LUNG CANCER Focus: INDIA
Tracing the evolution, prevalence, distribution, etiology, association, occurrence, types, manifestations & impact of lung cancer in India.
Contents

Introduction ..............................................................................................................................3
Evolution of lung cancer ........................................................................................................3
Incidence of lung cancer ........................................................................................................3
The Indian context ..................................................................................................................3
Literacy ..................................................................................................................................4
State-wise occurrence .............................................................................................................4
Occupation ..............................................................................................................................5
Why lung cancer in India? ......................................................................................................6
Smoking ....................................................................................................................................6
Other causes ...........................................................................................................................6
Types of lung cancer ...............................................................................................................7
Types of cancer and relationship with smoking ....................................................................8
Manifestations of lung cancer .................................................................................................8
Management of lung cancer ....................................................................................................9
Lung cancer scenario in India ................................................................................................10
Bibliography ..........................................................................................................................18
Lung cancer Focus: India

Lung cancer the Indian perspective

Introduction
Pakistan, India, Sri Lanka, Bangladesh, Nepal and Bhutan, with their total population of more than 1,500 million, make up the subcontinent of South Asia. Despite massive diversity across the region, there are sufficient similarities including occurrence of cancer. In males, oral and lung cancer are either number one or two, depending on the registry.¹

Evolution of lung cancer
Historically, in India, tobacco was introduced in Karnataka by the Portuguese during A.D 1600.²,³ A couple of centuries later, the British introduced commercially produced cigarettes and established tobacco production in the country. Beedi (0.2-0.3gm of tobacco wrapped in a temburni leaf and tied with a small string) smoking was reported as early as 1711 in India.²,⁴

One of the reasons for increased beedi consumption was the call for boycott of imported cigarettes as part of swadeshi movement (movement to boycott foreign goods) that enhanced a shift from cigarettes to beedies.²,⁵

Lung cancer was not recognized as a disease until 1761; the first link between lung cancer and smoking⁶ was reported way back in 1929 by physician Fritz Lickint from Germany.⁷

Incidence of lung cancer
Tobacco use is responsible for five million deaths (one in ten adults) in the world every year with 2.41 million being attributed to developing countries and 2.43 million in developed countries.²,⁸

The death toll due to lung cancer is projected to rise to ten million by 2030 with 7 out of 10 deaths in the developing world.²,⁹

The Indian context
One million of the current 5 million deaths in world, and 2.41 million in developing countries is contributed by India²,¹⁰ and, in 2020, this figure is projected at 1.5 million²,¹¹
On average, smokers increase their risk of lung cancer between 5 and 10-fold & 24% of men who smoke can expect to develop cancer during their expected life time.

**Literacy**

75.6% of Indians are literate;\(^2\) amongst these, the literacy rates are 75.6% and 54.0% for men and women respectively.\(^2,12\) The more illiterate the individual, the higher is the indulgence in tobacco use and smoking.\(^{13}\)

Fig: Data from Jaipur Heart Watch (JHW) – western Indian state of Rajasthan.\(^{13}\)

Other recent Indian studies and national surveys report similar associations.\(^{13}\) However, although the rural occurrence is higher, lung cancer sufferers are detectable across the Indian terrain and there is no geographical restriction either.

**State-wise occurrence**

The age-adjusted incidence of lung cancer is highest in the north eastern states, and lowest in Barshi – a rural registry in Western India.\(^{28}\)
In a trend that’s baffling scientists, the Indian council of medical research (ICMR), after studying lung cancer data of 24 years (1982-2005), has found that while new cases of lung cancer per one lakh male population has increased by around 160% in Chennai, 100% in Bangalore and 40% in Delhi during this period, such cases have fallen by 60% in Mumbai.

Graph: Lung cancer trend in 4 Indian metro cities over 24 years.

**Occupation**

Occupation-wise, lung cancer predominates amongst farmers as opposed to those engaged in other activities and professions. Maybe the link lies in the higher illiteracy amongst these field workers.
Why lung cancer in India?

