APPROACH TO LUNG CANCER

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Abstract: Lung cancer today is the leading cause of cancer related deaths and the 2nd most common cancer in both genders. The single most important causative factor for lung cancer is smoking. The most common pathological type in those below 40 yrs of age is small cell carcinoma. Above the age of 40 years, adenocarcinom is the most common subtype in both smokers and others. A high index of suspicion is important for its early diagnosis. A new onset cough, chest pain, hemoptysis and weight loss are often the presenting features of lung cancer. Histopathology is superior to sputum cytology for diagnosis. Biopsy / FNAC should be taken from the site that provides the highest staging. EBUS is a cytological sampling method, but has high yield for lung cancer. Early Palliative therapy should be initiated and patient performance status and preferences should guide investigations and therapy.

(INTRODUCTION)

The term lung cancer, or bronchogenic carcinoma, refers to malignancies that originate in the airways or pulmonary parenchyma. It is probably the most deadly disease associated with tobacco use and its impact on mankind today is massive. A lot of research has gone into this field leading to development of new diagnostic strategies, algorithms and treatment modalities. The aim of this review is to provide an overview of approach to a patient with lung cancer (with an emphasis on investigative strategies to obtain a diagnosis) along with a brief outline of management of this disease.

KEY POINTS

- Lung cancer should be an important differential when a smoker or ex-smoker over 40 years of age is found to have a lung opacity on X-ray or has new symptoms of worsening cough/hemoptysis.
- A new onset hemoptysis and change in character of cough in a person with tuberculosis / COPD should be viewed with suspicion.
- A high index of suspicion is necessary for an early diagnosis and optimal treatment. In most cases, the diagnosis is made late when the disease is advanced.
- Imaging modality should be chosen to obtain an anatomic location for biopsy and maximum information for staging.
- Biopsy / FNAC should be taken from the site that provides the highest staging. EBUS is a cytological sampling method, but has high yield for lung cancer.
- Early Palliative therapy should be initiated and patient performance status and preferences should guide investigations and therapy.
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BACKGROUND
Although nicotine has been used by man in many forms for a very long time, the first commercial cigarette was made in 1865. The first cigarette company – the American tobacco company was established in 1881. The world wars increased the popularity of this poison, when cigarettes were supplied free to soldiers. Women started working outside their homes during this period (in the western world) and started using cigarettes as well. The first scientific paper that explored the relation between smoking and lung cancer was published in the 1940s. Over the last century, the incidence of lung cancer rose parallel to the incidence of cigarette smoking, making it the single most contributory risk factor for the disease (Fig. 1).

EPIDEMIOLOGY:
Lung cancer today is the leading cause of cancer related deaths and the 2nd most common cancer in both genders (second only to prostate cancer in men and breast cancer in women). It is a rampant disease in India, with a male : female ratio of 4.5:1 and smoker : non-smoker ratio of 20:1. The most common pathological type in those below 40 yrs of age is small cell carcinoma. Above the age of 40 years, squamous cell carcinoma used to be the most common subtype in. However currently, in this age group, adenocarcinoma is more common in both smokers and others. Advances in immunohistochemistry that have led to better identification of many cases of adenocarcinoma (which would have previously been classified as other histological subtypes) is a probable contributing factor. The other pathological types include small-cell carcinoma (SCC), non-small-cell carcinoma (NSCLC), large cell carcinoma (LCC) and others.

CAUSES
There are many malignancies without a clear causative factor. Lung cancer is not one of them. Some of the important causes of lung cancer are enumerated below.

1. Smoking
The single most important causative factor for lung cancer is smoking. In India, 87% cases of Lung Cancer were in smokers and 3% cases were in Passive smokers. Beedi is more carcinogenic than cigarette (RR 2.64 vs 2.23) although the tobacco content is about 5 times lesser in beedi. Environmental Tobacco smoke exposure in childhood is also a risk factor (OR 3.9).

2. Occupational Factors
Asbestos is probably the most important among occupational carcinogens. There is substantial risk of developing lung cancer after 20yrs of exposure to asbestos. In the presence of concurrent smoking, the risk of developing lung cancer increases 90 times in those with occupational exposure to asbestos. This makes asbestos exposure and cigarette smoking a lethal combination.

Other occupational carcinogens implicated in lung cancer...
include Arsenic (Smelter and Vineyard workers), Nickel (Refinery), Uranium (Mining), Chromium, Ether and Mustard gas.

