National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Small Cell Lung Cancer

Version 2.2024 — November 21, 2023

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**Clinical Trials:** NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference.

**Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.**

**Updates in Version 2.2024 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2024 include:**

MS-1
- The discussion section has been updated to reflect the changes in the algorithm.

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**Updates in Version 1.2024 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2023 include:**

SCL-1
- Initial Evaluation
  - Bullet 9 modified: *Consider* molecular profiling ~~(only for patients who have never smoked tobacco with extensive stage SCLC)~~
  - Bullet 10 added: Integrate palliative care. See NCCN Guidelines for Palliative Care.
- Footnote g modified: ~~Molecular testing can be considered in rare cases for patients with extensive-stage SCLC who do not smoke tobacco, lightly smoke, or for pathologic dilemma because this may change management.~~ *Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management.*

SCL-3
- Adjuvant Treatment
  - Branch modified: N~~1~~+
  - Branch removed: N2, Systemic therapy + mediastinal RT (sequential or concurrent)

SCL-5
- Primary treatment, spinal cord compression
  - Bullet 1 added: Initiate steroids
  - Bullet 2 modified: *Systemic therapy* + RT *(typically sequential* ~~to symptomatic sites before systemic therapy unless immediate systemic therapy is required~~)
- Footnotes added
  - u: For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).
  - v: Initiate steroids for patients with symptomatic neurologic disease.
  - w: With neurologic symptoms, RT is preferred before systemic therapy. Systemic therapy may start first if RT cannot be started expeditiously or if controlling systemic symptoms is more urgent.

SCL-6
- Surveillance
  - Bullet 4 modified: Brain MRI (preferred) or CT with contrast every 3–4 mo during y 1, then every 6 mo ~~during y 2 and after y 2~~ *afterwards, then* as clinically indicated (regardless of PCI status)
  - Bullet 7 modified: *FDG*-PET/CT is not recommended for routine follow-up *unless contrast CT C/A/P is contraindicated*

SCL-7
- Footnotes added
  - ee: For CNS progression only, continue systemic therapy and treat the brain metastases with RT (see Principles of Radiation Therapy).
  - ff: Consider genomic profiling, if not previously done, to determine clinical trial eligibility.

SCL-A 2 of 2
- Neurologic

Continued

- Sub-bullet 1 added: Consider early subspecialty consultation for unusual paraneoplastic neurologic syndromes to ensure the most recent management is done
- Sub-bullet 2 modified: If paraneoplastic neurologic syndrome is suspected, consider obtaining *a neurologic consultation and/or* comprehensive paraneoplastic antibody panel

• Footnote added: Principles of Supportive Care (SCL-D).

**Updates in Version 1.2024 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2023 include:**

SCL-B 1 of 2

• Bullet 5 modified: Careful counting of mitoses is essential, because it is the most important histologic criterion for distinguishing SCLC from typical and atypical carcinoids. *Strongly recommend a second opinion—with a pathologist specializing in the diagnosis of thoracic malignancies—for diagnostic dilemma, including carcinoid.*

• Bullet 8 modified: ~~Molecular testing can be considered in rare cases for patients with extensive-stage SCLC who do not smoke tobacco, lightly smoke (<10 cigarettes/day), or for pathologic dilemma because this may change management~~ *Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke (<10 cigarettes/day), with remote smoking history, or diagnostic or therapeutic dilemma or at time of relapse—if not previously done, because this may change management.*

SCL-C

• Bullet 2, sub-bullet 2 modified: For patients undergoing definitive surgical resection, the preferred operation is lobectomy with mediastinal lymph node dissection or systematic lymph node sampling *(eg, ≥3 N2 and ≥1 N1 stations).*

• References added
- 3: Katz MHG, Francescatti AB, Hunt KK; Cancer Surgery Standards Program of the American College of Surgeons. Technical Standards for Cancer Surgery: Commission on Cancer Standards 5.3-5.8. Ann Surg Oncol 2022;29:6549-6558.
- 4: Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-670.
- 5: Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-1129.
- 6: Osarogiagbon RU, Decker PA, Ballman K, et al. Survival Implications of Variation in the Thoroughness of Pathologic Lymph Node Examination in American College of Surgeons Oncology Group Z0030 (Alliance). Ann Thorac Surg 2016;102:363-369.
- 7: Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. J Thorac Cardiovasc Surg 2014;147:747-752: Discussion 752-753.

SCL-D

• Bullet 2 modified: Granulocyte ~~colony-stimulating factor (G-CSF) or granulocyte-~~macrophage colony-stimulating factor (GM-CSF) ~~is~~ *or granulocyte colony–stimulating factor (G-CSF) are* not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).

• SIADH, sub-bullet removed: Antineoplastic therapy

• Cushing syndrom, sub-bullet 2 modified: ~~Try to control before initiation of antineoplastic therapy.~~ *Consider referral to an appropriate endocrinology subspecialist.*

• Bullet added: Consider early subspecialty consultation for unusual paraneoplastic neurologic syndromes to ensure the most recent management is done.

• Reference added: Wang C, Zhu S, Miao C, et al. Safety and efficacy of pegylated recombinant human granulocyte colony-stimulating factor during concurrent chemoradiotherapy for small-cell lung cancer: a retrospective, cohort-controlled trial. BMC Cancer 2022;22:542.

SCL-E 2 of 6

• Footnote b modified: Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. *For safety reasons, do not use ICIs in patients who have recently received tyrosine kinase inhibitors (TKIs).*

• Footnotes added:
- c: Included patients with asymptomatic untreated brain metastases.
- d: Maintenance immunotherapy with either atezolizumab or durvalumab should continue until progression or intolerable toxicity.

Continued

- e: For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).

SCL-E 3 of 6
- Page extensively revised.
- Vinorelbine and bendamustine (category 2B) were removed as subsequent therapy options.

Updates in Version 1.2024 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2023 include:

SCL-E 4 of 6
- Bullet added: Transformed SCLC from NSCLC with an Oncogenic Driver
- Sub-bullets added
  - This is a rare population of patients with very limited data to guide treatment.
  - Systemic cytotoxic chemotherapy is recommended using the NCCN Guidelines for Small Cell Lung Cancer.
  - The role of immunotherapy in this setting is unclear based on limited data.
  - If TKI is continued, ICI should be avoided, due to known toxicity.
  - Consider referral to a center with experience managing transformed SCLC.

SCL-E 6 of 6
- References added
  - 28: Edelman MJ, Dvorkin M, Laktionov K, et al. Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer. Lung Cancer 2022;166:135-142.
  - 40: Hoang T, Kim K, Jaslowski A, et al. Phase II study of second-line gemcitabine in sensitive or refractory small cell lung cancer. Lung Cancer 2003;42:97-102.
  - 41: Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. Ann Oncol 2019;30:839-844.
  - 42: Oshima Y, Tanimoto T, Yuji K, Tojo A~~ et al~~. EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer. JAMA Oncol 2018;4:1112-1115.
  - 43: Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: Clinical outcomes. J Clin Oncol 2019;37:278-285.
  - 44: Ferrer L, Giaj Levra M, Brevet M, et al. A brief report of transformation from NSCLC to SCLC: Molecular and therapeutic characteristics. J Thorac Oncol 2019;14:130-134.
  - 45: Chai X, Zhang X, Li W, Chai J. Small cell lung cancer transformation during antitumor therapies: A systematic review. Open Med (Wars) 2021;16:1160-1167.
  - 46: Zhang CY, Sun H, Su JW, et al. A potential treatment option for transformed small-cell lung cancer on PD-L1 inhibitor-based combination therapy improved survival. Lung Cancer 2023;175:68-78.
- References removed:
  - Furuse K, Kuboa K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Japan Lung Cancer Vinorelbine Study Group. Oncology 1996;53:169-172
  - Jassem J, Karnicka-Mlodkowska H, van Pottelsberghe C, et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. EORTC Lung Cancer Cooperative Group. Eur J Cancer 1993;29A:1720-1722.
  - Lammers PE, Shyr Y, Li CI, et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. J Thorac Oncol 2014;9:559-562.
  - Oxnard GR, Yang JCH, Yu H, et al. TATTON: a multi-arm, phase Ib trial of osimertinib combined with selumetinib, savolitinib, or durvalumab in EGFR-mutant lung cancer. Ann Oncol 2020;31:507-516.

SCL-F 1 of 6
- General treatment information, limited stage, bullet 2 modified: Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is

Continued

**Updates in Version 1.2024 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2023 include:**

made not to pursue surgery may be candidates for stereotactic ablative radiotherapy (SABR*), also known as stereotactic body RT (SBRT),* to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC (see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCLC-C).

SCL-F 2 of 6
- Extensive stage, bullet 1 modified: Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy *before immunotherapy*, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients. The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with ES-SCLC that responded to ~~systemic therapy~~ *chemotherapy (without immunotherapy)* demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved. Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.

SCL-F 3 of 6
- Extensive stage
  - Bullet removed: Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions up to definitive dosing regimens in patients with a longer life expectancy.
  - Bullet 1 modified: Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach, but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are ~~no~~ *limited* data on optimal sequencing or safety). The benefit of thoracic RT in the context of chemoimmunotherapy is under evaluation in the RAPTOR/NRG LU007 trial.

SCL-F 4 of 6
- Prophylactic Cranial Irradiation
  - Bullet 2 modified: When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases. The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening *(see the NCCN Guidelines for Central Nervous System Cancers)*
  - Bullet 3 modified: Hippocampal-avoidance (HA) PCI using IMRT may be considered as a potential strategy to improve cognitive preservation. A phase III randomized trial of HA-WBRT versus conventional WBRT demonstrated improved cognitive preservation and patient-reported outcomes with HA-WBRT in patients with brain metastases from mixed histologies. Conflicting data have been reported with HA-PCI versus conventional PCI in SCLC with one trial reporting no differences in cognition and a separate trial reporting improved cognitive preservation with HA-PCI. A larger randomized trial of HA-PCI versus conventional PCI, NRG CC003, ~~is ongoing~~ *has completed accrual with results pending.*
- Brain Metastases, bullet 4 modified: For patients with a better prognosis (eg, ≥4 months), hippocampal-sparing WBRT using IMRT plus memantine is preferred because it produces less cognitive function failure than conventional WBRT plus memantine. However, patients with metastases within 5 mm of the hippocampi, leptomeningeal metastases, and other high risk features were not eligible for hippocampal-sparing WBRT on NRG CC001. *Although CC001 did not include patients with brain metastases from SCLC, it is reasonable to extrapolate the findings to SCLC.*

SCL-F 5 of 6
- Reference modified: Bogart JA, Wang XF, Masters GA, et al. ~~Phase 3 comparison of high-dose once daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2021;39:8505-8505.~~ *High-dose once-daily thoracic radiotherapy in limited-stage small-cell lung cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2023;41:2394-2402.*

| DIAGNOSIS | INITIAL EVALUATION[a,b] | STAGE | |
|---|---|---|---|
| Small cell lung cancer (SCLC) or combined SCLC/non-small cell lung cancer (NSCLC) on biopsy or cytology of primary or metastatic site → | • History and physical (H&P)[c]<br>• Pathology review[d]<br>• Complete blood count (CBC)<br>• Electrolytes, liver function tests (LFTs), blood urea nitrogen (BUN), creatinine<br>• Chest/abdomen/pelvis (C/A/P) CT with contrast<br>• Brain MRI[a,e] (preferred) or CT with contrast<br>• FDG-PET/CT scan (skull base to mid-thigh), if needed to clarify extent of disease[a,f]<br>• Smoking cessation counseling and intervention. See the NCCN Guidelines for Smoking Cessation.<br>• Consider molecular profiling[g]<br>• Integrate palliative care. See NCCN Guidelines for Palliative Care | Limited stage (See ST-1 for TNM Classification) → | Additional Workup (SCL-2) |
| | | Extensive stage (See ST-1 for TNM Classification) → | Primary Treatment (SCL-5) |

[a] If extensive stage is established, further staging evaluation is optional. However, brain imaging MRI (preferred), or CT with contrast is recommended in all patients.
[b] Workup of SCLC should be expedited, with studies done in parallel whenever possible.
[c] Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[d] Principles of Pathologic Review (SCL-B).
[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[f] If FDG-PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by FDG-PET/CT that alter stage.
[g] Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management.

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**STAGE**

**ADDITIONAL WORKUP[b]**

**Limited stage (see ST-1 for TNM Classification)** →

- **If pleural effusion is present, thoracentesis is recommended; if thoracentesis inconclusive, consider thoracoscopy[h]**
- **Pulmonary function tests (PFTs) during evaluation for surgery or definitive RT**
- **Multidisciplinary evaluation is recommended before surgery**
- **Bone imaging (radiographs or MRI) as appropriate if FDG-PET/CT equivocal (consider biopsy if bone imaging is equivocal)**
- **Unilateral marrow aspiration/biopsy in select patients[i]**

→ **Limited stage: Clinical stage I–IIA (T1–2,N0,M0)** → **Pathologic mediastinal staging[j,k]** → **Primary Treatment (SCL-3)**

→ **Limited stage IIB–IIIC (T3–4,N0,M0; T1–4,N1–3,M0). Consider pathologic mediastinal staging (especially for cN0) if it would help determine RT fields[j,k]** → **Primary Treatment (SCL-4)**

→ **Bone marrow biopsy, thoracentesis, or bone studies consistent with malignancy** → **Extensive-Stage Disease (SCL-5)**

[b] Workup of SCLC should be expedited, with studies done in parallel whenever possible.

[h] While most pleural effusions in patients with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.

[i] Selection criteria include: nucleated red blood cells (RBCs) on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration.

[j] Principles of Surgical Resection (SCL-C).

[k] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

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| TESTING RESULTS[k] | PRIMARY TREATMENT | ADJUVANT TREATMENT |
|---|---|---|

**Limited stage: clinical stage I–IIA (T1–2,N0,M0)**

- **Pathologic mediastinal staging[j,k] negative** → **Lobectomy[j,l] (preferred) and mediastinal lymph node dissection or sampling**
  - **R0**
    - **N0** → **Systemic therapy[m]** → Response Assessment Following Primary Treatment (SCL-6)[o,p]
    - **N+** → **Systemic therapy[m] ± mediastinal RT[n] (sequential or concurrent)** → Response Assessment Following Primary Treatment (SCL-6)[o,p]
  - **R1/R2** → **Systemic therapy[m] + concurrent RT[n]** → Response Assessment Following Primary Treatment (SCL-6)[o,p]
- **Medically inoperable or decision made not to pursue surgical resection**
  - **SABR[n]** → **Systemic therapy[m,q]** → Response Assessment Following Primary Treatment (SCL-6)[o,p]
  - **Systemic therapy[m] + concurrent RT[n] (SCL-4)** → Response Assessment Following Primary Treatment (SCL-6)[o,p]
- **Pathologic mediastinal staging[j,k] positive** → SCL-4

Footnotes (SCL-3A)

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## FOOTNOTES

[j] Principles of Surgical Resection (SCL-C).

[k] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

[l] Select patients may be treated with systemic therapy/RT as an alternative to surgical resection.

[m] Principles of Systemic Therapy (SCL-E).

[n] Principles of Radiation Therapy (SCL-F).

[o] For patients receiving adjuvant systemic therapy ± RT, response assessment is recommended only after completion of adjuvant therapy (SCL-6); do not repeat scans to assess response during adjuvant treatment.

[p] For patients receiving systemic therapy + concurrent RT, response assessment is recommended only after completion of initial therapy (SCL-6); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by C/A/P CT with contrast is recommended after every 2 cycles of systemic therapy and at completion of therapy(SCL-6).

[q] Systemic therapy may be initiated first if time to initiation of stereotactic body radiotherapy (SABR) will be prolonged.

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## PRIMARY TREATMENT

**Limited stage IIB–IIIC (T3–4,N0,M0; T1–4,N1–3,M0)**

- **Good performance status (PS) (0–2)** → **Systemic therapy[m] + concurrent RT[n] (category 1)** → **Response Assessment Following Primary Treatment (SCL-6)[p]**
- **Poor PS (3–4) due to SCLC** → **Systemic therapy[m] ± RT[n] (concurrent or sequential)** → **Response Assessment Following Primary Treatment (SCL-6)[p]**
- **Poor PS (3–4) not due to SCLC** → **Individualized treatment including supportive care[r]**
  **NCCN Guidelines for Palliative Care**

[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[p] For patients receiving systemic therapy + concurrent RT, response assessment is recommended only after completion of initial therapy (SCL-6); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by C/A/P CT with contrast is recommended after every 2 cycles of systemic therapy and at completion of therapy (SCL-6).
[r] Principles of Supportive Care (SCL-D).

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**STAGE** — **PRIMARY TREATMENT**[u]

**Extensive stage (see ST-1 for TNM Classification)**[u]

- **Extensive stage without localized symptomatic sites or brain metastases**
  - • Good PS (0–2)
    • Poor PS (3–4) due to SCLC
    → Combination systemic therapy[m] including supportive care[r]
    NCCN Guidelines for Palliative Care
  - • Poor PS (3–4) not due to SCLC
    → Individualized therapy including supportive care[r]
    NCCN Guidelines for Palliative Care
- **Extensive stage + localized symptomatic sites**
  - • Superior vena cava (SVC) syndrome
    • Lobar obstruction
    • Bone metastases
    → Systemic therapy[m] ± RT[n] to symptomatic sites
    If high risk of fracture due to osseous structural impairment, consider orthopedic stabilization and palliative external beam RT (EBRT)[n]
    → Response Assessment Following Primary Treatment (SCL-6)[t]
  - Spinal cord compression
    → • Initiate steroids[v]
    • Systemic therapy[m] + RT[n] (typically sequential)[w]
    • NCCN Guidelines for Central Nervous System Cancers
    → Response Assessment Following Primary Treatment (SCL-6)[t]
- **Extensive stage with brain metastases**
  - Asymptomatic → Administer systemic therapy before initiating brain RT[m,n,s]
  - Symptomatic → • Brain RT[n] before systemic therapy,[w] unless immediate systemic therapy is indicated
    • Initiate steroids[v]

All primary treatment options → Response Assessment Following Primary Treatment (SCL-6)[t]

[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[o] For patients receiving adjuvant systemic therapy ± RT, response assessment is recommended only after completion of adjuvant therapy (SCL-6); do not repeat scans to assess response during adjuvant treatment.
[r] Principles of Supportive Care (SCL-D).
[s] Brain MRI (preferred) or CT with contrast is recommended to be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (SCL-6). If brain metastases progress while on systemic therapy, it is recommended that brain RT is initiated before completion of systemic therapy. Principles of Radiation Therapy (SCL-F).
[t] During systemic therapy, response assessment by C/A/P CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-6).
[u] For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).
[v] Initiate steroids for patients with symptomatic neurologic disease.
[w] With neurologic symptoms, RT is preferred before systemic therapy. Systemic therapy may start first if RT cannot be started expeditiously or if controlling systemic symptoms is more urgent.

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## RESPONSE ASSESSMENT FOLLOWING PRIMARY TREATMENT

- C/A/P CT with contrast
- Brain MRI[e] (preferred) or CT with contrast
- CBC
- Electrolytes, LFTs, BUN, creatinine

→ **Complete response or partial response**

→ **Limited stage**

**ADJUVANT RT:** Prophylactic cranial irradiation (PCI)[n,y,z] or Consider MRI brain surveillance[e,y]

→ After completion of initial therapy:
- Oncology follow-up visits every 3 mo during y 1–2, every 6 mo during y 3, then annually

→ **Extensive stage**

**ADJUVANT RT:** MRI brain surveillance[e,y] ±
- Consider PCI[n,y]
- Consider thoracic RT[n,aa]

→ After completion of initial or subsequent therapy:
- Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during 4–5, then annually

→ **Stable disease**

→ **Limited stage** → After completion of initial therapy:
- Oncology follow-up visits every 3 mo during y 1–2, every 6 mo during y 3, then annually

→ **Extensive stage** → After completion of initial or subsequent therapy:
- Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during y 4–5, then annually

→ **Primary progressive disease** → Subsequent Therapy/Palliative Therapy (SCL-7)

## SURVEILLANCE

- Provide survivorship care plan after completion of initial therapy[x]
- H&P[c]; blood work only as clinically indicated
- Surveillance CT[bb]
- Brain MRI (preferred)[e] or CT with contrast every 3–4 mo during y 1, then every 6 mo afterwards, then as clinically indicated (regardless of PCI status)
- New pulmonary nodule should initiate workup for potential new primary
- Smoking cessation intervention, see the NCCN Guidelines for Smoking Cessation
- FDG-PET/CT is not recommended for routine follow-up unless contrast CT C/A/P is contraindicated

→ Relapse, see Subsequent Therapy (SCL-7)

[c] Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[n] Principles of Radiation Therapy (SCL-F).
[x] NCCN Guidelines for Survivorship.
[y] PCI is not recommended in patients with poor PS or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close brain surveillance, MRI (preferrred) or CT with contrast, should be carefully discussed with these patients.
[z] The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0) SCLC. See Principles of Radiation Therapy (SCL-F).
[aa] Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.
[bb] Most NCCN Member Institutions use CT chest ± abdomen/pelvis every 2–6 months (more frequently in years 1–2 and less frequently thereafter).

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## PROGRESSIVE DISEASE — SUBSEQUENT THERAPY/PALLIATIVE THERAPY

**Relapse or primary progressive disease[ff]**

- **PS 0–2** → **Subsequent systemic therapy[m,cc]** or **Palliative symptom management[r,dd] including localized RT[n] to symptomatic sites**
  - **Response** → **Continue until progression[ee] or development of unacceptable toxicity** →
    - **PS 0–2** →
      - **Consider subsequent systemic therapy[m,cc]**
      - **Palliative symptom management,[r,dd] including localized RT[n] to symptomatic sites**
    - **PS 3–4** → **Palliative symptom management,[r,dd] including localized RT[n] to symptomatic sites**
  - **No response or unacceptable toxicity** →
    - **PS 0–2** →
      - **Consider subsequent systemic therapy[m,cc]**
      - **Palliative symptom management,[r,dd] including localized RT[n] to symptomatic sites**
    - **PS 3–4** → **Palliative symptom management,[r,dd] including localized RT[n] to symptomatic sites**
- **PS 3–4** → **Palliative symptom management,[r,dd] including localized RT[n] to symptomatic sites**

[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[r] Principles of Supportive Care (SCL-D).
[cc] Response assessment by C/A/P CT with contrast is recommended after every 2–3 cycles of systemic therapy.
[dd] NCCN Guidelines for Palliative Care.
[ee] For central nervous system (CNS) progression only, continue systemic therapy and treat the brain metastases with RT (see Principles of Radiation Therapy).
[ff] Consider genomic profiling, if not previously done, to determine clinical trial eligibility.