Smoking
Smoking is responsible for upwards of 80% of all lung cancers worldwide. In India, smoking is prevalent in:

- 29% of adult males
- 2.5% of adult females
- 11.7% of male collegians
- 8.1% Among school children and adolescents

A quarter of the cigarette or beedi smokers in India would be killed by tobacco at the ages of 25-69 years, losing 20 years of life expectancy.

Other causes
Non-smokers account for 15% of lung cancer cases and these cases are often attributed to a combination of genetic factors, radon gas, asbestos, pesticides and air pollution including passive and static smoking. Farmers mostly end up with lung cancer, may be because they rely heavily on the use of chemical pesticides to get rid of their pest problems. Farmers use 85% of the 2.6 million metric tons of active ingredient of pesticides produced annually in crop production in developing countries.
The risk is equal in smokers and non-smokers due to pesticide and other carcinogen exposures.\textsuperscript{15}

**Types of lung cancer**

90\% of lung content is air and only 10\% is solid tissue; the latter’s significant components include the bronchi, bronchioles and alveoli.\textsuperscript{18} There are 300 million alveoli and over a million bronchioles,\textsuperscript{18} and over 95\% of lung cancer is bronchogenic carcinoma.\textsuperscript{19} There are 40 types of cells in the lung of which 27 varieties make up the lung tissue itself. Four amongst these are unique for the lung and include:\textsuperscript{20}

- Non ciliated bronchiolar cells (Clara cells)
- Squamous cells (Type I)
- Great alveolar cells (Type 2)
- Alveolar macrophages

The Clara and squamous cells – present in epithelium, contribute to the secretion of airway mucus.\textsuperscript{21} Depending upon its origin from a certain cell type, the cancer of lung is classified as:\textsuperscript{22}

**Non-small cell lung cancer (NSCLC)**

- Squamous cell carcinoma: arises from cells lining the bronchi.
- Adenocarcinoma: arises from glands and cells lining the alveoli. \textbf{In those who have never smoked, and in women, adenocarcinoma is the commonest amongst lung cancers.}\textsuperscript{7,23}
- Large cell carcinoma: a form of adenocarcinoma but the cells appear much larger on microscope.
- Small cell lung cancer (SCLC): also called ‘oat cell’ carcinoma, it arises from neuroendocrine cells variety called “Kulchitsky” cells. Enterochromaffin cells (synonym for Kulchitsky cells) are present primarily in the linings of digestive and respiratory tracts; they store 90\% of the body’s serotonin content.\textsuperscript{24} Kulchitsky cells could release biologic amines and peptides which could regulate bronchial muscle tone and also control the pulmonary circulation.\textsuperscript{21}
Approximately 80% of cancers are NSCLC whilst 20% are SCLC.\textsuperscript{23,25} In Indians, however, SCLC is predominant over NSCLC having an occurrence ratio of 2.5:1 and 2.7:1.\textsuperscript{28}

**Types of cancer and relationship with smoking**

In India, squamous cell carcinoma is still the commonest histological type in India in contrast to the Western countries, although adenocarcinoma is becoming more common.

The smoker to non-smoker ratio is 20:1 for those having lung cancer.\textsuperscript{15}

**Manifestations of lung cancer**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>As per large Indian studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough with Expectoration</td>
<td>40.0-94.3%</td>
</tr>
<tr>
<td>Chest Pain</td>
<td>16.0-66.7%</td>
</tr>
<tr>
<td>Loss of Weight</td>
<td>11.4-90.0%</td>
</tr>
<tr>
<td>Breathlessness</td>
<td>24.0-59.0%</td>
</tr>
<tr>
<td>Weakness</td>
<td>4.0-90.0%</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>8.0-69.2%</td>
</tr>
<tr>
<td>Fever</td>
<td>19.6-68.6%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>20.5-90.0%</td>
</tr>
<tr>
<td>Hoarseness of Voice</td>
<td>9.0-33.0%</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>6.0-25.0%</td>
</tr>
<tr>
<td>Puffiness of Face</td>
<td>2.9-19.8%</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>2.9-20.8%</td>
</tr>
</tbody>
</table>