3. Pre-existing Pathologies
HIV increases the risk of adenocarcinoma lung. Coexistence of Idiopathic pulmonary fibrosis, COPD and Tuberculosis with lung cancer is now known. Change in pattern of cough, a new patch on chest x-ray or development of hemoptysis in individuals with these conditions should arouse suspicion of lung cancer.

Challenges in Diagnosis
Patients may present to the clinic with either symptoms suggestive of lung cancer or an incidentally detected pulmonary nodule on a chest x-ray. A high index of suspicion is required (based on history and clinical findings) to decide on further investigations in order to detect and confirm lung malignancy.

Lung cancer is an insidious disease, and hence highly lethal, because unlike in many other cancers, the clinical presentation is neither drastic nor specific. The illness is usually not diagnosed until the disease is advanced. A major reason for this is that a pathology in the lungs does not cause pain until it invades the pleura. Unfortunately lung cancer that has invaded the pleura is advanced and probably inoperable. Symptoms appear mostly in late stages only and studies have shown that, at the time of diagnosis of lung cancer, 20% of the patients have localized disease, 25% have regional metastasis and 55% distant metastasis.

However in a tertiary care set up in India, the vast majority (more than 90%) of patients have metastatic disease at the time of diagnosis and very few are eligible for operative management. The high prevalence of the great mimic called Tuberculosis is the major reason for this. It is common to see a patient with lung cancer who has been misdiagnosed to have TB and initiated on ATT, presenting after 2 or 3 months for further evaluation because of lack of relief from symptoms. However by the time a diagnosis of lung cancer is made, the disease has often progressed too far. Hence a high index of suspicion for lung cancer is important for its early diagnosis.

CLINICAL PRESENTATION

Primary Symptoms
A new onset cough, chest pain, hemoptysis and weight loss are often the presenting features of lung Cancer. A change in the character/pattern of cough and a new onset hemoptysis in patients with established Tuberculosis or COPD should also be viewed with high degree of suspicion.

Symptoms of Regional Invasion/distant Metastasis

As discussed earlier, often patients live with lung cancer without any symptoms until the cancer metastasizes. Local and lymph nodal metastasis may cause one or more of the following syndromes

• Superior venacava (SVC) syndrome due to mechanical compression (or invasive obstruction) of the SVC. Dyspnoea is the most common symptom. Some of the other characteristic clinical features are facial swelling, cough, arm swelling, chest pain, dysphagia and orthopnea. Individuals may also present with distorted vision, hoarseness, stridor, headache, nasal stuffiness, nausea, pleural effusions, and light-headedness.

• A high index of suspicion for lung cancer is important for its early diagnosis.
• A new onset cough, chest pain, hemoptysis and weight loss are often the presenting features of lung Cancer.
• A change in the character/pattern of cough and a new onset hemoptysis in patients with established Tuberculosis or COPD should also be viewed with high degree of suspicion.
Presence of a new opacity in a follow-up chest X-ray of a patient with TB or COPD should be treated with high index of suspicion.

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- Ptosis, miosis, anhydrosis, enophthalmos and loss of ciliospinal reflex.
- Stridor – due to airway narrowing / compression

The common presentations of lung cancer that have metastasized to distant regions are:
- Bone pain in case of bone metastasis
- Altered sensorium / seizures in brain metastasis
- Paraparesis in vertebral metastasis

**Para-Neoplastic Syndromes**

It is not uncommon for patients to present primarily with manifestations of a para-neoplastic syndrome. The well known para-neoplastic syndromes associated with lung cancer include the following

- Hypercalcemia - SCC
- Trousseau syndrome - Adenocarcinoma
- Clubbing - Seen in all types
- HPOA - NSCLC
- SIADH - SCC
- Ectopic ACTH - SCC
- Eaton Lambert syndrome - SCC

**Physical examination**

General examination may reveal cachexia, clubbing, signs of metastasis. A respiratory system examination may often pick up an effusion, collapse and rarely evidence of a mass. The importance of detecting palpable lymph nodes should be emphasized. Presence of palpable supraclavicular lymph nodes signifies inoperable disease. In their presence, a metastatic work up for staging is unwarranted. A palpable supraclavicular lymph node also gives an easy and less invasive portal for biopsy and identification of the tumour. Ordering a CT/ ultrasound guided biopsy in the presence of palpable lymph nodes is often not needed. Hence it is worth spending a few extra minutes, examining thoroughly for lymph nodes, as it helps saving both money and time.

**IMAGING**

Imaging is usually the initial step in the diagnosis of lung cancer. The aims of imaging are

1) to locate the anatomical site of the lesion,
2) to guide in obtaining tissue biopsy for confirmation of diagnosis and
3) staging the disease.

