SMALL CELL LUNG CANCER
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DISCLAIMER: The following are study notes compiled by the above PGY-5s medical oncology resident and reviewed by a staff medical oncologist. They reflect what we feel is relevant knowledge for graduating medical oncology residents preparing for their final examination. The information has not been surveyed or ratified by the Royal College.

A) PUBLIC HEALTH

EPIDEMIOLOGY
- Incidence: 52 per 100,000\(^1\). Highest incidence in Canada\(^1\).
- Mortality: Most common cause of cancer death in Canada (40 deaths per 100,000)\(^1\).

RISK FACTORS
- Environmental/Chemical/Infections: smoking, radiation therapy, air pollution, radon, metals (arsenic, chromium and nickel), ionizing radiation, asbestos, polycyclic aromatic hydrocarbons, pulmonary fibrosis, HIV infection
- Genetic: inherited susceptibility variants for lung cancer have been found on several chromosomal loci such as 15q25 (nicotinic acetylcholine receptor subunit CHRNA5) and 6q23-25

PREVENTION & SCREENING
- Prevention: Smoking cessation
- Screening: Evidence from the National Lung Screening Trial (NLST) found that screening high-risk patients (defined as >/= 30 pack year smoking history or quit smoking <15 years ago and aged between 55 and 74 years old) with an annual low dose CT scan reduced lung cancer mortality by 20% and all cause mortality by 6.7%.
- The Prostate, Lung, Colorectal, Ovarian (PLCO) trial found that Chest X-ray is not effective for lung cancer screening, when compared to no screening.
- Canadian Task Force guidelines are out – weak recommendation due to high rate of false positive results
- still pending as of July 4, 2015. BCCA, Cancer Care Ontario and Alberta Cancer Guidelines do not provide a clear stance on screening for lung cancer.

B) PRESENTATION & DIAGNOSIS

SYMPTOMS & SIGNS
- Common Symptoms:
  - Symptoms from local tumour effect: cough, hemoptysis, dyspnea, chest pain, hoarseness
  - Symptoms from extrathoracic metastases to supraclavicular lymph nodes, liver, adrenals, bone, brain
  - Symptoms from paraneoplastic syndromes: hypercalcemia symptoms, hyponatremia symptoms, cushings syndrome symptoms, hypertrophic osteoarthropathy symptoms, dermatomyositis/polymyositis symptoms, neurologic symptoms, hypercoagulable disorders
- Common Signs:
  - Signs from local tumour effect: airway compromise, hoarseness, superior vena cava syndrome, pancoast syndrome
  - Signs from extrathoracic metastases to supraclavicular lymph nodes, liver, adrenals, bone, brain
  - Signs from paraneoplastic syndromes
    - Non-small cell – hypertrophic pulmonary osteoarthropathy, hypercalcemia
- Small cell – SIADH (10%), ectopic ACTH, eaton-lambert syndrome
- **Common Presentations**: pancoast syndrome, paraneoplastic syndrome, majority of patients have advanced disease at presentation

**Prognostic factors:**
- weight loss, stage, performance status, sex (M worse than F), LDH
  - age is not a prognostic factor

**INVESTIGATIONS**
- **Laboratory**: anemia, leukocytosis, thrombocytosis, eosinophilia has been reported in patients with large cell carcinoma, features of microangiopathic hemolytic anemia can be seen (ex. DIC/TTP), electrolytes (can show features of SIADH/ectopic ACTH secretion in small cell lung cancer patients), calcium, albumin, LDH, SGOT, CEA if elevated can help with assessment of treatment in patients with difficult-to-evaluate index lesions (ex. Bone lesions)
- **Diagnostic Imaging**: CT Chest Enhanced that encompasses the liver and adrenal glands, CT head if neuro symptoms, MR brain if persistent neuro symptoms despite normal CT head, Bone scan if bony symptoms, consider PET for SCLC
- **Diagnostic Procedures**:
  - Tissue diagnosis – tissue biopsy preferred with bronchoscopy, percutaneous fine needle biopsy, excisional or needle biopsy as appropriate for the patient
  - Bone marrow aspirate is not recommended unless an otherwise unexplained hematologic abnormality is present.
- **Pretreatment Evaluation**:
  - Pulmonary function testing if patient is potentially operable.

**PATHOLOGY & MOLECULAR BIOLOGY**
- **Common Histology**:
  - Small cell lung cancer (SCLC): 13%
  - Non-small cell lung cancer (NSCLC):
    - Adenocarcinoma: 38%
    - Squamous cell carcinoma: 20%
    - Large cell carcinoma: 5%
    - Other NSCLC’s (ex. NSCLC NOS): 24%
- **Common Metastatic Sites**: liver, bone, brain, bone marrow
- **Relevant Molecular Biology**:
  - None for small cell lung cancer.
- **Relevant prognostic factors**: stage, performance status, serum LDH, gender.

