Review Article

Lung cancer in the Indian subcontinent

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Abstract

Smoking tobacco, both cigarettes and beedis, is the principal risk factor for causation of lung cancer in Indian men; however, among Indian women, the association with smoking is not strong, suggesting that there could be other risk factors besides smoking. Despite numerous advances in recent years in terms of diagnostic methods, molecular changes, and therapeutic interventions, the outcomes of the lung cancer patients remain poor; hence, a better understanding of the risk factors may impact the preventive measures to be implemented at the community level. There is a lack of comprehensive data on lung cancer in India. In this review, we attempt to collate the available data on lung cancer from India.

Key words: Epidemiology, India, lung cancer, nonsmokers

Introduction

There is a dearth in our current understanding of the changing epidemiological trends of lung cancer among Indian patients. While the global trend of a rise in adenocarcinoma appears to be paralleled in India, we do not completely understand the alarming rise in the incidence of lung cancer among the nonsmokers. We have, in particular, a limited understanding of the impact of the factors that are unique to our region such as the presence of indoor air pollution, the use of domestic or biomass fuel exposure, the presence or lack of micronutrients in our diet, occupational exposure, and the possible contribution of infectious pathogens such as *Mycobacterium tuberculosis*. Smoking tobacco, both cigarettes and beedis, is the principal risk factor for causation of lung cancer in Indian men; however, among Indian women, the association with smoking is not strong, suggesting that there could be other risk factors besides smoking. Despite numerous advances in recent years in terms of diagnostic methods, molecular changes, and therapeutic interventions, the outcomes of the lung cancer patients remain poor; hence, a better understanding of the risk factors may impact the preventive measures to be implemented at the community level. In this review, we attempt to collate the available data on lung cancer from India.

Epidemiology

Lung cancer is the most common cancer diagnosed worldwide. It is also the foremost contributor to cancer-related mortality, resulting in 1.38 million cancer deaths per year worldwide.[1] Lung cancer accounts for more deaths than any other type of cancer. Several epidemiological observations performed across varied demographic cohorts in India confirm the significant burden of lung cancer in India, contributing significantly toward the cancer morbidity and mortality.[2]

According to the GLOBOCAN 2012 report, the estimated incidence of lung cancer in India was 70,275 in all ages and both sexes; the crude incidence rate per 100,000 was 5.6, the age-standardized rate per 100,000 (world), i.e. ASR (W) was 6.9, and the cumulative risk was 0.85. In terms of incidence rates, lung cancer ranked fourth overall among the various types of cancer (excluding nonmelanoma skin cancer) after breast, cervical, and oral cavity cancer; in males, it ranked second while in females it was sixth in terms of cancer incidence. There were 53,728 new lung cancer cases among Indian males (crude incidence rate - 8.3, ASR (W) – 11, and cumulative risk - 1.36) and 16,547 new lung cancer cases among Indian females (crude incidence rate - 2.7, ASR (W) - 3.1, and cumulative risk - 0.37). The overall estimated lung cancer mortality in India in 2012 was 63,759, making it the third most common cause of cancer-related mortality in India after breast and cervical cancer. Among Indian males, lung cancer was the most common cause of cancer mortality at 48,697; the estimated lung cancer mortality among Indian females was 15,062 (ranking seventh in terms

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of cancer-related mortality in Indian women behind breast, cervix, colorectal, ovary, stomach, and lip/oral cavity cancer).[3] The quality of the data acquired from Indian hospital-based registries and regional cancer registries may be hindered by incomplete penetrance of disease registration across the different states of India, resulting in an underestimation of the overall burden. As per the GLOBOCAN 2008 report, males predominate with a male:female ratio of 4.5:1, and this ratio varies with age and smoking status. The ratio increased progressively till 51–60 years and then remained steady. Various reports have noted that the smoker:nonsmoker ratio is high at 20:1. After the age of 40 years, the squamous cell type was the most common in smokers and adenocarcinoma was common in the nonsmokers. The current demographic pattern of lung cancer in India appears to be similar to that seen in the Western countries approximately 40 years ago. There appears to be a marginal increase in the mean age of diagnosis of lung cancers in India over the years from 52.16 years during 1958–1985 to 54.6 years during 1985–2001.

The history of published data on lung cancer epidemiology in India reflects the impact of industrialization and smoking trends on cancer in the community. After the initial erroneous impression of the rarity of lung cancer likely resulting from paucity in lung cancer reporting, Viswanathan *et al.* in their seminal paper in 1962 made the observation of the increasing burden of lung cancer across different centers in the country. They collected data from different hospitals in India for the years 1950–1959. They drew parallels with Western data with regard to increasing lung cancer incidence among male smokers and the most common primary histology of squamous cell carcinoma in the period under observation (1950–1959). They noted that there was a significant rise in the number of cases of lung cancer during the 10 years from 1950 to 1959, and although the incidence had increased in both sexes, the increase in males was greater than that in females. They found that of a total of 95 necropsies on lung cancer patients, 78 were males and 17 were females; 64 (67.6%) were smokers and 31 (32.4%) were nonsmokers. The histopathologic distribution included 20 (21.05%) adenocarcinomas, 48 squamous (50.53%), 23 (24.21%) anaplastic, and 4 (4.21%) alveolar carcinoma. Regarding age distribution, the majority of the lung cancer patients, i.e. 38 (40%) were in the 50–59 years age group, 19 (20%) each were in the age groups of 40–49 years, and 60–69 years, while there were smaller numbers in the extreme age groups, i.e., 3 (3.16%) in the <30 years age group, 11 (11.6%) in the 30–39 years group, 3 (3.16%) in the 70–79 years age group, and 2 (2.1%) in the 80 + years group.[2]

