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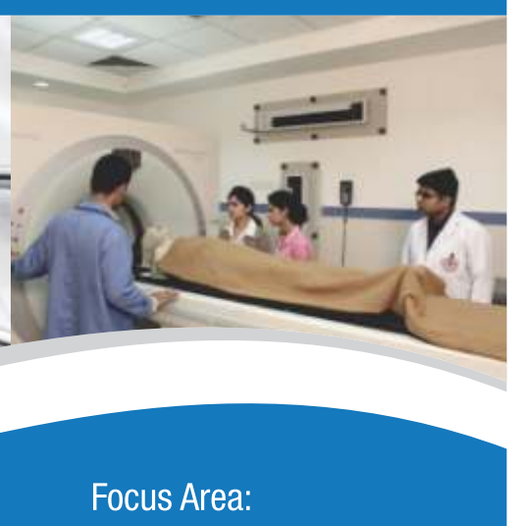

Focus Area:

LUNG CANCER

Rajiv Gandhi Cancer Institute and Research Centre
A Unit of Indraprastha Cancer Society
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From the Desk of Director Research

Globally, lung cancer is the largest contributor to new cancer diagnoses and to deaths from cancer. The estimated number of lung cancer cases worldwide has increased by 51% since 1985. Although there has been some improvement in the 5-year survival rate during the past few decades, the survival advances that have been achieved in other common malignancies are yet to be attained in lung cancer. There has been a large relative increase in the number of cases of lung cancer in developing countries. The most important single risk factor is smoking but second hand smoke or environmental tobacco smoke underpins lung cancer in non smokers. Other intriguing contributory factors include diet, radon, asbestos, arsenic, diesel, exhaust, silica & chromium exposures, which cannot be ignored and open up a corresponding potential for prevention.

Lung cancer arises from the cells of the respiratory epithelium and can be divided into two broad categories, that is small cell lung cancer (SCLC) which is a highly malignant tumor derived from cells exhibiting neuroendocrine characteristics and accounts for 15% of lung cancer cases; and non–small cell lung cancer (NSCLC), which accounts for the remaining 85% of cases. NSCLC is further divided into 3 major pathologic subtypes: adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. Adenocarcinoma by itself accounts for 38.5% of all lung cancer cases, with squamous cell carcinoma accounting for 20%, and large cell carcinoma accounting for 2.9%.

Abundant genetic diversity underlies this malignancy. New technologies have identified key and targetable genetic aberration not only in adenocarcinoma but also in squmaous cell carcinoma. However, complexity arises due to occurrence of mutational evolution overtime during the natural course of disease progression.

Lung cancer therapy has now emerged as a “role model” for precision cancer medicine with several important therapeutic breakthroughs occurring during 2015. These advances have occurred primarily in the immunotherapy field and in treatments directed against tumors harboring specific oncogenic drivers. The knowledge about molecular mechanisms for oncogene driven tumors and about resistance to targeted therapies has increased. As a result, several regulatory approvals of new agents that significantly improve survival and quality of life for lung cancer patients with advanced disease, have occurred. Prevention offers the greatest opportunity to fight lung cancer. Although decades have passed since the link between smoking and lung cancers became clear, smoking is still responsible for most lung cancer deaths. However, significant progress is underway in both the prevention and treatment of lung cancer. Research holds the key to discovering the causes of lung cancer, developing effective treatment options and delivering those treatments to patients in a timely manner.

The current issue of the Cancer News highlights the newer advances in the field of lung cancer and features the regular articles, such as Special Feature, Guest Article, Perspective and In Focus.We are grateful to Dr D Behera, Senior Professor & Head, Dept of Pulmonary Medicine, Postgraduate Institute of Medical Education & Research, Chandigarh, for the "Special Feature, Dr Praveen Paliwal, Junior Consultant in Medical Oncology and Dr Senthil J Rajappa, Senior Consultant in Medical Oncology, Indo American Cancer Hospital & Research Center, Hyderabad, for the "Guest Article" and Dr A K Anand, Dr Abhishek Gulia, Dr Amal Roy Chaudhary and Dr Rajender Kumar, Dept of Radiation Oncology, Max Cancer Centre, Max Super Speciality Hospital, Saket, New Delhi for the "Perspective" .

Suggestions/comments from the readers are welcome.

Dr D C Doval

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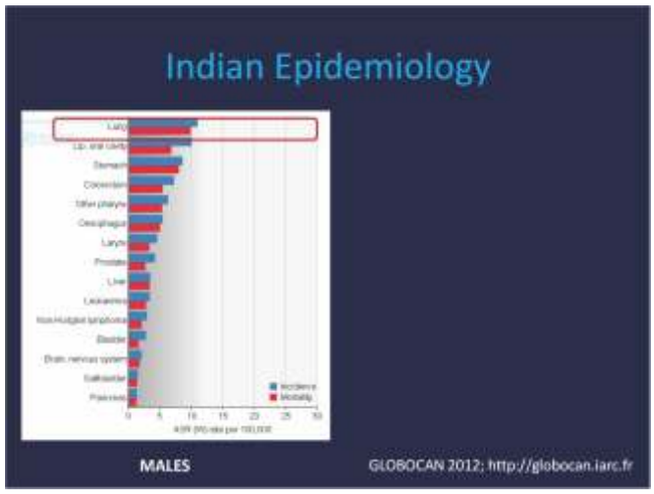
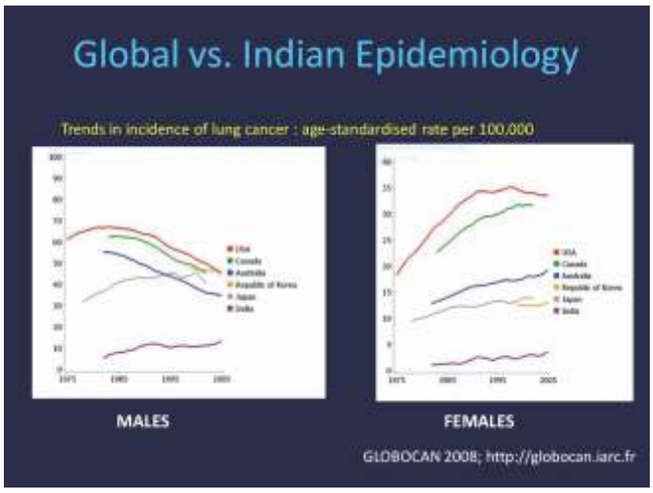
SPECIAL FEATURE

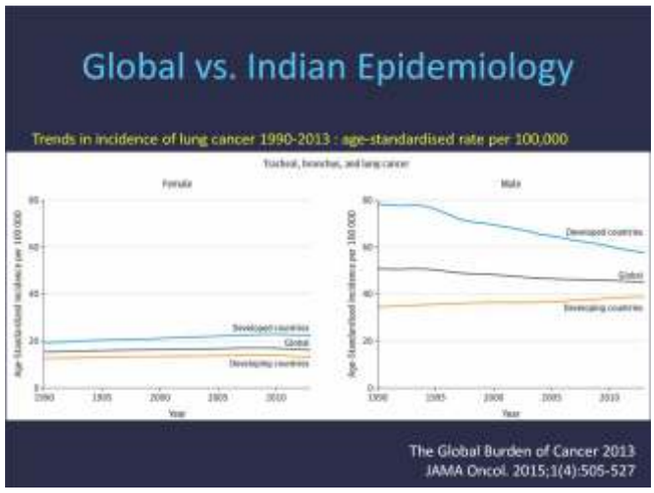
EPIDEMIOLOGY OF LUNG CANCER IN INDIA

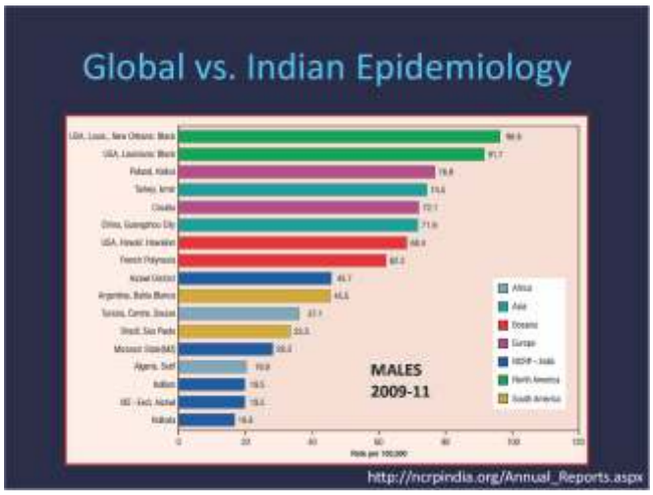
There is an increase in the burden of cancer in the world particularly in economically developing countries because of various factors like increase in cancer causing behaviors, adoption of cancer-associated lifestyle choices including smoking, physical inactivity, and ''westernized'' diets. Lung cancer has remained the most common cancer worldwide for several decades and represents 12.9% of all new cancers. Tracheal, bronchus, and lung (TBL) cancer are the most common type of cancer in men and remains a leading cause of cancer related mortality in both sexes, with 1.6 million deaths. For men, TBL cancer was the leading cause of disability-adjusted life-years (DALYs) (24.9 million) in 2013. Most patients with lung cancer present with advanced disease.[3] Although the cancer incidence rates in India are lower than in the developed world, the relative mortality rates are higher and this disparity results in a significant contribution to the world cancer deaths. Delay in diagnosis and inadequate, incorrect, or suboptimal treatment (due to lack of access to specialist care, financial constraints or lack of awareness) are the chief factors leading to poor cancer survival in India. In women, the incidence rates are generally lower than in men and the geographical pattern is somewhat different, depending on the uptake and consumption of tobacco.

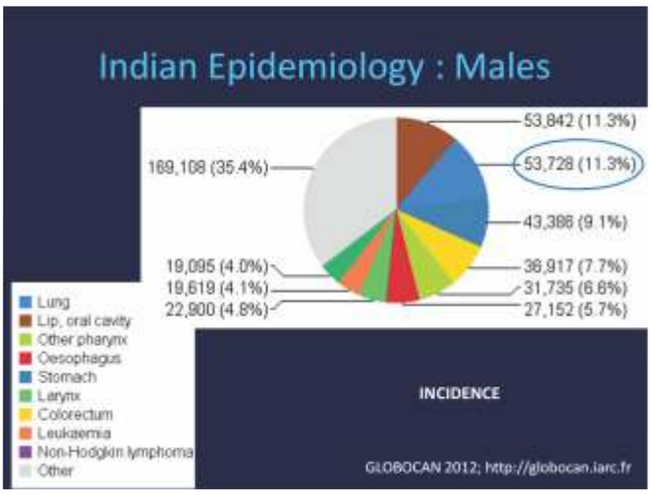


In contrast to a declining trend in men in developed countries with a plateau for females, in India the incidence continues to rise for both males and females. Data from the population based cancer registries developed under the National Cancer Registry Program of the Indian Council for Medical Research (ICMR) indicates that there is a wide geographical variability in the incidence of this disease in different parts of the country. The highest age adjusted incidence rates of 45 per 100000 population are seen in the North-East region of India and are similar to areas reporting the highest incidence rates in some parts of the US and Europe. In other areas of India, especially the western region, the age adjusted incidence rates are as low as 2 per 100000 population. The demographic profile, including age, gender, stage, histology and even the molecular epidemiology (prevalence of EGFR mutations and ALK rearrangements) varies considerably in different parts of India. However, the







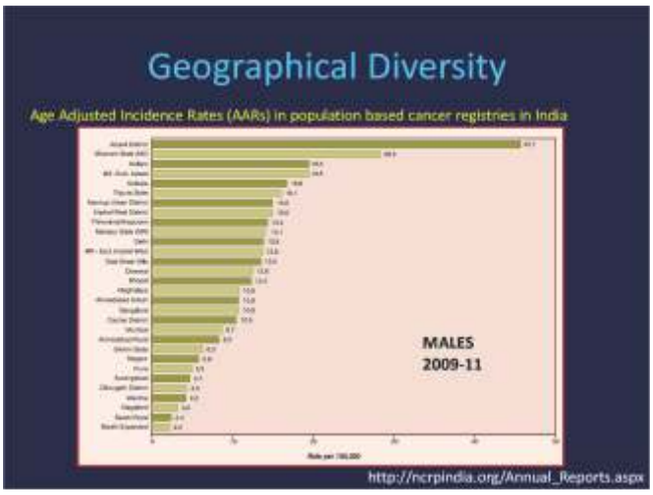


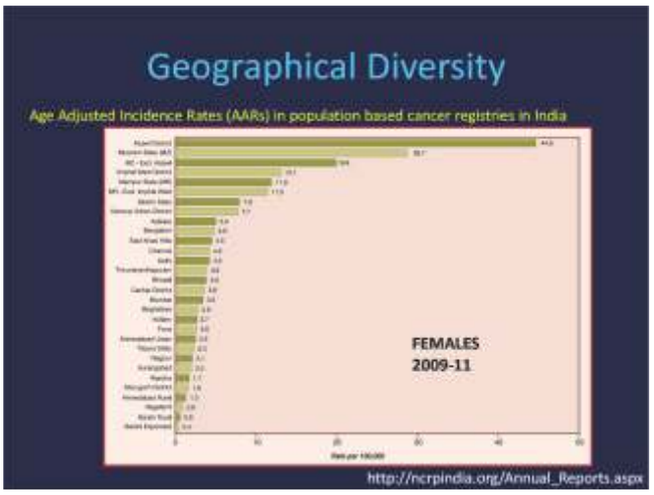
overall incidence is much lower than that compared to many western countries.