**STAGING**
- **1) SCLC Staging**
  - **Limited Stage** – tumour that is encompassable by a reasonable radiotherapy treatment volume. Usually limited to one hemithorax and may include mediastinal and ipsilateral supraclavicular nodes.
  - **Extensive Stage** – disease beyond limited stage criteria. Patients with “regional” extensive stage disease (such as pleural effusion, cervical lymph nodes or contralateral supraclavicular lymph nodes) may benefit from limited stage type treatment.
- **TNM staging** – same as NSCLC

**i) LIMITED STAGE**
- **Bottom Line General Approach**:
  - **First-line therapy**: Curative intent combined thoracic irradiation with 4 – 6 cycles of chemotherapy (cisplatin and etoposide). The combination of thoracic irradiation with chemotherapy improves long-term survival for patients with limited stage disease – controversial
  - Prophylactic cranial irradiation should follow treatment for patients with response to treatment. The integration of thoracic irradiation with chemotherapy early in the treatment program (ie, concurrently with cisplatin and etoposide at week 3) is superior to late addition of radiation
- **Recurrent disease:** See “SMALL CELL LUNG CANCER, EXTENSIVE STAGE” (below).
- **Prognosis:** median survival with treatment is 14 months for limited stage with treatment.
- **Important Phase III Clinical Trials:**

| Prophylactic Cranial Irradiation (PCI) for Patients with Small-Cell Lung Cancer in Complete Remission |

<table>
<thead>
<tr>
<th>Regimen</th>
<th>PCI or no PCI</th>
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<tbody>
<tr>
<td>Mechanism of Action of Experimental Drug</td>
<td>prophylactic cranial irradiation</td>
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<tr>
<td>Primary Endpoint</td>
<td>OS</td>
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<tr>
<td>Inclusion/Exclusion Criteria</td>
<td>Patients with SCLC in complete remission</td>
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<tr>
<td></td>
<td>No evidence of brain mets before randomization</td>
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<td></td>
<td>No previous cranial irradiation</td>
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<tr>
<td>Size (N)</td>
<td>987 patients</td>
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<tr>
<td>Results</td>
<td>Survival: rate of survival at 3 years 20.7% in treatment group vs 15.3% in control group (RR = 0.84).</td>
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<td>DFS: relative risk of recurrence or death was 0.75</td>
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<td>Toxicity</td>
<td>(e.g. common toxicities overall, common grade 3/4 toxicities)</td>
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<tr>
<td>Conclusion</td>
<td>Prophylactic cranial irradiation improves both overall survival and disease-free survival among patients with small-cell lung cancer in complete remission.</td>
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<td>Other Comments</td>
<td>(e.g. any criticisms about the study)</td>
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- **Other Important Published Data:** (e.g. meta-analysis, restrospective analyses, phase II)


**ii) EXTENSIVE STAGE**
- **Bottom Line General Approach:**
  - **First-line therapy:** Combination palliative intent chemotherapy with a platinum agent for 4 to 6 cycles. Thoracic irradiation is ONLY recommended for palliation of symptoms that are not controlled by chemotherapy. Prophylactic cranial irradiation for extensive stage small cell lung cancer with response to chemotherapy decreases the risk of brain metastases and prolongs survival. Consider consolidative thoracic radiation in patients who have achieved a favorable response to initial chemotherapy and who have residual disease limited to the chest. Consolidative thoracic RT has been associated with improved overall survival\(^1\).
  - **Recurrent disease/Second-line therapy:** Time of recurrence since completion of chemotherapy is an indicator of prognosis, with patients who relapse within 3 months of completing first-line treatment carrying the worst prognosis. Consider second-line chemotherapy in patients with an acceptable performance status.
Topotecan may be considered for recurrent disease. Irinotecan and temozolomide also demonstrate activity in second- and third-line settings. Single agent oral etoposide may also be considered for patients who are reluctant to receive IV chemotherapy. Patients with longer remissions (particularly those with one year or more) may be considered for retreatment with platinum and etoposide.

- **Prognosis:** Median survival with standard treatment is 9 months
- **Important Phase III Clinical Trials:**

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<td><strong>Regimen</strong></td>
<td>• PCI or no further therapy</td>
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<td><strong>Mechanism of Action of Experimental Drug</strong></td>
<td>• Prophylactic cranial irradiation</td>
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<td><strong>Primary Endpoint</strong></td>
<td>• Time to symptomatic brain mets</td>
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| **Inclusion/Exclusion Criteria** | • Patients between age 18 and 75 years of age with extensive stage SCLC who achieved response after 4 to 6 cycles of initial chemotherapy.  
• ECOG 0 to 2  
• No previous brain/leptomeningeal mets  
• No previous radiotherapy to the head and neck area |
| **Size (N)** | • 286 patients |
| **Results** | • **Survival:** Median survival, 5.4 mos in treatment group vs. 6.7 mos in control group  
• Symptomatic brain mets was observed in 16.8% in the treatment group vs 41.3% in the control group.  
• Cumulative risk of brain mets within 1 year was 14.6% in the treatment group vs 40.4% in the control group.  
• **DFS:** 14.7 weeks in treatment group vs. 12 weeks in control group  
• **Quality of Life:** irradiation did not have a clinically significant effect on global health status. |
| **Toxicity** | • Headache, nausea/vomiting, fatigue/lethargy |
| **Conclusion** | • PCI prolongs disease-free and overall survival and decreases the incidence of symptomatic brain metastases. |
| **Other Comments** | • (e.g. any criticisms about the study) |


N=498 ext stage SCLC with response to chemotherapy. Thoracic RT 30 Gy in 10 Fr vs no RT. No diff in 1-yr OS 33% vs 28% (ns). 2-yr OS was better in the RT group (13% vs 3%, s). 46% isolated intrathoracic progression in the control (no RT) group, vs 20% in the experimental (RT) group.

- **Other Important Published Data:** (e.g. meta-analysis, retrospective analyses, phase II)
  1. Consolidative thoracic radiation:


C) OTHER REFERENCES (not previously cited above)
1) Canadian Cancer Statistics 2015
2) UpToDate
3) Alberta Cancer Guidelines
4) BC Cancer Agency Clinical Practice Guidelines