As is expected, most Indian patients with lung cancer complain of cough with expectoration, breathlessness, fever and anorexia consistently.
**Management of lung cancer**

In spite of great advances in radiological and molecular diagnostic techniques, the ideal screening marker for early detection of lung cancer has still not been found. Histological diagnosis and staging is essential for selecting the mode of therapy in patients with lung cancer. Stages I and II are amenable to surgery. However, advanced stage III and IV need an individualized combination of surgery, chemotherapy and radiotherapy. Although NSCLC is sometimes treated with surgery, the advanced and metastatic NSCLC and SCLC usually respond better to chemotherapy and radiation.

**NCCN guidelines**

The National Comprehensive Cancer Network (NCCN), a not-for-profit alliance of 21 of the world’s leading cancer centers, is dedicated to improving the quality and effectiveness of care provided to patients with cancer. Forty-two Nobel Prize winners have served on the faculties of NCCN Member Institutions. As the arbiter of high-quality cancer care, NCCN promotes the importance of continuous quality improvement and recognizes the significance of creating clinical practice guidelines appropriate for use by patients, clinicians, and other health care decision-makers.

**Updated guidelines for non-small cell lung cancer (2010)**

Erlotinib has been added as a first-line treatment option for epidermal growth factor receptor (EGFR) mutation positive patients with advanced or metastatic disease with a category 2A designation. Bevacizumab and cetuximab have been added as treatment options for continuation maintenance with a category 1 designation. Pemetrexed and erlotinib have been added as treatment options for switch maintenance with a category 2B designation and docetaxel has been added as a treatment option for switch maintenance with a category 3 designation.

**Updated guidelines for small cell lung cancer (2010)**

As per the NCCN guidelines, the standard of care for first line treatment of extensive stage – small cell lung cancer (ES-SCLC) is platinum-based systemic chemotherapy. The NCCN guidelines indicate that for patients with localizing symptoms (superior vena cava syndrome, lobar obstruction, or painful bone metastases), concurrent radiation therapy can also be considered.

The NCCN Clinical Practice Guidelines for Small Cell Lung Cancer have been updated and published as v.1.2010.
Lung cancer scenario in India

- Sex distribution of smokers\(^{28}\)
  - Males: 33.4%
  - Females: 1.4%
- Smoking prevalence in varied areas\(^{28,38}\)
  - Rural areas: 31.3%
  - Urban areas: 21.5%
- Relative risk of developing lung cancer\(^{28,39}\)
  - *Beedi* smokers: 2.64
  - Cigarette smokers: 2.23
  - Overall: 2.45
- Incidence rates (age-standardized) per 100,000 population (2008)\(^{28}\)
  - Males: 10.9
  - Females: 2.5
- Increase in new cancer cases per 100,000 population each year over 24 years (till 2005)\(^{15}\)
  - Chennai: 160%
  - Bangalore: 100%
  - Delhi: 40%
  - Mumbai: (-)60%
- Disability Adjusted Life Years (DALYs) due to lung cancer (2004)\(^{28}\)
  - Males: 0.55 million
  - Females: 0.13 million
- Most prevalent is NSCLC amongst lung cancers\(^{7,27}\)
  - Squamous cell carcinoma: 44.73%
  - Adenocarcinoma: 30.26%

CANCER FACTS & FIGURES WITH FOCUS ON LUNG CANCER

- Detection and management facts in India
  - Oncologists available: 0.98 per 100,000 population\(^{40}\)
  - On-going (all) clinical trials: 1.5% of the world’s total\(^{41}\)
  - Number of patients currently undergoing (all) studies: 10,000\(^{42}\)
  - Number of LUNG CANCER being detected each year: 250,000 to 300,000!\(^{40,43}\)

Oncology research in India

The Central Drugs Standard Control Organization (CDSCO) has prepared a National List of Essential Medicines (NLEM) of India in 2011. For compiling the NLEM there were 87 experts including two medical oncologists. The NLEM is one of the key instruments in ensuring balanced healthcare delivery system for the nation. There are 354 medicines mentioned in the NLEM.
of 2003 whilst the same released in 2011 has 348. The 2003 NLEM included 23 anticancer products, and in the 2011 list, although pruned, 8 new oncology drugs have been added!