The incidence of lung cancer has paralleled the trends of tobacco smoking. Smoking tobacco remains the single most important risk factor (80–90%); a smaller proportion (10–20%) is attributed to occupational exposure to various carcinogenic agents. The smoker:nonsmoker ratios have been lower in most of the Indian studies compared to those in the West.[4] The percentage of tobacco-related products smoked in India are beedis (28.4–79%), cigarettes (9.0–53.7), hookah (3.4–77.3), and mixed (7.5–13.6).[5] The relative risk of developing lung cancer is 2.64 for beedi smokers and 2.23 for cigarette smokers, with 2.45 as the overall risk for smoking tobacco.[5] Passive smoking and environmental tobacco smoke are known

lung carcinogens. A meta-analysis of 41 studies showed that environmental tobacco exposure carries a relative risk of developing lung cancer of 1.48 (1.13–1.92) in males and 1.2 in females (1.12–1.29).[6] The risk increases with an increase in exposure. Exposure at the workplace results in a relative risk of 1.16. There is an increasing risk with an increase in the number of smokers in the house and in the duration of exposure. Environmental tobacco smoke exposure during childhood is strongly associated with the risk of developing lung cancer (odds ratio 3.9, 95% confidence interval [95% CI] 1.9–8.2).[7]

In the Western countries and most of the Asian countries, adenocarcinoma has surpassed squamous cell carcinoma as the most common histologic variant of lung cancer. This shift seems to be attributable partly to the changed smoking pattern and increasing incidence of lung cancer in women and nonsmokers. However, most of the older and some recent Indian series still report that squamous cell carcinoma is the most common histology. Single-center-based reporting from the established tertiary cancer centers points toward adenocarcinoma being the most common nonsmall cell lung cancer (NSCLC) subtype. Krishnamurthy *et al.* in their retrospective analysis of data extracted from a total of 258 consecutive hospital in-patients with lung cancer at Adyar in Chennai between January 2003 and December 2007 reported that the most common histology was adenocarcinoma (42.6%), followed by squamous cell carcinoma (15.6%), large cell carcinoma (2.3%), and others (7%). Subclassification was not possible in 49 patients (19%) primarily because the diagnosis was made cytologically. There was a very significant correlation found with adenocarcinoma among nonsmokers compared to smokers, and with squamous cell carcinoma among the smokers compared to nonsmokers ($P = 0.0002$).[8] Similarly, Malik *et al.* analyzed 434 pathologically confirmed lung cancer cases registered at the All India Institute of Medical Sciences, Delhi, over a period of 3 years between July 2008 and June 2011. Among the biopsy slides which were subjected to independent review, squamous cell carcinoma was the most common histological subtype (33.33%) as per the initial report, but after expert pathological review, adenocarcinoma was found to be the most common histology (37.3%). This emphasizes the critical role of pathology review in lung cancer in the present era of personalized treatment. This changing paradigm in epidemiological and pathological trend was also supported by the data published by our group at Tata Memorial Hospital, Mumbai, Maharashtra, India. We reported that of 489 patients, 52% were nonsmokers and the most common histology was adenocarcinoma at 43.8% followed by squamous cell carcinoma at 26.2%.[9]

The epidemiological description of lung cancer is not uniform throughout India, which is reflected in data collected from different cancer registries across the country. The population-based cancer registries (PBCRs) consolidated report from 1990 to 1996 reported that cancer of the lung is the number one cause of cancer in males and is the leading cancer site in Delhi, Mumbai, and Bhopal, wherein it accounts for 10% of all cancers. In Bengaluru and Chennai, lung cancer is the second and the third leading cancer site, respectively. In women, lung cancer is one of the 10 leading sites in 4 of

the 6 cancer registries, i.e., in Bhopal, Chennai, Delhi, and Mumbai.[10] The national cancer registry program under the Indian council of medical research, after studying the lung cancer incidence rate over 24 years (1982–2005), has found that lung cancer is the second leading cause of cancer in women and has increased by an annual percentage change of 2.7 in Bengaluru, 4.6 in Chennai, and 2 in Delhi.[11]

In a retrospective comparison study of the clinicoradiological profile from the first PBCR in Kolkata in the Eastern part of India, the most predominant histopathological subtypes of primary bronchogenic carcinoma were squamous cell carcinoma at 35.1% and adenocarcinoma at 30.8%, followed by small cell lung cancer at 16.5%, undifferentiated carcinoma 11.7%, and large cell carcinoma 5.9%. Of the total of 607 patients, 67.2% were current smokers, 26.8% were nonsmokers, and the rest were ex-smokers. The smoking status was found to have a strong correlation with primary lung cancer. Among all the smokers with lung cancer, 93.9% were male; the females with lung cancer were more commonly nonsmokers at 77.12%.[12]