There is a wide variability in the incidence of lung cancer throughout the country. The incidence rates of lung cancer in the PBCRs (Population Based Cancer Registries) in India are at least as of now much lower than the registries elsewhere in the world with the highest rates. However, the district-wise bar charts revealed that Aizawl in Mizoram State and Imphal West in Manipur State, had 1½ times the MAAR (Average annual ageadjusted incidence rates for microscopically diagnosed cases) of the highest urban PBCR - Delhi. Further, at least nine other districts had MAARs higher of comparable with that of Delhi.

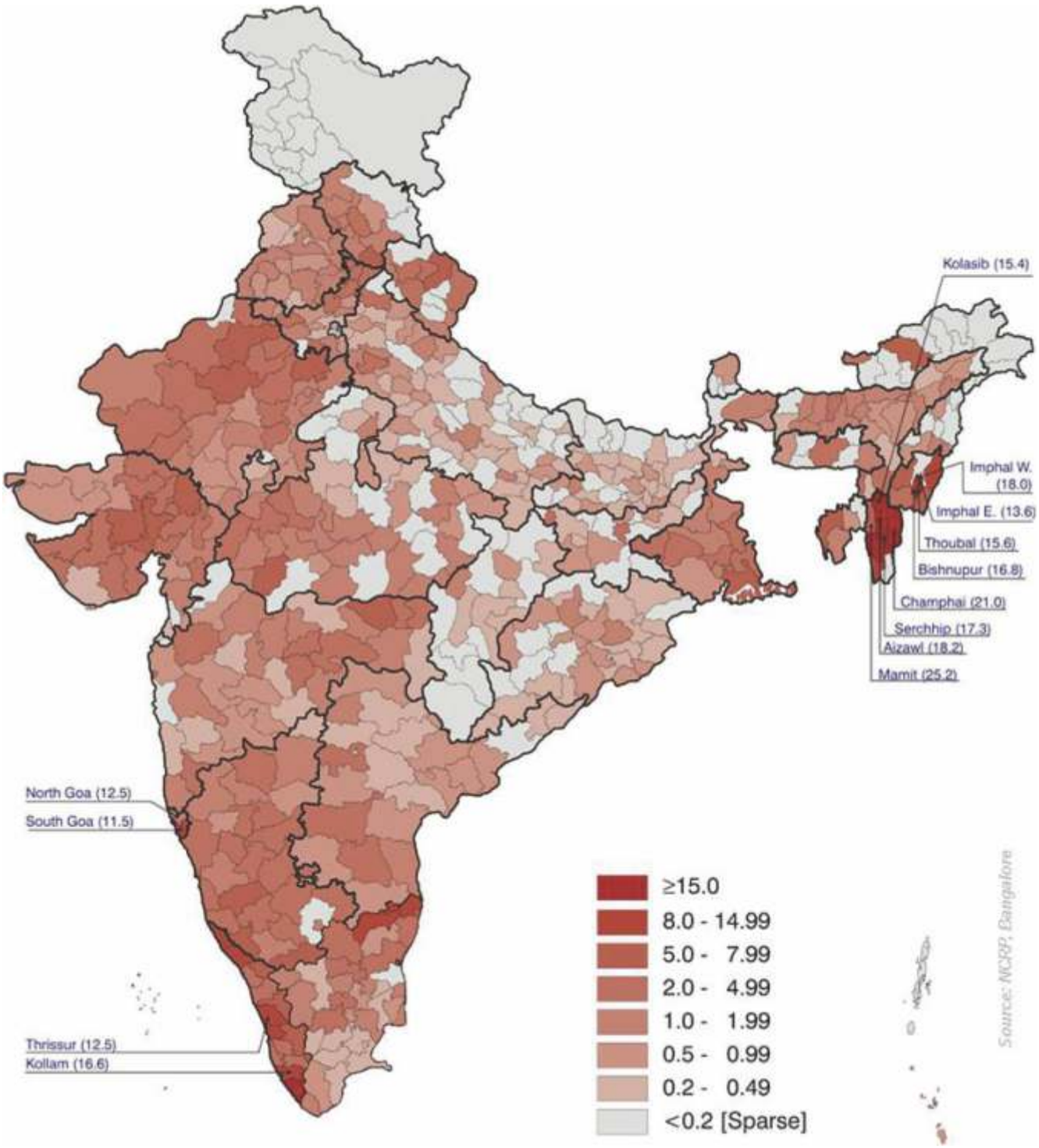
Except in Mumbai PBCR, cancer of the lung in females has not been a leading site of cancer in women in the PBCRs under NCRP. Even the rate (AAR of 4.2/100,000) in Mumbai is lower than that seen in Indians in Singapore and in other women in areas of high incidence in the world. Observation of the MAARs in the districts showed that Aizawl women had almost ten times the MAAR of women in Mumbai. Imphal West and East in Mizoram, State and South Goa had much higher MAARs than that seen in Mumbai.

The demographic profile of lung cancer seen in India needs special mention. In the past, a single-centre large series of 1009 patients presenting to our institute from 1977-86 had shown squamous histology as the commonest (34.3%), followed by adenocarcinoma (25.9%) and small cell lung cancer (SCLC; 20.3%). Subsequent analysis of 250 patients in the same center three decades later (2007-09) found that the histological pattern was largely unchanged with squamous still being the commonest (34.8%) followed by adenocarcinoma (26.0%) and SCLC (18.4%). The male-female ratio as well as the current/ex-smoker to never-smoker ratio was also similar between the two cohorts. A possible reason for the lack of change in demographic

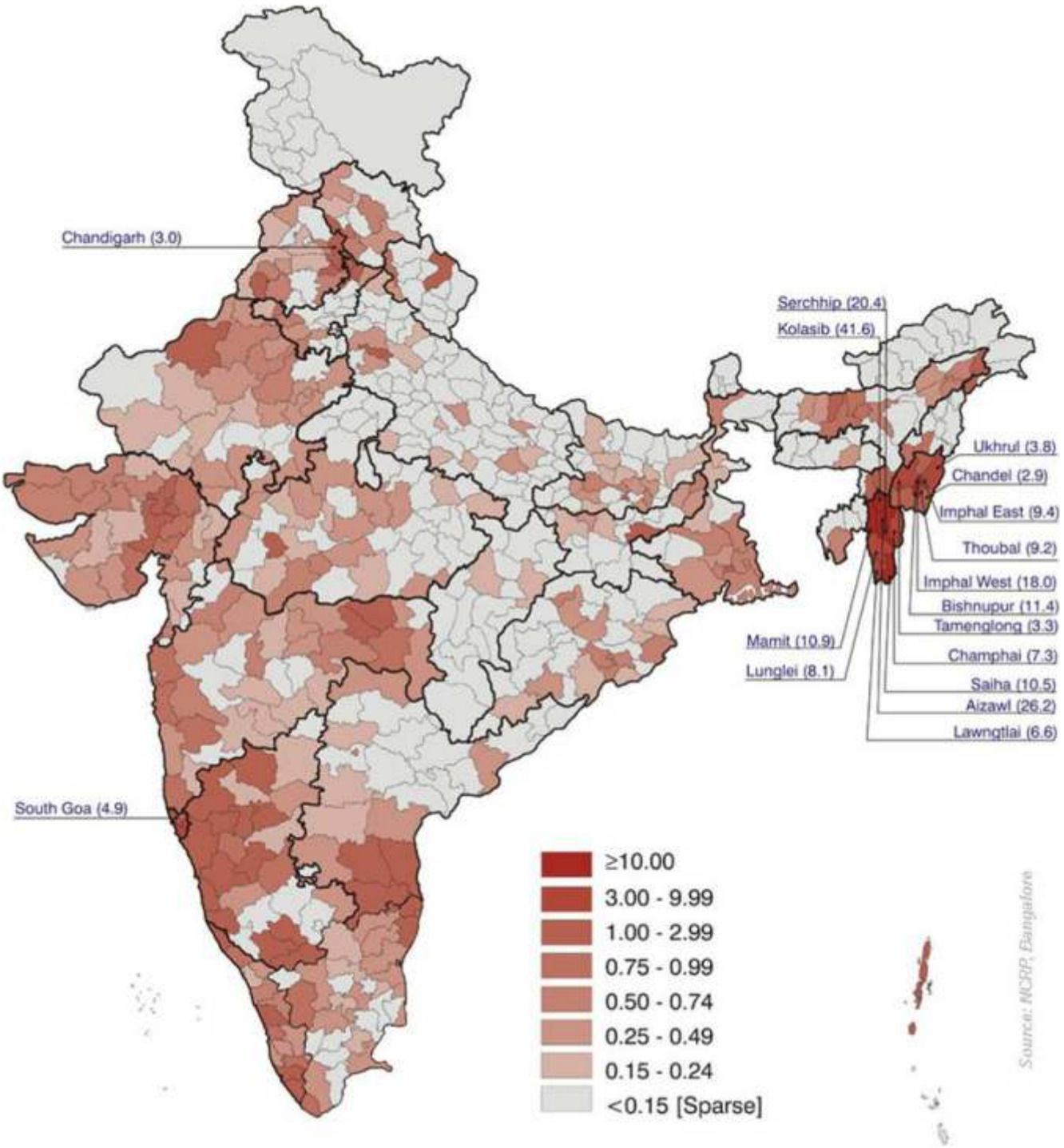




District-Wise Minimum Age Adjusted Incidence Rate Per 100,000 LUNG - Males



District-Wise Minimum Age Adjusted Incidence Rate Per 100,000 LUNG - Females



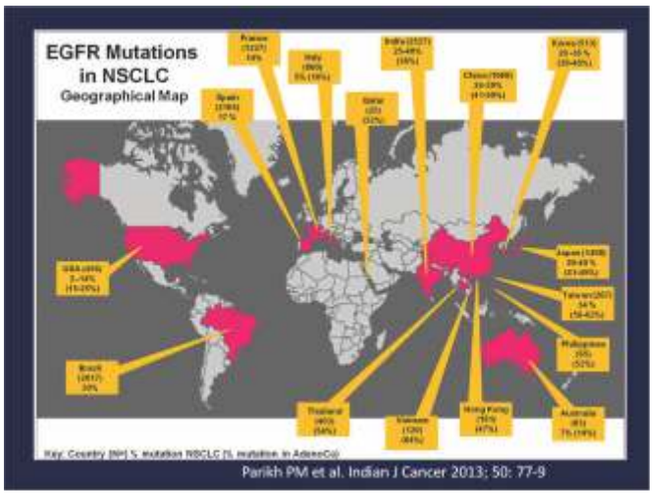
Geographical Diversity

Study	East	North	West	South
No of cases	607	654	489	258
Mean age (yrs)	58.9 (11.5) [M]	58.1% (10.8)	56 (11.9)	56.0 (10.1)
Males	80.6%	83.3%	77.7%	77.5%
Smokers	73.1%	76.9%	47.9%	60.4%
• SqCC	35.1%	38.1%	24.1%	15.9%
• ADC	30.8%	27.5%	40.3%	42.9%
• SCLC	16.5%	20.5%	8.0%	13.2%
• NSCLC-NOS	11.7%	10.9%	18.0%	19.0%
I-II	53.9% (I-IIIA)	3.1% (I-II)	15.5% (I-II)	11.2% (I-II)
IIIA		13.1% (IIIA)	46.6% (III)	35.7% (III)
IIIB	28.2% (IIIB)	35.4% (IIIB)		
IV	27.0% (IV)	48.5% (iv)	37.9% (IV)	53.1% (IV)

Singh N, et al. J Thorac Dis 2012;4:474-84
Dey A, et al. Indian J Cancer 2012;49:89-95
Noronha V, et al. Indian J Cancer 2012;49:74-81
Krishnamurthy A, et al. Indian J Cancer 2012;49:82-8

profile of lung cancer was thought to be related to the fact that 'bidi' and NOT cigarette is the most common form of tobacco smoking in India. The ratio of bidi to cigarette smoking in India ranges from 2.5:1 to 7.0:1 in different parts of India and unlike cigarette making, there has been no change in the process of bidi manufacturing which is primarily a cottage industry. However, there is a change in the histology reported from different regions.

