

Lung Cancer

B. Dingle MD, FRCPC, Brian Yaremko MD, FRCPC, R. Ash, MD, FRCPC, P. Truong, MD, FRCPC

EPIDEMIOLOGY

The estimated incidence of lung cancer in Canada for 2007 is 23,300 with 12,400 occurring in men and 10,900 in women. This makes lung cancer the leading type of cancer in the population. With the prevalence of cigarette smoking decreasing (now about 19% in Canada, compared to 30+% in the 70s), the incidence of lung cancer is decreasing in males, but still on the increase in females. Although the incidence of lung cancer is about half that of breast cancer in females, because the mortality rates are higher, lung cancer has now become the leading cause of death due to cancer among Canadian women.

Cigarette smoking is the single most important cause of lung cancer, although other agents have been associated, such as asbestos, coal tar fumes, nickel, chromium, arsenic and radioactive materials.

NATURAL HISTORY

- Exposure of host to carcinogenic agent → metaplasia → atypia and dysplasia → carcinoma in situ → invasive cancer
- Patterns of spread are local (within same lung), regional (hilar, mediastinal, and supraclavicular nodes) and distant (liver, adrenals, bone, brain, contralateral lung, other nodes)
- The recent decline of small cell and squamous cell carcinoma, in favour of adenocarcinoma may reflect changes in particulate size of cigarette smoke, with newer cigarette filtering resulting in greater peripheral penetration of carcinogens into the lung, and thus a change in histology of the presenting tumour
- Evidence is emerging that suggests non-small cell carcinoma may be of at least two different molecular types, In elderly, non-smoker females with adenocarcinoma, there is a trend toward tumours with EGFR alterations and better survival and response to tyrosine kinase inhibitors. In the rest, there seems to be a prevalence of K-RAS mutations and a worse prognosis (neither are particularly good)

CLINICAL PRESENTATION

- Signs and symptoms may arise from local tumour growth, invasion of adjacent structures, regional or distant metastasis, or from a secondary effect of the tumour (paraneoplastic syndrome).
- Cough, hemoptysis, dyspnea, and chest pain are common
- Systemic symptoms such as weight loss, weakness, anorexia and malaise

- Pancoast's tumour (superior sulcus tumour syndrome): involvement of cervical and thoracic nerves with shoulder pain, ulnar dysesthesias, destruction of adjacent ribs or vertebrae
- Sympathetic nerve involvement: Horner's syndrome with exophthalmos, ptosis, miosis and ipsilateral anhidrosis
- Recurrent laryngeal nerve involvement: hoarseness
- Phrenic nerve involvement: dyspnea from paralysis of the hemidiaphragm
- Compression of the esophagus: dysphagia
- Superior vena cava obstruction (SVCO): swelling of face, neck, and arms and collateral circulation over the anterior chest wall
- Pericardial involvement: pericardial tamponade and congestive heart failure
- Paraneoplastic syndromes:
 - SIADH (almost) exclusively in small cell cancer (5-10%)
 - Ectopic ACTH largely in squamous cell carcinoma (3-7%)
 - Hypercalcemia often secondary to PTHrp, often in squamous cell (10%)
 - Lambert Eaton (reverse myasthenia) in small cell (6%)
 - Hypertrophic pulmonary osteoarthropathy, mostly in adenocarcinoma
 - Hypercoagulable state

EVALUATION

- History and physical exam (be sure to ask about weight loss, performance status, smoking history)
- CBC, electrolytes, renal and liver function, pulmonary function tests
- CXR, CT chest and upper abdomen
- Bone scan, especially if symptomatic or advanced disease
- CT brain if signs or symptoms or advanced disease
- PET scan strongly suggested (though not yet funded at most centres in Canada); PET also replaces the bone scan (equivalent sensitivity & specificity)
- Bronchoscopy, thoracic fine needle aspiration biopsy, mediastinoscopy.