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## SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

### Signs and Symptoms Due to Local Primary Tumor Growth

- Cough – endobronchial irritation, bronchial compression
- Hemoptysis – usually central or cavitary lesion
- Wheezing – partially obstructing endobronchial lesion
- Fever – postoperative pneumonia
- Dyspnea – bronchial obstruction, pneumonia, pleural effusion

### Signs and Symptoms Due to Primary Tumor Invasion or Regional Lymphatic Metastases

- Hoarseness – left vocal cord paralysis due to tumor invasion or lymphadenopathy in the aortopulmonary window
- Hemidiaphragm elevation – due to phrenic nerve compression
- Dysphagia – due to esophageal compression
- Chest pain – involvement of pleura or chest wall, often dull and non-localized
- SVC syndrome – due to local invasion into mediastinum or lymphadenopathy in right paratracheal region
- Pericardial effusion and tamponade
- Cervical or supraclavicular lymph node enlargement

### Signs and Symptoms Due to Extrathoracic (Hematogenous) Metastases

- Brain metastases:
  - Headache, focal weakness or numbness, confusion, slurred speech, gait instability, incoordination
- Leptomeningeal carcinomatosis:
  - Headache, confusion, cranial nerve palsy, diplopia, slurred speech, radicular back pain, spinal cord compression
- Adrenal metastases:
  - Mid-back or flank pain, costovertebral angle tenderness
  - Adrenal insufficiency due to tumor involvement (rare)
- Liver metastases:
  - Right upper quadrant pain or tenderness, jaundice, fatigue, fever, hepatomegaly
- Bone metastases:
  - Bone pain
  - Spinal cord compression – back pain, muscle weakness, numbness, paresthesia, loss of bowel and bladder control
- Constitutional:
  - Anorexia/cachexia – weight loss
  - Fatigue

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Continued

## SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

**Signs and Symptoms of Paraneoplastic Syndromes**

- Presence does not imply metastases or incurability

- Endocrine:
  - Due to ectopic peptide hormone production
  - Usually reversible with successful anti-tumor therapy
  - Syndrome of inappropriate antidiuretic hormone secretion (SIADH)[a]:
    - ◊ Ectopic vasopressin (antidiuretic hormone, ADH) secretion
    - ◊ Clinically significant hyponatremia in 5%–10% of SCLC
    - ◊ Malaise, weakness, confusion, obtundation, volume depletion, nausea
    - ◊ Hyponatremia, euvolemia, low serum osmolality, inappropriately concentrated urine osmolality, normal thyroid and adrenal function
  - Cushing syndrome[a]:
    - ◊ Ectopic adrenocorticotropic hormone (ACTH) secretion
    - ◊ Weight gain, moon facies, hypertension, hyperglycemia, generalized weakness
    - ◊ High serum cortisol and ACTH, hypernatremia, hypokalemia, alkalosis

- Neurologic: All specific syndromes are rare
  - Consider early subspecialty consultation for unusual paraneoplastic neurologic syndromes to ensure the most recent management is done
  - If paraneoplastic neurologic syndrome is suspected, consider obtaining a neurologic consultation and/or comprehensive paraneoplastic antibody panel
  - Subacute cerebellar degeneration (anti-Yo antibody) – ataxia, dysarthria
  - Encephalomyelitis (ANNA-1 [anti-Hu] antibody) – confusion, obtundation, dementia
  - Sensory neuropathy (anti-dorsal root ganglion antibody) – pain, sensory loss
  - Lambert-Eaton myasthenic syndrome (LEMS)[a] (anti-voltage-gated calcium channel antibody) – weakness, autonomic dysfunction
  - Cancer-associated retinopathy (anti-recoverin antibody) – visual loss, photosensitivity

- Hematologic:
  - Anemia of chronic disease
  - Leukemoid reaction – leukocytosis
  - Trousseau syndrome – migratory thrombophlebitis

[a] Principles of Supportive Care (SCL-D).

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## PRINCIPLES OF PATHOLOGIC REVIEW

**Pathologic Evaluation**

- Pathologic evaluation is performed to determine the histologic classification of lung tumors and relevant staging parameters.
- The World Health Organization (WHO) tumor classification system provides the foundation for the classification of lung tumors, including histologic subtype, staging factors, clinical features, molecular characteristics, genetics, and epidemiology.[1-3]
- SCLC is a poorly differentiated neuroendocrine carcinoma. Distinguishing SCLC from other neuroendocrine tumors, particularly typical and atypical carcinoids, is important due to significant differences in epidemiology, genetics, treatment, and prognosis.[4-6]
- SCLC can be diagnosed on good-quality histologic samples via high-quality hematoxylin and eosin (H&E)-stained sections or on well-preserved cytologic samples.
  - SCLC is characterized by small blue cells with scant cytoplasm, high nuclear-to-cytoplasmic ratio, granular chromatin, and absent or inconspicuous nucleoli.
  - SCLC cells are round, oval, or spindle-shaped with molding and high mitotic counts.[7-9]
  - The most useful characteristics for distinguishing SCLC from large-cell neuroendocrine carcinoma (LCNEC) are the high nuclear-to-cytoplasmic ratio and paucity of nucleoli in SCLC.
- Careful counting of mitoses is essential, because it is the most important histologic criterion for distinguishing SCLC from typical and atypical carcinoids. Strongly recommend a second opinion—with a pathologist specializing in the diagnosis of thoracic malignancies—for diagnostic dilemma, including carcinoid.
  - SCLC (>10 mitoses/2 $mm^2$ field); atypical carcinoid (2–10 mitoses/2 $mm^2$ field); typical carcinoid (0–1 mitoses/2 $mm^2$ field)
  - Mitoses should be counted in the areas of highest activity and per 2 $mm^2$ field, rather than per 10 high-power fields.
  - In tumors that are near the defined cutoffs of 2 or 10 mitoses per 2 $mm^2$, at least three 2-$mm^2$ fields should be counted and the calculated mean (rather than the single highest mitotic count) should be used to determine the overall mitotic rate.[1,2]
- SCLC is often associated with necrosis. However, necrosis, usually punctate, is also seen in atypical carcinoid tumors. Counting mitotic figures helps to distinguish these two entities.
- Combined SCLC consists of both SCLC histology and NSCLC histology (squamous cell, adenocarcinoma, spindle/pleomorphic, and/or large cell). There is no minimal percentage of NSCLC histologic elements required; when any are present along with SCLC, this can be called combined SCLC, except in combination with LCNEC. At least 10% of the tumor should show LCNEC morphology to be classified as combined SCLC and LCNEC.[1]
- Comprehensive molecular profiling can be considered in rare cases—particularly for patients with extensive-stage/relapsed SCLC who do not smoke tobacco, lightly smoke (<10 cigarettes/day), have remote smoking history, or have diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management.

**Immunohistochemical Staining**

- Immunohistochemistry can be very helpful in diagnosing SCLC in limited samples.[5,7]
  - Nearly all SCLCs are positive for cytokeratin antibody mixtures with broad reactivity, such as AE1/AE3 and CAM5.2.[1,10]
  - The majority of SCLCs are reactive to markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), CD56/NCAM, synaptophysin, and chromogranin A. Fewer than 5% of SCLCs are negative for all neuroendocrine markers.[11,12]
  - Thyroid transcription factor-1 (TTF-1) is positive in 85% to 90% of SCLCs.[13-16]
  - Additional immunohistochemical markers are useful in distinguishing small cell carcinoma from poorly differentiated non-small cell carcinoma and combined carcinoma using Napsin A as a marker of adenocarcinoma, and p40 or p63 as a marker of squamous differentiation.[10] It should, however, be noted that p40 and p63 can be focally positive in small cell carcinoma.
- Ki-67 immunostaining can be very helpful in distinguishing SCLC from carcinoid tumors, especially in small biopsy samples with crushed or necrotic tumor cells in which counting mitotic figures is difficult.[4,5]
  - The Ki-67 proliferative index in SCLC is typically 50% to 100%.[1]

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References on SCL-B 2 of 2

## REFERENCES


[1] WHO Classification of Tumours Editorial Board. Thoracic Tumours. In: WHO classification or tumours series. 5th ed. Lyron, France. International Agency for Research on Cancer; 2021.

[2] Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. J Thorac Oncol 2015;10:1240-1242.

[3] Travis WD, Brambilla E, Nicholson AG, et al, and WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-1260.

[4] Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. J Thorac Oncol 2014;9:273-284.

[5] Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. Am J Surg Pathol 2005;29:179-187.

[6] Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. Endocr Relat Cancer 2013;21:1-16.

[7] Travis WD. Advances in neuroendocrine lung tumors. Ann Oncol 2010;21 Suppl 7:vii65-vii71.

[8] Zakowski MF. Pathology of small cell carcinoma of the lung. Semin Oncol 2003;30:3-8.

[9] Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. Am J Surg Pathol 2002;26:1184-1197.

[10] Masai K, Tsuta K, Kawago M, et al. Expression of squamous cell carcinoma markers and adenocarcinoma markers in primary pulmonary neuroendocrine carcinomas. Appl Immunohistochem Mol Morphol 2013;21:292-297.

[11] Rooper LM, Sharma R, Li QK, et al. INSM1 demonstrates superior performance to the individual and combined use of synaptophysin, chromogranin and CD56 for diagnosing neuroendocrine tumors of the thoracic cavity. Am J Surg Pathol 2017;41:1561-1569.

[12] Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol 2020;96:8-33.

[13] Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. Am J Surg Pathol 2000;24:1217-1223.

[14] Kaufmann O, Dietel M. Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinomas and other neuroendocrine carcinomas of various primary sites. Histopathology 2000;36:415-420.

[15] Lantuejoul S, Moro D, Michalides RJ, et al. Neural cell adhesion molecules (NCAM) and NCAM-PSA expression in neuroendocrine lung tumors. Am J Surg Pathol 1998;22:1267-1276.

[16] Wick MR. Immunohistology of neuroendocrine and neuroectodermal tumors. Semin Diagn Pathol 2000;17:194-203.


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## PRINCIPLES OF SURGICAL RESECTION

- **Stage I–IIA SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients most likely to benefit from surgery are those with SCLC that is clinical stage I–IIA (T1–2,N0,M0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and FDG-PET/CT imaging).[1,2]**
  - **Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.**
  - **For patients undergoing definitive surgical resection, the preferred operation is lobectomy with mediastinal lymph node dissection or systematic lymph node sampling (eg, ≥3 N2 and ≥1 N1 stations).[3,4,5,6,7]**
- **In patients who do not smoke, small lesions that are presumed to be small cell carcinoma on biopsy should be resected because they are likely carcinoids that have been misdiagnosed (NCCN Guidelines for Neuroendocrine and Adrenal Tumors).**
- **Surgery may be considered for selected patients with T3 (based on size), N0 SCLC, if invasive mediastinal lymph node staging is negative.**
- **Intraoperative diagnosis of likely SCLC in a patient with no prior biopsy**
  - **Mediastinal lymph node dissection or systematic lymph node sampling with frozen section is recommended to assess extent of disease and overall burden of disease.**
  - **If primary site and lymph nodes appear resectable, perform anatomic resection, preferably lobectomy. Should not do pneumonectomy if needed to encompass nodal metastatic disease.**
- **Patients who undergo complete resection should be treated with postoperative systemic therapy.[8] Patients without nodal metastases should be treated with systemic therapy alone. Patients with N2 or N3 nodal metastases should be treated with postoperative concurrent or sequential systemic therapy and mediastinal RT. Patients with N1 nodal metastases may be considered for postoperative mediastinal radiation.**
- **The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0); see SCL-F.**

[1] Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994;106:320S-323S.
[2] Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. Ann Surg 2018;268:1105-1112.
[3] Katz MHG, Francescatti AB, Hunt KK; Cancer Surgery Standards Program of the American College of Surgeons. Technical Standards for Cancer Surgery: Commission on Cancer Standards 5.3-5.8. Ann Surg Oncol 2022;29:6549-6558.
[4] Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-670.
[5] Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-1129.
[6] Osarogiagbon RU, Decker PA, Ballman K, et al. Survival Implications of Variation in the Thoroughness of Pathologic Lymph Node Examination in American College of Surgeons Oncology Group Z0030 (Alliance). Ann Thorac Surg 2016;102:363-369.
[7] Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. J Thorac Cardiovasc Surg 2014;147:747-752: Discussion 752-753.
[8] Yang CE, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-1064.

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## PRINCIPLES OF SUPPORTIVE CARE

- Smoking cessation advice, counseling, and pharmacotherapy
  - Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange (https://www.ahrq.gov/prevention/guidelines/tobacco/5steps.html)
  - See NCCN Guidelines for Smoking Cessation

- Granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte colony–stimulating factor (G-CSF) are not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1,2]
- Trilaciclib or G-CSF may be used as prophylactic options to decrease the incidence of chemotherapy-induced myelosuppression when administering platinum/etoposide ± immune checkpoint inhibitor (ICI)-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (ES-SCLC).

- SIADH
  - Fluid restriction
  - Saline infusion for symptomatic patients
  - Demeclocycline
  - Vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) for refractory hyponatremia

- Cushing syndrome
  - Consider ketoconazole. If not effective, consider metyrapone.
  - Consider referral to an appropriate endocrinology subspecialist.

- Leptomeningeal disease: See NCCN Guidelines for Central Nervous System Cancers

- Pain management: See NCCN Guidelines for Adult Cancer Pain

- Nausea/vomiting: See NCCN Guidelines for Antiemesis

- Psychosocial distress: See NCCN Guidelines for Distress Management

- See NCCN Guidelines for Palliative Care as indicated

- Consider early subspecialty consultation for unusual paraneoplastic neurologic syndromes to ensure the most recent management is done

[1] Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641.
[2] Wang C, Zhu S, Miao C, et al. Safety and efficacy of pegylated recombinant human granulocyte colony-stimulating factor during concurrent chemoradiotherapy for small-cell lung cancer: a retrospective, cohort-controlled trial. BMC Cancer 2022;22:542.

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## PRINCIPLES OF SYSTEMIC THERAPY

### PRIMARY OR ADJUVANT THERAPY FOR LIMITED-STAGE SCLC:

**Four cycles of systemic therapy are recommended.**
**Planned cycle length should be every 21–28 days during concurrent RT.**
**During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).**
**The use of myeloid growth factors is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]**

Preferred Regimens
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[3]

Other Recommended Regimens
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[2]
- Carboplatin area under the curve (AUC) 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]

### PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC[e]:

**Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.**

Preferred Regimens
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[b,d,5]
- Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[b,d]
- Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[b,c,d,6]
- Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[b,c,d,6]

Other Recommended Regimens
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[7]
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[8]
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[9]
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[10]

Useful in Certain Circumstances
- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[11]
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[12]
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[13]

Footnotes (SCL-E 2 of 6)
Subsequent Systemic Therapy (SCL-E 3 of 6)
Response Assessment (SCL-E 4 of 6)
References (SCL-E 5 of 6)

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## FOOTNOTES

[a] Cisplatin contraindicated or not tolerated.
[b] Contraindications for treatment with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. For safety reasons, do not use ICIs in patients who have recently received tyrosine kinase inhibitors (TKIs).
[c] Included patients with asymptomatic untreated brain metastases.
[d] Maintenance immunotherapy with either atezolizumab or durvalumab should continue until progression or intolerable toxicity.
[e] For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).

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## SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[f,]
**Consider dose reduction or growth factor support for patients with PS 2.**

### CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS

<u>Preferred Regimens</u>
- Clinical trial enrollment
- Re-treatment with platinum-based doublet[g,34,35,37-39]

<u>Other Recommended Regimens</u>
- Lurbinectedin[17,36]
- Topotecan oral (PO) or intravenous (IV)[14-16,28]
- Irinotecan[h,21,28]

### CTFI ≤6 MONTHS

<u>Preferred Regimens</u>
- Clinical trial enrollment
- Lurbinectedin[17,36]
- Topotecan oral (PO) or intravenous (IV)[14-16,28,37]
- Irinotecan[h,21,28]
- Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[g,37,38,39]

<u>Other Recommended Regimens</u>
- Nivolumab or pembrolizumab (if not previously treated with an ICI)[b, 29,30,31,32,33]
- Paclitaxel[18,19]
- Temozolomide[22,23]
- Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Docetaxel[20]
- Gemcitabine[26,27,40]
- Oral etoposide[24,25]

[b] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. For safety reasons, do not use ICIs in patients who have recently received TKIs.
[f] Subsequent systemic therapy refers to second-line and beyond therapy..
[g] Rechallenging with the original regimen or similar platinum-based regimen, as shown on SCL-E 1, is recommended if there has been a CTFI of more than 6 months and may be considered if there has been a CTFI of at least 3 to 6 months.
[h] For patients with CNS disease, consider using irinotecan.

References (SCL-E 5 of 6)

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## PRINCIPLES OF SYSTEMIC THERAPY

**Response Assessment**

- **Limited stage**
  - **For patients receiving adjuvant therapy, response assessment is recommended only after completion of adjuvant therapy; do not repeat scans to assess response during adjuvant treatment.**
  - **Response assessment after adjuvant therapy involves C/A/P CT with contrast and brain MRI (preferred) with contrast or brain CT with contrast (SCL-6).**
  - **For patients receiving systemic therapy + concurrent RT, response assessment is recommended only after completion of initial therapy; do not repeat scans to assess response during initial treatment.**
  - **For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by C/A/P CT with contrast is recommended after every 2–3 cycles of systemic therapy and at completion of therapy.**

- **Extensive stage**
  - **During systemic therapy, response assessment by C/A/P CT with contrast is recommended after every 2–3 cycles of systemic therapy and at completion of therapy.**
  - **For patients with asymptomatic brain metastases receiving systemic therapy before brain RT, it is recommended that brain MRI (preferred) or CT with contrast is repeated after every 2 cycles of systemic therapy and at completion of therapy.**

- **Subsequent systemic therapy**
  - **Response assessment by C/A/P CT with contrast is recommended after every 2–3 cycles of systemic therapy.**

- **Transformed SCLC from NSCLC with an Oncogenic Driver**
  - **This is a rare population of patients with very limited data to guide treatment.[43,44,45,46]**
  - **Systemic cytotoxic chemotherapy is recommended using the NCCN Guidelines for Small Cell Lung Cancer.[43,44]**
  - **The role of immunotherapy in this setting is unclear based on limited data.[43,44,45,46]**
  - **If TKI is continued, ICI should be avoided, due to known toxicity.[41,42,45]**
  - **Consider referral to a center with experience managing transformed SCLC.**

References (SCL-E 5 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

## PRINCIPLES OF SYSTEMIC THERAPY – References


[1] Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641.

[2] Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116-1125.

[3] Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-271.

[4] Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). Ann Oncol 2001;12:1231-1238.

[5] Horn L, Mansfield A, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-2229.

[6] Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51-65.

[7] Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small cell lung cancer. J Clin Oncol 1999;17:3540-3545.

[8] Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol 2011;29:2215-2222.

[9] Niell HB, Herndon JE 2nd, Miller AA, et al. Randomized phase III Intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte-colony stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B trial 9732. J Clin Oncol 2005;23:3752-3759.

[10] Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol 1985;3:1471-1477.

[11] Schmittel A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. Ann Oncol 2006;17:663-667.

[12] Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91.

[13] Hanna N, Bunn Jr. PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24:2038-2043.

[14] von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-667.

[15] O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 2006;24:5441-5447.

[16] Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 2007;25:2086-2092.

[17] Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020;21:645-654.

[18] Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998;77:347-351.

[19] Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006;26:777-781.

[20] Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 1994; 30A:1058-1060.

[21] Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992;10:1225-1229.

[22] Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res 2012;18:1138-1145.

[23] Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. Lung Cancer 2014;86:237-240.

[24] Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. Semin Oncol 1990;17:32-35.


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## PRINCIPLES OF SYSTEMIC THERAPY – References


25 Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 1990;8:1613-1617.
26 Van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. Ann Oncol 2001;12:557-561.
27 Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol 2003;21:1550-1555.
28 Edelman MJ, Dvorkin M, Laktionov K, et al. Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer. Lung Cancer. 2022;166:135-142.
29 Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (Checkmate 032): a multicentre, open-label phase 1/2 trial. Lancet Oncol 2016;17:883-895.
30 Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. J Thorac Oncol 2020;15:426-435.
31 Chung HC, Lopez-Martin JA, Kao S, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158 [abstract]. J Clin Oncol 2018;36(Suppl): Abstract 8506.
32 Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab After Two or More Lines of Previous Therapy in Patients With Recurrent or Metastatic SCLC: Results From the KEYNOTE-028 and KEYNOTE-158 Studies J Thorac Oncol 2020;15:618-627.
33 Ott PA, Elez E, Hiret S, et al. Pembrolizumab in patients with extensive-stage small-cell lung cancer: results from the phase Ib KEYNOTE-028 study. J Clin Oncol 2017;35:3823-3829.
34 Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol 1987;23:1409-1411.
35 Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol 1987;23:1697-1699.
36 Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. Lung Cancer 2020;150:90-96.
37 Baize N, Monnet I, Greillier L, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2020;21:1224-1233.
38 Naito Y, Yamada K, Imamura Y, et al. Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer. Med Oncol 2018;35:61.
39 Genestreti G, Tiseo M, Kenmotsu H, et al. Outcomes of platinum-sensitive small-cell lung cancer patients treated with platinum/etoposide rechallenge: a multi-institutional retrospective analysis. Clin Lung Cancer 2015;16:e223-e228.
40 Hoang T, Kim K, Jaslowski A, et al. Phase II study of second-line gemcitabine in sensitive or refractory small cell lung cancer. Lung Cancer 2003;42:97-102.
41 Schoenfeld AJ, Arbour KC, Rizvi H, et al. Severe immune-related adverse events are common with sequential PD-(L)1 blockade and osimertinib. Ann Oncol 2019;30:839-844.
42 Oshima Y, Tanimoto T, Yuji K, Tojo A EGFR-TKI-associated interstitial pneumonitis in nivolumab-treated patients with non-small cell lung cancer JAMA Oncol 2018;4:1112-1115.
43 Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: Clinical outcomes. J Clin Oncol 2019;37:278-285.
44 Ferrer L, Giaj Levra M, Brevet M, et al. A brief report of transformation from NSCLC to SCLC: Molecular and therapeutic characteristics. J Thorac Oncol 2019;14:130-134.
45 Chai X, Zhang X, Li W, Chai J. Small cell lung cancer transformation during antitumor therapies: A systematic review. Open Med (Wars) 2021;16:1160-1167.
46 Zhang CY, Sun H, Su JW, et al. A potential treatment option for transformed small-cell lung cancer on PD-L1 inhibitor-based combination therapy improved survival. Lung Cancer 2023;175:68-78.