Similarly, Singh *et al*. published their results based on patient information from single tertiary care center-based in North India. In their retrospective analysis of prospectively collected data from 250 newly diagnosed lung cancer patients, they found no significant differences in the demographical, histological, or smoking profiles of lung cancer patients compared to those seen three decades earlier. The mean (standard deviation [SD]) age was 57.9 (±11.3) years whereas previously it was 54.3 years. The male:female ratio was 4.43:1 (previously 4.48:1; $P = 0.952$) while the smoker:nonsmoker ratio was 2.67:1 (previously 2.68:1; $P = 0.980$). The most common histological types were squamous cell (34.8%), adenocarcinoma (26.0%), and small cell (18.4%) while previously these were 34.3%, 25.9%, and 20.3%, respectively; $P = 0.916$. However, significant differences were observed between smokers and nonsmokers in relation to distribution of gender, histology, and disease stage. They concluded that the absence of change in the smoking pattern of the population could be a possible reason.[13]

Molecular Pathology of Nonsmall Cell Lung Cancer

There has been a tremendous increase in interest in unraveling the molecular mechanisms resulting in the malignant phenotype of different cancer types in the past two decades. We now have a better understanding of the different interconnecting networks of signaling pathways involved in the cancer cells' ability to proliferate evading various cell cycle checks, to inhibit apoptosis, to invade and to generate distant metastases. This has led to intense pharmacological and clinical research in several cancer types including NSCLC. The newer agents for therapy target mostly the transmembrane receptors, which often have tyrosine kinase activity, inhibiting the successive cascade of kinases' activation preventing the subsequent transcriptional changes necessary or responsible for the malignant phenotype. These molecular alterations (gene amplification or mutations), which have the driver/transforming capability or property, represent potentially an early event in carcinogenesis that fuels further sufficient genetic alterations that lead to malignant characteristics of cancer cells.

Molecular Data from the Indian Population in Lung Cancer

The relative extent to which the ethnic and genetic background contribute to the disparity in prevalence in different receptor mutations remains unclear. Apart from the genetic background, various environmental influences such as cigarette smoking and tobacco chewing may modulate the relative frequencies of different activating mutations.

There have been multiple reports on molecular testing in lung cancer in the Indian population. Several tertiary care centers have significantly contributed the results of the molecular testing done in their patients to form impressions regarding various mutation frequencies and variations in comparison to the Western population.

Epidermal Growth Factor Receptors

Small molecule tyrosine kinase inhibitors (TKIs) (gefitinib and erlotinib) which target a mutant epidermal growth factor receptor (EGFR) have been approved by the Food and Drug Administration (FDA) as first-line agents in the treatment of advanced NSCLC patients, who tested positive for the activating driver mutation. These driver mutations occur in exons 18–21 of the EGFR, modifying the active site of the kinase domain in favor of increased activity (ligand-driven or constitutive activity). The earlier reporting from most Indian populations suggested an EGFR mutation rate varying between 22% and 51.8%, which possibly was an overestimation resulting from selection bias and small sample size. An initial report from 2011 published by Sahoo *et al*. from Triesta laboratories in Bengaluru, India, reported an EGFR mutation rate of 55% in 220 patient samples tested between January 2008 and July 2010. However, these patients were possibly selected for EGFR mutation testing based on their clinicodemographic profile, and hence was likely to be an enriched population.[14] Studies from tertiary care centers that catered to a much larger patient pool with a referral base from across the country and which reported EGFR testing in all NSCLC patients subsequently gave us a much more accurate estimation of mutation rates.

Chougule *et al*. in their retrospective analysis of 907 patients diagnosed with lung cancer in Tata Memorial Hospital in Mumbai, Maharashtra, India, between August 2011 and December 2012, revealed an overall mutation rate of 23.2% with a higher mutation rate in females as compared to males (29.8% vs. 20%) with $P = 0.002$. Of all the EGFR tyrosine kinase domain mutations, 50% were in-frame deletions in exon 19, 42% were missense mutations in exon 21, 7% of the mutations were in exon 18, and 3% in exon 20. Two patients harbored a mutation in exon 20 along with exon 21. The overall frequency of EGFR mutations in the adenocarcinoma population was 26% as compared to 3.8% in squamous cell carcinomas ($n = 103$). This EGFR mutation rate was less than that of East Asian patients (26–30%) and more than Western patients (10–15%).[15] Another retrospective analysis involving 500 patients treated at six different centers revealed a slightly higher EGFR mutation rate of 33%.[16] Regional differences have also been reported, with a higher incidence of 65% in the Southern Indian population as compared to 33% in Northern Indian population.[17] These

variations may be related to difference in smoking rates in the community.

