Chapter 14
Small Cell Lung Cancer

Michael Wahl and Adam Garsa

IV

PEARLS

- SCLC accounts for 15–20% of lung cancer cases with decreasing incidence.
- Approximately 1/3 of patients present with limited stage disease and the remainder present with extensive stage disease.
- More than 95% of cases are associated with a history of tobacco exposure.
- Ten to 15% of patients present with brain metastases and 2-year incidence after chemo-RT is 50–80%.
- SCLC is the most common solid tumor associated with paraneoplastic syndromes: SIADH, ACTH production syndrome, and Eaton–Lambert syndrome.
- Histopathologic hallmarks include dense sheets of small, round to fusiform cells with scant cytoplasm, extensive necrosis, and a high mitotic rate.
- Pathologic subtypes (pure or classic, variant, and mixed) carry the same prognosis.
- Most important prognostic factors are stage and performance status.

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WORKUP

- H&P.
- Labs: CBC, chemistries, BUN/Cr, LFTs, LDH.
- Diagnosis: sputum, FNA, bronchoscopic biopsy, or CT-guided biopsy.
- Pathologic mediastinal staging only if T1-2NO and patient is surgical candidate.
- Imaging: CT chest and abdomen, MRI brain, PET/CT.
- Additional: PFTs, pathology review, smoking cessation intervention.

STAGING

- See Chap. 15 for details of the AJCC Staging for Lung Cancer.
- In practice, SCLC has been divided into limited stage and extensive stage disease.
  - Limited Stage (LS): classically defined as disease fitting into a single radiation port, typically confined to one hemithorax and regional nodes.
  - With modern conformal radiotherapy techniques, LS now effectively characterized as stage I-III disease that can safely be treated with definitive radiotherapy.
  - Extensive Stage (ES): Any disease not meeting limited stage criteria.

TREATMENT RECOMMENDATIONS

Stage	Recommended treatment	Outcome
Limited	Concurrent cisplatin and etoposide (4c every 3 weeks) with early RT during cycle 1 or 2 (45 Gy/1.5 Gy b.i.d. or 6070 Gy QD). If CR or near-CR, prophylactic cranial RT (25 Gy in 10 fx) For <5% of patients with cT1-2 N0 disease with negative mediastinoscopy (or endoscopic biopsy), lobectomy and mediastinal node dissection/sampling may be performed initially. If pN0, chemotherapy alone. If pN+, concurrent chemoradiation as above. PCI (25 Gy in 10 fx) for all patients post-operatively	MS 20 months, 5-year OS 20–26%

Extensive	Combination platinum-based chemotherapy ± palliative RT to symptomatic sites. For patients with PR or CR to chemotherapy, prophylactic cranial RT (25 Gy in 10 fx), consider consolidative thoracic RT (ex. 30 Gy in 10 fx (Slotman *Lancet* 2015)). If brain metastases present, WBRT (30–37.5 Gy in 10–15 fx)	MS 12 months, 5-year OS <5–10%

STUDIES

LIMITED STAGE (LS-SCLC)

ROLE OF SURGERY

- Multiple older studies did not show benefit to surgical resection over chemoradiation, but recent data suggests it may play a role in patients with node negative disease after full staging with pathologic mediastinal evaluation, PET/CT and MRI.
- JCOG9101 (*J Thorac Cardiovasc Surg* 2005): Phase II study of 61 patients with stage I-IIIA SCLC (90% stage I/II) who underwent complete surgical resection followed by adjuvant chemotherapy (cisplatin/etoposide x 4c). 3y OS 61% (I: 68%, II: 56%, III: 13%).

THORACIC RADIATION

- Pignon (*NEJM* 1992): metaanalysis of 13 trials and 2140 patients with LS-SCLC treated with chemo ± thoracic RT. Thoracic RT improved 3-year OS by 5.4% vs. chemo alone (14.3 vs. 8.9%).
- Metaanalyses of randomized controlled trials performed on LS-SCLC patients receiving chemo and early vs. late timing of thoracic RT demonstrate improved survival for early concurrent integration of RT with platinum-based chemo (De Ruysscher *JCO* 2006a,b, Pijls-Johannesma *Cancer Treat Rev* 2007).
- *INT 0096* (Turrisi *NEJM* 1999): 417 patients with LS-SCLC randomized to concurrent cisplatin/etoposide with either 45 Gy/1.8 Gy QD or 45 Gy/1.5 Gy BID. Twice daily arm decreased local failure (36 vs. 52%) and increased 5-year OS (26 vs. 16%) compared to QD arm. Grade 3 esophagitis more frequent with b.i.d. regimen (27 vs. 11%). Criticism: hyperfractionation arm had higher BED than standard fractionation, so positive

result may be a consequence of dose escalation and not hyperfractionation per se.

