interstitial brachytherapy is used infrequently, but its use in selected patients appears to be promising.[21,22]

For palliation of obstructive symptoms in patients with peribronchial and endobronchial disease, other endoscopic techniques that may be used alone or in combination with endobronchial brachytherapy should also be considered. Neodymium: yttrium-aluminum-garnet (Nd:YAG) laser therapy controls bleeding and rapidly debulks obstructive airway lesions. The laser can open a completely occluded bronchus to allow passage of the endobronchial brachytherapy catheter beyond the tumor site, and endobronchial brachytherapy can address tumor beyond the bronchial lumen. Cryotherapy is another option which kills tumor cells by freezing them repeatedly to -80°C with liquid nitrogen or nitrous oxide. The cryoprobe must be able to reach the tumor through the bronchoscope. Silicon or metal airway stents mechanically maintain patency of the trachea and major bronchi but do not address tumor regrowth. Metal stents may induce inflammation and additional scarring, while silicon stents may become occluded with secretions. Stents may also migrate or require removal or replacement, which can be problematic if they are fixed to underlying tumor or scar.[23,24]

As more low-dose computed tomography (LDCT) lung cancer screening programs are implemented in the developed world, more patients with early-stage lung cancer who could benefit from surgical intervention will be identified. Although lobectomy currently remains the standard of care for early-stage NSCLC, thoracic surgeons are increasingly adopting minimally invasive surgery via thoracoscopy as a viable approach for select lung cancer resections. Video-assisted thoracic surgery (VATS) lobectomy has been associated with decreased perioperative morbidity, with similar rates of locoregional recurrence and cancer-free survival. More tailored, personalized therapy is increasingly been recommended as quality-of-life parameters and surgical quality indicators are gaining wide acceptance. The principal aim of surgical treatment for NSCLC is to obtain a complete resection which has been precisely defined by a working group of the International Association for the Study of Lung Cancer (IASLC). Intraoperative staging of lung cancer is of utmost importance to decide on the extent of resection according to the intraoperative tumour (T) and nodal (N) status. Systematic nodal dissection is generally advocated to evaluate the hilar and mediastinal lymph nodes. Lymph-node involvement not only determines prognosis but also the administration of adjuvant therapy.[25,26]

To conclude, development of predictive biomarkers, availability of targeted therapies for personalized treatment, better radiation delivery techniques, minimally invasive surgical approach and increasing awareness and screening programs can improve the outcome of lung cancer in the years to come.

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