The PIONEER study was a prospective, multinational, epidemiological study of EGFR mutations which enrolled patients from Asia with newly diagnosed advanced lung adenocarcinoma. This study included a proportion of patients from a single center from South India. PIONEER reported a lower EGFR mutation frequency in patients from India (22.2%) compared with other areas (47.2–64.2%).[18]

The clinical correlation and outcome to EGFR targeted therapy was reported in a retrospective study by Noronha *et al.* from Tata Memorial Hospital in Mumbai, Maharashtra, India.[19] In our analysis of patients who were managed with oral TKIs, the overall response to oral TKI therapy was 30%. Patients with an activating mutation of EGFR had a response rate of 74% while the response rate in patients with wild-type EGFR was 5% ($P = 0.001$). Progression-free survival (PFS) and overall survival (OS) were 10 months and 19 months, respectively, in patients with EGFR mutations compared to 2 months and 13 months, respectively, for EGFR mutation-negative patients.[19]

The correlation between various clinicopathological factors and the EGFR mutation status was also studied and reported by Bhatt *et al.* The authors retrospectively analyzed a cohort of 104 histologically confirmed NSCLC patients between January 2008 and December 2010 who also had formalin-fixed paraffin-embedded tissues available for EGFR mutational analysis. The prevalence of EGFR mutation in this population was 39.6% with exon 19 mutation being the most common (80%); exon 21 mutation was seen in 17% and exon 18 in 3%. There were no significant associations between those who were positive for mutations in either exon 19 or 21 when compared to age, gender, or histology. The response rates were superior in the EGFR mutation-positive group compared to mutation-negative group (90.5% vs. 70.3%), with the best response noted in those treated upfront with oral TKI (93.3% vs. 88.8%). This retrospective series further demonstrated better PFS in the EGFR mutation-positive patients who received chemotherapy, followed by TKI, as compared with EGFR mutation-positive patients who received only TKIs, which could be contributory evidence in support of studies assessing the best way to sequence chemotherapy and oral TKI in EGFR mutation-positive lung cancer patients.[20]

Our group at Tata Memorial Hospital, Mumbai, Maharashtra, India retrospectively analyzed the survival outcomes of 101 EGFR mutant patients with and without brain metastases. Fourteen (13.8%) patients had brain metastases. The overall response to therapy was 64% in the group of patients with extracranial metastases compared to 50% in the brain metastases group. Correspondingly, the median OS in the patients with extracranial metastases group was 18.7 months compared to 11.6 months in the brain metastases group, $P = 0.029$. Thus, even among the patients with EGFR driver mutation, the presence of brain metastases leads to an inferior outcome.[21]

A questionnaire-based survey of medical oncologists from India published by Parikh *et al.* in an abstract form in ASCO 2013 showed that the awareness about the need for EGFR mutation testing and use of TKIs among medical oncologists is increasing in India. However, the availability of sufficient tissue for molecular testing remains a problem.[22]

Echinoderm Microtubule-associated Protein-like 4-Anaplastic Lymphoma Kinase

The echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (EML4-ALK) protein results from the fusion of PTK EML-4 with a transmembrane tyrosine kinase, ALK. The genetic mechanism is an inversion of two closely located genes on chromosome 2p. The resulting constitutive oligomerization leads to persistent mitogenic signaling and malignant transformation. The presence of ALK mutation is reported in approximately 3–7% of lung cancers, found more commonly in young patients with adenocarcinomas with a history of never or light smoking. Clinically the presence of ALK rearrangement is detected by fluorescence *in situ* hybridization (FISH) with an ALK break-apart probe. In the majority of patients, ALK rearrangements are nonoverlapping with other oncogenic mutations. In 2011, crizotinib received accelerated approval from the US FDA because of its efficacy in ALK + NSCLC based on the results from the 2009 single-arm, global Phase II study of crizotinib (PROFILE 1005, NCT00932451).[23] Based on the impressive response rates attained in initial Phase I and Phase II trials with the dual ALK/MET TKI, crizotinib in patients harboring the ALK mutation, an international Phase III trial randomized patients with advanced lung cancer harboring ALK fusions to crizotinib versus standard chemotherapy after disease progression on first line treatment. This trial revealed an improved radiographic response rate with crizotinib (65% vs. 25%) and the study met its primary end-point of improved PFS with crizotinib (median PFS 7.7 vs. 3 months, hazard ratio [HR] for progression - 0.49, 95% CI 0.37–0.64).[24] In treatment naïve patients harboring ALK mutation, therapy with crizotinib resulted in an improved PFS, quality of life (QOL), and radiographic response rates. There was, however, no survival benefit among both pretreated and treatment naïve patients probably because the majority of patients on the chemotherapy arm crossed over to crizotinib at progression.

Desai *et al.* from Tata Memorial Hospital in Mumbai, Maharashtra, India, in their retrospective observational study provided the earliest literature of ALK mutations among Indian lung cancer patients. They observed ALK gene rearrangement among 5 (2.7%) of the total cohort of 227 patients with adenocarcinoma in whom ALK testing was performed, excluding the patients in whom the results of the test were uninterpretable. These ALK-positive patients were relatively younger than ALK-negative patients. The appearance of a solid pattern on histology was associated with ALK positivity.[25]

Doval *et al.* tested the ALK rearrangement by FISH among EGFR-negative patients with lung adenocarcinoma. A total of 500 patients were enrolled from six centers in India and tested for the EGFR mutations. One hundred sixty-four patients (32.8%) were found to be EGFR-positive. ALK mutation testing was performed on the 336 tissue blocks which tested negative for the EGFR mutation. ALK rearrangement was observed in 15 of 336 patients (4.5%). The overall incidence of ALK mutations was 3.0% (15/500).[16]