The increasing presence of anticancer drugs in the NLEM emphasizes the importance of oncology products in national health. Also the twelve New Drug Advisory Committees (NDAC) set up by the Drugs Controller General of India (DCGI) has a special committee (of ten experts) to deal with approval of anticancer product and combinations, including clinical studies.

Things are improving with government support and initiatives in cancer research from institutions such as Indian Council of Medical Research (ICMR), Council of Scientific and Industrial Research (CSIR) and Department of Biotechnology (DBT).

**Attitudes to oncology research**

Cancer incidence is generally much lower in India than in the developed world, the average national age adjusted rate being ~120 compared with >300 per 100,000 per year in developed countries. However, because of the sheer size of the population it is a safe estimate that India adds ~1 million new cases of cancer every year. Patients in India are often diagnosed in late stages and have bulky disease. Hence, acceptance by the medical oncologists of large population is devoid of significant roadblocks, and the cancer patients themselves are geared to subject themselves to any innovative intervention which lends hope of disease arrest or regression.

“These trials ultimately help Indian patients by giving them access to new anti-cancer agents at a much earlier stage than in the past,” says Dr Ashok Vaid, Senior Consultant, Medical Oncology, Rajiv Gandhi Cancer and Research Institute, a principle investigator in cancer trials at the institute.”
Importance of India as a hub for cancer clinical trials

Nearly 20% of cancer patients in many global cancer drug research trials are Indians from India. If India had not taken part these abovementioned trials would have taken 2-3 years more for patient recruitment.46

By contributing towards clinical trials on a global scale, India will find solutions for its own problem of cancer.44

Lung cancer management
Oncology trial sites
There are about 15-20 cancer centers in India,44 171 trial sites available and 200 ICH-GCP trained investigators for oncology drugs clinical evaluation.

As per data available in end-2011, there are as many as 175 cancer studies in progress in various stages. The first therapeutic vaccine study in India is slated to take off in early 2012 which will be a global research project with joint participation by Sloan Kettering Memorial (US).47

In fact, for lung cancer, India has been labeled as hub since the widespread use of tobacco products primarily triggers this malignancy.48

Standardized assessment methodologies
Lung cancer is frequently suggested from chest X-ray findings: eg a solitary pulmonary nodule, pulmonary or hilar mass, poorly resolving pneumonia or pleural effusion.49

Histological or cytological confirmation of the diagnosis is desirable, though not always possible, and can be achieved by a variety of methods: image guided percutaneous biopsy, bronchoscopy, mediastinoscopy or thoracoscopy. Tissue diagnosis should be followed by subtyping of the cancer according to the current WHO classification.49,50 It may not be possible to use this classification fully if biopsy specimens or cytology samples are small, and in most instances designation as SCLC or NSCLC is sufficient for planning further management.49
Chest X-ray
Patients with lung cancer often have obstructive features (37%) and pleural effusions (22%). Lung cancer patients rarely present with a normal chest X-ray (only 2% in one study).\textsuperscript{49,5} Chest radiography is a simple, cost-effective measure and it imparts very little radiation to the patient.\textsuperscript{52} Naturally, it is routinely carried out at every institute.

CT / MRI scanning
Results from computed tomography (CT) scanning are subject to variation caused by different scanning techniques, but suggest that CT scanning of the chest has a high sensitivity (89 to 100%) but a relatively low specificity (56 to 63%) and a poor negative predictive value (60 to 100%).\textsuperscript{49}

CT has now become the mainstay of staging chest malignancies\textsuperscript{52} and is routinely performed at all major centers in India. Superiority of magnetic resonance imaging (MRI) over CT scan for the detection of bronchial and chest wall invasion or for nodal staging is unestablished. Also as the CT is less expensive and widely available in India\textsuperscript{52} it is preferred and routinely advised.