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## PRINCIPLES OF RADIATION THERAPY

**General Principles:**
- General principles of RT for lung cancer—including commonly used abbreviations; standards for clinical and technologic expertise and quality assurance; and principles of RT simulation, planning, and delivery—are provided in the NCCN Guidelines for Non-Small Cell Lung Cancer (NSCL-C) and are applicable to RT for SCLC.
- RT has a potential role in all stages of SCLC, as part of either definitive or palliative therapy. Radiation oncology input, as part of a multidisciplinary evaluation or discussion, should be provided for all patients early in the determination of the treatment strategy.
- To maximize tumor control and to minimize treatment toxicity, critical components of modern RT include appropriate simulation, accurate target definition, conformal RT (CRT) planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3D-CRT conformal RT. Multiple fields should be used, with all fields treated daily.
- Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4D-CT and/or FDG-PET/CT simulation, intensity-modulated RT (IMRT)/volumetric modulated arc therapy (VMAT), image-guided RT (IGRT), and motion management strategies. IMRT is preferred over 3D conformal EBRT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.[1] Quality assurance measures are essential and are covered in the NCCN Guidelines for Non-Small Cell Lung Cancer (NSCL-C).
- Useful references include the ASTRO Guidelines and the American Radium Society.[2,53,54]

**General Treatment Information:**
**Limited Stage:**
- In patients with clinical stage I–IIA (T1–2, N0, M0) who have undergone lobectomy and are found to have regional nodal involvement on final pathology, postoperative RT is recommended in pathologic N2 and may be considered in pathologic N1 stage, either sequentially or concurrently with chemotherapy. Principles of postoperative RT for NSCLC, including target volumes and doses, are recommended.
- Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT), to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC (see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C).[3-5]
- Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[6] RT should start early, with cycle 1 or 2 of systemic therapy (category 1).[7] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[8]
- Target definition: RT target volumes should be defined based on the pretreatment FDG-PET scan and CT scan obtained at the time of RT planning, as well as any positive biopsies. FDG-PET/CT is recommended, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, FDG-PET/CT should be obtained in the treatment position.

Limited Stage (continued), Extensive Stage (SCL-F 2 of 6)
Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation (SCL-F 3 of 6)
Brain Metastasis (SCL-F 4 of 6)

Note: All recommendations are category 2A unless otherwise indicated.
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Continued
References (SCL-F 5 of 6)

## PRINCIPLES OF RADIATION THERAPY

**Limited Stage (continued):**

- Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Several more modern series, both retrospective and prospective, suggest that omission of elective nodal irradiation (ENI) results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating FDG-PET staging/target definition (1.7%–3%).[10-15] ENI has been omitted in recent prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial). Inclusion of the ipsilateral hilum in the target volume, even if not grossly involved, differs between these trials but may be reasonable.
- In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.[12,16]
- Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established.
  - Based on the randomized phase III trial, INT 0096, 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).[17,18] When BID fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
  - Retrospective and randomized phase II studies suggest that similarly accelerated doses of 40–42 Gy in 3 weeks but given in once-daily fractionation produce similar outcomes as 45 Gy in 3 weeks in BID fractionation.[19,20]
  - If using once-daily conventionally fractionated RT, higher doses of 66–70 Gy are preferred. [21-24] Two randomized phase III trials did not demonstrate superiority of 66 Gy in 6.5 weeks/2 Gy daily (the European CONVERT trial) or 70 Gy in 7 weeks/2 Gy daily (CALGB 30610/RTOG 0538) over 45 Gy in 3 weeks/1.5 Gy BID, but overall survival and toxicity were similar.[25,26,27]
  - Recent randomized phase II trials suggest that higher dose accelerated RT of 60–65 Gy in 4–5 weeks given in BID or daily fractionation may produce increased overall or progression-free survival compared to 45 Gy in 3 weeks in BID fractionation.[28,29]

**Extensive Stage:**

- Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy before immunotherapy, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.[30,31] The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with ES-SCLC that responded to chemotherapy (without immunotherapy) demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.[32] Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.[33]
- Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions up to definitive dosing regimens in patients with a longer life expectancy.

Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation (SCL-F 3 of 6)
Brain Metastasis (SCL-F 4 of 6)

Continued

References (SCL-F 5 of 6)

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## PRINCIPLES OF RADIATION THERAPY

**Extensive Stage (continued):**
- Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach,[34,35] but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are limited data on optimal sequencing or safety). The benefit of thoracic RT in the context of chemo-immunotherapy is under evaluation in the RAPTOR/NRG LU007 trial.

**Normal Tissue Dose Constraints:**
- Normal tissue dose constraints depend on tumor size and location. For similar RT prescription doses, the normal tissue constraints used for NSCLC are appropriate (see NSCLC-C).
- When administering accelerated RT schedules (eg, BID) or lower total RT doses (eg, 45 Gy), more conservative constraints should be used. When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol should be used as a guide: ie, the maximum spinal cord dose should be limited to ≤41 Gy (including scatter irradiation) for a prescription of 45 Gy BID in 3 weeks and limited to ≤50 Gy for more protracted schedules.

**Prophylactic Cranial Irradiation:**
- In patients with limited-stage SCLC (LS-SCLC) who have a good response to initial therapy, PCI decreases brain metastases and increased overall survival[36,37] in meta-analyses of past clinical trials. Of note, none of the past studies that have been used as the basis for PCI recommendations in LS-SCLC employed MRI staging of the brain nor did any utilize FDG-PET scans for overall staging.
- The benefit of PCI is unclear in patients who have undergone definitive therapy for very early LS-SCLC, ie, pathologic stage I–IIA (T1–2,N0,M0).[9] These patients have a lower risk of developing brain metastases than patients with more advanced, LS-SCLC and may not benefit from PCI.[9] Brain MRI surveillance is recommended in patients not receiving PCI.[9] However, PCI may have a benefit in patients who are found to have pathologic stage IIB or III SCLC after complete resection.[9,37] This issue is being evaluated in the ongoing NCI cooperative group trial SWOG S1827/MAVERICK (brain MRI surveillance ± PCI), which includes the population undergoing surgical resection (https://clinicaltrials.gov/ct2/show/NCT04155034).
- In patients with ES-SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) found improved overall survival with PCI.[38] However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection.[39] Surveillance imaging for brain metastases is recommended for all patients regardless of PCI status.
- The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions. A shorter course (eg, 20 Gy in 5 fractions) may be appropriate in selected patients with extensive-stage disease. In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy.[40,41]
- Neurocognitive function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients >60 years experienced chronic neurotoxicity 12 months after PCI versus 56% of patients <60 years (*P* = .009).[41] PCI is not recommended in patients with poor PS or impaired neurocognitive function.[40] The role of PCI in MRI and FDG-PET staged SCLC in fit patients with normal neurocognitive function is the subject of ongoing debate, particularly in limited stage, and is being evaluated in the phase III SWOG S1827/MAVERICK trial comparing PCI (active comparator) to MRI surveillance (experimental) in both limited and extensive stage (https://clinicaltrials.gov/ct2/show/NCT04155034).

Brain Metastasis (SCL-F 4 of 6)

Continued

References (SCL-F 5 of 6)

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## PRINCIPLES OF RADIATION THERAPY

**Prophylactic Cranial Irradiation (continued):**
- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor PS or impaired neurocognitive functioning.
- When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases.[42] The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening (see NCCN Guidelines for Central Nervous System Cancers).
- Hippocampal-avoidance (HA) PCI using IMRT may be considered as a potential strategy to improve cognitive preservation. A phase III randomized trial of HA-WBRT versus conventional WBRT demonstrated improved cognitive preservation and patient-reported outcomes with HA-WBRT in patients with brain metastases from mixed histologies.[43] Conflicting data have been reported with HA-PCI versus conventional PCI in SCLC with one trial reporting no differences in cognition[44] and a separate trial reporting improved cognitive preservation with HA-PCI.[45] A larger randomized trial of HA-PCI versus conventional PCI, NRG CC003, has completed accrual with results pending.[46]
- An ongoing randomized trial, SWOG S1827/MAVERICK, is evaluating whether brain MRI surveillance alone is non-inferior to MRI surveillance plus PCI with regard to overall survival for LS-SCLC and ES-SCLC.[47]

**Brain Metastases:**
- Brain metastases have conventionally been treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS).[48] A current randomized trial, NRG CC009, is comparing SRS to hippocampal-sparing WBRT plus memantine in this setting.
- Recommended dose for WBRT is 30 Gy in 10 daily fractions. Consider adding memantine during and after RT (see Prophylactic Cranial Irradiation for memantine dosing).[42]
- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[49,50] SRS is preferred, if feasible.[51,52]
- For patients with a better prognosis (eg, ≥4 months), hippocampal-sparing WBRT using IMRT plus memantine is preferred because it produces less cognitive function failure than conventional WBRT plus memantine.[43] However, patients with metastases within 5 mm of the hippocampi, leptomeningeal metastases, and other high-risk features were not eligible for hippocampal-sparing WBRT on NRG CC001.[43] Although CC001 did not include patients with brain metastases from SCLC, it is reasonable to extrapolate the findings to SCLC.

**Palliative Radiation for Extracranial Metastases:**
- Common radiation dose-fractionation regimens (eg, 30 Gy in 10 fractions, 20 Gy in 5 fractions, 8 Gy in 1 fraction) used for palliation of other solid tumors are appropriate for palliation of SCLC metastases in most patients.
- Conformal techniques, such as IMRT, and/or higher dose intensity approaches, including SABR or SRS, may be appropriate in selected patients (eg, tumors with close proximity to organs at risk, re-irradiation, or better prognosis).

References (SCL-F 5 of 6)

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## PRINCIPLES OF RADIATION THERAPY – References


[1] Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. J Clin Oncol 2017;35:56-62.

[2] Simone CB 2nd, Bogart JA, Cabrera AR, et al. Radiation Therapy for Small Cell Lung Cancer: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2020;10:158-173.

[3] Shioyama Y, Onishi H, Takayama K, et al. Clinical outcomes of stereotactic body radiotherapy for patients with stage I small-cell lung cancer: Analysis of a subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database. Technol Cancer Res Treat 2018;17:1533033818783904.

[4] Verma V, Simone CB 2nd, Allen PK, Lin SH. Outcomes of stereotactic body radiotherapy for T1-T2N0 small cell carcinoma according to addition of chemotherapy and prophylactic cranial irradiation: a multicenter analysis. Clin Lung Cancer 2017;18:675-681.e1.

[5] Verma V, Simone CB 2nd, Allen PK, et al. Multi-institutional experience of stereotactic ablative radiation therapy for stage I small cell lung cancer. Int J Radiat Oncol Biol Phys 2017;97:362-371.

[6] Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054-3060.

[7] Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4837-4845.

[8] De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. J Clin Oncol 2006;24:1057-1063.

[9] Yang Y, Zhang D, Zhou X, et al. Prophylactic cranial irradiation in resected small cell lung cancer: A systematic review with meta-analysis. J Cancer 2018;9:433-439.

[10] De Ruysscher D, Bremer RH, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. Radiother Oncol 2006;80:307-312.

[11] van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. Int J Radiat Oncol Biol Phys 2010;77:329-336.

[12] Hu X, Bao Y, Xu YJ, et al. Final report of a prospective randomized study on thoracic radiotherapy target volume for limited-stage small cell lung cancer with radiation dosimetric analyses. Cancer 2020;126:840-849.

[13] Shirvani SM, Komaki R, Heymach JV, et al. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;82:e91-97.

[14] Xia B, Chen GY, Cai XW, et al. Is involved-field radiotherapy based on CT safe for patients with limited-stage small-cell lung cancer? Radiother Oncol 2012;102:258-262.

[15] Colaco R, Sheikh H, Lorigan P, et al. Omitting elective nodal irradiation during thoracic irradiation in limited-stage small cell lung cancer - Evidence from a phase II trial. Lung Cancer 2012;76:72-77.

[16] Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small-cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. J Clin Oncol 1994;12:496-502.

[17] Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-271.

[18] Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;59:943-951.

[19] Grønberg, BH, Halvorsen TO, Fløtten Ø, et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta Oncol 2016;55:591-597.

[20] Turgeon GA, Souhami L, Kopek N, et al. Thoracic irradiation in 3 weeks for limited-stage small cell lung cancer: Is twice a day fractionation really needed? Cancer Radiother 2017;21:89-98.

[21] Choi NC, Herndon JE 2nd, Rosenman J, et al. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. J Clin Oncol 1998;16:3528-3536.

[22] Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;56:355-359.

[23] Roof KS, Fidias P, Lynch TJ, et al. Radiation dose escalation in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;57:701-708.

[24] Bogart JA, Herndon JE, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys 2004;59:460-468.

[25] Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116-1125.

[26] Bogart JA, Wang XF, Masters GA, et al. High-dose once-daily thoracic radiotherapy in limited-stage small-cell lung cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2023;41:2394-2402.


**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

## PRINCIPLES OF RADIATION THERAPY – References


[27] Ganti A, Dueck AC, Fruth B, et al. Comparison of quality of life in patients randomized to high-dose once daily (QD) thoracic radiotherapy (TRT) with standard twice daily (BID) TRT in limited stage small cell lung cancer (LS-SCLC) on CALGB 30610 (Alliance, Sub-study CALGB 70702) [abstract]. J Clin Oncol 2022;40:8504.

[28] Grønberg BH, Killingberg KT, Fløtten Ø, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol 2021;22:321-331.

[29] Qiu B, Li QW, Liu JL, et al. Moderately hypofractionated once-daily compared with twice-daily thoracic radiation therapy concurrently with etoposide and cisplatin in limited-stage small-cell lung cancer: a multi-center, Phase II, randomized trial. Int J Radiat Oncol Biol Phys 2021;111:424-435.

[30] Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol 1999;17:2092-2099.

[31] Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. Radiother Oncol 2012;102:234-238.

[32] Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42.

[33] Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer-Authors' reply. Lancet 2015;385:1292-1293.

[34] Horn L, Mansfield A, Szczęsna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-2229.

[35] Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet 2019;394:1929-1939.

[36] Arriagada R, Le Chevalier T, Rivière A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. Ann Oncol 2002;13:748-754.

[37] Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-484.

[38] Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-672.

[39] Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-671.

[40] Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 2009;10:467-474.

[41] Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:77-84.

[42] Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;10:1429-1437.

[43] Brown P, Gondi V, Pugh S, et al. Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. J Clin Oncol 2020;38:1019-1029.

[44] Belderbos JSA, De Ruysscher DKM, De Jaeger K, et al. Phase 3 randomized trial of prophylactic cranial irradiation with or without hippocampus avoidance in SCLC (NCT01780675). J Thorac Oncol 2021;16:840-849.

[45] Rodriguez De Dios N, Murica M, Counago F, et al. Phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer. Int J Radiat Oncol Biol Phys 2019;105:S35-S36.

[46] Gondi V, Pugh SL, Mehta MP, et al. NRG Oncology CC003: A randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer. J Clin Oncol 2019;37:TPS 8578-TPS 8578.

[47] SWOG S1827 (MAVERICK) Testing whether the use of brain scans alone instead of brain scans plus preventive brain radiation affects lifespan in patients with small cell lung cancer. https://clinicaltrials.gov/ct2/show/NCT04155034

[48] Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of first-line radiosurgery vs whole-brain radiotherapy for small cell lung cancer brain metastases: the FIRE-SCLC cohort study. JAMA Oncol 2020;6:1028-1037.

[49] Sadikov E, Bezjak A, Yi QL, et al. Value of whole brain re-irradiation for brain metastases--single centre experience. Clin Oncol (R Coll Radiol) 2007;19:532-538.

[50] Son CH, Jimenez R, Niemierko A, et al. Outcomes after whole brain reirradiation in patients with brain metastases. Int J Radiat Oncol Biol Phys 2012;82:e167-172.

[51] Harris S, Chan MD, Lovato JF, et al. Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:e53-e59.

[52] Wegner RE, Olson AC, Kondziolka D, et al. Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e21-e27.

[53] Chun SG, Simone CB 2nd, Amini A, et al. American Radium Society Appropriate Use Criteria: Radiation Therapy for Limited-Stage SCLC 2020. J Thorac Oncol 2021;16:66-75.

[54] Higgins KA, Simone CB 2nd, Amini A, et al. American Radium Society Appropriate Use Criteria on Radiation Therapy for Extensive-Stage SCLC. J Thorac Oncol 2021;16:54-65.


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***Table 1*** **- Definition of small cell lung cancer consists of two stages:**
(1) Limited-stage: Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
(2) Extensive-stage: Stage IV (T any, N any, M 1a/b/c), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

***Table 2*** **- American Joint Committee on Cancer (AJCC) Eighth ed., 2017 Definitions of TNM**

| **T** | | **Primary Tumor** |
|---|---|---|
| **TX** | | 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 |
| **T0** | | No evidence of primary tumor |
| **Tis** | | Carcinoma *in situ*<br>Squamous cell carcinoma *in situ* (SCIS)<br>Adenocarcinoma *in situ* (AIS): adenocarcinoma with pure lepidic pattern, ≤3 cm in greatest dimension |
| **T1** | | Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) |
| | T1mi | Minimally invasive adenocarcinoma: adenocarcinoma (≤3 cm in greatest dimension) with a predominantly lepidic pattern and ≤5 mm invasion in greatest dimension |
| | T1a | Tumor ≤1 cm in greatest dimension. A superficial, spreading tumor of any size whose invasive component is limited to the bronchial wall and may extend proximal to the main bronchus also is classified as T1a, but these tumors are uncommon. |
| | T1b | Tumor >1 cm but ≤2 cm in greatest dimension |
| | T1c | Tumor >2 cm but ≤3 cm in greatest dimension |
| **T2** | | Tumor >3 cm but ≤5 cm or having any of the following features: (1) Involves the main bronchus, regardless of distance to the carina, but without involvement of the carina; (2) Invades visceral pleura (PL1 or PL2); (3) Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, involving part or all of the lung. T2 tumors with these features are classified as T2a if ≤4 cm or if the size cannot be determined and T2b if >4 cm but ≤5 cm. |
| | T2a | Tumor >3 cm but ≤4 cm in greatest dimension |
| | T2b | Tumor >4 cm but ≤5 cm in greatest dimension |
| **T3** | | Tumor >5 cm but ≤7 cm in greatest dimension or directly invading any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or separate tumor nodule(s) in the same lobe as the primary |
| **T4** | | Tumor >7 cm or tumor of any size invading one or more of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, or carina; separate tumor nodule(s) in an ipsilateral lobe different from that of the primary |

**Continued**

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*Table 2.* **Definitions for T, N, M (continued)**

| N | Regional Lymph Nodes |
|---|---|
| NX | Regional lymph nodes cannot be assessed |
| N0 | No regional lymph node metastasis |
| N1 | Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension |
| N2 | Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s) |
| N3 | Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s) |

| M | | Distant Metastasis |
|---|---|---|
| MX | | Distant metastasis cannot be assessed |
| M0 | | No distant metastasis |
| M1 | | Distant metastasis |
| | M1a | Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion[a] |
| | M1b | Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node) |
| | M1c | Multiple extrathoracic metastases in a single organ or in multiple organs |

*Table 3.* **AJCC Prognostic Groups**

| | T | N | M |
|---|---|---|---|
| **Occult carcinoma** | TX | N0 | M0 |
| **Stage 0** | Tis | N0 | M0 |
| **Stage IA1** | T1mi | N0 | M0 |
| | T1a | N0 | M0 |
| **Stage IA2** | T1b | N0 | M0 |
| **Stage IA3** | T1c | N0 | M0 |
| **Stage IB** | T2a | N0 | M0 |
| **Stage IIA** | T2b | N0 | M0 |
| **Stage IIB** | T1a | N1 | M0 |
| | T1b | N1 | M0 |
| | T1c | N1 | M0 |
| | T2a | N1 | M0 |
| | T2b | N1 | M0 |
| | T3 | N0 | M0 |
| **Stage IIIA** | T1a | N2 | M0 |
| | T1b | N2 | M0 |
| | T1c | N2 | M0 |
| | T2a | N2 | M0 |
| | T2b | N2 | M0 |
| | T3 | N1 | M0 |
| | T4 | N0 | M0 |
| | T4 | N1 | M0 |

**Prognostic Stage Groups**

| | T | N | M |
|---|---|---|---|
| **Stage IIIB** | T1a | N3 | M0 |
| | T1b | N3 | M0 |
| | T1c | N3 | M0 |
| | T2a | N3 | M0 |
| | T2b | N3 | M0 |
| | T3 | N2 | M0 |
| | T4 | N2 | M0 |
| **Stage IIIC** | T3 | N3 | M0 |
| | T4 | N3 | M0 |
| **Stage IV** | Any T | Any N | M1 |
| **Stage IVA** | Any T | Any N | M1a |
| | Any T | Any N | M1b |
| **Stage IVB** | Any T | Any N | M1c |

[a] Most pleural (pericardial) effusions with lung cancer are a result of the tumor. In a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and not an exudate. If these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