Although imaging and sampling procedures are discussed separately, in practice these are used concurrently, for diagnosis and staging.

**Chest X-Ray**

Chest X-Ray remains an important modality that can provide important clues towards the diagnosis of lung cancer. Certain tell-tale signs of malignancy on chest x-ray include:

- Rib erosion
- ‘Golden S’ – Right upper lobar collapse with a right hilar central mass forming a reverse S shape in PA view
- Signs of lobar or lung collapse (Fig.2)
- Pleural effusion with fixed mediastinum (Pleural effusion pushes the mediastinum to opposite hemithorax, but if there is a large pleural effusion with central mediastinum, this indicates either a fixed mediastinum due to tumour invasion or presence of ipsilateral collapse with effusion)
- Cannon ball or rounded opacities in lungs indicating metastasis – usually large and in lower zone (Fig.1)
- Cavity – Cavity with thick or irregular wall can be a cavitating malignancy)

Presence of a new opacity in a follow up chest X-ray of a patient with TB or COPD should also be treated with high index of suspicion. An attempt must be made to review any previous X-rays of the patient and assess the probable age and progression of the disease.
Fig. 2 – X-ray chest of a lung malignancy
Chest radiograph PA view showing a large 8x7cm sized fairly well defined rounded mass in the right lower zone (arrows). It was diagnosed to be a large cell undifferentiated carcinoma on a CT guided biopsy specimen.

Computed Tomography
CT Thorax is recommended for further evaluation of findings suggestive of lung cancer on chest x-ray as it gives much more information than just the location and extent of the tumour. It is always advisable to perform a contrast CT to facilitate differentiation between a mediastinal lymph node and vessel and to aid in nodal staging. CT findings suggestive of a lung malignancy include mass like opacities or cavities with thick and irregular wall. CT is also useful in detecting recurrence on follow up.

Apart from the extent and location of the primary lesion in CT thorax, One should make an effort must also be made to visualize
1. Mediastinal invasion
2. Vertebral invasion
3. Nodule in other lung/ liver which signifies inoperability
4. Tracheal / main bronchus obstruction –which may warrant an Endobronchial bronchoscopic intervention to maintain bronchial lumen for symptom alleviation. A cancer that has invaded trachea and carina is also inoperable.

Upper abdominal cuts should preferably be included in a CT thorax to look for any metastatic lesions in the liver and adrenals (two common sites of lung cancer metastasis). In their presence, there is no requirement for further metastatic work up. Ultrasound guided liver biopsy may be the easiest and cheapest procedure to confirm and stage the diagnosis.

Low Dose CT (LDCT) is emerging as a screening modality for lung cancer and is worth mentioning. The ACCP recommends LDCT for screening in high risk patients. However widespread use of LDCT seems unreasonable because of its poor specificity in detecting early cancers and the risk-benefit ratio for exposing healthy individuals to unnecessary radiation is unfavourable. A lot of research is going on towards developing screening modalities that do not involve radiation, exhaled breath test being one of them. It aims at detecting specific chemical substances in exhaled air of individuals that can act as a tumor marker.

FDG-PET (Flurodeoxyglucose – Positron Emission Tomography)
FDG-PET is a good imaging modality with a reported sensitivity of 97%. However the specificity is low
Histopathological confirmation of diagnosis of lung cancer is mandatory for any form of therapy whether surgery / chemotherapy or radiation therapy of lung cancer.

**Bone scan**
Bones are common sites of metastasis. A bone scan can be useful adjunct to staging in patients who present with bone pain and in those with raised serum Alkaline Phosphatase levels.

Fig.3 – Bone scan showing multiple metastasis

**STAGING AND BIOPSY**
Histopathological confirmation of diagnosis of lung cancer is mandatory for any form of therapy whether surgery / chemotherapy or radiation therapy of lung cancer. Identifying the histopathological type of lung cancer also aids in prognosis.

**Selection of biopsy site:**
For selection of a biopsy site as well as for staging of lung cancer, a careful evaluation (physical examination) of patient and review of all radiological images is essential. The selection of biopsy modality should take into consideration the patient safety, diagnostic yield and expertise of the team. The histopathological specimen can also be used for immunohistochemistry and tumour marker studies for determining the type of lung cancer and is thus superior to cytopathology. The sample may be obtained from lung, lymph nodes or sites of distant metastasis. The commonly used procedures to obtain samples for biopsy are discussed briefly in Table 1.