- *RTOG 0239* (Komaki *JCO* 2009): phase II trial using accelerated high-dose thoracic RT (AHTRT) with concurrent etoposide/cisplatin. RT was given to large field to 28.8 Gy /1.8 Gy QD, then 14.4 Gy/1.8 Gy b.i.d. (1.8 Gy AP/PA in am; 1.8 Gy boost in pm). Total RT dose 61.2 Gy in 5 weeks. Two-year OS 37%, 2-year LC 80%, and 18% acute severe esophagitis, improved compared to INT 0096.
- CALGB 30610/RTOG 0538 (ongoing): Patients with LS-SCLC randomized to 3 RT regimens: standard fractionation (70 Gy/2 Gy daily), Turrisi regimen (45 Gy/1.5 Gy BID) or RTOG 0239 dose escalation (61.2 Gy in 5 weeks). RTOG 0239 based arm dropped at planned interim analysis to facilitate accrual.
- CONVERT (Faivre-Finn, ASCO 2016). 547 patients randomized to 45 Gy (1.5 Gy BID over 3 weeks) vs. 66 Gy (2 Gy daily over 6.5 weeks) on day 22 cycle 1 chemotherapy (4–6 cycles cisplatin etoposide), followed by PCI as indicated (received by ~87% of patients). No significant difference in 2-yr OS (BID 56%, QD 51%), MS (BID 30 mo, QD 25 mo), or toxicities (grade 2 esophagitis 55–63%, grade 3/4 esophagitis 19%, grade 3/4 pneumonitis 2.2–2.5%).

PROPHYLACTIC CRANIAL IRRADIATION

- Auperin (*NEJM* 1999): metaanalysis of seven trials of SCLC patients in CR comparing prophylactic cranial irradiation (PCI) vs. no PCI. PCI reduced the 3-year incidence of brain metastases (59 vs.33%) and increased 3-year OS (15.3 vs. 20.7). Neurocognitive function not assessed.
- RTOG 0212/Intergroup (Le Pechoux *Lancet* 2009): 720 LS-SCLC patients in CR to chemo-RT randomized to standard dose (25 Gy/2.5 Gy QD) vs. higher dose (36 Gy/2 Gy QD or 36 Gy/1.5 Gy b.i.d.) PCI. No significant difference in 2-year incidence of brains metastases. Reduced 2-year OS in higher dose group (37 vs. 42%) probably due to increased cancer-related mortality.

EXTENSIVE STAGE (ES-SCLC)

- Jeremic (*JCO* 1999): 210 ES-SCLC patients treated with three cycles cisplatin/etoposide with local PR or CR and distant CR randomized to accelerated hyperfractionated RT (54 Gy/1.5 Gy b.i.d.) and chemo vs. four cycles chemo alone. Patients receiving chemo-RT had improved 5-year OS (9.1 vs. 3.7%) and MS (17 vs. 11 months) vs. those treated with chemo alone.
- *EORTC* (Slotman *NEJM* 2007): 286 patients with ES-SCLC with response to chemotherapy randomized to PCI vs. no further treatment. PCI reduced 1-year incidence of symptomatic brain mets (14.6 vs. 40.4%) and improved OS (27.1 vs. 13.3%) compared to the control group.
- CREST (Slotman *Lancet* 2015): 498 patients with ES-SCLC without brain metastases with CR or PR to chemo randomized to PCI (25 Gy/10 fractions) and thoracic RT (30 Gy/10 fractions) vs. PCI alone. RT targeted post-chemo tumor volume plus any initially involved nodal stations. Trend towards improved 1y OS (33 vs. 28%), with improved 2y OS (13 vs. 3%), and improved PFS at 6 months (24 vs. 7%). Rate of isolated introthoracic progression was cut in half (46 vs. 20%).

RADIATION TECHNIQUES

SIMULATION AND FIELD DESIGN

- Supine, arms up with wingboard or alpha cradle.
- 4DCT to account for respiratory motion.
- GTV = Gross primary and nodal disease.
- CTV = GTV + 0.5–1 cm + pre-chemo involved nodal stations.
- Traditional mediastinal fields covered ipsilateral hilum and bilateral mediastinum from thoracic inlet to subcarinal region, but recent evidence suggests limited risk of isolated nodal failure away from clinically node positive disease.
  - Van Loon (*IJROBP* 2010): 60 patients with LS-SCLC prospectively treated chemo-RT to primary and pre-

chemo involved nodes on PET/CT only. 3% isolated nodal failure rate.
- MDACC (Shirvani *IJROBP* 2012): Retrospective analysis of 60 patients with LS-SCLC underwent chemo-RT to primary and pre-chemo involved nodes on PET/CT. 2% isolated nodal failure rate.

- If RT is preceded by chemotherapy, target volumes should be defined on the RT planning CT scan. However, the pre-chemotherapy originally involved lymph node regions should be included.

DOSE PRESCRIPTIONS

- LS-SCLC: 45 Gy in 1.5 b.i.d. fx (6 hour interval) or 60–70 Gy at 1.8–2.0 Gy QD.
- PCI: 25 Gy in 10 fx.
- Brain metastases: 30–37.5 Gy in 10–15 fx.

DOSE LIMITATIONS

- Spinal cord: limit maximum dose to ≤36 Gy with 1.5 Gy b.i.d. RT or ≤46 Gy at 1.8–2 Gy/fx QD.
- See Chapter 15 for additional dose limitations for thoracic RT.

COMPLICATIONS

- Acute: esophagitis, dermatitis, cough, fatigue.
- Subacute/late: radiation pneumonitis, pulmonary fibrosis, esophageal stricture or perforation, pericarditis, coronary artery disease, brachial plexopathy, rib fracture.

FOLLOW-UP

- Clinic visits every 2–4 months initially (H&P, CT chest/abdomen, and blood work at each visit), then decrease frequency to every 3–6 months, then annually.

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