Therapy of Lung Cancer

Early stage lung cancer

Neoadjuvant chemotherapy

Sharma *et al.* in their prospective randomized trial in 506 patients with locally advanced NSCLC compared

neoadjuvant chemotherapy, consisting of three cycles of three-drug combination regimen of cisplatin, ifosfamide, and mitomycin-C administered every 3 weeks followed by local-regional radiotherapy (study group) with radiotherapy alone (control group) up to a dose of 60 Gy. The response to neoadjuvant chemotherapy was complete response (CR) in 13 (5.7%), partial response (PR) in 103 (43.2%), stable disease (SD) in 48 (21%), and progressive disease (PD) in 74 patients (31.1%). The rates of disease progression were 27.6% and 42.3% in the study group and control group, respectively. Actuarial 2-year survival was 20% in the study group and 7.4% in the control group.[26]

Bahl *et al*. reported a smaller prospective trial in 40 patients with locally advanced inoperable NSCLC, who were treated with 3 cycles of neoadjuvant chemotherapy with cisplatin and etoposide, followed by restaging and definitive radiotherapy to 60 Gy in 30 fractions. There were 13 patients with Stage IIIA disease and 27 patients with Stage IIIB NSCLC. They reported that the most common toxicities were anemia in 81% of the patients (13.5% had Grade 3 anemia after the third cycle of chemotherapy), followed by nausea and vomiting – 97.2% experienced nausea after cycle 2, although the majority had Grade 1 nausea. Thirty-eight percent of the patients developed sensory neuropathy and 88% developed alopecia. 17.5% had febrile neutropenia. The response to induction chemotherapy was 45% (complete remission - 5.26%, partial remission - 40%); 28.94% had SD and 28.94% had PD.[27]

Radical chemoradiotherapy

Agarwal *et al*. from Tata Memorial Hospital, Mumbai, Maharashtra, India, recently described a retrospective audit of 171 consecutively treated NSCLC patients treated with definitive chemoradiotherapy between January 2008 and December 2012; 66% were treated concurrently and 28% received sequential therapy. The median radiotherapy dose was 60 Gy (range: 4–66) over a median duration of 44 days (2–85 days). 86.5% patients received chemotherapy, either concurrently (weekly) or sequentially as a 3-week regimen, of which 92% received platinum-based doublets. 95.5% patients completed chemoradiotherapy without a gap and with acceptable toxicity. Toxicities included Grade 2 acute radiation pneumonitis - 6.4%, Grade 2 esophagitis - 32.2%, Grade 3 esophagitis - 4.1%; chemotherapy-related grade ≥2 hematological toxicity - 23.5% and renal toxicity - 7.4%. At a median follow-up of 13 months (interquartile range 14 months, range: 0–54 months), the responses included complete remission - 36.2%, partial remission or SD - 49.1%, PD - 9.9%, and lost to follow-up: 4.7%. The median DFS was 7 months, OS 13 months, estimated 2 years DFS 17.5%, and the 2-year OS 61.5%. Nonsmoking status and the development of a CR to therapy significantly correlated with prolonged DFS and OS on multivariate analysis.[28]

Agrawal *et al*. from SGPGI (Lucknow, Uttar Pradesh, India) retrospectively analyzed 52 NSCLC patients who were treated with combined modality therapy with radical intent. The development of radiation pneumonitis correlated with ipsilateral (V20 ipsi, V5 ipsi, and MLD ipsi) and whole lung (V20, V5, and MLD) dose volume parameters. 35.3% of the patients developed grade >2 pneumonitis. On multivariate analysis, V5 ipsi was most strongly correlated with the development of radiation pneumonitis. The authors selected a cutoff of 65% for V5 ipsi, which had a sensitivity of 65% and a specificity of 91%. They also noted that concurrent chemoradiotherapy led to significantly more radiation pneumonitis that neoadjuvant chemoradiotherapy ($P = 0.004$).[29]

Stereotactic body radiotherapy

Kundu *et al*. from Tata Memorial Hospital in Mumbai, Maharashtra, India, treated 8 patients with early-stage lung cancer (T1-2N0M0) but could not undergo surgery due to age or comorbidities with hypofractionated high-dose stereotactic body radiotherapy between December 2007 and December 2010. At 3-month follow-up, seven patients had a complete metabolic response and one patient had a partial metabolic response. One patient developed Grade 2 pneumonitis. At a median follow-up of 18 months, the OS at 1.5 years was 87.5%.[30]