## ABBREVIATIONS

| | |
|---|---|
| ACTH | adrenocorticotropic hormone |
| AIS | adenocarcinoma in situ |
| ANNA-1 | antineuronal nuclear antibody-type 1 (also known as anti-Hu antibody) |
| AUC | area under the curve |
| BUN | blood urea nitrogen |
| C/A/P | chest/abdomen/pelvis |
| CBC | complete blood count |
| CNS | central nervous system |
| CONVERT | concurrent once-daily versus twice-daily radiotherapy |
| CREST | carotid revascularization endarterectomy versus Stenting Trial |
| CRT | conformal radiation therapy |
| CTFI | chemotherapy-free interval |
| EBRT | external beam radiation therapy |
| ENI | elective nodal irradiation |
| ES-SCLC | extensive-stage small cell lung cancer |
| 4D-CT | four-dimensional computed tomography |
| FDG | fluorodeoxyglucose |
| G-CSF | granulocyte colony-stimulating factor |
| GM-CSF | granulocyte-macrophage colony-stimulating factor |
| GTV | gross tumor volume |
| H&E | hematoxylin and eosin |
| H&P | history and physical |
| HA | hippocampal avoidance |
| ICIs | immune checkpoint inhibitors |
| IGRT | image-guided radiation therapy |
| IMRT | intensity-modulated radiation therapy |
| INSM1 | insulinoma-associated protein 1 |
| LCNEC | large-cell neuroendocrine carcinoma |
| LEMS | Lambert-Eaton myasthenic syndrome |
| LFT | liver function test |
| LS-SCLC | limited-stage small cell lung cancer |
| NSCLC | non-small cell lung cancer |
| PCI | prophylactic cranial irradiation |
| PD-1 | programmed cell death protein 1 |
| PD-L1 | programmed death ligand 1 |
| PFT | pulmonary function test |
| PS | performance status |
| RBC | red blood cell |
| SABR | stereotactic ablative radiotherapy |
| SBRT | stereotactic body radiation therapy |
| SCIS | squamous cell carcinoma in situ |
| SCLC | small cell lung cancer |
| SER | start of any therapy to the end of RT |
| SIADH | syndrome of inappropriate antidiuretic hormone secretion |
| SRS | stereotactic radiosurgery |
| SRT | stereotactic radiation therapy |
| SVC | superior vena cava |
| 3D | three dimensional |
| TKIs | tyrosine kinase inhibitors |
| TNM | tumor node metastasis |
| TTF-1 | thyroid transcription factor-1 |
| VMAT | volumetric modulated arc therapy |
| WBRT | whole brain radiation therapy |

| NCCN Categories of Evidence and Consensus | |
|---|---|
| **Category 1** | Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2A** | Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate. |
| **Category 2B** | Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate. |
| **Category 3** | Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate. |

All recommendations are category 2A unless otherwise indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

**Note: All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

# Discussion

This discussion corresponds to the NCCN Guidelines for Small Cell Lung Cancer. Last updated: November 21, 2023

## Table of Contents

## Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; of which nearly 14% are small cell lung cancer (SCLC).[1-3] In 2023, an estimated 33,000 new cases of SCLC were diagnosed in the United States.[1,2,4] During the COVID-19 pandemic, the diagnosis and treatment of lung cancer were hampered; however, this has not been reflected in the 2023 estimates for incidence and mortality because of the typical delays in collecting, calculating, and reporting of data.[1] Although the incidence of SCLC has been decreasing, the frequency in females is increasing and the male-to-female incidence ratio is now 1:1.[1-3]

Nearly all cases of SCLC are attributable to cigarette smoking.[5] Patients with SCLC who also continue to smoke tobacco during treatment have increased toxicity and shorter survival.[6] Therefore, tobacco smoking cessation counseling and intervention should be strongly promoted in patients with SCLC and other high-grade neuroendocrine carcinomas (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[7] Patients who previously smoked tobacco should be strongly encouraged to remain abstinent. Programs using behavioral counseling combined with U.S. Food and Drug Administration (FDA)-approved medications that promote smoking cessation can be very useful.

SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present with limited disease confined to the chest. Although 95% of small cell carcinomas originate in the lung, they can also arise from extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract.[8,9] Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior with increased potential for widespread metastases. Management of SCLC is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer that includes the algorithm and this supporting Discussion text. Management of other lung neuroendocrine tumors (LNTs) and Non-Small Cell Lung Cancer (NSCLC) are described in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors and Non-Small Cell Lung Cancer, respectively, available at www.NCCN.org.

The definitions for limited-stage and extensive-stage SCLC incorporate TNM staging (see the algorithm and *Staging* in this Discussion). The panel recommends that the workup for SCLC should be expedited and if possible, studies should be performed in parallel. In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiation therapy (RT). However, some patients with resectable tumors (stage I–IIA) are eligible for curative surgery followed by systemic therapy with or without mediastinal RT.[10,11] The panel recommends multidisciplinary evaluation before any surgery. In other patients with stage I–IIA SCLC, including medically inoperable circumstances or when the decision not to pursue surgical resection is made, stereotactic ablative radiotherapy (SABR) followed by systemic therapy is an option.[12-17] The benefits of prophylactic cranial irradiation (PCI) are unclear in patients with stage I SCLC (T1–2a, N0, M0) who have received definitive therapy. The NCCN Panel recommends that MRI brain surveillance be considered for all patients with limited-stage SCLC who do not receive PCI. In most patients with extensive-stage SCLC, systemic therapy with or without RT can palliate symptoms and prolong survival; however, long-term survival is rare.[18] SCLC is highly sensitive to initial chemotherapy and RT; however, most patients eventually die of recurrent disease.[19] Despite recent advances, the recommended therapy options for SCLC need improvement. Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Thus, participation in clinical trials is strongly encouraged.

## Guidelines Update Methodology

The NCCN Guidelines® for Small Cell Lung Cancer were originally published in 1996 and have been subsequently updated at least once every year.[20] The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

## Literature Search Criteria

Prior to the update of the NCCN Guidelines for Small Cell Lung Carcinoma, an electronic search of the PubMed database was performed to obtain key literature in SCLC using the following search term: *(small cell lung cancer OR small cell carcinoma lung) NOT (non-small)*. The PubMed database was chosen because it is the most widely used resource for medical literature and it indexes peer-reviewed biomedical literature.

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 1; Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Practice Guidelines; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these NCCN Guidelines and discussed by the NCCN SCLC Panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

## Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[21] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in subsequent analyses.

## Diagnosis

### Screening

Ideally, a screening test should detect disease at an early stage when it is still curable. The National Lung Screening Trial reported that screening with annual, low-dose, spiral CT scans detected early-stage NSCLC and decreased lung cancer-specific mortality in asymptomatic high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).[22] Low-dose CT is probably not useful for SCLC screening because symptomatic disease can develop between annual scans due to the aggressive nature of the disease; thereby limiting the potential reduction of mortality through screening.[22-25]

### Manifestations

Patients with SCLC typically present with a large hilar mass and bulky mediastinal lymphadenopathy that causes cough and dyspnea.[26] Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. The *Signs and Symptoms of Small Cell Lung Cancer* section in the algorithm lists the manifestations based on tumor location and type of metastases. It is uncommon for patients to present with a solitary peripheral nodule without central adenopathy. In this situation, fine-needle aspiration (FNA) may not adequately differentiate small cell carcinoma (which is a high-grade neuroendocrine carcinoma) from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or large-cell neuroendocrine carcinoma (LCNEC) (which is also a high-grade neuroendocrine carcinoma) (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).[27,28]

Many neurologic and endocrine paraneoplastic syndromes, including Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy, are associated with SCLC.[29-31] Given the occurrence of paraneoplastic neurologic syndromes in individuals with SCLC, the panel recommends considering early subspecialty consultation for most recent management in v1.2024. Patients with Lambert-Eaton Myasthenic Syndrome present with proximal leg weakness that is caused by antibodies directed against the voltage-gated calcium channels.[32,33] Paraneoplastic encephalomyelitis and sensory neuropathy-related neurologic deficits are caused by the production of an antibody (anti-*Hu*) that cross-reacts with both small cell carcinoma antigens and human neuronal RNA-binding proteins. Paraneoplastic encephalomyelitis may precede a diagnosis of SCLC.[34] The NCCN SCLC Panel recommends considering a comprehensive paraneoplastic antibody panel and/or neurologic consultation if neurologic paraneoplastic syndrome is suspected.

SCLC tumors sometimes produce polypeptide hormones, including vasopressin and adrenocorticotropic hormone that cause syndrome of inappropriate ADH secretion (SIADH) and Cushing syndrome, respectively.[35,36] In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Primary treatment for SIADH includes fluid restriction (which is difficult for patients because of increased thirst) and demeclocycline. Cancer treatment (eg, cisplatin) and/or supportive care (eg, opiates) may also cause hyponatremia.[37] Hyponatremia usually improves after successful treatment of SCLC. However, vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) can be used for refractory hyponatremia (see *Principles of Supportive Care* in the algorithm).[37-39]

## Pathology

SCLC is a poorly differentiated malignant epithelial tumor that is categorized as a high-grade neuroendocrine carcinoma.[27,40] Up to 30% of tumors from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma).[41] This finding is more common in patients who have received previous treatment. The classic and distinctive histology on hematoxylin and eosin (H&E), including small blue cells with scant cytoplasm, high nuclear/cytoplasmic ratio, fine granular nuclear chromatin, and absent or inconspicuous nucleoli, may be sufficient for identifying SCLC in good-quality histologic samples.[27,42] The mitotic count is high in SCLC compared with the count in atypical and typical carcinoids. However, mitotic figures are difficult to count in small biopsy samples with crushed or necrotic cells. In such samples immunohistochemistry is useful.[43] In cases of diagnostic dilemma, including carcinoids, the panel strongly recommends getting a second opinion with a pathologist specializing in diagnosis of thoracic malignancies.

Using immunohistochemistry as one of the tools to diagnose and distinguish SCLC from NSCLC or other neuroendocrine tumors is important; especially because these cancer types have different treatment recommendations. [27,43-47] Ki-67 is useful for distinguishing SCLC from carcinoid tumors.[43,47-49] Nearly all SCLCs are immunoreactive for cytokeratin (AE1/Ae3, CAM5.2) and 85% to 90% of SCLCs are positive for thyroid transcription factor-1 (TTF-1).[27,50-52] Most SCLCs (~95%) stain positively for markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), chromogranin A, NCAM (CD56), and synaptophysin.[27,53,54] However, at least one of these neuroendocrine markers will be immunoreactive in approximately 10% of NSCLCs and therefore cannot be used alone to distinguish SCLC from NSCLC.[55] Napsin A (adenocarcinoma marker) and p40 (or p63, squamous cell carcinoma marker) are generally negative in SCLC and useful for distinguishing SCLC from poorly differentiated NSCLC and combined SCLC.[56] However, p40 (or p63) can be focally positive in SCLC. For the v1.2024 update, the panel clarified that molecular profiling may be considered in rare cases, particularly for patients with extensive-stage/relapsed SCLC who have never smoked or lightly smoked, remote smoking history, for diagnostic/pathologic dilemma, or at time of relapse if not done previously because this may change management.[57-62]

The WHO classification recognizes two types of SCLC: pure and combined SCLC.[47,58,63-66] Combined SCLC, which consists of both SCLC and NSCLC histology (squamous cell, adenocarcinoma, spindle/pleomorphic, and/or large cell carcinoma), is more frequent in patients with limited-stage SCLC.[47,58,65,67] Any presence of NSCLC histology (no minimal percentage) results in a classification of combined SCLC. The only exception is combined SCLC and LCNEC where at least 10% of the tumor should show LCNEC morphology.[41,68] Patients with combined SCLC are treated using regimens for SCLC, because it is the more aggressive cancer.[68] Patients with NSCLC can also transform to SCLC after treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors or immune checkpoint inhibitors.[69,70]

## Evaluation

### Staging Systems

The Veterans Administration (VA) Lung Study Group's 2-stage classification scheme has historically been used to define the extent of disease in patients with SCLC: 1) limited-stage is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage is disease beyond the ipsilateral hemithorax, including malignant pleural/pericardial effusion or hematogenous metastases.[71] Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage SCLC, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial and treatment is individualized.[19,72,73] Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. Most studies use the VA definitions of limited-stage or extensive-stage SCLC, for clinical decision-making. However, the TNM system is useful for selecting patients with T1–2, N0 disease who are eligible for surgery and RT.[72] The American Joint Committee on Cancer (AJCC) revised the TNM staging system (8$^{th}$ edition) for lung cancer in 2017 (see *Staging* in the algorithm).[74,75] Clinical research studies that include use of the TNM system will allow for more precise assessments of prognosis and specific therapy.[74]

The NCCN SCLC Panel adopted a combined approach of using both the AJCC TNM staging system and the older VA scheme for SCLC staging.[19,72] *Limited-stage* SCLC is defined as stage I to III (T any, N any, M0) that can be safely treated with definitive RT. This excludes T3–4 due to multiple extensive lung nodules or disease with tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan (see Table 1 in the algorithm). *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3–4 as previously described.

**Initial Evaluation**

The workup for SCLC should be expedited with studies done in parallel whenever possible. Staging should not delay the onset of treatment for more than 1 week because of the aggressive nature of SCLC. Many patients may become more seriously ill in the interval, with a significant decline in their performance status (PS). Staging primarily provides a therapeutic guideline for thoracic RT for patients with limited-stage SCLC. For v1.2024, the panel recommends integration of palliative care so that management of cancer-related symptoms and goals of care are discussed during initial evaluation.

The initial diagnostic evaluation includes a history and physical examination; pathology review; clinical laboratory tests; CT scan with intravenous contrast of the chest/abdomen/pelvis; and MRI (preferred) or CT scan with intravenous contrast for brain imaging.[73,76] An FDG-PET/CT scan (skull base to mid-thigh), which is superior to PET alone, is recommended to clarify the extent of disease if needed.[19,72,77] For most metastatic sites, FDG-PET/CT is superior to CT imaging; however, FDG-PET/CT is inferior to MRI (or contrast-enhanced CT as an alternative when MRI is not possible) for the detection of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[78] FDG-PET scans can also increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.[77,79,80] Approximately 19% of patients who undergo FDG-PET are upstaged from limited-stage to extensive-stage SCLC, whereas 8% are down staged from extensive-stage to limited-stage SCLC.[73] Although FDG-PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for FDG-PET/CT-detected lesions. Additionally, FDG-PET staging altered the planned radiation field because of improved detection of intrathoracic disease sites in approximately 27% of patients.[73,80,81]

Once a patient has been found to have extensive-stage SCLC, further staging is optional, except for brain imaging.[19] Brain imaging (preferably MRI or CT with contrast) can identify central nervous system (CNS) metastases in 10% to 15% of patients at diagnosis, of which approximately 30% are asymptomatic. Therefore, staging should not focus only on sites of symptomatic disease or on sites suggested by laboratory tests. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the usefulness of early diagnosis in asymptomatic patients.

Bone imaging with radiographs or MRI can be performed if FDG-PET/CT is equivocal or not available; bone biopsy can be further considered if bone imaging is also equivocal. Bone scans are positive in up to 30% of patients without bone pain or without abnormal alkaline phosphatase levels. However, less than 5% of patients have bone marrow involvement as the only site of extensive-stage SCLC. Unilateral bone marrow aspirates and biopsies may be indicated in select patients with no other evidence of metastatic disease, with nucleated red blood cells on peripheral blood smear and neutropenia, or thrombocytopenia suggestive of bone marrow infiltration.

Before surgical resection in patients with clinical limited stage I–IIA SCLC (T1–2, N0, M0), pathologic mediastinal staging is recommended to confirm FDG-PET/CT scan results and rule out occult nodal disease.[19] To help determine RT fields, mediastinal staging can be considered for clinical stage IIB–IIIC SCLC (T1–4, N0, M0; T1-4, N1-3, M0), especially for those with clinical N0 disease. Invasive mediastinal staging can be performed either by conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound-guided FNA (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), or video-assisted thoracic surgery (VATS).[82,83] If the endoscopic lymph node biopsy is positive, then additional mediastinal staging is not recommended.

Thoracentesis with cytologic analysis is recommended if pleural effusion is large enough to be safely accessed via ultrasound guidance. If thoracentesis does not show malignant cells, then thoracoscopy can be considered to document pleural involvement, which is suggestive of extensive-stage SCLC. The effusion should be excluded as a staging element if: 1) multiple cytopathologic examinations of the pleural fluid are negative for cancer; 2) the fluid is not bloody and not an exudate; and 3) clinical judgment concludes that the effusion is not directly related to the cancer. Pericardial effusions are classified using the same criteria.

## Prognostic Factors

Poor PS (3–4), extensive-stage SCLC, weight loss, and markers, such as lactate dehydrogenase (LDH), associated with bulky disease are the most important adverse prognostic factors. Age <70 years, normal LDH, and stage I disease are associated with favorable prognosis in patients with limited-stage SCLC. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage SCLC.[84,85]

## Treatment

Surgery is only recommended for certain patients with stage I–IIA SCLC; with only about 5% of patients eligible for surgery. Concurrent chemoradiation or SABR is recommended for patients with limited-stage I–IIA (T1–2, N0) SCLC who are medically inoperable or do not want to pursue surgical resection (see *Systemic Therapy, Radiation Therapy,* and *SABR* in this Discussion). Systemic therapy alone (with or without palliative RT) is recommended for patients with extensive-stage SCLC.

### Surgical Resection of Stage I to IIA SCLC

The *Principles of Surgical Resection* for SCLC are described in the algorithm and the studies supporting these recommendations are described in this section. Most of the data regarding the role of surgery in SCLC are from retrospective studies.[86-91] These studies report favorable 5-year survival rates of 40% to 60% in patients with stage I disease. In most series, survival rates decline significantly in patients with advanced disease with lymph node involvement. Therefore, the general recommendation for surgery is restricted to certain patients with stage I–IIA disease (T1–2, N0, M0). Fewer than 5% of patients with SCLC have true stage I–IIA disease.[92] Analyses of the SEER database suggest that surgery is appropriate for some patients with localized disease.[17,93] However, retrospective studies and analyses of the SEER database are limited by the lack of information on chemotherapy. In addition, comparison of the survival of surgical patients to those who did not undergo surgery is inherently flawed by selection bias. Ultimately, the role of surgery in SCLC will not be fully delineated until prospective trials in patients who are rigorously staged compare surgery plus adjuvant chemotherapy versus concurrent chemoradiotherapy.

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[94] Patients with limited-stage SCLC, excluding those with solitary peripheral nodules, that responded to 5 cycles of chemotherapy with cyclophosphamide, doxorubicin, and vincristine (CAV) were randomly assigned to undergo thoracic RT with or without resection. The overall survival rates of patients on the two arms were equivalent, suggesting no benefit to surgery in this setting. However, only 19% of enrolled patients had clinical limited stage I (T1–2, N0, M0) disease. Data show that patients with SCLC who have nodal disease (ie, T1–3, N1–3, M0–1) do not benefit from surgery.[94]

The NCCN Panel recommends that in patients who do not smoke tobacco, small lesions—that are presumed to be small cell carcinoma on biopsy—should be resected because they are likely carcinoids that have been misdiagnosed (see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org). The NCCN SCLC Panel also recommends surgery for certain patients with clinical stage I to IIA (T1–2, N0) SCLC with negative mediastinal lymph nodes that have been confirmed by mediastinal staging.[15,86,95] Surgery can include patients with clinical limited stage IIA SCLC based on the staging criteria that includes tumors up to 5 cm in diameter (T2b) without lymph node involvement (N0). The NCCN Panel added recommendations for patients who did not have a preoperative biopsy but have an intraoperative diagnosis of likely SCLC. If resection is performed, the NCCN SCLC Panel recommends lobectomy (preferred) with mediastinal lymph node dissection or systematic lymph node sampling (eg, ≥3 N2 and ≥1 N1 stations). The panel does not recommend pneumonectomy if nodal metastatic disease needs to be encompassed or under other circumstances. Chemoradiation is the preferred alternative over any resection requiring pneumonectomy.

Following surgery, adjuvant chemotherapy or chemoradiation is recommended based on the absence or presence of nodal metastases for patients with limited stage I to IIA (T1–2, N0) SCLC with negative margins (R0 resection) (see *Systemic Therapy* in this Discussion).[89,96-98] Adjuvant chemotherapy alone is recommended for patients without nodal metastases (N0). Concurrent or sequential chemotherapy and postoperative mediastinal RT are recommended for patients with N+ disease (see *Adjuvant Treatment* in the algorithm). Although panel members agree that postoperative mediastinal RT is recommended for nodal metastases, it should be based on the extent of nodal sampling/dissection and extent of nodal positivity; however, there are no data to support this recommendation. The benefit of PCI is unclear in patients with pathologic stage I (T1–2a, N0, M0) who have had definitive therapy (see *Prophylactic Cranial Irradiation* in this Discussion and *Adjuvant Treatment* in the algorithm).[99,100] For patients with limited stage I–IIA (T1–2, N0) SCLC with positive margins (R1/R2 resection), the panel recommends concurrent chemoradiation following surgery. The NCCN SCLC Panel recommends response assessment following adjuvant therapy to establish new disease baseline.

## Systemic Therapy

For all patients with SCLC, systemic therapy is an essential component of appropriate treatment (see *Principles of Systemic Therapy* in the algorithm). The NCCN SCLC Panel has preference stratified the adjuvant, first-line, and subsequent therapy options for patients with SCLC into 1) *Preferred*, 2) *Other recommended*, and 3) *Useful under certain circumstances*.

Adjuvant chemotherapy is recommended for patients with early-stage SCLC who have had surgery or SABR. For patients with limited-stage SCLC who are not eligible for surgery or SABR, chemotherapy with concurrent thoracic RT (category 1 for patients with PS 0–2) is the recommended primary treatment.[11,101,102] For patients with extensive-stage SCLC, systemic therapy alone is recommended. RT may be used in select patients for palliation of symptoms (see NCCN Guidelines for Palliative Care, available at www.NCCN.org). These options are rationalized based on studies described in the following sections.