PET scanning
Positron emission tomography (PET) scanning has a diagnostic sensitivity of 96% and a specificity of 78% but there is considerable variation within the studies included.\textsuperscript{49,53} The diagnostic studies indicate negative predictive values as low as 47%.\textsuperscript{49}

The considerable cost of the instrument imaging agents as well as the short half-life of positron emitting isotopes (which require a nearby cyclotron for generation), has prevented widespread acceptance and hence these units are available only at a few specialized centers.\textsuperscript{52}

Bronchoscopy
The value of bronchoscopy depends on the location of the primary tumor.\textsuperscript{49} Peripheral tumors in subsegmental bronchi may not be visible.\textsuperscript{49} Flexible bronchoscopy has good diagnostic sensitivity (83% to 88%) for central lesions.\textsuperscript{49,54,55}

Bronchoscopy is done in India, and the overall diagnostic yield of bronchial forceps biopsy and brushings for central lesions ranges from 70% to 90% depending on the site and visibility of the lesion.\textsuperscript{52,56}

FNA / percutaneous biopsy
Percutaneous fine needle aspiration (FNA)/biopsy is a highly sensitive technique for diagnosing
lung cancer (sensitivity of 88% to 92%). Fine needle aspirations can be done as blind percutaneous biopsy or guided by fluoroscopy, ultrasound, CT or magnetic resonance imaging (MRI). There is a high false negative rate (25%) resulting in limited ability to confirm a benign diagnosis.

In India, mediastinal lymph nodes can be staged by transbronchial needle aspiration (TBNA), which if positive, can preclude the need for further surgical staging.

**Sputum cytology**

There is a wide variation (10% to 97%) in the sensitivity of sputum cytology in the diagnosis of lung cancer. High sensitivity is only achieved by the use of specific and carefully controlled protocols for sample collection.

**Thoracoscopy / Mediastinoscopy**

Thoracoscopy is to be considered for patients with suspected lung cancer where less invasive means have not achieved histological and cytological confirmation of diagnosis. If the CT scan of the chest does not reveal any mediastinal lymph node greater than one centimeter in size, the likelihood of N2 disease is small and mediastinoscopy or mediastinotomy is not required before surgery.
Staging of lung cancer
With the assistance of the diagnostic procedures elaborated the NSCLC can be staged.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy.</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor.</td>
</tr>
<tr>
<td>T1</td>
<td>Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than lobar bronchus (i.e., not in the main bronchus).</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor with any of the following features of size or extent. More than 3 cm in greatest dimension. Involving main bronchus, 2 cm or more distal to the carina. Invading the visceral pleura. Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the whole lung.</td>
</tr>
<tr>
<td>T3</td>
<td>• Tumor of any size that directly invades the chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, phrenic nerve or parietal pericardium. • Tumors in the main bronchus less than 2 cm distal to the carina but without involvement of carina. • Associated atelectasis or obstructive pneumonitis of the entire lung.</td>
</tr>
<tr>
<td>T4</td>
<td>• Tumor of any size, which invades the mediastinum, heart, great vessels, trachea, esophagus, vertebral body or carina. • Tumor with a malignant pleural effusion. • Secondary nodules in the same lobe of the lung.</td>
</tr>
</tbody>
</table>
Regional Lymph Nodes

NX  Regional nodes cannot be assessed.

N0  No regional node metastasis.

N1  Ipsilateral peribronchial and/or ipsilateral hilar nodes including direct extension.

N2  Ipsilateral mediastinal and/or subcarinal nodes.

N3  Ipsilateral scalene, contralateral mediastinal, hilar, scalene or supraclavicular nodes.

Distant Metastasis

M0  Presence of metastasis cannot be assessed.

M1  No distant metastasis.

M2  Distant metastasis present; secondary nodules in a different lobe of the lung other than that of primary.