Palliative chemotherapy
First-line chemotherapy

In a retrospective analysis published in 2008, Rajappa *et al*. reported treatment outcomes for locally advanced and metastatic NSCLC, treated at a single center from South India. Patients with Stages III and IV NSCLC, who were diagnosed between the years 2002 and 2006, who had radiological response evaluation after minimum of two cycles of palliative chemotherapy, were analyzed for response rates, survival outcomes, and factors related to prognosis. A total of 294 patients received palliative chemotherapy, of which 66% (194 patients) were eligible for the outcome analysis. The authors concluded that the outcomes with platinum doublet chemotherapy remain less than ideal with a median OS of 7–9 months and a modest improvement to 12.5 months with the addition of monoclonal antibodies. They also added that the ability to deliver second-line chemotherapy (pemetrexed, erlotinib, and docetaxel) improved the OS (15 months vs. 7 months $P < 0.0001$) as well as the QOL. About 20.6% of the patients who were eligible for the outcome analysis were suitable for the second-line chemotherapy at progression. Through the univariate analysis, the strongest factors predictive of survival were female, nonsmoker and performance status. In multivariate analysis, only performance status retained prognostic significance with an OS of 6.5 months for patients with poor performance status (3 or 4) compared to 8 months for patients with better performance status (0 or 1) ($P = 0.0013$). The survival was similar for patients treated with either 1st generation or 2nd generation chemotherapy agents in platinum doublets.[31]

The objective response rate of 35.4% reported in this retrospective analysis was comparable to that reported internationally with various platinum doublets in advanced NSCLC. However, the median PFS of 6 months (range: 2–70 months) and OS of 7 months (2–72 months) for all evaluable patients noted in this retrospective series were lower than those reported in various trials with the 2nd generation platinum doublets. The probable reason as noted by authors could be below average rates for delivery of the second-line chemotherapy (20.6% vs. 45% internationally). Further in another published report, based on the same cohort of patients,

the authors attempted to identify "the true clinical trial effect" or the superior outcomes related to clinical trial enrollment. In their retrospective review, the difference in response rates and median PFS were not significant among the patients treated on trial as compared to the patients in the nontrial group. However, the median OS of patients treated on a clinical trial was superior at 9.5 months compared to 7 months for those treated out of clinical trial ($P = 0.0052$). The 1-year OS was also superior for patients treated on a clinical trial (25% vs. 42.5% $P = 0.022$). The survival benefit was still significant after censoring the effect for the second-line chemotherapy delivery rates which were superior in patients treated on a clinical trial.[32]

In 2013, Tiwana *et al.* reported the demographic profile and survival outcomes of 138 consecutively diagnosed North Indian (from Dehradun) NSCLC patients between November 2008 and January 2012. The median age was 60 years, males formed 90% of the cohort, 35% of the patients had a Karnofsky performance status <70, 59% had NSCLC not otherwise specified (squamous - 25%, adenocarcinoma - 16%), and Stage IIIA constituted 20%, Stage IIIB - 31%, and Stage IV - 49%. The treatment protocol followed for the Stage III patients was 4–6 cycles of induction chemotherapy (paclitaxel/carboplatin or cisplatin/etoposide) followed by radical radiotherapy. Stage IV patients were treated with systemic chemotherapy. They found that the median OS and 2-year survival for patients with Stage III NSCLC were 9.26 ± 1.85 months and 13%, respectively; the median OS and 2-year survival rate for Stage IV patients were 5 ± 1.5 months and 8%, respectively. On a multivariate analysis, they found that delivery of a higher biologically equivalent radiotherapy dose (BED) correlated with better OS in patients with Stage III disease; in the Stage IV patients, nonsquamous histology, administration of chemotherapy, PR to chemotherapy, presence of skeletal metastases, and a higher BED significantly correlated with a better OS.[33]

It is well recognized that delivery of chemotherapy on time and on schedule leads to the best possible outcomes. Singh *et al.* from the Postgraduate Institute of Medical Education and Research in Chandigarh, India, evaluated the intercycle delays (ICD) during first-line chemotherapy in 118 (of whom 100 patients received at least 2 chemotherapy cycles and were included in the analysis) NSCLC patients treated during a 12-month period. Of a total of 441 chemotherapy cycles, 57 patients had ICD of 683 days during 84 (19.1%) cycles of chemotherapy. The common reasons for ICD included unavailability of blood reports (25.5%), anemia (20.2%), and hospital holidays on the scheduled chemotherapy cycle days (9.6%). There was no significant difference in the groups of patients who had ICD and no-ICD in terms of age, gender smoking histology, disease stage, baseline performance status, chemotherapy regimen, or the number of cycles administered. The median survival was also similar – ICD group: 247 days (95% CI: 188–306 days) and non-ICD group: 232 days (95% CI: 196–268 days).[34]

The therapy of lung cancer had evolved from the one-size-fits-all therapy used in the previous decade when all patients with NSCLC with a good performance status were treated with first-line platinum-based doublet chemotherapy to

an exquisitely tailored approach.[35,36] The decision regarding the type of chemotherapy is now based on the type of NSCLC, i.e., patients with adenocarcinoma histology are preferentially treated with a pemetrexed-based regimen. Scagliotti *et al.* reported this in a Phase III study that recruited a significant number of patients from India. The investigators compared gemcitabine and cisplatin (CG) to pemetrexed and cisplatin (CP). In patients with advanced chemotherapy-naive NSCLC, they found that the OS of the patients treated with CP was noninferior at 10.3 months to that of patients treated with CG (10.3 months), HR - 0.94, 95% CI - 0.84–1.05. Patients with adenocarcinoma had a superior OS when treated with CP (12.6 months) versus CG (10.9 months) while patients with squamous cell carcinoma had a better survival when treated with CG (10.8 months) as compared to when they were treated with CP (9.4 months).[37] In a follow-up report, the authors confirmed that histology was predictive of the efficacy of CP and may also serve as a prognostic marker.[38]