The other important aspect related to is its association of quantified tobacco smoke exposure. The smoking index (SI; number of combined bidis and cigarettes smoked per day multiplied by number of years smoked) has been developed for this purpose. Patients can be categorized as either never-smokers (SI=0), light to moderate smokers (SI=1-300), and heavy smokers (Sie"301). In a cohort of 520 non-small cell lung cancer (NSCLC) patients, we observed that age, gender, histological type and stage differed significantly between the three groups. Never-smokers had significantly more females (52%), were younger (mean age 54.5 years), lesser squamous histology (28%), more advanced stage (IIIB/IV; 92%), more metastatic disease (67.4%) and more extra-thoracic metastases (42%), while group of heavy smokers had more males (98%), were older (mean age 61.2 years), more squamous histology (58%), lesser advanced stage (81%), lesser metastatic disease (39%) and lesser extra-thoracic metastases (17%). We have identified another risk factor in women to be the exposure to biomass fuel.



Parikh PM et al. Indian J Cancer 2013; 50: 77-9

Majority of patients (approximately 83% of NSCLC histology) present with advanced stage(IIIB/IV) at the time of diagnosis and are managed non-surgically. Misdiagnosis as tuberculosis and empirical treatment with anti-tubercular drugs prior to referral to higher centre are the important causes for delayed diagnosis of this disease in India.

Etiology

Smoking: Smoking is byfar the most common cause of lung cancer. The life time risk of developing lung cancer varies widely (1% - 15%) even amongst smokers. The factors which modify this risk include: (a) the duration of smoking (number of years smoked); (b) the age at initiation of smoking; (c) the intensity of smoking (number of cigarettes smoked per day);

	Sahoo, 2011	Veldore, 2013	Bhatt, 2013	Doval, 2013	Mehta, 2013	Chougule, 2013	Chougule, 2013
Centre	Triesta, Bangalore	Triesta, Bangalore	CMC, Vellore	RGCI, Delhi	SRL, Mumbai	TMH, Mumbai	TMH, Mumbai
N	220 NSCLC	1036 NSCLC	106 NSCLC	166 ADC	367 NSCLC	1018 NSCLC (885 ADC)	907 NSCLC (780 ADC)
Duration	2.5 y (Jan 08 – Jul 10)	3 y (2009 – 2012)	3 y (2008 – 2010)	2.5 y (Nov 09 – Apr 12)	3 y (2010 – 2013)	2 y (2011 – 2012)	1.5 y (Aug 11 – Dec 12)
Source	FFPE, FNAC, Pl fluid, Br. wash	FFPE, FNAC, BAL, Pl fluid	FFPE blocks	FFPE blocks	FFPE blocks	FFPE blocks	FFPE blocks
Mutation analysis	Scorpion ARMS-PCR	Scorpion ARMS-PCR	Direct sequencing	Direct sequencing	Direct sequencing	Direct sequencing	Direct sequencing
Exons covered	18, 19, 20, 21	18, 19, 20, 21	18, 19, 20, 21	18, 19, 20, 21	19, 21	18, 19, 20, 21	18, 19, 20, 21
Total EGFR+	(51.8%)	418/1036 (40.3%)	42/106 (39.6%)	43/166 (25.9%)	118/367 (32%)	255/1018 (25%)	210/907 (23%)
Exon 19	51.6%	255/418 (61%)	32/42 (76.2%)	22/43 (51.2%)	76%	135/255 (53%)	50%
Exon 21	26.2%	133/418 (31.8%)	7/42 (16.7%)	15/43 (34.9%)	24%	97/255 (38%)	42%
EGFR +ve ADC	44%	Not specified	33/76 (43.4%)	43/166 (25.9%)	106	245/885 (27.7%)	202/780 (25.9%)
EGFR +ve (NS vs current smoker)	48% vs 55.2%	N/A	49.3% vs 20%	34.7% vs 9.3%	33.9% vs 24.1%	31.5% vs 16%	29.4% vs 15.3%
EGFR +ve: F vs M	59.8% vs 45.5%	51.5% vs 33.5%	45.5% vs 37%	32.7% vs 22.5%	36.9% vs 24.4%	34% vs 21%	29.8% vs 20.4%
	Indian J Cancer 2013; 50(2): 87-111						
	Lung Cancer 2011; 73: 316-9			PLoS ONE 2013; 8: e61561			
	J Carcinogen 2013: 12: 12			PLoS ONE 2013; 8: e76164			

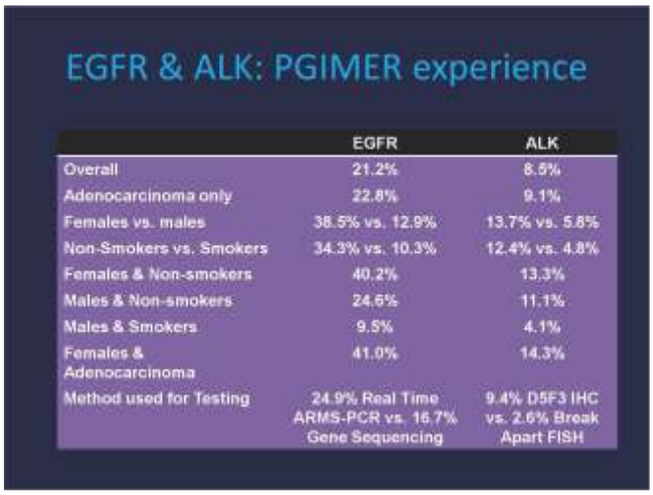
(d) the total exposure to smoke (smoking index or pack years); (e) exposure to co-carcinogens (radon, asbestos, silica etc..); (f) genetic susceptibility; and (g) years since cessation of smoking (for reformed smokers). A recent meta-analysis involving 287 studies observed that although RR estimates were markedly heterogeneous, it demonstrated a relationship of smoking with lung cancer risk and the relationship was as follows:

- Ever smoking(random-effects RR 5.50, CI 5.07-5.96)
- Current smoking (8.43, CI7.63-9.31),
- Ex smoking (4.30, CI 3.93-4.71), and
- Pipe/cigar only smoking (2.92, CI 2.38-3.57)

In many of the developing countries, including India, a majority of smokers use indigenous forms of tobacco (bidi, chutta, khaini, hooka and many more). These forms of smoking also predispose to development of lung cancer. In fact, a review of eight studies from different parts of India has concluded that bidi smoking poses a higher risk for lung cancer than cigarette smoking.

Environmental Tobacco Smoke: Environmental tobacco smoke (ETS), also known as second hand smoke (SHS) is also a known lung carcinogen. The chemical composition of the side stream smoke is qualitatively similar to the main stream smoke but is quantitatively different with certain carcinogenic agents, such as aromatic amines being present at a higher concentration in the side stream smoke. 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). This risk increases with increase in duration of exposure. Exposure to ETS before the age of 25 years is associated with a higher risk of developing lung cancer than exposure after the age of 25 years.

Indoor and Outdoor Airpollution: Use of biomass fuels has been implicated as a causative agent for lung cancer. The International Agency for Research on Cancer (IARC) had identified coal as group1 (known) pulmonary carcinogen and biomass fuels as group 2A (probable) pulmonary carcinogen. A recent meta-analysis of 28 studies has shown that both coal and biomass fuels are associated with lung cancer though the odds ratio was greater for coal (OR 1.82, 95% CI 1.60–2.06) as compared to biomass fuels (OR 1.50, 95% CI 1.17–1.94. The IARC in 2013 also included exposure to outdoor particulate matter air pollution as a group 1 lung carcinogen. Though the risk associated with air pollution is much lesser than the risk associated with active smoking, as almost everyone is exposed to outdoor air pollution, the anticipated public health effect is quite large. An Indian study has highlighted the fact that exposure to biomass fuel-cooking is an important risk factor in women even if they may be nonsmokers.



Other Causes: In addition to the above mentioned causes, several other factors have also been implicated in the development of lung cancer. These include occupational exposures to organic and inorganic dusts, radiation and exposure to radon, long standing structural lung diseases, HIV infection, and genetic factors.

There is also a variability in the molecular profiling of adenocarcinoma of lung in the country as shown below.

In a multicentre study, Doval et al studied a total of 500 NSCLC adenocarcinoma patients across six centers. There were 337 (67.4%) men and 163 (32.6%) women with a median age of 58 years. One hundred and sixty four (32.8%) blocks were positive for EGFR mutations, whereas 336 (67.2%) were EGFR wild-type. Of the 336 EGFR-negative blocks, EML4-ALK fusion gene was present in 15 (4.5%) patients, whereas 321 (95.5%) tumors were EML4-ALK negative. The overall incidence of EML4-ALK fusion gene was 3% (15/500).

They concluded that the incidence of EGFR mutations (33%) in this Indian population is close to the reported incidence in Asian patients. EML4-ALK gene fusions are present in lung adenocarcinomas from Indian patients, and the 3% incidence of EML4-ALK gene fusion in EGFR mutation-negative cases is similar to what has been observed in western and other asian populations. The mutual exclusivity of EML4-ALK and EGFR mutations suggests implementation of biomarker testing for tumors harboring ALK rearrangements in order to identify patients that can benefit from newer targeted therapies.

Conclusion

Developing and under-developing countries are often constrained with regards to availability of healthcare and other resources necessary for appropriate management of the health related requirements of their population. This holds true for lung cancer as well. Some of the challenges in resource constrained settings include:

- Large population with high population density
- Illiteracy and poor health awareness
- Sub-optimal economic and infrastructure inputs for health care
- Suboptimal ratios of doctors and nurses for populations
- Overburdened hospitals and healthcare facilities
- Huge burden of TB that hinders differentiation of patients by the primary physician of with lung cancer

Important issues in resource constrained settings include choosing the platinum agent as well as the non platinum agent. Decision on dose intensity may also be influenced by similar factors, such as (efficacy, tolerance, toxicity profile and packaging strengths of marketed drugs).

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GUEST ARTICLE

CHEMOTHERAPY IN ADVANCED LUNG CANCER

Introduction

Lung cancer is second most common cancer in both men and women worldwide. Lung cancer is also the most common cause of death from cancer worldwide, estimated to be responsible for nearly one in five deaths from cancer (1.59 million deaths, 19.4 % of the total)[1]. The vast majority of non small cell lung cancer (NSCLC) patients are diagnosed with advanced, unresectable disease that remains incurable.In the last decade lot of progress has been made in improving the outcome of patients with advanced NSCLC. Median overall survival (OS) has improved from 4-6 months to 12-14 months. This has been possible because of improvement in supportive care, combination chemotherapy and use of molecular targeted therapy. Most guidelines recommend use of histology and molecular characteristics for selection of first-line treatments. We have moved from single agent chemotherapy to platinum based combination chemotherapy which has resulted in better response rates and overall survival[2]. This review will cover first-line systemic chemotherapy in advance NSCLC, histology driven chemotherapy, maintenance chemotherapy, chemotherapy after progression and future perspectives.

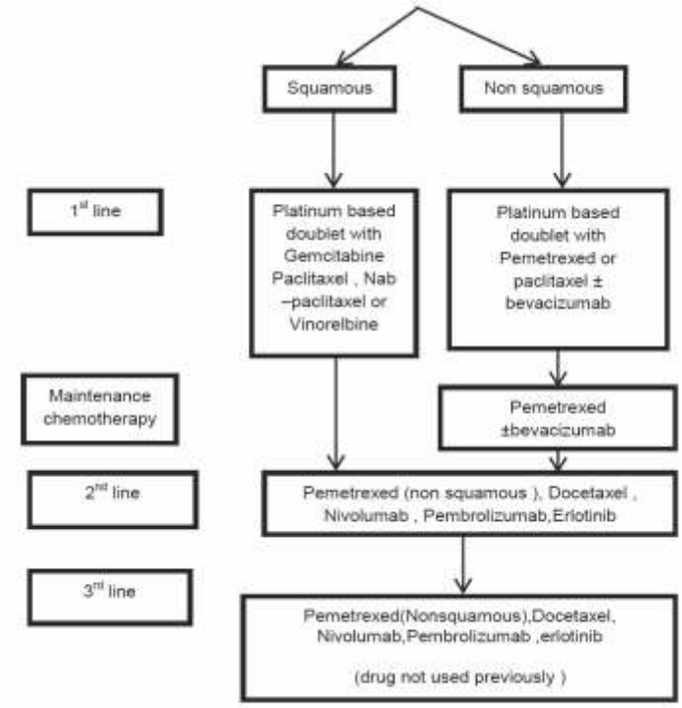
First-line Chemotherapy

After assessment for local therapy if any (e.g. pleurocentesis ,radiotherapy).patients with performance status (PS) of 0-1without a targetable driver mutation (EGFR and ALK) should be offered cytotoxic platinum based doublet chemotherapy. Patients with PS 2 may be offered single agent chemotherapy, while some may benefit from doublets. Patients with PS 3-4 do not benefit from chemotherapy and are offered best supportive care (BSC) only[2]. Benefit of cytotoxic chemotherapy compared to BSC was shown in a meta analysis where the one-year survival was 29% and 20% for chemotherapy and BSC respectively. This was independent of histology, performance status, and age.[3] Chemotherapy recommended is a platinum-based (cisplatin, carboplatin) doublet. A meta analysis showed that use of platinum based doublet was associated with better survival at 1 year (RR -1.16), CR (RR- 2.29), PR (RR-1.19) compared to non platinum doublet[4]. Compared to cisplatin, carboplatin has a lower response rate (24 % vs 30 %), statistically non-significant shortening of survival (median 8.4 vs 9.1 months) but a more favorable toxicity profile. Carboplatin is preferred in elderly and those with significant comorbidities and poor PS[5]. Platinum-free regimens can be considered in patients who cannot tolerate platinum-based treatment[2]. Direct comparison of several doublets [platinum with gemcitabine, paclitaxel and vinorelbine] in randomized phase III trials has failed to demonstrate the superiority of one doublet over the other. Thus, no particular regimen can be recommended as the gold standard. Choices between regimens may be based on potential toxicities[6]. Addition of third cytotoxic drug to platinum doublet increases response rate but with increased toxicity and inconsistent impact on survival[7]. Optimum number of cycles of first line chemotherapy recommended is 4-6.[2] Paik et al have shown non inferiority of 4 cycles compared to 6 cycles in the first line setting[8]. Elderly patients (age>70 years) also derive benefit from platinum based doublet chemotherapy[9].