PATHOLOGY

There are 2 broad classes of lung cancer. They differ both histologically and clinically.

- | | |
|------------------------------------|------------|
| • Non-small cell carcinoma (NSCLC) | 80% |
| • Squamous cell carcinoma | 30% |
| • Adenocarcinoma | 40% |
| • Large cell carcinoma | 10% |
| • Small cell carcinoma (SCLC) | 20% |

STAGING

Non Small Cell Lung Cancer (NSCLC) Staging

The TNM system is the only system used to stage NSCLC.

TX	Not assessed, or evident by sputum or bronchial washings only
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour < 3 cm in greatest dimension
T2	Tumour with any of the following: <ul style="list-style-type: none">• > 3 cm• involves main bronchus, > 2 cm distal to the carina• invades visceral pleura• associated with atelectasis or obstructive pneumonitis that extends to hilum but does not involve entire lung
T3	Any size, invades any of the following: chest wall, diaphragm, mediastinal pleura, parietal pericardium; or tumour in main bronchus < 2 cm distal to the carina, or associated atelectasis or obstructive pneumonitis of the entire lung
T4	Any size; invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumour nodules in the same lobe or malignant pleural effusion
NX	Not assessed
N0	No regional nodal metastasis
N1	Ipsilateral peribronchial or hilar or intrapulmonary nodes
N2	Ipsilateral mediastinal or subcarinal nodes
N3	Contralateral mediastinal, hilar nodes; or ipsilateral or contralateral scalene or supraclavicular nodes
MX	Not assessed, or evident by sputum or bronchial washings only
M0	No distant metastasis
M1	Distant metastasis present, nodule in a separate lobe

Stage groupings are given in detail in the next section. Use the following simplified rules to define stage:

- (T1 or T2)N0 = Stage I
- Any N2M0 = stage IIIA
- Any N3M0 = stage IIIB
- Any T4M0 = stage IIIB
- Any M1 = Stage IV
- Any thing else = Stage II

Small cell lung Cancer Staging

The TNM system (identical to the one used for NSCLC) can be used for Small cell Lung cancer, but this is rarely if ever done. Instead, most oncologists use the following simplified system.

- **Limited Stage:**
 - disease which is encompassed by a reasonably sized radiation treatment plan, usually ipsilateral chest
- **Extensive Stage:**
 - disease that cannot be encompassed by a standard radiation treatment plan

note:

- This definition of “extensive stage” is now archaic and open to interpretation as modern RT delivery technology has drastically improved our ability to deliver treatment to larger volumes.
- Most radiation oncologists consider a pleural effusion to represent extensive stage.

TREATMENT

General Considerations (all types of lung cancer, all stages)

- For early stage disease, one treatment modality is adequate.
 - e.g. surgery alone; radiotherapy (RT) alone
- For advanced disease, more than one treatment modality is required.
 - e.g. surgery and chemotherapy; chemotherapy and RT
 - e.g. surgery, chemotherapy and RT (trimodality therapy)
- Radiotherapy toxicity & dose
 - Potential toxicities are considered very carefully in RT treatment planning.
 - Higher RT doses = improved local control and survival, but normal tissue toxicity limits the dose that can be delivered using standard technology to around 74 Gy (Is this enough? Many say no!).
- Radiotherapy targets
 - Traditionally we encompassed the visible disease within large regional nodal volumes (elective nodal irradiation).
 - Many Radiation Oncologists now treat only the visible disease plus a margin (limited-field irradiation),

Non-Small Cell Lung Cancer

a) Stage 0 (Tis) & Stage 1 (T1N0, T2N0)

Surgery

- The best approach for all patients with early stage disease if medically fit.
- May consist of a lobectomy or pneumonectomy.
- Lesser resections (e.g. wedge resection, segmental resection) result in a higher recurrence rate.
- Locoregional relapse <10% with complete resection.