The spectrum of toxicity in different ethnic patient populations may vary. We found that 16 of 46 patients (35%) treated with 6 cycles of pemetrexed-platinum at Tata Memorial Center, Mumbai, Maharashtra, India, followed by maintenance pemetrexed until progression developed at least 1 episode of grade >3 hyponatremia. There were 24 episodes of grade >3 hyponatremia in 200 cycles of pemetrexed-platinum chemotherapy. The plasma exposure of pemetrexed was significantly higher in patients with high-grade hyponatremia as compared to those with low-grade ($P = 0.063$) or no hyponatremia ($P = 0.055$), respectively. The median pemetrexed exposure in our patient cohort was much higher than that reported from prior Western studies.[39]

In an attempt to help predict which patients are chemoresponsive, Kumar *et al.* from the All Institute of Medical Sciences in New Delhi, India, quantified the plasma nucleosome levels in 134 patients with advanced NSCLC at baseline and 42 patients before the second and third cycles of first-line chemotherapy. They found that high plasma nucleosome levels and insufficient decrease in levels during chemotherapy correlated with a poor outcome. Patients who went into remission had significantly lower nucleosome levels at baseline and before cycles 2 and 3 as compared to patients who had SD or PD. They reported that nucleosome levels before cycle 2 could predict early disease progression with a sensitivity and specificity of 85.7% and 92.2%, respectively.[40]

Immunotherapy

Lynch *et al.* reported the results of a randomized double-blind Phase II multicenter study evaluating the role of ipilimumab in combination with paclitaxel and carboplatin as first-line therapy in patients with Stage IIIB/IV NSCLC. Thirty patients of a total of 204 patients were from Christian Medical College in Vellore, Tamil Nadu, India. This study found an improvement in immune-related PFS and PFS for patients who were treated with phased ipilimumab (2 doses of placebo with paclitaxel and carboplatin followed by 4 doses of ipilimumab with paclitaxel and carboplatin) (HR - 0.72, $P = 0.05$ and HR - 0.9, $P = 0.02$).[41]

Digumarti *et al.* studied the use of weekly bavituximab in combination with first-line paclitaxel and carboplatin as

first-line therapy for 49 patients with advanced NSCLC. The objective response rate was 40.8% (CR - 2%, PR - 38.8%), and the median PFS and OS were 6 and 12.4 months, respectively. 40.8% developed adverse events, most commonly anemia (10.2%), asthenia, vomiting, paresthesia, anorexia, and fatigue (each 6.1%).[42]

Maintenance therapy

Pemetrexed maintenance therapy after first-line chemotherapy has been shown to improve the outcome of patients with advanced NSCLC. Pandey *et al*. from Tata Memorial Hospital in Mumbai, Maharashtra, India, reported that of 384 patients with advanced adenocarcinoma of the lung treated between June 2011 and March 2014, 66 (17%) progressed after 3 cycles and 78 (20%) progressed after 6 cycles of first-line chemotherapy. A total of 188 patients (49%) received maintenance pemetrexed for a median of 6 cycles, range: 1–38. The reasons for discontinuation of maintenance pemetrexed included PD in 127 patients, social or financial constraints in seven patients, and renal toxicity in four patients. At a median follow-up of 14 months, the median PFS was 8 months and the median OS was 20 months. Patients with baseline pleural effusion appeared to benefit more from maintenance pemetrexed.[43]

Even when patients receive the best possible chemotherapy for their specific individual disease, their outcome may not be optimal especially if the basic principles of medical oncology are not adhered to. Prasad *et al*. compared the outcome of patients with advanced NSCLC treated with platinum-based combination chemotherapy in two different setups – first, patients treated by medical oncologists at Tata Memorial Hospital, Mumbai, Maharashtra, India, versus patients treated by a nonmedical oncologist in the community setup. They found that the patients treated by medical oncologist had a higher dose intensity and consequently had a significantly better response rate to chemotherapy and a longer OS, 13 months versus 6 months for the patients treated by nonmedical oncologists in the community, *P* = 0.004.[44]

Relapsed refractory lung cancer

Patients with NSCLC who progress on first-line therapy still have numerous therapeutic options. In a randomized Phase II study performed at 11 centers in India, Parikh *et al*. reported that patients with advanced NSCLC who had failed one or two lines of systemic therapy had an improvement in OS when treated with oral talactoferrin, an oral novel immunomodulatory protein. Specifically, the OS improved from 3.7 months in the placebo-treated group to 6.1 months in the group of patients treated with talactoferrin, HR - 0.68, 95% CI - 0.47–0.98, *P* = 0.04 with one-tailed log-rank test.[45] Talactoferrin appeared to be efficacious in the first-line setting in combination with chemotherapy as well. Digumarti *et al*. conducted a randomized placebo-controlled Phase II study in patients with advanced untreated NSCLC. All patients received carboplatin and paclitaxel and were randomized to receive oral talactoferrin in combination with the chemotherapy versus placebo plus chemotherapy. The combination of paclitaxel and carboplatin chemotherapy with oral talactoferrin led to a superior response rate (42% vs. 27%, *P* = 0.08), duration of response (7.6 months vs. 5.5 months), median PFS (7 months vs. 4.2 months), and median OS (10.4 months vs. 8.5 months) although the differences were not statistically significant.[46]