Histology Based Chemotherapy

Historically. all NSCLC patients were treated with same platinum based chemotherapy. Initial trials of platinum based chemotherapy did not observe differential response or survival based on histological subtypes. Scagliotti et al in their study compared pemetrexed/ cisplatin to gemcitabine/cisplatin in advanced NSCLC and demonstrated longer survival with pemetrexed platinum doublet in nonsquamous histology and inferior outcome in squamous histology[10]. Similar interaction of histology and treatment efficacy of pemetrexed as maintenance therapy was also seen in JMEN trial[11]. Based on these studies, a pemetrexed platinum doublet is the combination of choice in those with non squamous histology while a gemcitabine platinum doublet is preferred in squamous histology. However, a taxane platinum doublet may also be used in the non squamous group. The treatment outcome difference using pemetrexed in different histologies is likely to be due to an underlying difference in enzyme thymidylates synthase. Nabpaclitaxel in combination with carboplatin was associated with better ORR in squamous histology compared to solvent based paclitaxel and carboplatin but without improving PFS and OS[12].

Chemotherapy algorithm for patients with advanced NSCLC without driver mutations



Predictive Markers

A predictive maker is one that predicts for differential benefit from a particular therapy. Excision repair cross complementation group 1 (ERCC1) and ribonucleotide reductase M1 (RRM1) protein are essential for nucleotide excision repair pathway. Low expression of ERCC and RRM 1 is associated with increased sensitivity to platinum agents and gemcitabine respectively and vice versa in early and advanced stage NSCLC. A high expression of â Tubulin III correlates with resistance to antimicrotubule reagents. However, these predictive biomarkers need validation in prospective randomized clinical trials and are not recommended to be used in daily practice[13].

Maintenance Chemotherapy

In patients who have responded to first-line chemotherapy-either continuing the same non-platinum chemotherapy partner (continuous maintenance) or a different chemotherapy drug not used in the initial combination chemotherapy (switch maintenance) have shown to improve the outcome without affecting QOL, particularly in adenocarcinoma histology. Continuing induction therapy doublet until progression failed to show improvement in OS but was associated with deterioration in quality of life. Switch maintenance using gemcitabine, docetaxel, pemetrexed and erlotinib showed statistically but not clinically significant improvement in PFS and OS[2].Role of continuation maintenance using pemetrexed was established in landmark PARAMOUNT trial in non squamous NSCLC. Both PFS (4.1vs 2.8 months, $p<0.0001$) and OS (16.9 vs 14 month Sp=0.019) were significantly better in pemetrexed arm compared to placebo[14]. Combination maintenance using pemetrexed and bevacizumab was better as single agent chemotherapy in AVAPREL and POINTBREAK trial but cost and toxicity were high significantly[15-16].

II Line chemotherapy

Though maintenance chemotherapy has been shown to improve overall survival, most patients will ultimately progress. Docetaxel, pemetrexed and erlotinib (non squamous only) are active drugs in this setting. In the II line setting, combination chemotherapy is not superior to single agents[17]. Ramucirumab and nintedanib in combination with docetaxel have shown statistically significant improvement in clinical outcomes compared to decetaxel alone[18-19]. Recently, immune check point inhibitors have become drugs of choice in most patients. Nivolumab and pembrolizumab, both PD-1 inhibitors improved the response rate and overall survival compared to docetaxel[20]. In patients having rapid progression (<3 months) of disease and those who have progressive disease as their best response to first-line therapy, docetaxel with nindetenib or ramucirumab may be preferable. This is based on exploratory sub-set analysis from the REVEL and LUXLUNG studies.

Future Perspective

Landscape of advanced NSCLC management is changing rapidly. Histology and oncogenic driver mutation play an important role in determining and sequencing of chemotherapy. There is need for predictive markers in order to further optimize efficacy of chemotherapy. As the number of druggable targets increase, the number of patients receiving first-line chemotherapy is likely to decrease. While plenty of basic research is ongoing to identify mechanisms of resistance to chemotherapy and to avoid unnecessary toxicity from chemotherapy drugs, we eagerly await the results of phase III trials using immunotherapy in combination with chemotherapy upfront for advanced NSCLC.

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OUTLOOK

ROLE OF SURGERY IN LUNG CANCER

Lung cancer is amongst the most common cancers in India and also the most common cause of cancer-related deaths. Approximately 85% of lung cancers are non small cell lung cancers (NSCLCs) and only 25-30% of these are eventually suitable for surgical resection with a curative intent [1]. Small cell lung carcinoma (SCLC) represents 15–20% of all lung cancers and it is characterized by rapid growth and early metastatic dissemination. Because of the advanced disease at presentation, systemic chemotherapy, with or without radiotherapy, has been typically accepted as the cornerstone of therapy in SCLC [2].

The current treatment strategy for NSCLC depends on clinical staging [Table 1]. Surgery remains the best curative option in patients with early stage lung cancer (stage 1 and 2) and is considered the treatment of choice in patients with stage 1 and 2 disease whose performance status allows for general anaesthesia and a lung resection [3, 4]. Surgery is also an accepted treatment modality in a fair proportion of patients with clinical stage 3A disease, and in a small proportion of selected patients with stage 3B and stage 4 disease.

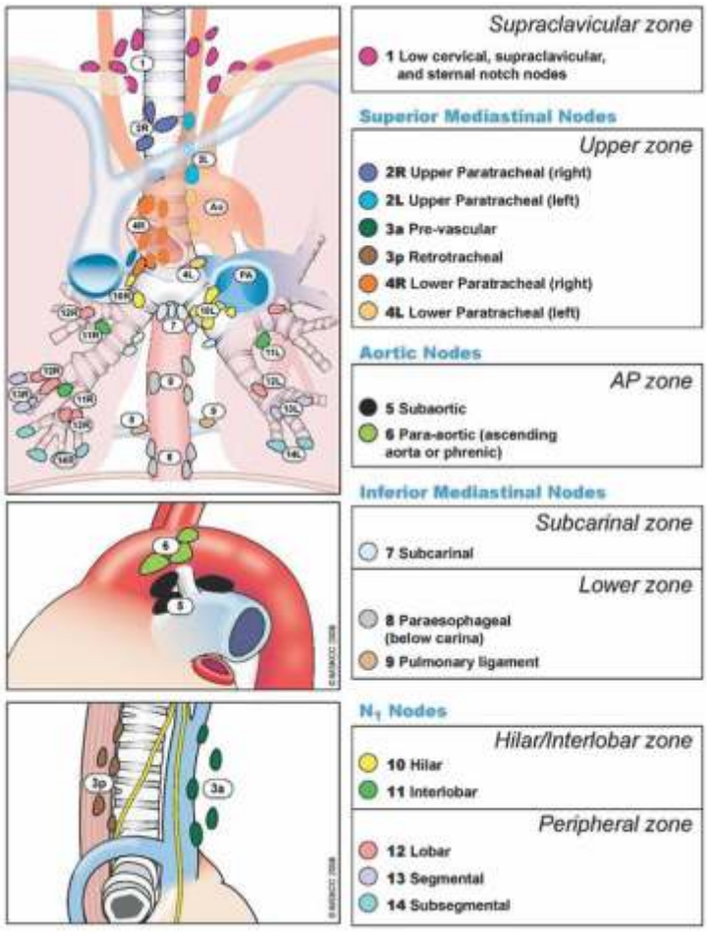
The availability and development of stappling devices have made lung resection safer, faster while maintaining oncological principles. With surgeons gaining experience and confidence in lung resections and thoracic anaesthesia techniques becoming more developed, it can be safely performed. More and more procedures are now being performed using a minimally invasive technique of thoracoscopy and also using the Da vinci robot [5].

Table 1. TNM Stage

	T-Primary tumor		N-Lymph nodes		M-Metastasis
T1	Tumor size less than or equal to 3 cm across, surrounded by lung or visceral pleura, without invasion proximal to the lobar bronchus	N0	No regional lymph node metastasis	M0	No distant metastasis
T1a	Tumor size less than or equal to 2 cm across	N1	Metastasis to ipsilateral peribronchial and/or hilar lymph nodes	M1a	Separate tumor nodule in other lung, pleural nodules Malignant pleural or pericardial effusion
T1b	Tumor size more than 2 cm but less than or equal to 3 cm across	N2	Metastasis to ipsilateral mediastinal and/or subcarinal lymph nodes	M1b	Distant metastasis
T2	Tumor size more than 3 cm but less than or equal to 7 cm across Involvement of the main bronchus at least 2 cm distal to the carina Invasion of visceral pleura Atelectasis/obstructive pneumonitis extending to the hilum but not involving the whole lung	N3	Metastasis to scalene or supraclavicular lymph nodes Metastasis to contralateral hilar or mediastinal lymph nodes		
T2a	Tumor size more than 3 cm but less than or equal to 5 cm across				
T2b	Tumor size more than 5 cm but less than or equal to 7 cm across				
T3	Tumor size more than 7 cm across nvasion into the chest wall, diaphragm, phrenic nerve, mediastinal pleura or parietal pericardium Tumor less than 2 cm distal to the carina, but not involving the carina Atelectasis/obstructive pneumonitis of the whole lung Separate tumor nodule in the same lobe				
T4	nvasion of the mediastinum, heart, great vessels, trachea, carina, recurrent laryngeal nerve, esophagus, or vertebra Separate tumor nodule in a different lobe of the same lung				

TNM	Stage group
T1a–T1b N0 M0	IA
T2a N0 M0	IB
T1a–T2a N1 M0	IIA
T2b N0 M0	
T2b N1 M0	IIB
T3 N0 M0	
T1a–T3 N2 M0	IIIA
T3 N1 M0	
T4 N0–N1 M0	
N3 M0	IIIB
T4 N2 M0	
M1	IV

Fig 1 – Mediastinal node station



Surgery for lung cancer is indicated in the following conditions:

1. Tissue for diagnosis
2. Surgical staging of mediastinal nodes
3. Thoracoscopy for undiagnosed pleural effusion
4. Definitive surgery for lung cancer
5. Palliative procedures

1. Tissue for Diagnosis: Tissue diagnosis is the most important initial step in diagnosis of lung cancer, and the tissue obtained should be adequate for histopathology, immuno-histochemistry and targeted mutation testing. Adequate tissue to establish a diagnosis is usually obtained using CT guided trucut biopsy or bronchoscopic forcep biopsy. It is only when these less invasive procedures fail to establish a diagnosis that a surgical biopsy is indicated. When surgical biopsy is needed, it can be safely done using minimally invasive thoracoscopy. For small peripheral T1 and ground glass lesion, a frozen section examination with curative surgical resection and mediastinal node dissection can be done in the same setting.