Treatment guidelines

Stage I & II
Surgery (pneumonectomy, lobectomy and segmental wedge or sleeve resection) is the treatment of choice for stages I and II.\textsuperscript{52,60,61}

Inoperable patients with sufficient pulmonary reserve may be considered for radiotherapy with curative intent. Recently, use of three or four cycles of cisplatin-based chemotherapy after complete surgical resection in early stage NSCLC have shown significant improvement in survival (44.5% vs 40.4% without adjuvant chemotherapy) at five years and higher disease free survival (39.4% vs 34.4% at five years).\textsuperscript{52} Based on this, it is recommended to give three or four cycles of cisplatin-based chemotherapy as adjuvant to surgery.\textsuperscript{52,62}

Stage IIIA
Only some patients in Stage IIIA are resectable. Cisplatin-based chemotherapy has been combined with concomitant radiotherapy in an effort to improve the prognosis. The results are encouraging & treatment with neoadjuvant chemotherapy combined with chest radiotherapy should be considered for all patients with good performance status prior to surgery.\textsuperscript{52,63}
Stage IIIB

Patients with stage IIIB disease do not benefit from surgery alone and are best managed by initial chemotherapy with or without radiotherapy, depending upon the site of the tumor and performance status.\textsuperscript{52}

Stage IV

Newer drugs like paclitaxel and carboplatin have sparked great interest in the management of advanced NSCLC. Combination regimen of these drugs has been demonstrated to be very helpful.\textsuperscript{52}

Six new drugs were discovered in the early 1990s for the management of lung cancer - docetaxel, gemcitabine, vinorelbine, irinotecan and topotecan. Recently, a few other agents have also been identified with activity in lung cancer. These include tirapazamine, multitargeted antifolate (MTA), oxaliplatin, tegafur and uracil (UFT). The one-year survival of advanced NSCLC patients has gradually increased with the use of these novel chemotherapeutic agents in select groups of patients.\textsuperscript{52,64}

Treatment modalities

Surgery

Training in oncology surgery has been especially incorporated as a distinct entity (MCh course) and approved by the Medical Council of India (MCI). The approved centers include:\textsuperscript{65}

- Gujarat Cancer Research Institute, Ahmedabad
- Kidwai Memorial Institute of Oncology, Bangalore
- King George’s Medical University, Lucknow
- Regional Cancer Center, Thiruvananthapuram
- Tata Memorial Hospital, Mumbai
- Women’s Cancer Initiative, Chennai

Radiotherapy

Radiotherapy has an established role in management of lung cancer, both on its own and in combination with chemotherapy. Radiotherapy has a well-documented effect in palliating thoracic symptoms and, in selected cases with NSCLC, it may be curative.\textsuperscript{49}

Radiotherapy can also be useful in treating locally symptomatic metastases.\textsuperscript{49}

At least 185 centers having radiotherapy facility in India have been documented.\textsuperscript{66}
Chemotherapy

NSCLC
- Chemotherapy with a platinum-based combination double regimen should be considered in all patients who are not suitable for curative resection or radical radiotherapy and are fit enough to receive it.
- Second-line chemotherapy with docetaxel should be considered for stage IIIA/IV patients with good performance status.

SCLC
- A regimen containing a platinum agent with etoposide is recommended for first line treatment.
- Second-line in SCLC cases must be considered depending upon the duration of response to first line chemotherapy and on patient’s performance status and desire.

Logistical considerations

Cancer incidence shows significant variations in various regions, but more importantly the incidence of various types and organs affected also varies very widely. For example, in males stomach cancer is the most common in the south, whereas lung cancer is most common in the north. In females, cancer of the cervix is more common in the south, whereas breast cancer is more common in the north. Other common cancers are head and neck in males and gall bladder in females, both comparatively uncommon in the West. Hence, global studies including India as an important cancer site needs recognition of the geographic variability which expert clinical research organizations would be well placed to guide.

Summary

Lung cancer is one of the leading causes of cancer deaths. It carries a greater mortality than colorectal, breast and prostate cancers collectively! Approximately 85% of lung cancer patients in India are diagnosed at an advanced stage that is not amenable to surgical intervention. As a result, these patients require chemotherapy and/or radiotherapy and constitute a huge resource pool for clinical research.

Cancer research is well established, but requires a detailed understanding of both national and local requirements and practices, using a research team that is experienced in conduct of oncology studies, with a track record of delivery of project goals.
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