### *Cisplatin Versus Carboplatin*

Randomized trials in a small number of patients with SCLC and retrospective analysis of patients with extensive-stage SCLC suggest similar efficacy between cisplatin and carboplatin regimens.[103-105] In a meta-analysis of 663 patients with limited-stage SCLC (32%) and extensive-stage SCLC (68%), no significant difference was observed in response rate (67% vs. 66%), progression-free survival (PFS) (5.5 vs. 5.3

months), or overall survival (9.6 vs. 9.4 months) between cisplatin- versus carboplatin-containing regimens.[106] Carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.[107] However, the use of carboplatin carries a greater risk of myelosuppression.[107]

***Limited-Stage SCLC***

Adjuvant chemotherapy alone is recommended for patients who have undergone surgical resection (N0) or SABR for early-stage SCLC (see *Principles of Systemic Therapy* in the algorithm). However, most patients with limited-stage SCLC are not eligible for surgery or SABR. Etoposide plus cisplatin is the most commonly used first-line combination chemotherapy regimen for patients with limited-stage SCLC.[108,109] Etoposide plus cisplatin replaced alkylator plus anthracycline-based regimens based on its superiority in both efficacy and toxicity.[110-112] If pathologic lymph node involvement is found at surgery (N1 or N2) for patients with stage I–IIA (T1–2, N0, M0), then thoracic RT can be added concurrently or sequentially to etoposide/cisplatin. Treatment with etoposide/cisplatin plus definitive thoracic RT showed response rates of 70% to 90% with a median overall survival of 25 to 30 months and 5-year overall survival rates of 31% to 34%.[108] Thoracic RT improves local control rates by 25% in patients with limited-stage SCLC and is associated with improved survival.[101,102] Data suggest that chemoradiotherapy may also be indicated for patients with limited-stage SCLC who have cytologically negative or indeterminate pleural effusions but not for those with pericardial effusions.[113,114] Etoposide/cisplatin in combination with thoracic RT increases the risk of esophagitis, pulmonary toxicity, and hematologic toxicity.[115]

For patients with limited-stage IIB–IIIC (T3–4, N0, M0; T1–4, N1–3, M0) SCLC, the NCCN Guidelines recommends different etoposide/cisplatin regimens plus concurrent thoracic RT (category 1).[101,102,116,117] The preferred etoposide/cisplatin regimens for limited-stage SCLC are based on the dosing used in the CONVERT trial.[108] Other recommended options for limited-stage SCLC include carboplatin/etoposide and other cisplatin/etoposide doses. The use of myeloid growth factors is not recommended in patients undergoing concurrent chemoradiation (category 1 for not using granulocyte-macrophage colony-stimulating factor [GM-CSF]).[118] Thus far, there are no data to support the use of immunotherapy in patients with limited-stage SCLC.

Response assessment is an important aspect of the management of SCLC. For patients with limited-stage SCLC, the panel recommends response assessment using CT with contrast only after completion of adjuvant chemotherapy alone or chemotherapy with concurrent RT and not during therapy. Response assessment can be measured using CT with contrast of the chest/abdomen/pelvis and brain MRI (preferred) or brain CT with contrast. For systemic therapy alone or sequential systemic therapy followed by RT in patients with limited-stage SCLC, the panel recommends response assessment using CT with contrast of the chest/abdomen/pelvis after every 2 to 3 cycles of systemic therapy and again at completion of therapy.

***Extensive-Stage SCLC***

The NCCN SCLC Panel recommends certain combination chemotherapy plus immunotherapy regimens as preferred options for patients with extensive-stage SCLC.[119-121] In patients with extensive-stage SCLC and brain metastases, systemic therapy can be given either before or after brain RT depending on whether the patient has neurologic symptoms (see *Primary Treatment* in the algorithm).[18,122] If systemic therapy is given first, brain RT is administered after completion of systemic therapy.

For many years, platinum plus etoposide had been the only recommended therapy for patients with extensive-stage SCLC; however, the preferred regimens now include the programmed death ligand 1 (PD-L1)–targeted immune checkpoint inhibitors, atezolizumab or durvalumab. Contraindications for treatment with programmed cell death protein 1 (PD-1)/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. For v1.2024, recent use of tyrosine kinase inhibitors (TKIs) is added as a contraindication for treatment with immune checkpoint inhibitors. The panel recommends continuation of maintenance immunotherapy until disease progression or intolerable toxicity. Atezolizumab or durvalumab may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy. Therefore, health care providers should be aware of the spectrum and management of potential immune-mediated adverse events and have a discussion with patients about possible side effects. High-dose corticosteroids are generally recommended for immune-mediated adverse events based on the severity of the reaction. Atezolizumab or durvalumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information) (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).

The panel recommends steroid initiation for patients with spinal cord compression or brain metastasis who have symptomatic neurologic disease. Systemic therapy with or without RT to localized symptomatic sites is recommended for patients with extensive disease, which includes the superior vena cava (SVC), lobar obstruction, and bone metastasis. Prophylactic external beam RT (EBRT) can be considered for patients with high fracture risk due to osseous structural impairment.

During systemic therapy for patients with extensive-stage SCLC, the panel recommends response assessment using CT with contrast of the chest/abdomen/pelvis after every 2 to 3 cycles of systemic therapy and again at completion of therapy. Serial brain imaging is also recommended for patients with extensive-stage SCLC who have asymptomatic brain metastases and are receiving systemic therapy before brain RT. Brain MRI (preferred) or brain CT with contrast is recommended after every 2 cycles of systemic therapy and again at completion of therapy.

*Atezolizumab Plus Chemotherapy*

IMpower133, a phase 3 randomized trial, assessed the addition of atezolizumab (treatment and maintenance) to carboplatin plus etoposide in 403 patients with previously untreated extensive-stage SCLC and compared outcomes to carboplatin plus etoposide alone.[121] The 1-year overall survival rate was 51.9% for the atezolizumab regimen versus 39.0% for chemotherapy alone. The median overall survival was 12.3 months (95% CI, 10.8–15.8) with the addition of atezolizumab versus 10.3 months (95% CI, 9.3–11.3) with chemotherapy alone (hazard ratio [HR], 0.76; 95% CI, 0.6–0.95; *P* = .0154).[119] Response rates were similar in both arms (60% with chemotherapy plus atezolizumab vs. 64% with chemotherapy alone). The rate of grade 3 or 4 adverse events was similar in both groups (67.7% for the atezolizumab regimen vs. 63.3% for chemotherapy alone). There were 4 deaths (2%) in the atezolizumab group versus 11 deaths (5.6%) in the chemotherapy alone group. Different doses for maintenance atezolizumab have been FDA-approved for patients with extensive-stage SCLC. In light of these data and FDA approval, the NCCN SCLC Panel recommends carboplatin plus etoposide plus atezolizumab as a category 1 and preferred first-line systemic therapy option followed by maintenance atezolizumab for patients with extensive-stage SCLC.[119,121] The NCCN Panel recommends either 1200 or 1680 mg of maintenance atezolizumab. The category 1 recommendation is only for 1200 mg of maintenance atezolizumab based on the dose used in the clinical trial.[119,121]

*Durvalumab Plus Chemotherapy*

CASPIAN, a phase 3 randomized trial, assessed adding durvalumab to etoposide and either carboplatin or cisplatin followed by maintenance durvalumab in 537 patients with previously untreated extensive-stage SCLC and compared response to platinum plus etoposide alone regimens.[120,123] Most patients received carboplatin (78%). A 3-year analysis showed that the median overall survival was 13.0 months (95% CI, 11.5–14.8) in the durvalumab plus chemotherapy group and 10.3 months (95% CI, 9.3–11.2) in the chemotherapy alone group (HR, 0.73; 95% CI, 0.59–0.91; *P* = .0047).[124] The 1-year overall survival rate was 52.8% for the durvalumab regimen versus 39.3% for chemotherapy alone. The rate of serious adverse events was similar in both groups (32% vs. 36%). The death rate from adverse events was also similar (2% vs. 1%). In this trial, adding tremelimumab to durvalumab/etoposide carboplatin (or cisplatin) did not improve overall survival compared with platinum/etoposide (10.4 vs. 10.5 months; HR, 0.82; 95% CI, 0.68–1.0). Based on the data and FDA approval, the NCCN SCLC Panel recommends durvalumab plus etoposide plus (carboplatin or cisplatin) as a category 1 and preferred first-line systemic therapy option followed by maintenance durvalumab for patients with extensive-stage SCLC, including those with asymptomatic untreated brain metastases.[120,123-125]

*Other Primary Systemic Therapies*

Other recommended first-line systemic therapy regimens for extensive-stage SCLC include etoposide with either cisplatin or carboplatin. Additional chemotherapy combination regimens evaluated in patients with extensive-stage SCLC show inconsistent evidence of benefit compared with etoposide/cisplatin. For example, the combination of irinotecan and cisplatin initially appeared to be better than etoposide/cisplatin. A phase 3 trial in Japan reported that patients with extensive-stage SCLC treated with irinotecan plus cisplatin had a median survival of 12.8 months compared with 9.4 months for patients treated with etoposide/cisplatin (*P* = .002).[126] The 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the etoposide/cisplatin group.[126] Two subsequent large phase 3 trials performed in the United States comparing irinotecan plus cisplatin versus etoposide/cisplatin showed no significant difference in response rate or overall survival.[127,128] A phase 3 randomized trial of 220 patients with extensive-stage SCLC found that median overall survival slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs. 7.1 months; *P* = .04).[129] In addition, a meta-analysis suggested an improvement in PFS and overall survival with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.[130] The NCCN SCLC Panel recommends the irinotecan-based regimens as primary therapy options (useful in certain circumstances) for patients with extensive-stage SCLC. However, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens.

The use of maintenance or consolidation chemotherapy beyond the recommended 4 to 6 cycles results in a minor increase in the duration of response without improving survival and carries a greater risk of cumulative toxicity.[131,132] The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. Alternating or sequential combination therapies have been designed to overcome drug resistance by exposing the tumor to as many active cytotoxic agents as possible during initial treatment.[133] However, this approach has not improved PFS or overall survival in randomized trials.[134,135] Therefore, the NCCN SCLC Panel recommends 4 cycles of systemic cytotoxic therapy for patients with limited-stage (with concurrent radiation) and extensive-stage (with concurrent immunotherapy) SCLC. However, some patients with extensive-stage SCLC may receive up to 6 cycles based on response and tolerability.

Attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have not shown significant advantages compared to recommended approaches. In two trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to etoposide/cisplatin showed a modest survival advantage.[136,137] However, these findings have not been uniformly observed, and the addition of an alkylating agent, with or without an anthracycline, significantly increases hematologic toxicity when compared to etoposide/cisplatin alone.[138] Two different phase 3 trials assessing the combination of ifosfamide, etoposide, and epirubicin versus etoposide/cisplatin, and carboplatin plus etoposide with or without palifosfamide confirmed the lack of improvement in survival with three-drug chemotherapy regimens in patients with extensive-stage SCLC.[139,140] Similarly, the addition of paclitaxel to either cisplatin or carboplatin plus etoposide yielded promising results in phase 2 studies, but did not improve survival and was associated with unacceptable toxicity in a phase 3 trial.[141]

The role of high dose chemotherapy for patients with SCLC remains controversial. Patients receiving high chemotherapy doses compared with those given conventional doses of the same agents had higher complete and partial response rates, and modestly longer median survival times.[142] However, randomized trials comparing conventional chemotherapy doses to incremental increases in dose intensity (up to 2 times the conventional dose) have not consistently shown an increase in response rate or survival.[143-146] In addition, a meta-analysis of trials that studied dose-intense variations of the CAV and etoposide/cisplatin regimens found that increased relative dose intensity resulted in only a small, clinically insignificant enhancement of median survival in patients with extensive-stage SCLC.[147] Early phase 2 results designed to increase dose intensity by weekly cyclic multidrug chemotherapy were promising, but favorable patient selection was of some concern.[148,149] No survival benefits were documented in randomized trials, and excessive treatment-related mortality were noted with weekly cyclic multidrug chemotherapy regimens.[150-153]

Despite the recent success with atezolizumab/chemotherapy or durvalumab/chemotherapy regimens, other immunotherapy-based strategies have not been as favorable. A phase 3 randomized trial in patients with extensive-stage SCLC reported that the addition of ipilimumab to etoposide with either cisplatin or carboplatin as first-line therapy did not improve either overall survival or PFS compared with chemotherapy alone.[154] Likewise, another phase 3 randomized trial showed no improvement in overall survival in patients with extensive-stage SCLC treated with first-line pembrolizumab plus etoposide/platinum followed by maintenance pembrolizumab compared with chemotherapy alone.[58]

Antiangiogenic therapy has also been evaluated in SCLC. In patients with limited-stage SCLC, a phase 2 study of irinotecan, carboplatin, and bevacizumab with concurrent RT followed by maintenance bevacizumab was terminated early because of an unacceptable incidence of tracheoesophageal fistulae. In extensive-stage SCLC, phase 2 trials of platinum-based chemotherapy plus bevacizumab showed promising response and survival data.[155-158] However, at least two randomized trials have demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.[159,160] Currently, the NCCN SCLC Panel does not recommend use of bevacizumab in patients with SCLC.

Cytokines (eg, GM-CSF, granulocyte colony-stimulating factor [G-CSF]) can ameliorate chemotherapy-induced myelosuppression and reduce the incidence of febrile neutropenia, but cumulative thrombocytopenia remains dose-limiting. Although trials involving patients with SCLC were instrumental in obtaining FDA approval for the clinical use of cytokines,[161] maintenance of dose intensity with growth factors does not prolong disease-free survival or overall survival.[162,163] The panel does not recommend GM-CSF (category 1 for not using it) or G-CSF for patients with limited-stage SCLC receiving systemic therapy/RT.[118,164] Trilaciclib or G-CSF may be used as prophylactic supportive care options to decrease the incidence of chemotherapy-induced myelosuppression when administering certain regimens for patients with extensive-stage SCLC (see *Principles of Supportive Care* in the algorithm).[118,164-168] It is important to note that trilaciclib or G-CSF are not treatment options.

*Transformed SCLC from NSCLC with an Oncogenic Driver*

The panel recognizes that transformed SCLC from NSCLC is a rare population of patients with limited data including treatment options. The panel recommends considering referral to a center with expertise in managing transformed SCLC. The panel recommends systemic cytotoxic chemotherapy using SCLC Guidelines due to lack of data for transformed SCLC. The role of immunotherapy in transformed SCLC is unclear and should be avoided if tyrosine kinase inhibitors are being used.

### Older Patients

The incidence of SCLC increases with age with the median age at diagnosis being >70 years.[169] The functional status of an individual patient is more useful than chronological age in guiding clinical decision-making that includes considering treatment tolerance (see the NCCN Guidelines for Older Adult Oncology, available at www.NCCN.org). Greater attention to the needs and support systems of a patient's functional status is recommended to provide optimal care. Patients who are able to perform activities of daily living (ADLs) should be treated with combination systemic therapy and RT, if indicated.[170-172] For example, a subgroup analysis of the CONVERT trial suggests that concurrent chemoradiation yields equivalent median survival in patients <70 years versus patients ≥70 years and limited-stage SCLC (29 vs. 30 months; *P* = .38).[170] However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in patients ≥70 years. Therefore, the study recommended closer surveillance for patients ≥70 years during treatment to avoid excessive risk.[170]

Randomized trials have indicated that less-intense treatment (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in patients of all ages with good PS (0–2).[173,174] A retrospective analysis in 8637 patients ≥70 years with limited-stage SCLC reported that chemoradiation increased survival compared with chemotherapy alone.[171] Several other strategies have been evaluated in patients ≥65 years with SCLC.[105,175-177] The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve (AUC) dosing of carboplatin takes into account the declining renal function of the patient.[177] However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in the population >70 years.[178] A short 2-week course, full-intensity chemotherapy showed acceptable results in patients (median age, 73 and poor PS); but this approach has not been directly compared with 4 to 6 cycles of therapy.[179]

PCI should be used with caution in older patients. A Dutch analysis of more than 5000 patients suggests that median survival is lower in patients ≥70 years compared with patients <70 years treated with PCI, regardless of stage.[180] Patients aged ≥60 years are at increased risk for cognitive decline after PCI; therefore, the risks and benefits of PCI versus close MRI surveillance need to be discussed.[181-184]

### Surveillance for Relapse

Although SCLC responds to initial treatment, disease relapse is observed in most patients.[185,186] Therefore, surveillance recommendations to assess for relapse in patients with SCLC are outlined in the algorithm. Most

NCCN Member Institutions use chest CT (± abdomen/pelvis) every 2 to 6 months (more frequently in years 1 to 2 and less frequently thereafter). The frequency of surveillance decreases during subsequent years because of the declining risk of recurrence.[187] If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors frequently occur in patients with no evidence of SCLC post-treatment.[188,189] It is important to monitor for brain metastases, prior to the development of potentially debilitating neurologic symptoms, which allows for early treatment. The NCCN SCLC Panel recommends brain MRI (preferred) or CT with contrast every 3 to 4 months during year 1 for all patients and then every 6 months as clinically indicated, regardless of the PCI status. MRI is more sensitive than CT for identifying brain metastases.[76] The panel maintains that FDG-PET/CT is not recommended for routine follow-up unless contrast CT chest/abdomen/pelvis is contraindicated. Tobacco smoking cessation intervention is recommended for all patients with SCLC, because second primary tumors occur less commonly in patients who quit smoking (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[190-192] Patients who previously smoked tobacco should be encouraged to remain abstinent. The NCCN SCLC Panel also recommends the survivorship guidelines for appropriate patients (see the NCCN Guidelines for Survivorship, available at www.NCCN.org).

## Subsequent Systemic Therapy

Patients with disease relapse or with primary progressive disease may be treated with subsequent systemic therapy. Recommended subsequent systemic therapy options are based on chemotherapy-free interval (CTFI) of 1) 6 months or less; or 2) more than 6 months (see *Principles of Systemic Therapy* in the algorithm). Clinical trial enrollment is the preferred regimen for both CTFI >6 months and CTFI ≤6 months. For v1.2024, the panel recommends considering genomic profiling of relapsed tumors, if not previously performed, to determine clinical trial eligibility.

Subsequent systemic therapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse.[193] If the interval is 6 months or less (refractory or resistant disease), response to most agents or regimens is poor (≤10%). If more than 6 months have elapsed (sensitive disease), expected response rates are approximately 25%. Response rates are higher with newer agents, such as lurbinectedin. Unfortunately, most patients relapse in 6 months or less.[194,195] Note that the European Society for Medical Oncology (ESMO) Guidelines use cutoffs of 3 months or more for sensitive SCLC and less than 3 months for resistant SCLC.[196] The NCCN SCLC Panel recommends additional subsequent therapy options for patients with SCLC based on clinical expertise and trial data. Other recommended subsequent therapy options, described in the following sections, include topotecan (oral [PO] or IV), lurbinectedin, CAV, docetaxel, oral etoposide, gemcitabine, irinotecan, nivolumab, paclitaxel, pembrolizumab, and temozolomide (category 2A for all agents).The optimal duration of subsequent systemic therapy has not been fully explored. For cytotoxic chemotherapy agents, the duration of treatment is usually short, and the cumulative toxicity is frequently limiting even in patients who experience response. For these reasons, subsequent systemic therapy should be continued until progression of disease or development of unacceptable toxicity. The panel recommends response assessment using CT with contrast of the chest/abdomen/pelvis after every 2 to 3 cycles. Dose reduction or growth factor support should be considered for patients with a PS of 2. For CNS progression only, the panel recommends continuing systemic therapy and treat brain metastases with RT. Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0 to 2.