2. Mediastinal Node Staging [FIG 1]: Initial mediastinal node assessment is done using non-invasive CT and PET CT modality. Pathological mediastinal node staging is a requirement in all cases of lung cancer who can be offered curative treatment except for small solid peripheral nodules <1cm. The presence of mediastinal lymph node or metabolic activity is not diagnostic of diseased nodes N2, N3 which is critical in the staging and management of lung cancer. This scenario is especially true in India where granulomatous involvement of lymph nodes is very common. If tissue diagnosis is not done there is a high probability of upstaging such cases and denying a curative surgical resection. A tissue diagnosis of the lymph node can be done using bronchoscopy needle biopsy or endo bronchial using guided needle biopsy [EBUS] where available. When these lesser invasive modalities are unavailable or tissues are inadequate for pathological examination, then a surgical mediastinal node staging should be done. Video-mediastinoscopy is able to access mediastinal node at level 2R, 4R, 2L, 4L, 7, extended mediastinoscopy can access level 5,6 nodes. Similary,

Table 2: Current recommendation and future directions of NSCLC management

Stage	Current recommendation	Future direction
Stage 1	surgery	Adjuvant therapy chemoprevention
Stage 2	Surgery	Adjuvant therapy Chemoprevention
Stage 3 A	Surgery in select cases Chemo-radiation	Neoadjuvant combined modality to downstage primary tumor
Stage 3 B	Chemo-radiation	Neoadjuvant combined modality to downstage primary tumor
Stage 4	Chemotherapy, Gene therapy Surgery in solitary metastasis with resectable primary	More efficacious single agent chemotherapy Combination chemotherapy Gene therapy

a right sided thoracoscopy can access lymph nodes at 2R, 4R, 7, 9 and a left sided thoracoscopy can access level 5, 6, 7, 9 nodes. This mediastinal node pathological staging is very crucial as management of lung cancer is stage dependent. The other advantage of a surgical mediastinal staging for resectable primary is the ability to do surgical resection of the primary tumor in the same sitting where N2 nodes are reported as negative for disease on frozen section examination.

3. Thoracoscopy for Undiagnosed Pleural Effusion: Pleural effusion in lung cancer is an indicator of metastatic disease and is usually diagnosed using pleural fluid examination; pleural fluid cytology has a sensivity of about 40-70 % which increases to about 55-85 % when using cell block study [6]. However reactive pleural effusion can also arise due to associated collapse consolidation of lung segments. For lesions with no other extra pulmonary lesions a diagnostic thoracoscopy helps in getting a pleural biopsy from the site of lesion or disproves pleural disease.

4. Definitive Surgery for NSCLC: Surgery is definitive treatment of choice for early stage disease patients who are able to withstand surgery [Table 2]. It is very important to evaluate such patients before surgery to look for resectability, cardiopulmonary reserve and perioperative risk. As a general guideline, most patients with a preoperative forced expiratory volume in one second (FEV1) of greater than 2.5 L are able to tolerate pneumonectomy. With an FEV1 of 1.1-2.4L, a lobectomy is possible. Patients with an FEV1 of less than 1 L and DLCO < 40 % are not considered candidates for surgery. These factors are further modified by the presence of cardiac disease or other comorbid conditions. In those patients undergoing surgical resection for lung cancer, lesser invasive techniques are being used. With the improvement in endovision, instruments and stappling devices such procedures can now be safely done using thoracoscopy / VATS. Robotic thoracic surgery is also now in use for lung cancer surgery with all the advantages of minimally invasive approach and shorter hospital stay. The various surgical procedures for lung cancer are segmental resection, lobectomy, bilobectomy, sleeve resection, and pneumonectomy. All these lung resections should be done with a systemic mediastinal node dissection to accurately stage the disease. Lobectomy is still the procedure of choice for lung cancer. For very early lesion < 2cm, a segmental resection may be done in those with poor pulmonary reserve. Sleeve resection of bronchus or vessels is now routinely used in order to preserve lung parenchyma and avoid a pneumonectomy.

Stages 1, 2: Surgery is the preferred treatment of choice.

Stage 3 A: The N2 disease is a heterogeneous group of patients with some having a better prognosis than others. It is recognized that patients who present with bulky N2 disease at clinical staging have a different prognosis from those with microscopic N2 disease diagnosed at thoracotomy or final pathology [7]. N2 disease patients who are most likey to benefit with surgery are: (a)- single station < 3cm size; (b) < 2 nodal station involvement, (c)no extracapsular extension on imaging, (d) response to induction therapy. It is now recognised that patients with single station N2 node have a similar survival as those with multiple N1 disease [8]. Riquet et al. [9] have also reported that patients with skip mediastinal lymphadenopathy (N2) have a better survival than those with N1 plus N2 disease.

Stage 3 B: At present, there is no role for definitive surgery in patients with N3 disease, outside of a clinical trial.

Stage 4: Surgery with curative intent for lung cancer is indicated for solitary metastasis to the adrenal or limited metastasis (<3) in the brain. The primary lesion should be T1,2,N0,1 or T3,N0.

5. Palliative procedures: Malignant pleural effusion is a common occurrence in those with advanced lung cancer. Most of the cases can be managed by draining the pleural fluid using image guided needle aspiration, pleural catheter or placement of a chest drain. Once the lung is expanded pleurodesis using talc 4gm can be done to prevent fluid reaccumilation. However in a few cases, complications such as empyema with trapped lung and bronchopleural fistula can arise. In such scenario neither chemotherapy nor radiotherapy can be offered until the empyema has resolved. When the patient has a life expectancy of >3 months it seems justified to offer a surgical intervention to drain the empyema, close the bronchopleural fistula. Such cases can now be routinely managed using minimally invasive thoracoscopic decortications and wedge / segmental resection for closure of bronchopleural fistula. A thoracoscopy technique avoids morbid thoracotomy incisions in these patients and such therapeutic plans should ideally be approved in a multidisciplinary meeting and should be documented in the patient's notes.

Surgery for Limited Disease Small Cell Lung Cancer (SCLC)

Most cases of small cell lung cancer present at an advanced stage because of its rapid growth and early dissemination. Surgery has a role in limited disease small cell carcinoma as part of the multimodality treatment approaches and it is justified to offer primary surgery followed by chemoradiotherapy in stage T1, N0 and possibly in stage T2, N0. The rational for surgery in limited disease small cell carcinoma [10] is as follows:(1)-Small peripheral lung nodules that are in fact typical or atypical carcinoids tumors may be misdiagnosed as SCLC (2)-Histologically mixed tumors with both SCLC and NSCLC components may fail to chemoradiation protocols since there is less sensitivity of the NSCLC component to chemotherapy. (3)-Surgical resection for T1-2, N0, M0 SCLC could offer better local control of the disease compared to chemotherapy alone. Indeed current chemoradiotherapy protocols have demonstrated local failure rates approximating 50%. (4)-Second primary, histologically proven NSCLC.

Conclusion

Surgical resection remains the mainstay of treatment for all patients with stages 1 and 2 NSCLC- that is, those patients with no evidence of mediastinal disease or invasion of local organs. Lobectomy is the procedure of choice with outcomes better when the procedure is performed by a surgeon with speciality training, or is done in a higher volume center or in a teaching facility [11]. The role of surgery for stage 3A disease is limited to single station, microscopic N2 disease. Patients with stage 3B or 4 tumors are almost never surgical candidates.

Survival in lung cancer remains poor, except in patients with early-stage disease where cancer can be cured in more than 60–70% of cases. Nonetheless, surgery remains the best choice of cure for lung cancer patients and an invaluable palliative treatment modality in many. As surgical techniques are unlikely to change dramatically in the next decade, our efforts should concentrate on early diagnosis, better understanding of tumour biology, development of biomarkers and effective systemic and targeted therapies [table 2].

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PERSPECTIVE

STEREOTACTIC BODY RADIATION THERAPY (SBRT) FOR EARLY STAGE LUNG CANCER AND LUNG METASTASES

Introduction

Lung cancer is the most common cancer in men and overall second most common cancer if age standardised incidence in both sexes is considered[1]. In India, it is the commonest cancer and cause of cancer related mortality in men, with time trends of lung cancer showing a significant rise in Delhi, Chennai and Bengaluru in both sexes[2]. Lung cancer mainly occurs in older people with 2 out of 3 people diagnosed with lung cancer being 65years or older and the average age at the time of diagnosis of about 70 years[3].

Currently, surgery is the standard treatment option for patients with stage 1 Non Small Cell Lung Cancer (NSCLC). Long term results of surgical resection show survival rates of 60-70% at 5 years and as high as 80% in some series[4]. However, a substantial number of patients are ineligible for surgery due to the presence of respiratory or cardiovascular comorbities.

Conventional radiotherapy has been tried in stage 1 NSCLC, where surgery is not an option. Grutters et al in a meta-analysis, compared conventional radiotherapy, stereotactic body radiotherapy (SBRT) and particle therapy (proton and carbonion) in patients of lung cancer[5]. The meta-analysis found that five-year overall survival for CRT (20%) was statistically significantly lower than that for SBRT (42%), proton therapy (40%) and carbon-ion therapy (42%). Severe adverse events (grade > 3) were infrequent for all modalities, with the majority of studies reporting no adverse events.

Surgery versus SBRT in NSCLC Stage 1: Till date, there has been no randomised controlled trial comparing SBRT with surgery in stage 1 NSCLC cases. The radiation therapy oncology group (RTOG) in its 0236 trial, prospectively studied early stage NSCLC (T_1 or T_2, N_0) medically inoperable cases, treated with SBRT to a dose of approximately 45Gy in 3 fractions. The 2-year local control rate of the primary tumor was 97.6% and the 3-year rate of local control (defined as absence of recurrence at the primary site or involved lobe) was 90.6%. Overall survival (OS) at 2 years was 55.8%, with a median survival of 48.1 months. The reported 5-year OS was 40%[6].

Senthi et al, reported on outcomes of 676 patients of inoperable stage 1 NSCLC (56% T_1, 44% T_2 tumors), treated with SBRT. Dose delivered ranged from 54-60Gy in 3-8 fractions. The predominant pattern of failure was out of field, with a 5-year actuarial local control rate of 89.5%[7].

Solda F et al, in their systemic review of 3771 patients of stage 1 NSCLC treated with SBRT, observed that the 2-year local control rate post SBRT was 91% while the 2-year OS was 70%[8]. In comparison, the surgical cohort (n=2038) had a 2-year survival of 68% in stage I patients. The authors concluded that survival outcome in the short and medium term was equivalent in case of SBRT as well as with surgery.

Literature is limited on outcomes of SBRT in potentially operable stage 1 NSCLC patients, who declined surgery. In a retrospective analysis, Lagerwaard et al analysed 177 such cases and observed that local control rates at 1 and 3 years were 98% and 93%, respectively. Regional and distant failure rates at 3 years were 9.7% each. Toxicity was mild, with gradee "3 radiation pneumonitis and rib fractures in 2% and 3%, respectively[9].

Two independent, randomised, phase 3 trials of SABR in patients with operable stage 1 NSCLC (STARS and ROSEL) closed early due to slow accrual[10]. Chang et al assessed overall survival for SABR versus surgery by pooling data of 58 enrolled patients from these trials (31 received SBRT and 27 underwent surgery). The estimated overall survival at 3 years was 95% in the SBRT group and 79% in the surgery group (p=0.037). Recurrence-free survival at 3 years was 86% (95% CI 74–100) in the SBRT group and 80% in the surgery group (p=0.54). In the surgery group, one patient had regional nodal recurrence and two had distant metastases; in the SABR group, one patient had local recurrence, four had regional nodal recurrence, and one had distant metastases. Three (10%) patients in the SABR group had grade 3 treatment-related adverse events (three [10%] chest wall pain, two [6%] dyspnoea or cough, and one [3%] fatigue and rib fracture). No patient given SABR had grade 4 events or treatmentrelated death. In the surgery group, one (4%) patient died of surgical complications and 12 (44%) patients had grade 3-4 treatment related adverse events. Grade 3 events occurring in more than one patient in the surgery group were dyspnoea (four [15%] patients), chest pain (four [15%] patients), and lung infections (two [7% patients])[10].

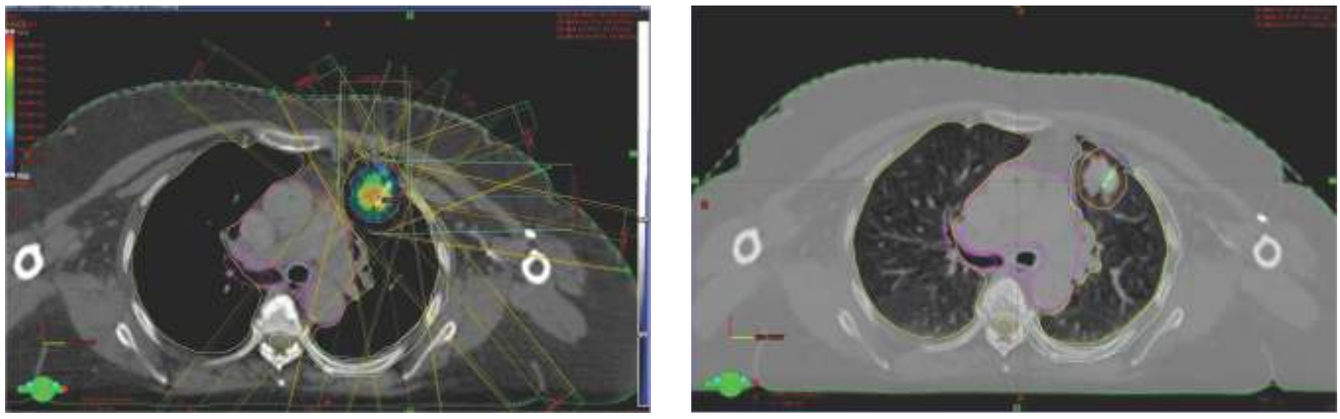

Figure – 1 A & B : 73year old female, adenocarcinoma left upper lobe, stage-I, with visicoil marker (A) and SBRT radiation planning (B).