We reported that in patients with refractory and relapsed NSCLC, metronomic scheduling of paclitaxel using a continuous 80 mg/m^2 weekly schedule resulted in a response rate of 35%, a median PFS of 4 months and an estimated median OS of 7 months. The most common Grade 3 or higher toxicities included sensory neuropathy in 8%, anemia in 8%, and neutropenia in 5.4%.[47]

The Iressa Survival Evaluation in Lung Cancer (ISEL) study was a Phase III study which compared the efficacy of gefitinib versus placebo in patients with refractory NSCLC. This study also recruited a significant number of Indian patients. A total of 1692 patients were randomized in a 2:1 fashion to gefitinib versus placebo. At a median follow-up of 7.2 months, there was no significant difference in median OS between the two groups in the overall population (5.6 months in the patients treated with gefitinib vs. 5.1 months in the placebo-treated patients, HR - 0.89, 95% CI - 0.77–1.02, *P* = 0.087) or in the adenocarcinoma patients, 6.3 versus 5.4 months, 0.84 (0.68–1.03), *P* = 0.089. However, never-smokers (8.9 vs. 6.1 months, *P* = 0.012) and patients of Asian origin (9.5 vs. 5.5 months, *P* = 0.01) had a significantly longer survival when treated with gefitinib.[48] Parikh *et al*. reported on the clinical experience with gefitinib in patients who were enrolled on the ISEL study or were treated with gefitinib as part of an expanded-access program. They found that the median survival of the patients treated with gefitinib was 6.4 months as compared 5.1 months in the patients treated with placebo. The objective response rate of Indian patients treated with gefitinib in the relapse setting was 14% compared to 0% for placebo. Gefitinib was well tolerated.[49] Our own group at Tata Memorial hospital in Mumbai, Maharashtra, India, have reported on the outcome of patients treated with EGFR directed therapy. The overall response rate to gefitinib was 30%. Thirty-nine of the 111 patients had an activating EGFR mutation and the response rate to gefitinib in these EGFR-positive patients was 74% while the response rate in EGFR-wild-type patients was 5%.[19] The nuclear medicine group from Tata Memorial Hospital in Mumbai, Maharashtra, India, reported that in patients with advanced lung cancer treated with targeted therapy, the use of metabolic criteria from restaging positron emission tomography-computed tomography scans can accurately predict response as well as disease progression early as compared to standard morphologic criteria. Early metabolic response assessment can also predict refractoriness to therapy.[50]

Louis *et al*. retrospectively reviewed the outcomes of 120 patients with Stage IIIB and IV advanced NSCLC treated between January 2009 and December 2010 at Adyar in Chennai, Tamil Nadu, India. They reported that the median age was 60 years, males predominated (69.2%), 55% of the patients were smokers, 90.8% had adenocarcinoma, and 54.2% had performance status of 2 or 3. Forty-seven patients (39.2%) were treated with upfront gefitinib and 60.8% received upfront chemotherapy. 23% of the patients who progressed after first-line chemotherapy received gefitinib in the second line. The response rate to gefitinib was 23% (CR - 0, PR - 23%; SD - 42.5%, PD - 34%) and that for chemotherapy was 6.8% (CR - 0, PR - 6.8%, SD - 39.7%, PD - 3.4%). At a median follow-up of 7.5 months, the median PFS and OS

were 5 months (0–23 months) and 7.5 months (1–26 months), respectively. On univariate analysis, nonsmoking status, female gender, and upfront treatment with gefitinib significantly prolonged PFS; female gender significantly prolonged OS. However, no factor was significant on the multivariate analysis. In the patients with performance status 2–3, gefitinib led to a significantly longer PFS than chemotherapy (PFS of 10 months vs. 4 months, $P = 0.017$).[51]

Palliative radiotherapy

Mallick *et al.* in a retrospective study analyzed 95 previously untreated patients with locally advanced NSCLC who were treatd with palliative radiation using endobronchial brachytherapy with or without palliative external radiation therapy. Symptomatic response rates, duration of symptom palliation, obstruction scores, and complications were assessed and compared. QOL outcomes, measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and LC13 questionnaires, were analyzed. The median time to symptom relapse was 4–8 months for all symptoms, and the median time to symptom progression was 6–11 months. QOL showed significant improvement in symptom scores, functional scales, and overall QOL. Complication rates were low. Only one patient died of fatal hemoptysis. The overall symptom response rates were 93% for dyspnea, 81% for cough, 97% for hemoptysis, and 91% for obstructive pneumonia.[52]

Early Detection

Fernandes *et al.* in their review elaborated the utility of the naso – nose-based volatile organic compound (VOC) biomarker testing in the samples of exhaled breath. Exhaled breath VOC analyzers are devices used for the detection of the VOCs, whose abnormal levels point to the presence of cancer in the human body. With proper scientific validation, the analysis of VOCs in the exhaled breath shows a great potential in being an noninvasive and cost-effective diagnostic technique for early detection of lung cancer.[53]

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Conflicts of interest
There are no conflicts of interest.

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