### *Platinum-Based Therapy*

A phase 3 randomized trial assessed carboplatin plus etoposide compared with oral topotecan in 162 patients with SCLC relapse after more than 3 months on first-line platinum/etoposide therapy.[197] The median PFS was 4.7 months (90% CI, 3.9–5.5) in the carboplatin/etoposide group versus 2.7 months (90% CI, 2.3–3.2) in the oral topotecan group (HR, 0.57; 90% CI, 0.41–0.73; *P* = .004). Grade 3–4 adverse events included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and asthenia. In the topotecan group, two treatment-related deaths occurred; no deaths occurred in the carboplatin/etoposide group. The NCCN SCLC Panel recommends subsequent therapy with platinum-based regimens based on the clinical trial data.[194,197-200] The NCCN Panel maintains that rechallenging with the original regimen, or similar platinum-based regimen, is recommended for subsequent systemic therapy, if CTFI >6 months and may be considered if there has been a CTFI of at least 3 to 6 months.[194,197-200] The NCCN Panel maintained that platinum-based doublets are the preferred subsequent therapy options for patients with SCLC and a PS of 0 to 2.[194,197,198]

***Lurbinectedin***

A phase 2 basket trial assessed lurbinectedin (3.2 mg/m$^2$ every 3 weeks) as second-line therapy in 105 patients with SCLC who previously received platinum/etoposide; 57% of patients had not received chemotherapy for 3 months or more.[201] The overall response rate with lurbinectedin was 35% (95% CI, 26.2%–45.2%). The response rate was 22% (95% CI, 11.2%–37.1%) if CTFI was less than 3 months. The response rate was 45% (95% CI, 32.1%–58.4%) if CTFI was 3 months or more. Common grade 3–4 adverse events included anemia, leucopenia, neutropenia, and thrombocytopenia. There were no reported treatment-related deaths. In a subset analysis of this trial, lurbinectedin was assessed as second-line therapy in 20 patients with SCLC who had received platinum/etoposide more than 6 months ago.[195] The overall response rate with lurbinectedin was 60% (95% CI, 36.1%–86.9%). The median overall survival was 16.2 months (95% CI, 9.6–upper level not reached). After 1 year, 60.9% of patients were alive and after 2 years, 27.1% were alive. Common grade 3–4 adverse events included neutropenia, anemia, thrombocytopenia, fatigue, and increased liver function tests. The FDA granted approval for lurbinectedin at a dose of 3.2 mg/m$^2$ every 3 weeks based on clinical trial data.[201]

ATLANTIS, a phase 3 randomized trial, assessed lurbinectedin plus doxorubicin versus control therapy with either CAV or topotecan in 613 patients with relapsed SCLC.[202] Most patients had received first-line platinum-based therapy more than 3 months ago. The median overall survival was 8.6 months (95% CI, 7.1–9.4) with lurbinectedin/doxorubicin versus 7.6 months (95% CI, 6.6–8.2) with CAV or topotecan (HR, 0.97; 95% CI, 0.82–1.15). Grade 3 or higher adverse events occurred in 66% of patients receiving lurbinectedin/doxorubicin versus 86.5% of patients in the control group. Grade 3 or worse adverse events included neutropenia (lurbinectedin/doxorubicin: 37%; control: 69%). Two patients (<1%) died because of treatment-related adverse events in the lurbinectedin/doxorubicin group and 10 (3%) patients died in the control group. The dose of lurbinectedin was 2 mg/m$^2$ in the ATLANTIS trial, which is less than the dose used in the phase 2 trial discussed earlier.[195,201]

The NCCN SCLC Panel recommends lurbinectedin as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred).[195,201] The NCCN Panel decided to continue recommending lurbinectedin at the higher dose based on the FDA approval and since the lower dose of lurbinectedin did not perform well in ATLANTIS.[201,202]

***Topotecan***

Topotecan is also recommended as a subsequent therapy option based on clinical trial data.[197] A randomized phase 3 trial for subsequent treatment for patients with SCLC relapse at least 60 days after therapy compared single-agent IV topotecan with the combination regimen CAV.[203] Both arms had similar response rates (topotecan, 24.3%; CAV, 18.3%)

and survival (25.0 vs. 24.7 weeks). Compared to CAV, topotecan caused less grade 4 neutropenia (37.8% vs. 51.4%; $P < .001$) and improved symptoms of dyspnea, anorexia, hoarseness, and fatigue. There is conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.[204,205] Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m$^2$ of IV topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.[206] In another phase 3 trial, oral topotecan improved overall survival compared with best supportive care (26 vs. 14 weeks).[207] The efficacy and toxicity of oral and IV topotecan seem to be similar and therefore either route may be used.[207,208] The NCCN SCLC Panel recommends oral or IV topotecan as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤ 6 months (preferred).[197,202,203,207,209]

***Irinotecan***

47% of patients responded (95% CI, 21.4%–71.9%) to irinotecan in a phase 2 study in patients with refractory or relapsed SCLC.[210] Myelosuppression, diarrhea, and pulmonary toxicity were reported in patients receiving irinotecan.[210] Another phase 2/3 trial showed that irinotecan and topotecan had comparable activity in patients with relapsed or refractory SCLC and metastasis.[211] The NCCN SCLC Panel recommends irinotecan as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred). The panel added a consideration for irinotecan for patients with CNS disease.

***Nivolumab and Pembrolizumab***

Immune checkpoint inhibitors have been evaluated in patients with relapsed SCLC.[212-215] CheckMate 032, a phase 1/2 trial, assessed nivolumab alone (n = 147) or various doses of nivolumab plus ipilimumab (n = 96) for relapsed SCLC.[212,213] Response rates were 11.6% for nivolumab and 21.9% for nivolumab plus ipilimumab.[212] The 12- and 24-month overall survival rates were similar (nivolumab, 30.5% and 17.9%; nivolumab plus ipilimumab, 30.2% and 16.9%, respectively). Grade 3–4 adverse events were 12.9% for nivolumab alone and 37.5% for nivolumab plus ipilimumab. In patients receiving nivolumab alone, the most common grade 3 or 4 treatment-related adverse events were pneumonitis and increased levels of lipase and aspartate aminotransferase.

CheckMate 331, a randomized phase 3 trial, assessed nivolumab monotherapy versus topotecan or amrubicin in 569 patients with relapsed SCLC.[209,216] Data show that overall survival was 7.5 months in patients receiving nivolumab versus 8.4 months in those receiving chemotherapy (HR, 0.86; 95% CI, 0.72–1.04; $P = .11$).[209] Overall survival was similar regardless of PD-L1 levels. Response rates were 13.7% for nivolumab compared with 16.5% for chemotherapy. Treatment-related deaths occurred in two patients receiving nivolumab and in three patients receiving chemotherapy. Fewer grade 3–4 adverse events occurred in patients receiving nivolumab compared with chemotherapy (14% vs. 73%, respectively). A study reported that third-line therapy with nivolumab was associated with longer survival (5.7 months; 95% CI, 3.5–8.0) compared with other treatments such as paclitaxel or topotecan (3.8 months; 95% CI, 2.8–4.9; HR, 0.63; 95% CI, 0.44–0.90).[217] The 1-year overall survival rate is 28% with nivolumab versus 4% with the other treatments.

A combined analysis of two trials, phase Ib (KEYNOTE-028) and phase 2 (KEYNOTE-158), evaluated the activity of pembrolizumab in 83 patients with relapsed SCLC who had received two or more lines of therapy. 56% of patients were positive for PD-L1 (≥1%) and 84% patients did not have brain metastases.[218,219] This analysis reported a response rate of 19.3% (95% CI, 11.4%–29.4%). The median overall survival was 7.7 months (95% CI, 5.2–10.1); the estimated 12-month overall survival rate was 34%.

Both overall survival and response rate were higher in those who were PD-L1 positive; however, one patient with a complete response had a tumor that was PD-L1 negative. Grade 3 or 4 adverse events occurred in 9.6% (8/83) of patients; two patients died from treatment-related adverse events (pneumonitis and encephalitis).

The FDA has withdrawn the subsequent therapy indications for nivolumab or pembrolizumab for patients with relapsed SCLC, because phase 3 randomized trial data did not show an improvement in overall survival.[209,213,214,216,218-221] However, the NCCN SCLC Panel lists these agents as subsequent systemic therapy options (other recommended regimens) for patients with CTFI ≤6 months. The panel decided that nivolumab or pembrolizumab are just as effective as (sometimes better than) and less toxic than the other subsequent therapy options.[209,217] In addition, many agents recommended as subsequent therapy options for patients with SCLC do not have an FDA indication in this setting but data show that they are effective (see *Other Subsequent Therapy Options* in this Discussion). Patients with limited-stage SCLC who relapse and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. However, the use of nivolumab and pembrolizumab is discouraged in patients whose disease progresses while on maintenance atezolizumab or durvalumab as part of first-line therapy. There are no data to suggest that giving patients subsequent immune checkpoint inhibitors is effective if their disease previously progressed on other immune checkpoint inhibitors.

Immunotherapeutic agents, such as nivolumab and pembrolizumab, may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy. Therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage these events, and discuss possible side effects with patients (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[222,223] For patients with immune-mediated adverse events, high-dose corticosteroids are generally recommended based on the severity of the reaction. Nivolumab or pembrolizumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

***Other Subsequent Therapy Options***

Paclitaxel and docetaxel that belong to the taxane class of drugs have been assessed in patients with refractory or relapsed SCLC. In a phase 2 study in patients with refractory or relapsed SCLC; 24% of patients responded to paclitaxel.[224] Grade 3–4 toxicity included neutropenia, infection, rash, neuropathy, and pulmonary toxicity. Another phase 2 study of paclitaxel in patients with refractory SCLC yielded a response rate of 29% (95% CI, 12%–51%).[225] A retrospective study in 185 patients showed a response rate of 17% during third-line or fourth-line therapy with paclitaxel. Toxicity rates were similar in patients with PS 2 compared with PS 0 to 1 (63% vs. 62%).[226] 25% of patients responded to docetaxel in a phase 2 trial in patients with previously treated SCLC. Reported toxicities included neutropenia and asthenia.[227]

Oral etoposide was assessed in a phase 2 trial in 22 patients with recurrent SCLC.[228] Ten patients (45%; 95% CI, 27%–65%) had a complete or partial response. Median survival was 3.5 or more months (range, 1 to 15+). Five patients were hospitalized because of neutropenia and fever. Two patients died from sepsis. Another phase 2 trial assessed oral etoposide in 26 patients with refractory SCLC.[229] The overall response rate was 23%; there was one complete response and five partial responses.

Gemcitabine was assessed in a phase 2 trial in 42 patients with sensitive or refractory SCLC.[230] The median survival was 7.1 months. The overall objective response rate was 11.9%. One patient with refractory SCLC and four patients with sensitive SCLC responded. Grade 3–4 toxicities included neutropenia (27%), thrombocytopenia (27%), neurologic toxicity (14%), and pulmonary (9%). Another phase 2 trial assessed gemcitabine in 38 patients with resistant SCLC that progressed within 3 months of last therapy.[231] The median survival was 17 weeks (range, 4–84). The response rate was 13% (95% CI, 6%–27%); there were five partial responses and no complete responses. Grade 3 toxicities included thrombocytopenia (29%) and leukopenia (18%).

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated $O^6$-methylguanine-DNA methyltransferase (MGMT).[232-234] Temozolomide was assessed in a phase 2 trial in patients with relapsed or refractory SCLC. In patients with sensitive SCLC, the overall response rate was 23% (95% CI, 12%–37%). The response rate improved for patients with methylated MGMT compared to those with unmethylated MGMT (38% vs. 7%; *P* = .08).

A phase 3 trial (JCOG0605) from Japan in patients with sensitive, relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival compared with topotecan (median survival, 18.2 vs. 12.5 months; HR, 0.67; 90% CI, 0.51–0.88; *P* = .0079). However, the toxicity of this regimen was significant and it is not recommended for subsequent therapy.[235] The NCCN Panel recommends CAV as a subsequent therapy options based on clinical trial data.[203]

## Radiation Therapy

The *Principles of Radiation Therapy* section in the algorithm, including PCI and treatment of brain metastasis, describes the radiation doses, target volumes, and normal tissue dose-volume constraints for limited-stage SCLC and includes references to support the recommendations. RT is not recommended as primary treatment for patients with extensive-stage SCLC, however consolidative or palliative RT is an option for these patients. The American Radium Society appropriate use criteria and the American Society for Radiation Oncology (ASTRO) guidelines are useful resources.[236-239] The *Principles of Radiation Therapy* section in the NSCLC algorithm may also be useful (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).

### *Thoracic Radiation Therapy*

Achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge. The addition of thoracic RT has improved survival for patients with limited-stage SCLC. Meta-analyses that include more than 2000 patients show that thoracic radiation for limited-stage SCLC yields a 25% to 30% reduction in local progression, and a corresponding 5% to 7% improvement in 2-year overall survival compared with chemotherapy alone.[101,102] A phase 3 trial has reported 5-year overall survival of more than 30%, which is close to outcomes of locally advanced NSCLC of similar stage.[108]

#### *Timing of Radiation with Chemotherapy*

Optimal thoracic RT is impacted by several factors, including the timing of chemotherapy and RT (concurrent vs. sequential), timing of RT (early vs. late), the RT target volume (original tumor volume vs. shrinking field as the tumor responds), dose of radiation, and fractionation of RT. Early concurrent chemoradiotherapy is recommended for patients with limited-stage SCLC based on randomized trials. A randomized phase 3 trial by the Japanese Cooperative Oncology Group (9104) assessed sequential versus concurrent thoracic RT combined with etoposide/cisplatin for 231 patients with limited-stage SCLC. Overall survival was 27.2 months for those receiving concurrent chemoradiation versus 19.7 months for those receiving sequential chemoradiation (*P* = .097).[115] Patients receiving concurrent chemoradiation had more severe hematologic toxicity. Severe esophagitis occurred in 9% of patients receiving concurrent chemoradiation and 4% receiving sequential chemoradiation.

Several systematic reviews and meta-analyses on the timing of thoracic RT in limited-stage SCLC have reported that early concurrent chemoradiation results in a small, but significant improvement in overall survival compared with late concurrent or sequential chemoradiation.[240,241] A randomized phase 3 trial (by the National Cancer Institute of Canada) compared RT beginning with either cycle 2 or cycle 6 of chemotherapy and showed that early RT was associated with improved local and systemic control and longer survival.[242] Another meta-analysis in patients with limited-stage SCLC showed that survival improved with rapid completion of the chemoradiotherapy regimen (start of any chemotherapy until the end of RT [SER]).[243] A meta-analysis of individual patient data from 12 trials (2668 patients) reported that early concurrent chemoradiation, associated with increase in acute esophagitis, had higher 5-year overall survival (HR, 0.79; 95% CI, 0.69–0.91) compared with late concurrent chemoradiation.[244]

*Radiation Fractionation*

The Eastern Cooperative Oncology Group (ECOG)/Radiation Therapy Oncology Group (RTOG) compared accelerated to conventionally fractionated RT with etoposide/cisplatin.[245] In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiation using a total dose of 45 Gy delivered either twice daily over 3 weeks (accelerated) or once daily over 5 weeks (conventional). Median overall survival was 23 versus 19 months (*P* = .04), and 5-year survival rates were 26% versus 16% in the accelerated and conventional RT arms, respectively.[245] A higher incidence of grade 3–4 esophagitis was seen with the accelerated regimen compared with the conventional regimen.[245] A significant criticism of this trial is that the 45 Gy conventional regimen provided suboptimal dose intensity compared to modern conventionally fractionated regimens using higher total doses.

CONVERT, a phase 3 randomized trial, compared accelerated 45 Gy (given twice daily over 3 weeks) with higher dose conventionally fractionated 66 Gy (given once daily over 6.5 weeks) in 547 patients with limited-stage SCLC.[108] Median overall survival was similar between the 2 groups (30 vs. 25 months). However, the CONVERT trial was not powered to show equivalence. Although toxicity was generally similar between the arms, patients receiving accelerated 45 Gy had more grade 4 neutropenia compared with those receiving conventional 66 Gy (49% vs. 38%; *P* = .05).

CALGB 30610 (Alliance)/RTOG 0538, a randomized phase 3 trial, compared high-dose conventional 70 Gy (once daily over 7 weeks) with accelerated 45 Gy (twice daily over 3 weeks) in 638 patients with limited-stage SCLC.[246] Originally, there was a 61.2 Gy concomitant boost group in this trial, but it was removed based on a planned interim toxicity analysis.[247] Median overall survival was 30.5 months in the conventional 70 Gy arm versus 28.5 months in the accelerated 45 Gy arm (HR, 0.94; 95% CI, 0.75–1.17; *P* = .591). There were 5 deaths in the conventional 70 Gy arm and 2 deaths in the accelerated 45 Gy arm. Overall survival and toxicity were similar. The conventional 70 Gy arm had better quality-of-life scores at 3 weeks with patients reporting it to be more convenient. The study was not designed to assess whether the conventional 70 Gy arm was superior to the accelerated 45 Gy arm.

A randomized phase 2 trial assessed concurrent chemoradiation with two similarly accelerated regimens, 42 Gy given as once-daily fractions over 3 weeks compared with 45 Gy given as twice-daily fractions also over 3 weeks in 157 patients with limited-stage SCLC.[248] The overall survival curves overlapped with median overall survival of 18.8 months in the once-daily arm and 25.1 months in the twice-daily arm (*P* = .61). A retrospective study assessed concurrent chemoradiation with accelerated 40 Gy in 3 weeks given as once-daily fractionation in 68 patients with limited-stage SCLC.[249] The median survival was 28 months which is comparable to outcomes of similarly accelerated twice-daily fractionation.

Two randomized phase 2 trials compared high-dose accelerated RT with standard-dose accelerated RT. One trial compared concurrent chemoradiation with high-dose accelerated 65 Gy given as once-daily fractions over approximately 5 weeks with standard-dose accelerated 45 Gy given as twice-daily fractions over 3 weeks in 182 patients with limited-stage SCLC.[250] Estimated PFS was 17.2 months in the high-dose group versus 13.4 months in the standard-dose group ($P$ = .031). Overall survival was 39.3 months in the high-dose group versus 33.6 months in the standard-dose group ($P$ = .137). Grade 3 or higher esophagitis (high-dose, 17.4% vs. standard-dose, 15.3%), grade 3 or higher pneumonitis (high-dose, 3.3% vs. standard-dose, 2.4%), and treatment-related deaths (high-dose, 2.2% vs. standard-dose, 1.2%) were similar in each group. The second trial compared concurrent chemoradiation using high-dose accelerated RT with 60 Gy given as twice-daily fractions over 4 weeks with standard-dose accelerated 45 Gy given as twice-daily fractions over 3 weeks in 176 patients with limited-stage SCLC.[251] After 2 years, 74.2% (95% CI, 63.8%–82.9%) of patients were alive in the 60 Gy group versus 48.1% (95% CI, 36.9%–59.5%) in the 45 Gy group. Three treatment-related deaths occurred in each group.

Despite multiple trials, the optimal dose and fractionation of thoracic RT for SCLC remains unresolved. Higher dose accelerated RT may be advantageous, and this remains to be confirmed in larger studies. Two randomized trials have not shown that high dose without acceleration (66 Gy or 70 Gy over 6.5–7 weeks) is superior to moderate dose accelerated fractionation (45 Gy over 3 weeks); however, survival and toxicity are similar.[108,246,252] Overall, accelerated RT (whether given once or twice daily) is superior to similar doses of conventionally fractionated RT and comparable to higher dose conventionally fractionated RT. The NCCN SCLC Panel recommends that either accelerated 45 Gy given as twice-daily fractions over 3 weeks (category 1) or conventionally fractionated 66 to 70 Gy given as once-daily fractions over 6.5 to 7 weeks are acceptable options depending on individual patient circumstances.[108,246,252] The NCCN SCLC Panel maintains that higher doses of 66 to 70 Gy are preferred if using once-daily fractionation,[252] since the twice-daily thoracic radiation is logistically challenging for many patients and RT centers.

## Radiation for Limited-Stage SCLC

***External-Beam RT***

For limited-stage IIB to IIIC disease (T3–4, N0, M0; T1–4, N1–3, M0), the NCCN Guidelines recommend that RT should be used concurrently with chemotherapy and that RT should start with the first or second cycle (category 1 for patients with PS 0–2).[237,240] The optimal dose and schedule of RT have not been established. For accelerated RT, the recommended schedule is 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks. For conventionally fractionated RT, the recommended schedule is 2.0 Gy once daily to a total dose of 66 to 70 Gy.[108,252-255]

The minimum technical requirement for thoracic irradiation is CT-planned 3D-conformal RT. Intensity-modulated RT (IMRT) is preferred over 3D-conformal external-beam RT (EBRT) because of lower toxicity. The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar RT doses (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).[256-261] More advanced technologies, such as 4D-CT and proton therapy, may also be appropriate to limit normal tissue toxicity. The radiation target volumes can be defined on the FDG-PET/CT scan obtained at the time of RT planning, as well as any positive biopsies, using definitions in Reports 50 and 62 from the International Commission on Radiation Units & Measurements (ICRU).[262,263] However, the pre-chemotherapy FDG-PET/CT scan should be reviewed to include the original involved lymph node regions in the treatment fields if chemotherapy begins before RT.[255,264] When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol can be used as a guide.[252,265-267]

***SABR***

Emerging data suggest that SABR (also known as stereotactic body RT [SBRT]) is effective for patients with clinical limited-stage I–IIA (T1–2, N0) SCLC, especially for medically inoperable circumstances or refuse surgery.[14,268-273] A meta-analysis of 7 studies (399 patients) summarized outcomes in patients with early-stage SCLC who received SABR; 94% of the patients in this study were deemed inoperable.[273] 44% of patients received chemotherapy and 13.8% of patients received PCI. Overall survival was 86% (95% CI, 74%–95%) and 64% (95% CI, 46%–80%) at 1 year and 2 years, respectively. The nodal and distal recurrence rates were 18% (95% CI, 7.5%–31%) and 27% (95% CI, 7.4%–53%), respectively. Grade 3 toxicity was observed in 1.4% of patients (95% CI, 0%–5.3%). A multicenter analysis of 74 patients suggested that the addition of chemotherapy typically after SABR improves survival for patients with clinical limited-stage SCLC.[16,274] Most of these patients had FDG-PET staging but not pathologic nodal staging. Patients who received chemotherapy after SABR had a median overall survival of 31.4 months versus 14.3 months for those who received SABR alone (*P* = .02).

An analysis of 2107 patients with histologically confirmed T1–T2, N0, M0 from the National Cancer Database found that 7.1% had upfront SABR followed by adjuvant chemotherapy and 92.9% had concurrent chemoradiation.[12] Compared with patients receiving upfront concurrent chemoradiation, those receiving SABR were often older, had T1 disease, and treated recently in academic medical settings. Median survival was 29.2 months in those receiving SABR/chemotherapy versus 31.2 months in those receiving chemoradiation (*P* = .77). Both ASTRO and the American Radium Society recommend SABR followed by adjuvant chemotherapy as an option for medically inoperable patients with clinical limited stage I–IIA SCLC (T1–2, N0).[237,238]

The NCCN SCLC Panel recommends (category 2A) SABR followed by systemic therapy as an option for select patients with clinical limited stage I–IIA (T1–2, N0) ie who are medically inoperable or decline surgery.[14,274] The NCCN SCLC Panel added a caveat that systemic therapy may be initiated first, if time to initiation of SABR will be prolonged. The NCCN Guidelines for NSCLC provide detailed recommendations for SABR that may be useful for SCLC (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC, available at www.NCCN.org).