So it can be reasonably concluded that while in inoperable stage 1 NSCLC, SBRT is the treatment of choice but the same cannot be extrapolated to operable cases as yet, even though the local control rates achieved with SBRT are non-inferior to those achieved with surgery.

SBRT in Lung Metastasis: In oligometastatic disease, local therapies have a potentially curative role and also as per the Norton-Simon hypothesis, reducing tumor burden by local therapies may increase the efficacy of subsequent systemic therapy. Local treatments used for oligometastases in the lung (surgery, SBRT, radiofrequency ablation) have shown to increase survival in selected cases. The international registry of lung metastases records 5206 cases of lung metastatectomy. The 5-year overall survival rate for the series was 36% in completely resected cases, with a 15-year survival rate of 22%, supporting the possibility of long-term survival in this group of patients with oligometastatic disease[11].

Brown et al analysed 35 patients lung metastases (up to 8) in a retrospective study. Prescribed dose was 5-60 Gy in 1-4 fractions (according to the number of metastases for treatment and the tolerance of OARs). At a median follow-up of 18 months, the local control rate was 71%, with an overall survival rate of 77%. Grade 4 pneumonitis was observed in one patient with 2 adjacent lung metastases[12].

Okunieff et al reported outcomes of 49 patients having < 5 metastases, with a total of 125 lung metastases. All patients were treated with curative intent to a dose of

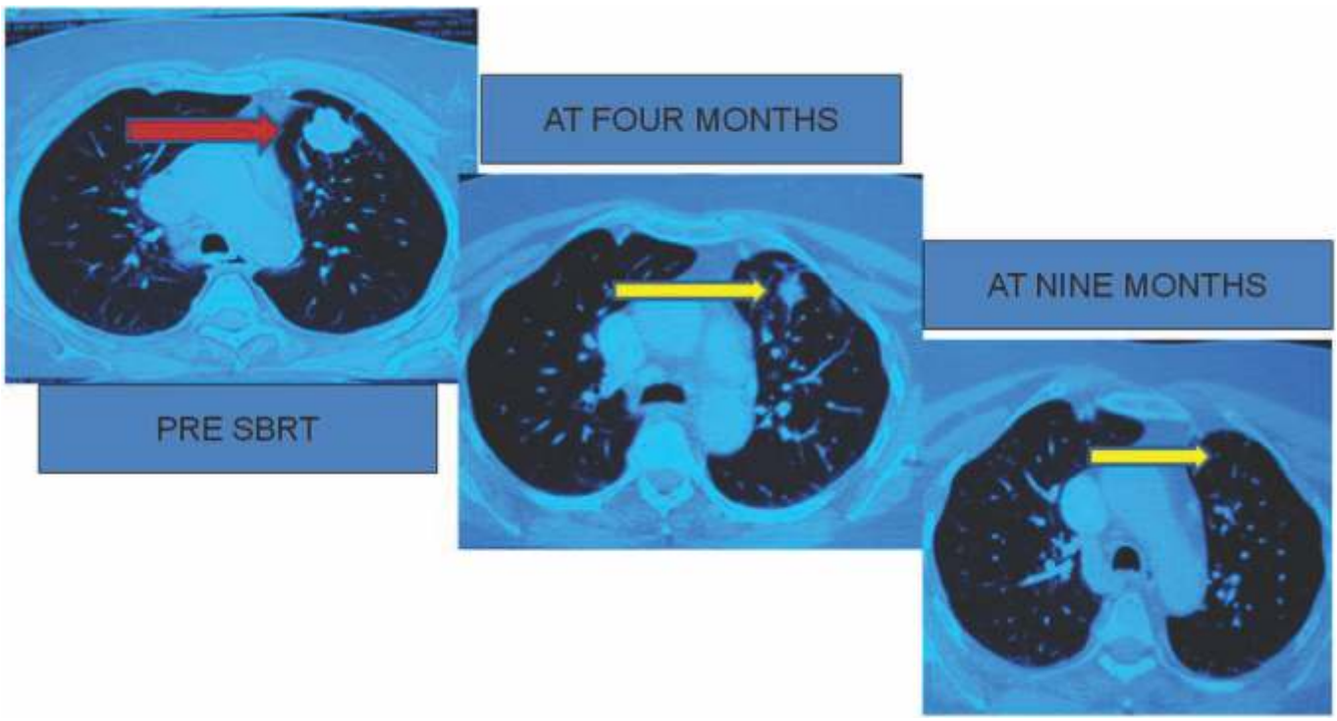

Figure - 2: Pre and post SBRT follow-up CT scans. Last follow up 14.02.2015 (38 months) - in CR

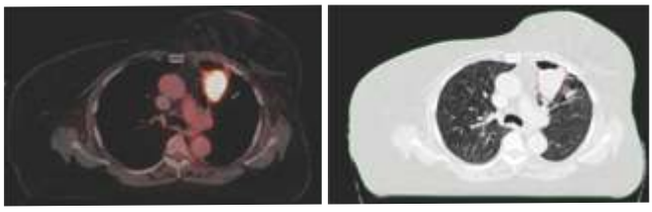

Figure 3: 85 year old female, CT and CT-PET shows stage - I, Lung cancer – Adenocarcinoma. CT PET (A) and CT scan of thorax (B) of a patient treated with SBRT

50 Gy in 5 fractions (BED 100 Gy). The local control rate at 3 years was 91%, with an overall survival of 75% at 3 years. There was no reported grade 3+ toxicity[13].

Norihisa et al. treated 35 patients with 1-2 lung metastases. The starting dose of 48 Gy in 4 fractions was escalated to 60 Gy in 5 fractions achieving a 2-year local control rate of 90%, and a 2-year overall survival rate of 84%. One patient was reported to have grade 3 lung toxicity[14].

In other studies with smaller number of patients, the reported local control rates at 3 years were in the range of 39–84%. SBRT in lung metastases was well tolerated in most reports, with a incidence of grade 3 toxicity of 4%. Better outcomes were achieved with regimes prescribing a BED of >100 Gy.

There are no randomized trials comparing SBRT with surgery in these cases and the patients treated with SBRT were invariably medically inoperable. Also, these patients have often received multiple previous chemotherapy, affecting their tolerance.

Figure 1: Novalis Tx with "Exac Trac" gating system The **tumor motion** is tracked with implanted gold visicoil marker (Figure 2) in or preferably near the tumour. As the relation between external breathing signal and tumour motion can change during treatment, this relationship needs to be verified constantly during treatment and multiple images are acquired on a regular basis at the reference level.

Figure 2b: Tumor tracking by implanted gold visicoil markers Respiratory correlated 4DCT uses multi-slice CT scanners combined with a respiratory surrogate to develop a series of 3DCT scans, each representing the patient in a different respiratory phase. The entire 4DCT dataset can be used to determine an envelope of tumor motion which can be expanded to include areas of expected tumour position in various respiratory phases.

In cases where implanting / inserting a visicoil marker is not feasible/ clinically advisable, we can restrict the respiratory motion with abdominal compression device or breath hold technique. However, many patients with lung cancer have an associated poor pulmonary function and may not be able to adequately comply with the breath hold instructions or tolerate abdominal compression. In such cases the Internal Target Volume (ITV) is determined by the maximal tumour motion as visualized on the fluoroscopy done with compression device.

At our centre we treat patients with 1-3 metastases in lungs, from any primary tumor, having a maximum cumulative tumor diameter smaller than 5 cm. A disease well controlled with systemic therapies, with a limited number of metastatic foci, reasonable life expectancy, with adequate lung function and a KPS at least 70, are prerequisites for SBRT delivery in lung metastases.

SBRT Technique

The technique of SBRT allows delivery of high ablative doses of radiation to a target with tight margins thereby sparing the surrounding organs at risk (OAR). The technique, also known as stereotactic ablative body radiotherapy (SABR), involves precise radiation delivered in 3-5 fractions, with a much higher dose delivered per fraction as compared to the conventional radiotherapy resulting in a considerably high biological effective dose (BED) to the tumour.

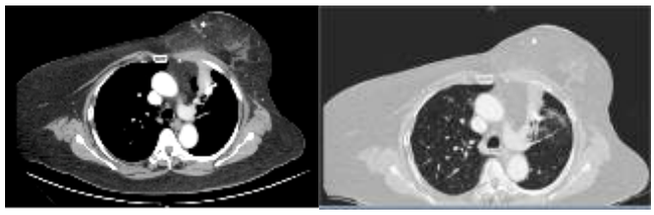

Figure 4: Same patient, post SBRT - 42 months-with scar like fibrosis

SBRT is well tolerated with a favourable toxicity profile reported in most series. Senthi et al in their review of central lung tumors treated with SBRT observed that, amongst the toxicities observed, respiratory toxicity including pneumonitis, pneumonia, dyspnoea (typically increased oxygen requirement in patients already using oxygen) and bronchial stricture were the most prevalent and grade 1 or 2 in most cases. There was one reported case of grade 3 esophagitis, rib fracture and peri card it is each. Grade 3 or 4 toxicity occurred in 8.6% (36/418) of central tumors treated with SBRT. Higher toxicity rates have been reported in a few series, this may be attributed to use of higher doses (60Gy or more in 3 or 4 fractions) without a substantial dose and/or fractionation adjustment for central tumors[7]. Higher toxicity may also be due to a compromised baseline respiratory function in these mostly elderly, inoperable patients.

Image Guidance Techniques to Track "Moving" Tumors: The aim while treating a patient with SBRT is to try and deliver an ablative dose (very high biologically equivalent doses BED >100Gy) to the target volume.

Prerequisites to deliver SBRT is to:

1. accurately identify and delineate the target and OARs
2. to employ a strategy to deal with respiratory motion
3. ensure precise and daily delivery of radiation to the intended target

Accurately Identify and Delineate the Target and OARs: Due to respiratory motion, standard free breathing CT scan both distorts and generally underestimates the tumor volume(). Therefore, contouring the gross tumor volume (GTV) on a free breathing CT scan leads to both an inaccurate representation of the tumour dimensions and the tumour position relative to other organs. In defining the tumor and OARs, it is important to delineate volumes on both mediastinal and lung windows and to co-register the PET CT images to distinctly identify tumor from collapsed lung.

Strategies to Deal with Respiratory Motion: Our centre uses both 4DCT based respiratory gating using the" Varian RPM" system as well as "Exactrac" based infra red tracking with stereoscopic X Rays for the respiratory movement of implanted markers (Figure1).

Number	14 Primary, 7 Metastatic
Age Median Range	 65 years (29-81)
Sex Male Female	 13 8
Gross tumor volume equivalent Diameter	0.41-81cc 0.2-5.4 centimetre
Histology Primary Metastatic	 8 – Adenocarcinoma, 6 – Squamous 4- Adenocarcinoma, 2 – Squamous 1-Sarcoma
Dose Schedules	50Gy /10 # - 5 patients 55Gy /5 # - 13 patients 60Gy /3 # - 3 patients
Frequency of treatment delivery	Alternate days
Follow up	Median – 16 months (range 4-29 months)
Local control	95% (1 – local failure)
Toxicity: Marker related	1 Patient – Self resolving Pneumothorax
Toxicity: SBRT related	1 Patient – Asymptomatic pneumonitis 1 Patient – Grade I skin toxicity No grade II-IV Toxicity

Table1: Patient Demographics and Clinical Characteristics at Max Cancer Centre, Max Hospital Saket, New Delhi

Marker placement in lung tumors is performed by intervention radiologists under CT guidance. The SBRT marker is a 2cm gold coil (visicoil) and is implanted inside lung, in proximity to the tumor(s). A single visicoil marker is enough for tracking the tumor by the Exac trac device.

The ExacTrac/NovalisBody System (Brain LAB AG), (Figure 1) combines:

- An infrared tracking system including two infrared cameras mounted to the ceiling
- Reflective markers that are placed on the patient's surface allowing real-time monitoring of the patient's position in space and extraction of a respiratory signal
- A pair of orthogonal X-ray tube/detector imagers to subtract 3D information of the patient's anatomy on the basis of bony structures or implanted radioopaque markers
- A robotic couch to adjust translational and rotational set-up errors before and during treatment. The beam on-off signal of the linear accelerator (LINAC) can be triggered by the respiratory signal that is obtained from the real-time tracking of the infrared reflective markers.

Respiratory correlated 4DCT uses multi-slice CT scanners combined with a respiratory surrogate to develop a series of 3DCT scans, each representing the

patient in a different respiratory phase. The entire 4DCT dataset can be used to determine an envelope of tumor motion which can be expanded to include areas of expected tumour position in various respiratory phases. In cases where implanting / inserting a visicoil marker is not feasible / clinically advisable, we can restrict the respiratory motion with abdominal compression device or breath hold technique. However, many patients with lung cancer have an associated poor pulmonary function and may not be able to adequately comply with the breath hold instructions or tolerate abdominal compression. In such cases the Internal Target Volume (ITV) is determined by the maximal tumor motion as visualized on the fluoroscopy done with compression device.