**Table 1: Procedures for histopathology and cytopathology**

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<thead>
<tr>
<th>Site</th>
<th>HISTO PATHOLOGY</th>
<th>CYTO PATHOLOGY</th>
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<tbody>
<tr>
<td>LUNG</td>
<td>Bronchoscopic Biopsy, Transthoracic (CT or Ultrasound guided) biopsy, Surgical biopsy</td>
<td>Sputum Transthoracic needle aspirates, Bronchoscopic washings/brushings Bronchoscopic needle aspirates</td>
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<tr>
<td>LYMPH NODE</td>
<td>Surgical Biopsy of peripheral lymph nodes EBUS TBNA or CT guided biopsy of mediastinal lymph nodes</td>
<td>Transthoracic Aspirate Transbronchial Aspirate</td>
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<tr>
<td>DISTANT METASTASIS</td>
<td>Core Needle Biopsy of Metastatic Lesions (Liver/Adrenals/Bone)</td>
<td>Pleural fluid Needle aspirates of metastatic tissue (eg. liver)</td>
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**Bronchoscopy**
Bronchoscopy is an excellent diagnostic test as it also helps in the staging of the disease (TNM staging) and obtaining a specimen for biopsy. A bronchial biopsy of a central lesion is easily obtained. Alternatively brush smears of central lesions can be taken. Bronchial wash and Bronchioalveolar lavage are also useful cytological
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Tools in expert hands. A transbronchial biopsy can be attempted for a peripheral lesion. However this is a blind procedure and requires expertise.

**Endobronchial Ultrasound (EBUS)**

Endobronchial ultrasound (EBUS) is a technique where the use of ultrasound is coupled with a bronchoscope to visualize the airway wall and adjacent structures. Any lesion touching the trachea or main bronchi can be visualized using this technique. An Endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) can be used for cytology. It should be remembered that this technique is a counterpart of FNAC and a cytopathological specimen is obtained rather than a biopsy for histopathology. However the yield is good with EBUS-TBNA (>90%) for cancer and TB. In cases of lymphoma, the diagnostic yield is only 50 to 70%. Hence if lymphoma is strongly suspected, it is probably better to attempt a biopsy – either image guided or open. In case a biopsy is not possible, a trial of EBUS-TBNA is reasonable.

Even for peripheral lesions, a radial EBUS guided transbronchial lung biopsy (EBUS-TBLB) can be attempted. After localizing the lesion with EBUS (the ultrasound probe can negotiate smaller airways as compared to a bronchoscope), the ultrasound probe is withdrawn and biopsy probe is introduced so that it traverses the same path as the ultrasound probe. EBUS-TBLB is also a blind procedure in its real sense and requires a high degree of expertise.

**Mediastinoscopy**

Once a popular procedure, mediastinoscopy is currently limited to patients in whom EBUS is negative or when EBUS is not available. The mediastinoscope is a rigid tube, and its extent of reach is limited. It can reach paratracheal and carinal nodes and may reach paraesophageal nodes but cannot reach interlobar lymph nodes. It also requires general anesthesia and can be done only in Operation Theater. Hence its best avoided when a better modality like EBUS TBNA is available.

**Thoracoscopy**

In this technique, a scope is introduced to the pleura and the lesion is directly visualized. It is superior to any USG guided technique as the lesion is directly visualized and biopsy can be taken from the lesion rather than from the vicinity of the lesion. The diagnostic yield is about 98% for malignancy and 100% for TB.

Thoracoscopy is not only diagnostic, but can also be therapeutic. Pleurodesis with Talc Powder can be done in cases of recurrent rapid filling malignant pleural effusion. It can also help clear adhesions.

Hence it is a suitable technique for individuals presenting with malignant pleural effusion.

**Sputum Cytology**

The usefulness of sputum cytology is dependent on the level of expertise of the examining pathologist. Studies have shown that sputum cytology can detect malignancy in 71% of central tumours and < 50% of peripheral tumours.

However the yield can be considerably lower in non-expert hands and discordant results are common. A minimum of 3 samples should be examined to increase yield. It is a good test to attempt in patients with high risk for complications with bronchoscopy / image-guided biopsy (when the patient is very sick, on antiplatelet drugs like Clopidogrel etc.)