Radiotherapy

- Operable patients
 - Post-operative RT not required if complete resection
 - Post-operative RT not required detrimental to survival.
- Inoperable patients
 - Consider RT alone (outcomes equivalent to surgery).
 - Standard approach = RT over 6-7 weeks (60-64 Gy in 30-32 fractions).
 - This will likely soon be supplanted by Hypofractionated RT.
 - smaller dose over a shorter time (e.g. 48 Gy in 4 fractions).
 - standard at many centres (but not yet here).

Systemic

- Systemic relapse in 30% or more after surgery.
- Recent studies (BR 10, ANITA and IALT studies) suggest chemotherapy in good performance patients with resected stage II to IIIA (we extend to resected IIIB by extrapolation); these patients may experience a relative risk reduction with the use of Cisplatin/Vinorelbine based adjuvant chemotherapy of about 30%
- The original enthusiasm about adjuvant treatment of stage IB disease stemmed from the premature reporting of the CALGB study, where interim analysis suggested a positive result, but subsequent follow-up proved to be negative, resulted in a short period where stage IB disease did receive adjuvant treatment. Even now, patients with stage IB but with > 4cm tumours are offered chemotherapy because of their higher risk.

b) Stage II (T1N1, T2N1, T3N0)

Surgery

- N1 signifies involvement of ipsilateral hilar lymph nodes which has higher impact on risk of systemic relapse
- If patients are medically fit, surgery is still the treatment of choice

Radiotherapy

- Inoperable patients

- Concurrent chemotherapy and RT is the standard curative treatment approach (60-64 Gy in 30-32 fractions).
- Sequential chemotherapy and RT is less toxic (but slightly less effective)
- Consider palliative RT alone in patients with poor performance status, highly symptomatic patients (typically 30 Gy in 10 fractions)
- Operable patients (adjuvant RT)
 - Consider adjuvant RT for patients with N1 disease
 - no randomized data but probably improves local control (but not overall survival).
 - 50Gy in 25 fractions to tumor bed,(usually with chemotherapy).
 - Consider adjuvant RT for patients with positive margins
 - 60-64 Gy in 30-32 fractions, usually with chemotherapy.
- Borderline operable patients:
 - Consider neoadjuvant chemoradiation then surgery (trimodality approach)
 - May shrink disease, enabling an easier surgery
 - Will improve local control; no clear improvement in overall survival.

Systemic

- Rate of systemic relapse is 55%
- Recent studies (BR 10, ANITA, and former IALT studies) all suggest adjuvant chemotherapy in good performance patients with stage II (IB with > 4cm) to IIIA (and IIIB extrapolated) resected may experience a relative risk reduction with the use of Cisplatin based adjuvant chemotherapy of about 30%

c) Stage IIIA (T1N2, T2N2, T3N1 or N2)

Surgery

- N2 signifies involvement of mediastinal lymph nodes
- Most patients with grossly enlarged mediastinal nodes on CT ("bulky N2") or N2 disease on mediastinoscopy are not candidates for primary surgery.
- Primary surgery can be done on a small subset of patients with resectable tumours and no nodal enlargement on CT
 - Patients with microscopic N2 disease after thoracotomy have a better prognosis compared to patients with gross N2 involvement.
 - Adjuvant chemotherapy is indicated (see below).
 - Consider adjuvant RT (see below)..

Chemotherapy/Radiotherapy

- Inoperable patients
 - If medically fit, the standard approach is combined modality chemotherapy and RT given with curative intent.
 - Sequential chemoradiation:
 - considered standard until recently
 - 2 cycles of cisplatin and vinblastine