Ensure Precise and Daily Delivery of Radiation to the Intended Target: In case we are using Exactrac system, first we determine the motion of internal marker with patient breathing freely. The treatment window is then decided as per our PTV margins, PTV margin being more than the treatment window so as to encompass the target during the treatment. A snap verification from both the orthogonal X-ray tubes is advisable for intrafraction motion detection and correction and repositioning if required.

If RPM is used, then at first we select the phases of respiration for treatment. Usually the expiratory phase is selected, since it is the most stable for tumor motion. Initial positioning is done by cone beam CT scan. Intrafraction motion is managed with RPM system and beam being on in selected phases of breathing cycle.

In case we are using abdominal compression device, we must verify the target motion with fluoroscopy on treatment couch. The patient positioning is verified with CBCT.

Max Cancer Centre Experience

Retrospective analysis was done for 21 patients treated with SBRT for primary and metastatic lung lesions. Their characteristics are listed in Table 1.

Demographics

Out of 21 cases, 14 had primary lung cancer (4 central, 10 peripheral) while the remaining seven were metastatic, age of patients ranged from 29-81 years (median - 65 years), 13 patients were > 65 years, 6 patients were > 75 years. The GTV volume and the equivalent diameter for primary lung lesions ranged from 11-81cc and 2.8–5.4cm respectively. Seven patients had oligometastatic disease with tial 12 lesions. Primary sites were larynx, breast, cervix, gall bladder, rectum and one patient had extremity soft tissue sarcoma. GTV volume ranged from 0.41-81cc while equivalent diameter was 0.2-5.4cm. Median follow-up was of 16 months (range 4-29 months). One patient with metastasis disease was lost to follow-up, 1 patient treated with SBRT for primary lung cancer had local failure. Remaining 20 patients were locally controlled till last follow up as confirmed by follow up CT/PET-CT scan done after 3-4 months of SBRT and then three monthly CECT scans.

Long term follow-up of two patients of stage I NSCLC treated with SBRT at our institution is shown in Figure 1 to 4.

Toxicity

The adverse events resulting from SBRT were classified using the common terminology (CTC) criteria for adverse events, version. Pulmonary toxicity was observed as cough, dyspnea, pneumothorax and radiographic changes. The symptoms of most patients were mild and did not interfere with their activities of daily living. Grade I skin toxicity with faint erythemia was observed only in one patient in which lesion was close to chest wall. No patient had fracture of the rib and musculitis of the chest wall. No adverse effects of the spinal cord, great vessels or esophagus were observed. One patient had asymptomatic pneumonitis at 3 months which was detected on follow-up CT scan. It was managed conservatively. One patient had asymptomatic pneumothorax after visicoil gold marker placement which resolved spontaneously and did not required any intervention. None of the patient developed grade 3 or 4 toxicity.

Conclusion

SBRT has emerged as a viable treatment option for patients with inoperable stage 1 NSCLC and lung oligometastases. SBRT scores over other treatment modalities with a high local control rate with minimal toxicity. Prospective randomised controlled trials comparing outcomes of SBRT with surgery in potentially operable NSCLC are warranted to further validate SBRT as an equally effective local modality in such cases.

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Frontiers in Cancer Immunotherapy	27–28 Feb 2017 Conference	New York City, US
2nd Exploring DNA Repair Pathways as Targets for Cancer Therapy Conference	27–02 Mar 2017 Conference	Cancun, Mexico
Tumor Metabolism: Mechanisms and Targets	05–09 Mar 2017 Conference	Whistler, Canada
Immune Regulation in Autoimmunity and Cancer	26–30 Mar 2017 Conference	Whistler, Canada
Molecular Chaperones in Cancer	02–04 May 2017 Conference	Madrid, Spain
Integrating science into oncology for a better patient outcome	Madrid - Spain	08 Sep - 12 Sep 2017
ESMO Summit Africa 2017 – Oncology Updates: From Evidence to Practice	Cape Town, South Africa	10 Feb - 12 Feb 2017
ESMO Update for Practising Oncologists 2017	Lisbon, Portugal	03 Mar - 05 Mar 2017
6th ICHNO: International Conference on Innovative Approaches in Head & Neck Oncology	Barcelona, Spain	16 Mar - 18 Mar 2017
11th International Symposium on Advanced Ovarian Cancer: Optimal Therapy. Update	Valencia, Spain	03 Mar 2017
ESMO Symposium on Signalling Pathways in Cancer 2017	Sitges, Barcelona, Spain	17 Mar - 18 Mar 2017
IMPAKT 2017 Breast Cancer Conference	Brussels, Belgium	04 May - 06 May 2017
ELCC 2017 European Lung Cancer Conference	Geneva, Switzerland	05 May - 08 May 2017
ESMO World Congress on Gastrointestinal Cancer 2017	Barcelona, Spain	28 Jun - 01 Jul 2017
American Society of Clinical Oncology (ASCO) Annual Meeting 2017	Chicago, Illinois	Jun 02 - 06, 2017

IN FOCUS

MOLECULAR DIAGNOSTICS IN LUNG CANCER

Introduction

Lung cancer is the commonest cancer globally and has been so for over several decades. Globocan estimated 1.8 million new cases in 2012 representing 12.9% of annual cancers worldwide. It has a high mortality, with estimated 1.59 million deaths across the globe, making an upto for 19.4% of all cancer deaths. In the Indian scenario, it is the commonest cancer in men and the 9th most common cancer in women while overall it is the fourth most common cancer national wide.

Till about 3 decades back, there was just one lung cancer to be treated by surgery or radiation whenever possible. A decade and a half back, the practice of dividing lung cancers into "Small Cell Lung Carcinoma (SCLC)" and "Non Small Cell Lung Carcinoma (NSCLC)" emerged; with the former being treated by chemotherapy and the latter as before. The last decade and a half saw the emergence of pemetrexed based chemotherapy and the use of bevacizumab in adenocarcinoma of lung (LADC). This has also been a period of rapid stride in personalized medicine based on identifying 'Driver Mutations'. Many of these driver mutations are effectively druggable, though currently effective only in LADC. Several others, including those in squamous cell carcinoma (SCC), are known and are being engaged in various trials. The lung cancer today is, therefore, a more complex disease requiring correct histogenetic typing and a search for novel driver mutations.

NSCLC accounts for ~85% all lung cancers of which more than 50% are LADC. More than 70% of these are discovered as advanced cancers with a median survival of 16 weeks. Despite the best advances in conventional management; the 5-year survival rate across all stages of lung cancer is just 17% and less than 4% in the subset presenting with distant metastases. This gruesome scenario has shown some positive change with the advent of targeted therapy. The overall survival has been extended by >1 yr in patients receiving genotype directed therapy- (Lung cancer mutation consortium).

What are Driver Mutations?

A cancer cell is a witch's brew of genetic alterations. Hundreds to thousands of genetic alterations are present in any one cancer cell (Fig1). While most of these are inconsequential, a few, usually from one to six, are necessary for cancer cell survival and its autonomy from regulatory controls. A cancer cell is addicted to these alterations, a phenomenon called 'Oncogene Addiction' Deprivation of the effect of these oncogenic driver mutations brakes the growth and proliferation of cancer cells.

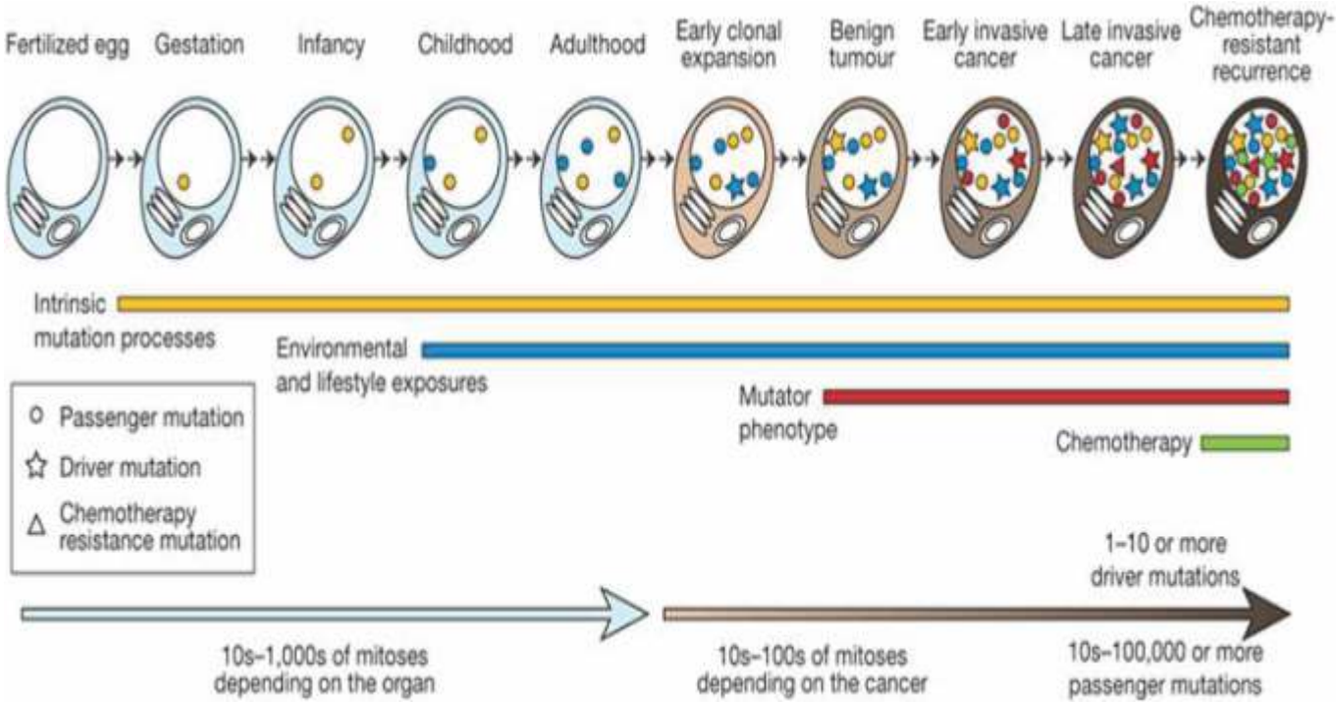


Figure 1: A cancer cell journey to a witch's brew of genetic alteration

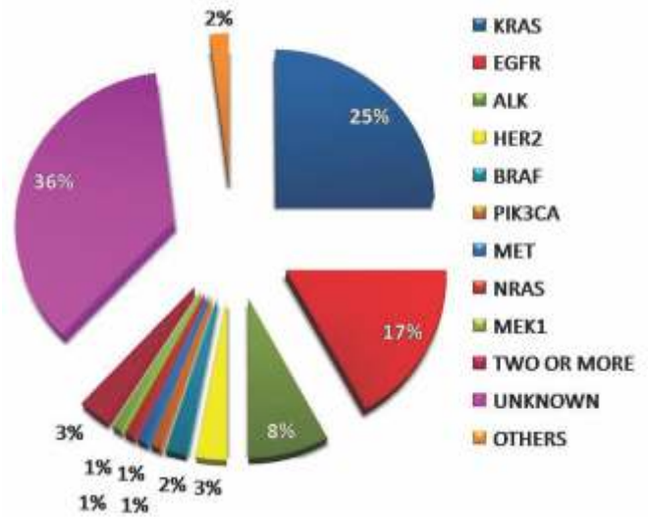


Figure 2: Driver mutations in LADC- based on lung cancer mutation consortium data 2012

A large number of driver mutations have been identified in lung cancer. The LADC has around 18 driver mutations. These are largely mutually exclusive and currently about 7 of these are actionable. Fig 2 depicts the driver mutations in lung cancer as identified by lung cancer mutation consortium.

Ethnicity and smoking habits are the two important determinants of the incidence of these driver mutations. The incidence of the driver mutations is different in the Asian population. Figure 3 highlights the incidence of driver mutations in the Asian population and as seen at RGCI & RC.

Similarly, many driver mutations have also been noted in SCC. It is another matter that as of now none is actionable beyond the confines of clinical trials. The data shall mature soon and several of these drivers in SCC shall also become actionable. Figure 4 depicts the drivers of SCC.