## Radiation for Extensive-Stage SCLC

***Sequential Thoracic Radiation for Extensive-Stage SCLC***

A randomized trial by Jeremic et al[275] assessed sequential (consolidative) thoracic RT in patients experiencing a complete response at distant metastatic sites after 3 cycles of etoposide/cisplatin. Patients were randomized to receive either 1) further etoposide/cisplatin; or 2) accelerated hyperfractionated RT (ie, 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide.[275] The addition of RT resulted in improved median overall survival (17 vs. 11 months). The Dutch CREST trial, a phase 3 randomized trial in patients with extensive-stage SCLC, reported that the addition of consolidative thoracic RT (30 Gy in 10 fractions) did not improve the primary endpoint of 1-year overall survival (33% vs. 28%; *P* = .066). A secondary analysis found improvement in 2-year overall survival (13% vs. 3%; *P* = .004) and 6-month PFS compared with patients who did not receive consolidative thoracic RT.[276] A trial involving 32 patients who received consolidative thoracic RT reported that only 16% of patients had symptomatic chest recurrences.[277] Consolidative thoracic RT appears to mainly benefit patients with residual thoracic disease after chemotherapy (without immunotherapy) and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.[278] The American Radium Society recommends that consolidative thoracic RT be considered for select patients with extensive-stage SCLC based on the limited data.[236] European experts (International Association for the Study of Lung Cancer [IASLC] and European Society Radiation Oncology [ESTRO]) recommend consolidative thoracic RT in select patients with stage IV SCLC who have responded to first-line chemotherapy and have limited extrathoracic tumor burden.[279]

The NCCN SCLC Panel recommends that consolidative thoracic RT be considered in select patients with low bulk extra thoracic metastatic extensive stage disease who have a complete or near complete response after initial systemic therapy before maintenance immunotherapy.[236,275,276] Sequential thoracic RT can be considered for selected patients, during or before maintenance immunotherapy; however, there are limited data on optimal sequencing. The benefit of thoracic RT in the context of chemoimmunotherapy is under evaluation in the RAPTOR/NRG LU007 trial (NCT04402788).

***Prophylactic Cranial Irradiation***

Intracranial metastases occur in greater than 50% of patients with SCLC. Randomized studies show that PCI is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to show a meaningful survival advantage.[280] Several meta-analyses suggest that PCI after complete resection may benefit patients with pathologic stage IIB or stage III SCLC.[99,100,281] A meta-analysis of all randomized PCI trials reported a nearly 50% reduction in the 3-year incidence of brain metastases, from 58.6% in the control group to 33.3% in the PCI-treated group.[100] Thus, PCI seems to prevent, and not simply delay, the emergence of brain metastases. This meta-analysis also reported an increase in 3-year overall survival from 15.3% in the control group to 20.7% in the PCI group.[100] Although the number of patients with extensive-stage SCLC was small, the observed benefit was similar in patients with both limited-stage and extensive-stage SCLC. A retrospective study of patients with limited-stage SCLC also found that PCI increased survival at 2, 5, and 10 years compared with those who did not receive PCI.[282] A study of 184 patients with limited-stage SCLC assessed PCI versus no PCI in patients who responded to chemoradiotherapy and had no brain metastases on MRI imaging, before and after primary treatment.[283] In patients receiving PCI, median overall survival was 26 months (range, 19.4–32.6 months) versus 14 months (range, 11.4–16.6 months; $P < .0001$) for those without PCI.

None of the abovementioned studies in limited-stage SCLC used MRI staging of the brain or FDG-PET scans for overall staging. A retrospective study included 49 patients with limited-stage SCLC who were staged with brain MRI before treatment.[284] The median overall survival was 55 months in patients with limited-stage SCLC who received PCI versus 24 months in those who did not receive PCI ($P < .05$). At 1 year, the probability of developing symptomatic brain metastases was 4% in patients with limited-stage SCLC who received PCI versus 22% in those who did not receive PCI ($P < .05$). For patients with extensive-stage SCLC, but without brain metastases, a large retrospective analysis of 4257 patients showed that PCI improved median overall survival compared with no PCI (13.9 vs. 11.1 months; $P < .0001$).[285] Another analysis of patients with extensive-stage SCLC (n = 397) reported that PCI improved overall survival compared with no PCI (13.5 vs. 8.5 months, respectively; HR, 0.55; 95% CI, 0.39–0.77; $P = .0005$); however, these patients did not receive routine surveillance brain imaging.[286]

The EORTC performed a randomized trial that assessed PCI versus no PCI in 286 patients with extensive-stage SCLC that had responded to initial chemotherapy. PCI decreased symptomatic brain metastases (14.6% vs. 40.4%) and increased the 1-year survival rate (27.1% vs. 13.3%) compared with controls.[287] However, the study did not require brain imaging prior to PCI and did not standardize the PCI dose or fractionation. Conflicting data from a randomized phase 3 trial in Japan found that median overall survival is not improved in patients receiving PCI compared with MRI surveillance (11.6 months; 95% CI, 9.5–13 vs. 13.7 months; 95% CI, 10.2–16.4) (HR, 1.27; 95% CI, 0.96–1.68; *P* = .094).[288] In this trial, patients were required to have an MRI to confirm that they did not have brain metastases prior to PCI, and the PCI regimen was standardized at 25 Gy in 10 fractions. In addition, the study required close MRI surveillance imaging in patients to allow for the early treatment of brain metastases. The American Radium Society recommends either PCI or brain MRI surveillance for patients with extensive-stage SCLC and without brain metastases based on the limited data.[236] A randomized trial (SWOG S1827/MAVERICK) is currently assessing brain MRI surveillance alone compared to brain MRI surveillance plus PCI for patients with late-stage SCLC and early-stage SCLC. Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrently with chemotherapy.[182,289,290] Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.[98,291] PCI has also been associated with chronic neurotoxicity in patients who are aged ≥60 years.[181,183]

The NCCN SCLC Panel has gradually revised the adjuvant recommendations for patients whose disease showed a complete or partial response after primary treatment based on conflicting clinical trial data and concerns about using PCI. Before a decision is made to administer PCI, a balanced discussion is necessary between the patient and physician.[182,292] The NCCN Panel recommends PCI for patients with limited-stage SCLC that shows a complete or partial response.[98,100,287] The NCCN Panel maintains that the benefit of PCI is unclear in patients with very early-stage SCLC (pathologic limited-stage I [T1–2a, N0, M0]) who have had definitive therapy (ie, surgery, SABR). These patients have a lower risk of developing brain metastases than patients with more advanced limited-stage SCLC and may not benefit from PCI.[99,274,293] The NCCN Panel recommends MRI brain surveillance for all patients with limited-stage SCLC who do not receive PCI. In patients with extensive-stage SCLC, the NCCN Panel recommends MRI brain surveillance with or without consideration of PCI based on the conflicting trial results from Japan and the EORTC.[287,288] Brain imaging surveillance for metastases is recommended using either MRI (preferred) or CT with contrast in patients who are unable to undergo MRI.[288]

Higher PCI doses (eg, 36 Gy) increased mortality and toxicity compared with lower doses (25 Gy).[181,294] Therefore, the preferred dose for PCI is 25 Gy in 10 daily fractions (2.5 Gy/fraction).[100,287,294] A shorter course of PCI may be appropriate (eg, 20 Gy in 5 fractions) for selected patients with extensive-stage SCLC.[287] PCI should not be given concurrently with chemotherapy, and high total RT dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity.[181] After the acute toxicities of initial systemic therapy have resolved, PCI can be administered. When given after the completion of chemotherapy and at a low dose per fraction, PCI may cause less neurologic toxicity. Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.[291,294]

The NCCN SCLC Panel recommends that memantine be considered for patients receiving PCI or therapeutic whole-brain irradiation. Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist that may delay cognitive dysfunction in patients receiving brain RT.[295] Patients receiving memantine have a longer time before cognitive decline (HR, 0.78; 95% CI, 0.62–0.99; *P* = .01). NRG Oncology CC001, a phase 3 randomized trial, assessed hippocampal-avoidance (HA) whole-brain IMRT plus memantine compared with conventional whole-brain RT plus memantine in patients with brain metastases who were not diagnosed with SCLC.[296] Cognitive preservation and patient-reported outcomes were improved with HA IMRT (HR, 0.74; 95% CI, 0.58–0.95; *P*=.02). However, conflicting data have been reported with HA PCI versus conventional PCI. PREMER, a phase 3 randomized trial, reported improved cognitive preservation with HA PCI.[297] However, another phase 3 randomized trial (NCT01780675) reported no differences in cognition with HA PCI.[298] A large randomized trial (NRG CC003) is assessing HA-PCI versus conventional PCI.[299]

***Palliative Radiation Therapy***

For patients with localized symptomatic sites of disease (ie, painful bony lesions, spinal cord compression, obstructive atelectasis) or with brain metastases, RT can provide excellent palliation (see the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).[300-302] Orthopedic stabilization may be useful in patients at high risk for fracture because of osseous structural impairment. Because patients with SCLC often have a short life span, surgery is not usually recommended for spinal cord compression. Radiation dose and fractionation for extracranial metastases include 30 Gy in 10 fractions, 20 Gy in 5 fractions, or 8 Gy in 1 fraction based on common dose-fractionation regimens used for other solid tumors (see the NCCN Guidelines for NSCLC, available at www.NCCN.org). IMRT, SABR, or stereotactic radiosurgery (SRS) may be appropriate for select patients (eg, those whose tumors are in close proximity to organs at risk).

Brain metastases have conventionally been treated with whole brain RT in patients with SCLC due to the frequent occurrence of multiple metastases (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[303] The recommended dose for whole-brain RT is 30 Gy in 10 daily fractions.[303]

A retrospective multicenter cohort study assessed SRS versus whole-brain RT in 710 patients with SCLC who had a limited number of brain metastases; overall survival was 6.5 months (95% CI, 5.5–8.0) for SRS and 5.2 months (95% CI, 4.4–6.7) for whole-brain RT (*P* = .003).[304] A meta-analysis of nine observational studies (1638 patients) also reported favorable lesion control and survival outcomes with SRS versus whole-brain RT.[305] A randomized trial (NRG CC009) is comparing SRS to HA whole-brain IMRT plus memantine in this setting. The NCCN Panel decided that SRS may be used for selected patients with a small number of brain metastases based on available data, pending outcomes of the ongoing trials.[304] In patients who develop brain metastases after PCI, SRS (preferred) or repeat whole-brain RT (in carefully selected patients) may be considered.[306,307] For patients with a better prognosis (eg, ≥4 months), HA whole-brain IMRT plus memantine is preferred because it produces less of a decrease in cognitive function than conventional whole-brain RT plus memantine. However, patients with metastases within 5 mm of the hippocampi, leptomeningeal metastases, and other high-risk features were not eligible for HA whole-brain IMRT in the phase 3 NRG CC001 trial.[296]

## Summary

In summary, the NCCN Guidelines for SCLC v1.2024 has recommendations for diagnosis, evaluation, therapy options and surveillance for both limited-stage and extensive-stage SCLC. These recommendations are based on data from clinical trials and panel expertise.

## References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. CA Cancer J Clin 2022;72:7-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35020204.

2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2018, based on November 2020 SEER data submission, posted to the SEER web site, April 2021. Bethesda, MD: National Cancer Institute. Available at: https://seer.cancer.gov/csr/1975_2018/.

3. Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. J Clin Oncol 2006;24:4539-4544. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17008692.

4. SEER*Explorer: An interactive website for SEER cancer statistics [Internet]. Surveillance Research Program National Cancer Institute. Available at: https://seer.cancer.gov/statistics network/explorer/.

5. Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. Int J Cancer 2012;131:1210-1219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22052329.

6. Videtic GMM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol 2003;21:1544-1549. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12697879.

7. Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e61S-e77S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23649454.

8. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol 2004;22:2730-2739. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15226341.

9. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer 1997;79:1729-1736. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9128989.

10. Kalemkerian GP. Advances in the treatment of small-cell lung cancer. Semin Respir Crit Care Med 2011;32:94-101. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21500128.

11. Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. Oncologist 2010;15:187-195. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20145192.

12. Verma V, Hasan S, Wegner RE, et al. Stereotactic ablative radiation therapy versus conventionally fractionated radiation therapy for stage I small cell lung cancer. Radiother Oncol 2019;131:145-149. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30773182.

13. Haque W, Verma V, Polamraju P, et al. Stereotactic body radiation therapy versus conventionally fractionated radiation therapy for early stage non-small cell lung cancer. Radiother Oncol 2018;129:264-269. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30031630.

14. Shioyama Y, Onishi H, Takayama K, et al. Clinical outcomes of stereotactic body radiotherapy for patients with stage I small-cell lung cancer: analysis of a subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database. Technol Cancer Res Treat 2018;17:1533033818783904. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29983096.

15. Yang CF, Chan DY, Shah SA, et al. Long-term Survival After Surgery Compared With Concurrent Chemoradiation for Node-negative Small Cell Lung Cancer. Ann Surg 2018;268:1105-1112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28475559.

16. Verma V, Simone CB, 2nd, Allen PK, et al. Multi-Institutional Experience of Stereotactic Ablative Radiation Therapy for Stage I Small Cell Lung Cancer. Int J Radiat Oncol Biol Phys 2017;97:362-371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28011047.

17. Yu JB, Decker RH, Detterbeck FC, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. J Thorac Oncol 2010;5:215-219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20101146.

18. Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. Eur Respir J 2010;35:202-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20044461.

19. Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e400S-e419S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23649448.

20. Demetri G, Elias A, Gershenson D, et al. NCCN Small-Cell Lung Cancer Practice Guidelines. The National Comprehensive Cancer Network. Oncology (Williston Park) 1996;10:179-194. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8953602.

21. Freedman-Cass DA, Fischer T, Alpert AB, et al. The value and process of inclusion: Using sensitive, respectful, and inclusive language and images in NCCN content. J Natl Compr Canc Netw 2023;21:434-441. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37156485.

22. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21714641.

23. Cuffe S, Moua T, Summerfield R, et al. Characteristics and outcomes of small cell lung cancer patients diagnosed during two lung cancer computed tomographic screening programs in heavy smokers. J Thorac Oncol 2011;6:818-822. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21623258.

24. Thomas A, Pattanayak P, Szabo E, Pinsky P. Characteristics and Outcomes of Small Cell Lung Cancer Detected by CT Screening. Chest 2018;154:1284-1290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30080997.

25. Kondo R, Yoshida K, Kawakami S, et al. Different efficacy of CT screening for lung cancer according to histological type: analysis of Japanese-smoker cases detected using a low-dose CT screen. Lung Cancer 2011;74:433-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21663995.

26. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e142S-e165S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23649436.

27. Travis WD. Advances in neuroendocrine lung tumors. Ann Oncol 2010;21 Suppl 7:vii65-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20943645.

28. Renshaw AA, Haja J, Lozano RL, et al. Distinguishing carcinoid tumor from small cell carcinoma of the lung: correlating cytologic features and performance in the College of American Pathologists Non-Gynecologic Cytology Program. Arch Pathol Lab Med 2005;129:614-618. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15859631.

29. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. J Natl Compr Canc Netw 2006;4:631-638. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16813730.

30. Kazarian M, Laird-Offringa IA. Small-cell lung cancer-associated autoantibodies: potential applications to cancer diagnosis, early detection, and therapy. Mol Cancer 2011;10:33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21450098.

31. Marchioli CC, Graziano SL. Paraneoplastic syndromes associated with small cell lung cancer. Chest Surg Clin N Am 1997;7:65-80. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9001756.

32. Titulaer MJ, Wirtz PW, Willems LN, et al. Screening for small-cell lung cancer: a follow-up study of patients with Lambert-Eaton myasthenic syndrome. J Clin Oncol 2008;26:4276-4281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18779614.

33. Meriney SD, Hulsizer SC, Lennon VA, Grinnell AD. Lambert-Eaton myasthenic syndrome immunoglobulins react with multiple types of calcium channels in small-cell lung carcinoma. Ann Neurol 1996;40:739-749. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8957015.

34. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001;124:1138-1148. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11353730.

35. Delisle L, Boyer MJ, Warr D, et al. Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. Arch Intern Med 1993;153:746-752. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8383484.

36. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. Am J Respir Crit Care Med 1997;156:1669-1678. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9372692.

37. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. Oncologist 2012;17:756-765. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22618570.

38. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-2112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17105757.

39. Verbalis JG, Zeltser D, Smith N, et al. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolaemic hyponatraemia: subgroup analysis of a randomized, controlled study. Clin Endocrinol (Oxf) 2008;69:159-168. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18034777.

40. Travis WD. Pathology and diagnosis of neuroendocrine tumors: lung neuroendocrine. Thorac Surg Clin 2014;24:257-266. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25065926.

41. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. Am J Surg Pathol 2002;26:1184-1197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12218575.

42. Zakowski MF. Pathology of small cell carcinoma of the lung. Semin Oncol 2003;30:3-8. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12635085.

43. Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. Am J Surg Pathol 2005;29:179-187. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15644774.

44. Bellizzi AM. Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you? Hum Pathol 2020;96:8-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31857137.

45. Thunnissen E, Borczuk AC, Flieder DB, et al. The Use of Immunohistochemistry Improves the Diagnosis of Small Cell Lung Cancer and Its Differential Diagnosis. An International Reproducibility Study in a Demanding Set of Cases. J Thorac Oncol 2017;12:334-346. Available at: https://pubmed.ncbi.nlm.nih.gov/27998793.

46. Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. Endocr Relat Cancer 2014;21:1-16. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24344249.

47. Travis WD, Brambilla E, Burke AP, et al. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Fourth edition. Geneva, Switzerland: World Health Organization; 2015.

48. Rindi G, Klimstra DS, Abedi-Ardekani B, et al. A common classification framework for neuroendocrine neoplasms: an International Agency for Research on Cancer (IARC) and World Health Organization (WHO) expert consensus proposal. Mod Pathol 2018;31:1770-1786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30140036.

49. Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. J Thorac Oncol 2014;9:273-284. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24518085.

50. Masai K, Tsuta K, Kawago M, et al. Expression of squamous cell carcinoma markers and adenocarcinoma markers in primary pulmonary neuroendocrine carcinomas. Appl Immunohistochem Mol Morphol 2013;21:292-297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23060301.

51. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. Am J Surg Pathol 2000;24:1217-1223. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10976695.

52. Kaufmann O, Dietel M. Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinomas and other neuroendocrine carcinomas of various primary sites. Histopathology 2000;36:415-420. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10792482.

53. Rooper LM, Sharma R, Li QK, et al. INSM1 Demonstrates Superior Performance to the Individual and Combined Use of Synaptophysin, Chromogranin and CD56 for Diagnosing Neuroendocrine Tumors of the Thoracic Cavity. Am J Surg Pathol 2017;41:1561-1569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28719469.

54. Sakakibara R, Kobayashi M, Takahashi N, et al. Insulinoma-associated Protein 1 (INSM1) Is a Better Marker for the Diagnosis and Prognosis Estimation of Small Cell Lung Carcinoma Than Neuroendocrine Phenotype Markers Such as Chromogranin A, Synaptophysin, and CD56. Am J Surg Pathol 2020;44:757-764. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32118626.

55. Guinee DG, Jr., Fishback NF, Koss MN, et al. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. Am J Clin Pathol 1994;102:406-414. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7524299.

56. Rekhtman N, Pietanza CM, Sabari J, et al. Pulmonary large cell neuroendocrine carcinoma with adenocarcinoma-like features: napsin A expression and genomic alterations. Mod Pathol 2018;31:111-121. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28884744.

57. George J, Lim JS, Jang SJ, et al. Comprehensive genomic profiles of small cell lung cancer. Nature 2015;524:47-53. Available at: https://pubmed.ncbi.nlm.nih.gov/26168399.

58. Rudin CM, Brambilla E, Faivre-Finn C, Sage J. Small-cell lung cancer. Nat Rev Dis Primers 2021;7:3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33446664.

59. Su S, Zou JJ, Zeng YY, et al. Tumor mutational burden and genomic alterations in chinese small cell lung cancer measured by whole-exome sequencing. Biomed Res Int 2019;2019:6096350. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31781628.

60. Wakuda K, Kenmotsu H, Serizawa M, et al. Molecular profiling of small cell lung cancer in a Japanese cohort. Lung Cancer 2014;84:139-144. Available at: https://pubmed.ncbi.nlm.nih.gov/24657128.

61. Liguori NR, Lee Y, Borges W, et al. Absence of biomarker-driven treatment options in small cell lung cancer, and selected preclinical candidates for next generation combination therapies. Front Pharmacol

2021;12:747180. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34531756.

62. Ogino A, Choi J, Lin M, et al. Genomic and pathological heterogeneity in clinically diagnosed small cell lung cancer in never/light smokers identifies therapeutically targetable alterations. Mol Oncol 2021;15:27-42. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32191822.

63. Tsao MS, Nicholson AG, Maleszewski JJ, et al. Introduction to 2021 WHO classification of thoracic tumors. J Thorac Oncol 2022;17:e1-e4. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34930611.

64. WHO Classification of Tumours Editorial Board. Thoracic Tumours. In: WHO classification or tumours series. 5th ed. WHO classification or tumours series. Lyon, France: International Agency for Research on Cancer; 2021.

65. Sanguedolce F, Zanelli M, Palicelli A, et al. The classification of neuroendocrine neoplasms of the lung and digestive system according to WHO, 5th edition: similarities, differences, challenges, and unmet needs. Panminerva Med 2022;64:259-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35146989.

66. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. J Thorac Oncol 2015;10:1243-1260. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26291008.

67. Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. J Thorac Oncol 2015;10:1240-1242. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26291007.

68. Qin J, Lu H. Combined small-cell lung carcinoma. Onco Targets Ther 2018;11:3505-3511. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29950855.

69. Marcoux N, Gettinger SN, O'Kane G, et al. EGFR-mutant adenocarcinomas that transform to small-cell lung cancer and other neuroendocrine carcinomas: Clinical outcomes. J Clin Oncol 2019;37:278-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30550363.

70. Sehgal K, Varkaris A, Viray H, et al. Small cell transformation of non-small cell lung cancer on immune checkpoint inhibitors: uncommon or under-recognized? J Immunother Cancer 2020;8:e000697. Available at: https://pubmed.ncbi.nlm.nih.gov/32581048.

71. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer 2002;37:271-276. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12234695.

72. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. J Natl Compr Canc Netw 2013;11:99-104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23307985.

73. Kalemkerian GP. Staging and imaging of small cell lung cancer. Cancer Imaging 2012;11:253-258. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22245990.

74. Amin MB, Greene FL, Byrd DR, et al. AJCC Cancer Staging Manual, 8th edition: Springer International Publishing; 2016:1-1024.

75. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: Proposals for the Revision of the Clinical and Pathologic Staging of Small Cell Lung Cancer in the Forthcoming Eighth Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:300-311. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26723244.