- followed by RT (60Gy/30 fractions)
- Median survival (MS) of 14 months
- Concurrent chemoradiation:
 - has largely replaced sequential chemoradiation
 - improves MS to approximately 16-18 months
 - offers about 17% five year disease free survival, which may translate into a cure for these patients.
- Palliative RT alone if poor performance status, highly symptomatic (30 Gy in 10 fractions).
- Operable patients (Adjuvant chemotherapy; Adjuvant RT)
 - Recent studies (BR 10, ANITA and former IALT studies) all suggest adjuvant chemotherapy in good performance patients as above
 - Consider adjuvant RT for patients with N2 disease.
 - no good randomized data but probably improves local control and overall survival (cf. N1).
 - 50Gy in 25 fractions to tumor bed,(usually with chemotherapy).
- Borderline operable patients
 - Consider neoadjuvant chemoradiation then surgery (trimodality approach)
 - May shrink disease, enabling an easier surgery
 - Will improve local control; no clear improvement in overall survival.

d) Stage IIIB (T4 or N3 disease)

Surgery

- Surgery not indicated (exception = Pancoast's; see below)
- In patients with malignant pleural effusions, consider thoracentesis and pleurodesis for symptom control

Chemotherapy/Radiotherapy

- Intent depends on patient and tumour factors (radical vs. palliative)
- concurrent (or sequential) chemoradiation as above for well-selected patients (though with less expectation of success overall)
- Palliative chemotherapy alone for the malignant effusion
- Palliative RT in patients with poor performance status, highly symptomatic (30 Gy in 10 fractions).

Special Case: Pancoast's Tumor

- Standard treatment approach is neoadjuvant chemoradiation followed by surgery.
- Outcomes are superior to surgery alone.

e) Stage IV (M1 disease)

- Palliation
- Options include chemotherapy and local RT
- Common indications for local RT:
 - bronchial obstruction, hemoptysis
 - SVCO
 - pain
 - CNS: spinal cord compression, brain metastasis
- Involve supportive care
- No treatment (best supportive care): MS=3-6 mo; 1 yr O.S. =10%
- With cisplatin-based chemotherapy: MS= 8 mo; 1 yr O.S. =20-40%
- Second line chemotherapy with Docetaxel or Pemetrexed can improve quality of life in good performance status patients
- Third line therapy with Tarceva, a new oral tyrosine kinase inhibitor, can improve survival and QoL briefly.

f) Locally Recurrent Disease

- All patients must be restaged fully (consider PET)
- Aggressive salvage therapy (chemoRT, RT, surgery) may be offered to well selected patients with clearly localized recurrences and good performance status.
- chance of cure is less

Small Cell Lung Cancer

a) Limited Stage Disease

- 1/3 of small cell cases
- No defined role for surgery (this is likely a systemic disease at presentation and chemotherapy is the primary treatment)
- REGIMEN: 5-6 wks thoracic RT delivered concurrently (usually early in chemo course) with 4-6 cycles of EP (epirubicin/cisplatin).
- Standard RT dose is not consistent: most treat to 50Gy in 25 fractions.
- Some advocate a higher dose (60 Gy in 30 fractions), or a hyperfractionated approach (45 Gy in 30 fractions given twice daily).
- MS = 20 mo with treatment; 5Y OS = 15-20% (these patients may be cured)

b) Extensive Stage Disease

- Most will soon be dead of disease without treatment (MS= 6 wks).
- Palliative chemotherapy as above
- Palliative RT for bone pain (2000/5 or 800/1), brain mets, hemoptysis, etc.

- MS with treatment improves to 9 months

c) Role of Prophylactic Cranial Irradiation (PCI)

- 50-60% of small cell patients have CNS mets at 2 yrs
- Whole brain RT (25-30 Gy in 10 fractions) prior to developing CNS metastases decreases CNS relapse by 50%, with a 5% improvement in OS.
- Usual candidates for PCI:
 - limited stage disease, excellent response to chemoradiation, good performance status
- Some Radiation Oncologists now offer PCI to patients with extensive stage disease, provided they have good performance status, with a good response to palliative treatment. For such patients, there is still a significant reduction in CNS metastases, though with no clear benefit upon OS.

d) Locally Recurrent Disease

- In principle, aggressive salvage therapy may be offered to well selected patients with clearly localized recurrences and good performance status.
- However, these patients are very rarely encountered.