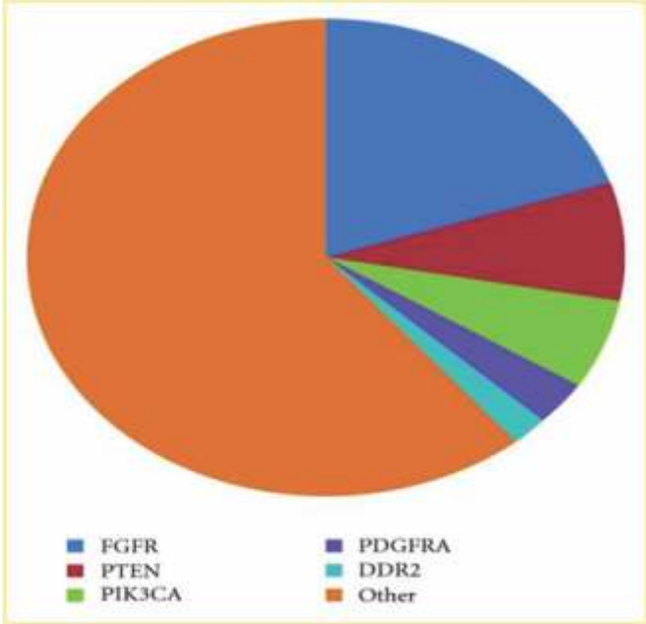
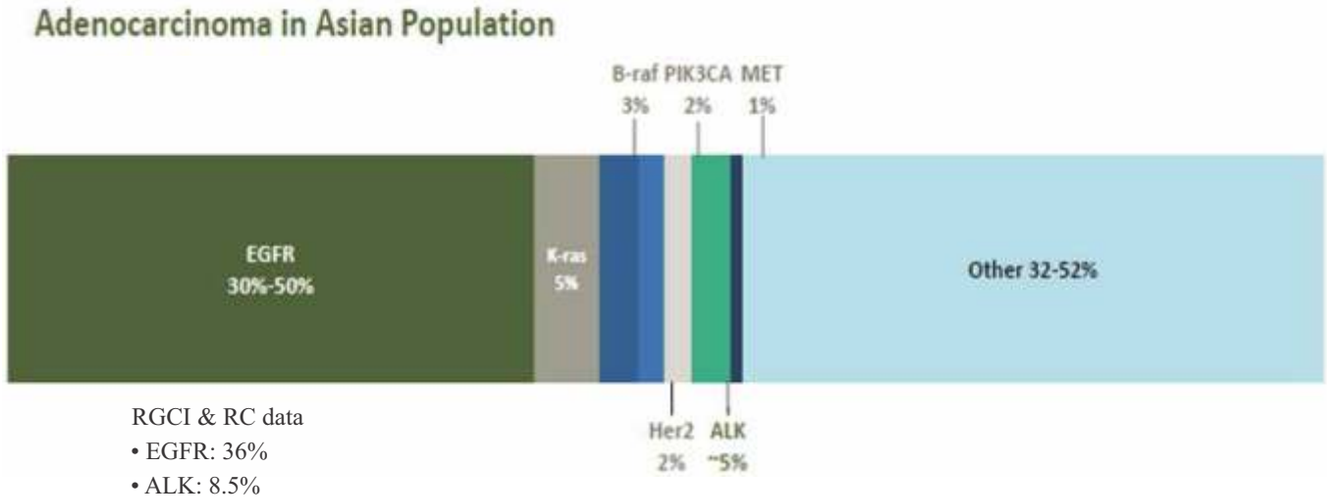


Figure 4: Driver mutations in SCC

What Driver Mutations need to be Tested?

Of all the genetic alterations, not all are druggable. The druggable mutations, as approved currently, by USA Food and Drug authority for the treatment of advanced LADC are listed below along with their corresponding small molecule inhibitor(s).

- EGFR sensitizing mutations- EGFR TKIs like Gefitinib, Erlotinib, Afitinib
- Alk1 gene rearrangement-Alk TKIs like Crizotinib, Ceritinib, Alectinib, Brigatinib, Lorlatinib



RGCI & RC data
- EGFR: 36%
- ALK: 8.5%
- ROS1: ~3%
- MET: ~ 3%

Figure 3: The incidence of driver mutations in LADC in asian patients and patients tested at RGCI&RC

Table1: The current genetic alterations to be tested and the best method along with possible alternative strategies for testing.

Biomarker	Genetic aberration for testing	Most suited method	Alternate tests
EGFR	Mutation	ARMS	Sequencing/NGS
EML4-ALK	Rearrangement	IHC	FISH
Ros-1	Rearrangement	FISH	IHC- D4D6. Lack specificity
C-Met	Amplification(CNG) Mutation- exon 14 silencing	FISH c-DNA – amplicon- sequencing	? IHC
BRAF	Mutation	Pyrosequencing RT PCR	NGS/ IHC- lacks both sensitivity and specificity
RET	Rearrangement	FISH- Not optimal	Multiplex PCR/NGS

- Ros 1 rearrangement.-Alk/Ros TKIs like Crizotinib, Cabozantinib

In addition, the following drivers have also been shown to respond to small molecule Tyrosine Kinase inhibitors in (TKIs) studies and also have been tested and treated at severall smaller centers.

- Met amplification-Crizotinib
- Met exon 14 skipping mutation(Met14ex)-Crizotinib
- C- Ret rearrangement-Cabozanitinib
- BRAF V600E- Dabrafenib, Vemurafenib

How are Driver Mutations Tested for?

The best method (gold standard) to test for a genetic alteration is the one that was used in drug development and clinical trial. It may however, not always be possible to adopt that method by all clinical laboratories aspiring to test for such drivers. Alternative methods are acceptable but these must pass the test on the touch stone of:

- ***Analytical validity:*** refers to a sensitivity, specificity, Negative predictive value and positive predictive value almost similar to that of the gold standard.
- ***Clinical validity:*** refers to the test being able to identify the attribute actually being looked for
- ***Clinical utility:*** The test outcome converts into the expected response on administration of the cognate treatment.

Optimizing Lung Cancer Molecular Testing

The molecular testing in lung cancer is already exhaustive. Several new rearrangements are being identified. Many more drivers are soon going to be druggable. This will mean a lot of testing with limited tissue. Two strategies will become important in the near future in order to ensure that necessary testing is carried out with limited tissue. The first and foremost is economizing on the use of tissue while the second imperative strategy is using tissue proficient testing methodologies.

Optimization of testing is also fraught with several other problems. To list a few, see Figure5.

How can the Lung Cancer Molecular Testing be Optimized?

- ***Care of pre-analytical variables:*** Ensure timely fixation- within a few minutes of extraction in neutral

Figure 5: Problems in optimizing molecular testing in lung cancer

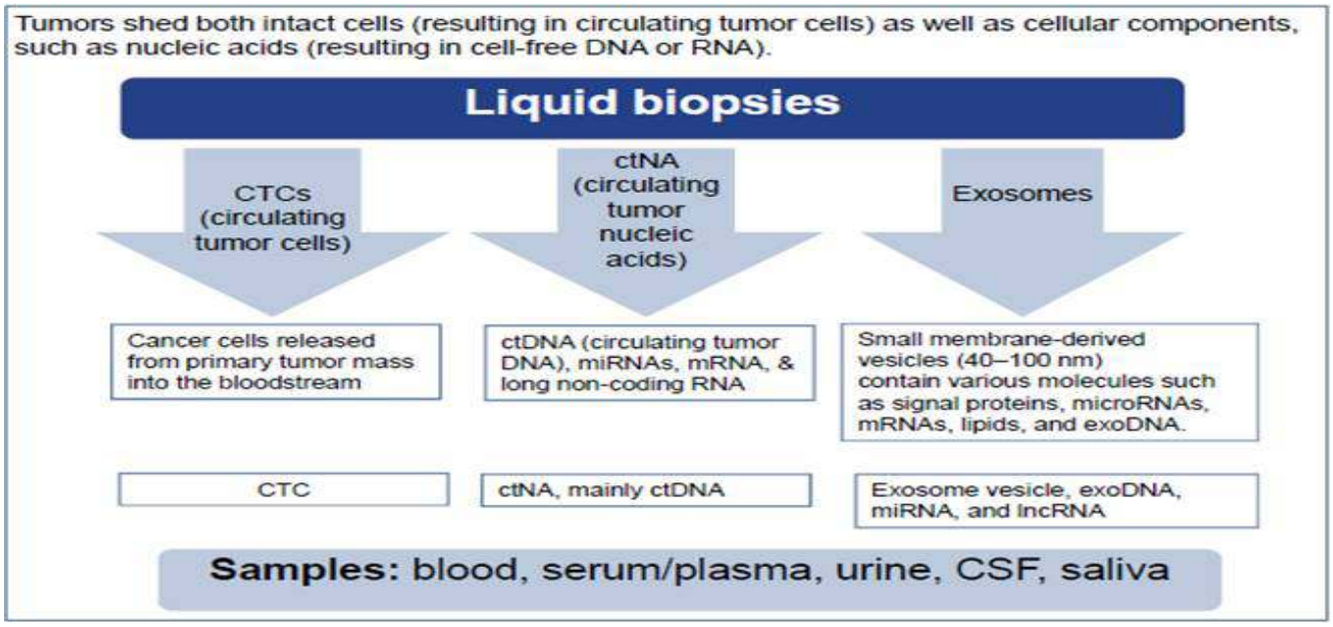


Figure 6: Liquid biopsy components

buffered formalin for not less than 6 hours and not more than 72 hours. Avoid usage of metallic fixatives.

- ***Economize on the use of tissue:*** Don't waste tissue. Ribbons on a slide look good but are a wastage of tissue. Cut necessary sections upfront. Refacing the tissue repeatedly leads to depletion.
- ***Use cytology material:*** For all molecular diagnostics it is as good as FFPE tissue sections. Tissue blocks are no different from FFPE sections. Ensure that 100 tumor cells are present if FISH is to be done for Alk, ROS or Ret rearrangement. 30 cells are sufficient for looking at amplification.
- ***Macrodissection*** to increase tumor fraction to 50% of the biopsy volume is necessary if Sanger based sequencing methodology is the testing platform for mutational analysis. Avoid laser micro dissection. It is still unknown as to what effect the laser micro dissection has on DNA.
- ***Be ready*** to use "Liquid Biopsy".
- ***Testing strategy:*** Use of appropriate & tissue efficient testing methodologies. Next generation sequencing capable of detecting rearrangements and fusions will be the next big step forward.
- ***Make yourself aware*** of cost effective strategies without compromising on turn around time (TAT). College of American Pathologist recommends a TAT of 10 working days. It also recommends that testing for biomarker be initiated in 1 day and if the sample is to be outsourced, 3 days is the upper limit.
- ***Extracting sufficient tissue:*** Have guidelines for adequate quality and quantity of biopsy material.

Something about Liquid Biopsy

Liquid biopsy is the latest chart buster on the lung cancer scene. It refers to testing blood and/or body fluid(s) to identify the molecular alterations that are happening real time in the cancer, not only at the primary site but also at all the sites of metastatsis. Liquid biopsy alludes to any biofluid used to detect "circulating tumor cells" or "cell-free DNA (cfDNA)" released by tumors into the bloodstream (Figure 6). Liquid biopsy can obviate the need for tissue biopsy, especially for the purpose of monitoring the response real time and identifying the molecular signature of acquired resistance. It is also useful in cases where the patient has an inaccessible tumor or is unwilling for any more biopsies.

cfDNA can be used to demonstrate point mutations, copy number variations (CNVs), chromosomal rearrangements, and methylation patterns. In several studies, it has shown a sensitivity of 80% with the specificity reaching beyond 95%. In lung cancer it is especially relevant in seeking out T790M mutation as a cause of acquired resistance.

What Shall be the Final Answer to Molecular Testing in Lung Cancer?

Doing several single gene assays to search for an actionable target is likely to be too time consuming and costly. With a median survival of 16 weeks, it is truly hard to complete testing without jeopardizing the chances of a patient to receive chemotherapy in case of a biomarker

Figure 7: A combo to look at lung cancer drivers in a tissue friendly way

negative lung cancer. The alternative to this unsuitable extensive single gene assays will be "Targeted NGS" capable of identifying "all changes including rearrangements, large deletions and CNVs. The capability of NGS to seek out fusion and CNVs however, Figure7: A combo to look at lung cancer drivers in a tissue friendly way requires extremely sophisticated bioinformatics. One answer could be to use a combination of NGS along with nanostring platform capable of finding fusions and CNVs (Figure 7).

Summary & Conclusion

- Biomarker based individualized therapy is feasible in > 60% of patients.
- Genomic based therapy provides at least one year of survival benefit over cytotoxic therapy with a better tolerance as an additional benefit.
- Actionable biomarker search is necessary.
- Tissue conservation is of utmost importance.
- Labs must develop the habit of tissue conservation.
- Reflex testing: Costly, but economizes on tissue and time. prevents refacing and loss of tissue in trimming.
- Cytology material is a good alternative for non FISH based tests. For FISH based tests, ensure that adequate tumor cells are available.
- Liquid biopsy will have a major role in the coming times.
- Possibility of a larger number of targets becoming actionable, a multi-gene profiling will be inevitable.

(Dr Anurag Mehta, Director- Lab Services and Molecular Diagnostics; RGCIRC)

Next issue :Lung Cancer

Molecular heterogenity and Immuno oncology

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