**Image Guided Biopsy**

A CT or Ultrasound (USG) guided biopsy can be performed in peripheral lesions which are in contact with or near the chest wall. It can be performed with a trucut biopsy needle under CT guidance or ultrasound guidance. When compared to CT guided biopsy, USG guided biopsy is a real time biopsy with no radiation exposure. A Chest physician can do USG guided biopsy and obtain cytology slides as well in same sitting, which can be read by cytologist within few hours. Thus USG guided biopsy has potential to provide same-day confirmation of diagnosis of lung cancer.
MOLECULAR TESTING

Molecular diagnosis and immunohistochemistry has been gaining importance due to development of targeted monoclonal antibodies against certain receptors. Adenocarcinomas are known to be associated with upregulation of specific receptors which can be targeted for therapy. Such examples include

1. EGFR – Epidermal growth factor receptor - Erlotinib, Gefitinib
2. ALK – Anaplastic lymphoma kinase - Crizotinib
3. RAS mutation - Salumetinib

The EURTAC study has shown that the progression free survival is significantly increased by adding Erlotinib to the standard therapy (10.4 months) as compared to only Standard Therapy (5.4 months).

This highlights the need for obtaining adequate tissue sample to perform molecular testing as well when compared to only a cytology for histopathological diagnosis.

OVERVIEW OF TREATMENT

Like in most other malignancies, the choice of modality of treatment depends on tumour type and the staging of the tumour. (An overview of TNM staging of Lung Cancer is available at https://cancerstaging.org/references-tools/quickreferences/Documents/LungMedium.pdf)

Treatment of Non-small cell lung cancer:

Stage I & II

The treatment of choice is surgery and this is often curative.

Stage IIIA

Stage IIIA implies lymph nodal involvement. In good centres surgery can be undertaken to remove the tumour and affected nodes. However if the nodes cannot be resected surgically these are treated by chemoradiation. The relapse rate are high after surgery, which is countered by giving adjuvant chemotherapy

Stage IIIB and IV

These are inoperable and are treated with Chemotherapy

Stage IV

If the disease is localized with a single metastasis in any one organ – liver, adrenal or brain, then surgery can be offered with good outcomes. Patients unfit for surgery should receive radiotherapy.

Treatment of Small cell lung cancer:

1. Limited stage SCLC: Platinum based chemotherapy and radiotherapy + Prophylactic cranial irradiation
2. Extensive stage SCLC: Platinum based chemotherapy
Role Of Performance Scale in Deciding Investigations and Treatment

It is important to assess the performance status of the patient, preferably at the first contact. For this, validated performance indicators like the Zubrod scale and Karnofsky (Fig. 4) may be used. A patient who is already debilitated and bed-ridden may not be fit for chemotherapy. Such patients should not be investigated aggressively, since there is probably not much more that can be offered. Hence it is best that patients with a poor performance scale be investigated and treated less aggressively, without adding to their suffering. Palliative therapy and symptom alleviation should be the major goals of treatment in these individuals.

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<tr>
<th>Role of Palliative Care</th>
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<td>Pain is managed by medications (eg: Morphine) or nerve blocks. It is not acceptable to let the patient wait for chemoradiation therapy without receiving adequate pain relief.</td>
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<tr>
<td>SVC syndrome can be managed by Dexamethasone/stent insertion in severe cases and with simple maneuvers like starting an IV line in lower limbs, raising the head end etc in cases that are less severe.</td>
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<tr>
<td>Tracheal or Main bronchial stenosis may warrant tumour debulking or stenting. The patient may get back the comfort of breathing normally which can be quite satisfying.</td>
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<td>It should be remembered that smoking which is a major risk factor for Lung cancer is also a major risk factor for COPD. Metered dose inhalers should be initiated in patients with co-existing COPD and can provide remarkable symptomatic relief.</td>
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**Symptom alleviation is often more important for the patient than diagnostic work up and curative therapy**

PROGNOSIS

The 5 year survival rate for lung cancers is 11%

- 49% for local disease
- 16% for regional disease
- 2% for distant stage disease

**The 3 major predictors of 5 year survival are**

1. Staging
2. Performance status
3. Weight loss

Majority of our patients present at an advanced stage and have poor performance status and hence often have
a poor prognosis. This fact reiterates two concepts that have already been discussed – high index of suspicion leading to early diagnosis and early initiation of palliative care and symptom alleviation.13.

CONCLUSIONS

- Lung cancer should be an important differential when a smoker or ex-smoker over 40 years of age is found to have a lung opacity on x-ray or has new symptoms of worsening cough/ hemoptysis.
- Imaging modality should be chosen so obtain an anatomic location for biopsy and maximum information for staging.
- Biopsy / FNAC should be taken from the highest staging site. EBUS is a cytological sampling method, but has high yield for lung cancer. However biopsy is preferred when a lymphoma is suspected.
- Early Palliative therapy should be initiated and patient performance status and preferences should guide investigations and therapy.

References