76. Seute T, Leffers P, ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). Cancer 2008;112:1827-1834. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18311784.

77. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol 2007;18:338-345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17060487.

78. Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. Eur J Nucl Med Mol Imaging 2004;31:1614-1620. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15258700.

79. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw 2009;7 Suppl 2:S1-26. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19555588.

80. Bradley JD, Dehdashti F, Mintun MA, et al. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. J Clin Oncol 2004;22:3248-3254. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15310768.

81. Kamel EM, Zwahlen D, Wyss MT, et al. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. J Nucl Med 2003;44:1911-1917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14660716.

82. Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. J Thorac Oncol 2009;4:44-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19096305.

83. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. Curr Opin Pulm Med 2009;15:334-342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19395972.

84. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. Cancer 2009;115:2721-2731. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19402175.

85. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. J Clin Oncol 1990;8:1563-1574. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2167954.

86. Schneider BJ, Saxena A, Downey RJ. Surgery for early-stage small cell lung cancer. J Natl Compr Canc Netw 2011;9:1132-1139. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21975913.

87. Rostad H, Naalsund A, Jacobsen R, et al. Small cell lung cancer in Norway. Should more patients have been offered surgical therapy? Eur J Cardiothorac Surg 2004;26:782-786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15450573.

88. Inoue M, Miyoshi S, Yasumitsu T, et al. Surgical results for small cell lung cancer based on the new TNM staging system. Thoracic Surgery Study Group of Osaka University, Osaka, Japan. Ann Thorac Surg 2000;70:1615-1619. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11093496.

89. Brock MV, Hooker CM, Syphard JE, et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. J Thorac Cardiovasc Surg 2005;129:64-72. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15632826.

90. Lim E, Belcher E, Yap YK, et al. The role of surgery in the treatment of limited disease small cell lung cancer: time to reevaluate. J Thorac Oncol 2008;3:1267-1271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18978561.

91. Shields TW, Higgins GA, Jr., Matthews MJ, Keehn RJ. Surgical resection in the management of small cell carcinoma of the lung. J Thorac Cardiovasc Surg 1982;84:481-488. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6289013.

92. Ignatius Ou SH, Zell JA. The applicability of the proposed IASLC staging revisions to small cell lung cancer (SCLC) with comparison to the current UICC 6th TNM Edition. J Thorac Oncol 2009;4:300-310. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19156001.

93. Schreiber D, Rineer J, Weedon J, et al. Survival outcomes with the use of surgery in limited-stage small cell lung cancer: should its role be re-evaluated? Cancer 2010;116:1350-1357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20082453.

94. Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest 1994;106:320S-323S. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7988254.

95. Inoue M, Nakagawa K, Fujiwara K, et al. Results of preoperative mediastinoscopy for small cell lung cancer. Ann Thorac Surg 2000;70:1620-1623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11093497.

96. Shepherd FA, Evans WK, Feld R, et al. Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung. J Clin Oncol 1988;6:832-838. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2835443.

97. Tsuchiya R, Suzuki K, Ichinose Y, et al. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: the Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101). J Thorac Cardiovasc Surg 2005;129:977-983. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15867769.

98. Yang CF, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population-based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-1064. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26786925.

99. Yang Y, Zhang D, Zhou X, et al. Prophylactic cranial irradiation in resected small cell lung cancer: A systematic review with meta-analysis. J Cancer 2018;9:433-439. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29344290.

100. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. N Engl J Med 1999;341:476-484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10441603.

101. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med 1992;327:1618-1624. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1331787.

102. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. J Clin Oncol 1992;10:890-895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1316951.

103. Hatfield LA, Huskamp HA, Lamont EB. Survival and Toxicity After Cisplatin Plus Etoposide Versus Carboplatin Plus Etoposide for Extensive-Stage Small-Cell Lung Cancer in Elderly Patients. J Oncol Pract 2016;12:666-673. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27352949.

104. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol 1994;5:601-607. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7993835.

105. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer 2007;97:162-169. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17579629.

106. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. J Clin Oncol 2012;30:1692-1698. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22473169.

107. Griesinger F, Korol EE, Kayaniyil S, et al. Efficacy and safety of first-line carboplatin-versus cisplatin-based chemotherapy for non-small cell

lung cancer: A meta-analysis. Lung Cancer 2019;135:196-204. Available at: https://www.sciencedirect.com/science/article/pii/S0169500219305501.

108. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. Lancet Oncol 2017;18:1116-1125. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28642008.

109. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol 1985;3:1471-1477. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2997406.

110. Pujol JL, Carestia L, Daures JP. Is there a case for cisplatin in the treatment of small-cell lung cancer? A meta-analysis of randomized trials of a cisplatin-containing regimen versus a regimen without this alkylating agent. Br J Cancer 2000;83:8-15. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10883661.

111. Mascaux C, Paesmans M, Berghmans T, et al. A systematic review of the role of etoposide and cisplatin in the chemotherapy of small cell lung cancer with methodology assessment and meta-analysis. Lung Cancer 2000;30:23-36. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11008007.

112. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. J Clin Oncol 2002;20:4665-4672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12488411.

113. Niho S, Kubota K, Yoh K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with ipsilateral pleural effusion. J Thorac Oncol 2008;3:723-727. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18594317.

114. Niho S, Kubota K, Yoh K, et al. Clinical outcome of small cell lung cancer with pericardial effusion but without distant metastasis. J Thorac Oncol 2011;6:796-800. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21258253.

115. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol 2002;20:3054-3060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12118018.

116. Kubota K, Hida T, Ishikura S, et al. Etoposide and cisplatin versus irinotecan and cisplatin in patients with limited-stage small-cell lung cancer treated with etoposide and cisplatin plus concurrent accelerated hyperfractionated thoracic radiotherapy (JCOG0202): a randomised phase 3 study. Lancet Oncol 2014;15:106-113. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24309370.

117. Saito H, Takada Y, Ichinose Y, et al. Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. J Clin Oncol 2006;24:5247-5252. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17114657.

118. Bunn PA, Jr., Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7602352.

119. Liu SV, Reck M, Mansfield AS, et al. Updated overall survival and PD-L1 subgroup analysis of patients with extensive-stage small-cell lung cancer treated with atezolizumab, carboplatin, and etoposide (IMpower133). J Clin Oncol 2021;39:619-630. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33439693.

120. Paz-Ares L, Dvorkin M, Chen Y, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-

label, phase 3 trial. Lancet 2019;394:1929-1939. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31590988.

121. Horn L, Mansfield AS, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med 2018;379:2220-2229. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30280641.

122. Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. Radiother Oncol 1998;46:29-32. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9488124.

123. Goldman JW, Dvorkin M, Chen Y, et al. Durvalumab, with or without tremelimumab, plus platinum-etoposide versus platinum-etoposide alone in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): updated results from a randomised, controlled, open-label, phase 3 trial. Lancet Oncol 2021;22:51-65. Available at: https://pubmed.ncbi.nlm.nih.gov/33285097.

124. Paz-Ares L, Chen Y, Reinmuth N, et al. LBA61 - Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): 3-year overall survival update from the phase III CASPIAN study [abstract] Annals of Oncology 2021;32 (suppl_5):S1283-S1346. Available at: https://oncologypro.esmo.org/meeting-resources/esmo-congress-2021/durvalumab-tremelimumab-platinum-etoposide-in-first-line-extensive-stage-sclc-es-sclc-3-year-overall-survival-update-from-the-phase-iii-casp.

125. Mathieu L, Shah S, Pai-Scherf L, et al. FDA Approval Summary: Atezolizumab and Durvalumab in Combination with Platinum-Based Chemotherapy in Extensive Stage Small Cell Lung Cancer. Oncologist 2021;26:433-438. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33687763.

126. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. N Engl J Med 2002;346:85-91. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11784874.

127. Lara PN, Jr., Natale R, Crowley J, et al. Phase III trial of irinotecan/cisplatin compared with etoposide/cisplatin in extensive-stage small-cell lung cancer: clinical and pharmacogenomic results from SWOG S0124. J Clin Oncol 2009;27:2530-2535. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19349543.

128. Hanna N, Bunn PA, Jr, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer 10.1200/JCO.2005.04.8595. J Clin Oncol 2006;24:2038-2043. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16648503.

129. Hermes A, Bergman B, Bremnes R, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. J Clin Oncol 2008;26:4261-4267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18779613.

130. Lima JP, dos Santos LV, Sasse EC, et al. Camptothecins compared with etoposide in combination with platinum analog in extensive stage small cell lung cancer: systematic review with meta-analysis. J Thorac Oncol 2010;5:1986-1993. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20978445.

131. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol 2001;19:2114-2122. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11304763.

132. Zhou H, Zeng C, Wei Y, et al. Duration of chemotherapy for small cell lung cancer: a meta-analysis. PLoS One 2013;8:e73805. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24023692.

133. Goldie JH, Coldman AJ. A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 1979;63:1727-1733. Available at: https://www.ncbi.nlm.nih.gov/pubmed/526911.

134. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst 1991;83:855-861. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1648142.

135. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1992;10:282-291. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1310103.

136. Loehrer PJ, Sr., Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: a Hoosier Oncology Group study. J Clin Oncol 1995;13:2594-2599. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7595712.

137. Pujol JL, Daures JP, Riviere A, et al. Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. J Natl Cancer Inst 2001;93:300-308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11181777.

138. Miyamoto H, Nakabayashi T, Isobe H, et al. A phase III comparison of etoposide/cisplatin with or without added ifosfamide in small-cell lung cancer. Oncology 1992;49:431-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1334539.

139. Berghmans T, Scherpereel A, Meert AP, et al. A Phase III Randomized Study Comparing a Chemotherapy with Cisplatin and Etoposide to a Etoposide Regimen without Cisplatin for Patients with Extensive Small-Cell Lung Cancer. Front Oncol 2017;7:217. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28975084.

140. Jalal SI, Lavin P, Lo G, et al. Carboplatin and Etoposide With or Without Palifosfamide in Untreated Extensive-Stage Small-Cell Lung Cancer: A Multicenter, Adaptive, Randomized Phase III Study (MATISSE). J Clin Oncol 2017;35:2619-2623. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28605291.

141. Niell HB, Herndon JE, 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. J Clin Oncol 2005;23:3752-3759. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15923572.

142. Cohen MH, Creaven PJ, Fossieck BE, Jr., et al. Intensive chemotherapy of small cell bronchogenic carcinoma. Cancer Treat Rep 1977;61:349-354. Available at: https://www.ncbi.nlm.nih.gov/pubmed/194691.

143. Johnson DH, Einhorn LH, Birch R, et al. A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol 1987;5:1731-1738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2824707.

144. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 1994;12:2022-2034. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7931470.

145. Arriagada R, Le Chevalier T, Pignon JP, et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med 1993;329:1848-1852. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8247036.

146. Thatcher N, Girling DJ, Hopwood P, et al. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. J Clin Oncol 2000;18:395-404. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10637255.

147. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol 1991;9:499-508. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1847968.

148. Miles DW, Earl HM, Souhami RL, et al. Intensive weekly chemotherapy for good-prognosis patients with small-cell lung cancer. J Clin Oncol 1991;9:280-285. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1846406.

149. Murray N, Gelmon K, Shah A. Potential for long-term survival in extensive stage small-cell lung cancer (ESCLC) with CODE chemotherapy and radiotherapy [abstract]. Lung Cancer 1994;11 (Suppl 1):99 Abstract 377. Available at:

150. Sculier JP, Paesmans M, Bureau G, et al. Multiple-drug weekly chemotherapy versus standard combination regimen in small-cell lung cancer: a phase III randomized study conducted by the European Lung Cancer Working Party. J Clin Oncol 1993;11:1858-1865. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8410110.

151. Souhami RL, Rudd R, Ruiz de Elvira MC, et al. Randomized trial comparing weekly versus 3-week chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. J Clin Oncol 1994;12:1806-1813. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8083704.

152. Fukuoka M, Masuda N, Negoro S, et al. CODE chemotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. Br J Cancer 1997;75:306-309. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9010043.

153. Murray N, Livingston RB, Shepherd FA, et al. Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an Intergroup Study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. J Clin Oncol 1999;17:2300-2308. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10561291.

154. Reck M, Luft A, Szczesna A, et al. Phase III Randomized Trial of Ipilimumab Plus Etoposide and Platinum Versus Placebo Plus Etoposide and Platinum in Extensive-Stage Small-Cell Lung Cancer. J Clin Oncol 2016;34:3740-3748. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27458307.

155. Petrioli R, Roviello G, Laera L, et al. Cisplatin, Etoposide, and Bevacizumab Regimen Followed by Oral Etoposide and Bevacizumab Maintenance Treatment in Patients With Extensive-Stage Small Cell Lung Cancer: A Single-Institution Experience. Clin Lung Cancer 2015;16:e229-234. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26072097.

156. Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol 2011;29:2215-2222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21502556.

157. Spigel DR, Greco FA, Zubkus JD, et al. Phase II trial of irinotecan, carboplatin, and bevacizumab in the treatment of patients with extensive-stage small-cell lung cancer. J Thorac Oncol 2009;4:1555-1560. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19875975.

158. Horn L, Dahlberg SE, Sandler AB, et al. Phase II study of cisplatin plus etoposide and bevacizumab for previously untreated, extensive-stage small-cell lung cancer: Eastern Cooperative Oncology Group Study E3501. J Clin Oncol 2009;27:6006-6011. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19826110.

159. Tiseo M, Boni L, Ambrosio F, et al. Italian, Multicenter, Phase III, Randomized Study of Cisplatin Plus Etoposide With or Without Bevacizumab as First-Line Treatment in Extensive-Disease Small-Cell Lung Cancer: The GOIRC-AIFA FARM6PMFJM Trial. J Clin Oncol 2017;35:1281-1287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28135143.

160. Pujol JL, Lavole A, Quoix E, et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial†. Ann

Oncol 2015;26:908-914. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25688059.

161. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med 1991;325:164-170. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1711156.

162. Berghmans T, Paesmans M, Lafitte JJ, et al. Role of granulocyte and granulocyte-macrophage colony-stimulating factors in the treatment of small-cell lung cancer: a systematic review of the literature with methodological assessment and meta-analysis. Lung Cancer 2002;37:115-123. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12140132.

163. Sculier JP, Paesmans M, Lecomte J, et al. A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. Br J Cancer 2001;85:1444-1451. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11720426.

164. Wang C, Zhu S, Miao C, et al. Safety and efficacy of pegylated recombinant human granulocyte colony-stimulating factor during concurrent chemoradiotherapy for small-cell lung cancer: a retrospective, cohort-controlled trial. BMC Cancer 2022;22:542. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35562713.

165. Ferrarotto R, Anderson I, Medgyasszay B, et al. Trilaciclib prior to chemotherapy reduces the usage of supportive care interventions for chemotherapy-induced myelosuppression in patients with small cell lung cancer: Pooled analysis of three randomized phase 2 trials. Cancer Med 2021;10:5748-5756. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34405547.

166. Hussein M, Maglakelidze M, Richards DA, et al. Myeloprotective Effects of Trilaciclib Among Patients with Small Cell Lung Cancer at Increased Risk of Chemotherapy-Induced Myelosuppression: Pooled Results from Three Phase 2, Randomized, Double-Blind, Placebo-Controlled Studies. Cancer Manag Res 2021;13:6207-6218. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34408488.

167. Weiss J, Goldschmidt J, Andric Z, et al. Effects of Trilaciclib on Chemotherapy-Induced Myelosuppression and Patient-Reported Outcomes in Patients with Extensive-Stage Small Cell Lung Cancer: Pooled Results from Three Phase II Randomized, Double-Blind, Placebo-Controlled Studies. Clin Lung Cancer 2021;22:449-460. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33895103.

168. Hart LL, Ferrarotto R, Andric ZG, et al. Myelopreservation with Trilaciclib in Patients Receiving Topotecan for Small Cell Lung Cancer: Results from a Randomized, Double-Blind, Placebo-Controlled Phase II Study. Adv Ther 2021;38:350-365. Available at: https://pubmed.ncbi.nlm.nih.gov/33123968.

169. Hurria A, Kris MG. Management of lung cancer in older adults. CA Cancer J Clin 2003;53:325-341. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15224973.

170. Christodoulou M, Blackhall F, Mistry H, et al. Compliance and Outcome of Elderly Patients Treated in the Concurrent Once-Daily Versus Twice-Daily Radiotherapy (CONVERT) Trial. J Thorac Oncol 2019;14:63-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30391573.

171. Corso CD, Rutter CE, Park HS, et al. Role of Chemoradiotherapy in Elderly Patients With Limited-Stage Small-Cell Lung Cancer. J Clin Oncol 2015;33:4240-4246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26481366.

172. Gridelli C, Casaluce F, Sgambato A, et al. Treatment of limited-stage small cell lung cancer in the elderly, chemotherapy vs. sequential chemoradiotherapy vs. concurrent chemoradiotherapy: that's the question. Transl Lung Cancer Res 2016;5:150-154. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27186510.

173. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party.

Lancet 1996;348:563-566. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8774567.

174. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst 1997;89:577-580. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9106647.

175. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with Eastern Cooperative Oncology Group Performance Status of 2, or age > or = 70 years. J Clin Oncol 2004;22:1872-1877. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15143079.

176. Westeel V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: a phase II study of the PAVE regimen. J Clin Oncol 1998;16:1940-1947. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9586913.

177. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol 1999;17:3540-3545. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10550152.

178. Matsui K, Masuda N, Yana T, et al. Carboplatin calculated with Chatelut's formula plus etoposide for elderly patients with small-cell lung cancer. Intern Med 2001;40:603-606. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11506300.

179. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer. J Clin Oncol 1998;16:3323-3328. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9779708.

180. Damhuis RAM, Senan S, Belderbos JS. Usage of Prophylactic Cranial Irradiation in Elderly Patients With Small-cell Lung Cancer. Clin Lung Cancer 2018;19:e263-e267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29208355.

181. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:77-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20800380.

182. Le Pechoux C, Laplanche A, Faivre-Finn C, et al. Clinical neurological outcome and quality of life among patients with limited small-cell cancer treated with two different doses of prophylactic cranial irradiation in the intergroup phase III trial (PCI99-01, EORTC 22003-08004, RTOG 0212 and IFCT 99-01). Ann Oncol 2011;22:1154-1163. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21139020.

183. Farooqi AS, Holliday EB, Allen PK, et al. Prophylactic cranial irradiation after definitive chemoradiotherapy for limited-stage small cell lung cancer: Do all patients benefit? Radiother Oncol 2017;122:307-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28073578.

184. Lok BH, Ma J, Foster A, et al. Factors influencing the utilization of prophylactic cranial irradiation in patients with limited-stage small cell lung cancer. Adv Radiat Oncol 2017;2:548-554. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29204521.

185. Hurwitz JL, McCoy F, Scullin P, Fennell DA. New advances in the second-line treatment of small cell lung cancer. Oncologist 2009;14:986-994. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19819917.

186. Schneider BJ. Management of recurrent small cell lung cancer. J Natl Compr Canc Netw 2008;6:323-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18377850.

187. Manapov F, Klocking S, Niyazi M, et al. Timing of failure in limited disease (stage I-III) small-cell lung cancer patients treated with chemoradiotherapy: a retrospective analysis. Tumori 2013;99:656-660. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24503787.

188. Johnson BE, Linnoila RI, Williams JP, et al. Risk of second aerodigestive cancers increases in patients who survive free of small-cell

lung cancer for more than 2 years. J Clin Oncol 1995;13:101-111. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7799009.

189. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. J Natl Cancer Inst 1998;90:1335-1345. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9747865.

190. Richardson GE, Tucker MA, Venzon DJ, et al. Smoking cessation after successful treatment of small-cell lung cancer is associated with fewer smoking-related second primary cancers. Ann Intern Med 1993;119:383-390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8393311.

191. Kawahara M, Ushijima S, Kamimori T, et al. Second primary tumours in more than 2-year disease-free survivors of small-cell lung cancer in Japan: the role of smoking cessation. Br J Cancer 1998;78:409-412. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9703291.

192. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ 2010;340:b5569. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20093278.

193. Owonikoko TK, Behera M, Chen Z, et al. A systematic analysis of efficacy of second-line chemotherapy in sensitive and refractory small-cell lung cancer. J Thorac Oncol 2012;7:866-872. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22722788.

194. Genestreti G, Tiseo M, Kenmotsu H, et al. Outcomes of platinum-sensitive small-cell lung cancer patients treated with platinum/etoposide rechallenge: A multi-institutional retrospective analysis. Clin Lung Cancer 2015;16:e223-228. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25983005.

195. Subbiah V, Paz-Ares L, Besse B, et al. Antitumor activity of lurbinectedin in second-line small cell lung cancer patients who are candidates for re-challenge with the first-line treatment. Lung Cancer 2020;150:90-96. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33096421.

196. Dingemans AC, Fruh M, Ardizzoni A, et al. Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up(). Ann Oncol 2021;32:839-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33864941.

197. Baize N, Monnet I, Greillier L, et al. Carboplatin plus etoposide versus topotecan as second-line treatment for patients with sensitive relapsed small-cell lung cancer: an open-label, multicentre, randomised, phase 3 trial. Lancet Oncol 2020;21:1224-1233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32888454.

198. Naito Y, Yamada K, Imamura Y, et al. Rechallenge treatment with a platinum-based regimen in patients with sensitive relapsed small-cell lung cancer. Med Oncol 2018;35:61. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29610997.

199. Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol 1987;23:1697-1699. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2828074.

200. Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. Eur J Cancer Clin Oncol 1987;23:1409-1411. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2824211.

201. Trigo J, Subbiah V, Besse B, et al. Lurbinectedin as second-line treatment for patients with small-cell lung cancer: a single-arm, open-label, phase 2 basket trial. Lancet Oncol 2020;21:645-654. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32224306.

202. Aix SP, Ciuleanu TE, Navarro A, et al. Combination lurbinectedin and doxorubicin versus physician's choice of chemotherapy in patients with relapsed small-cell lung cancer (ATLANTIS): a multicentre, randomised, open-label, phase 3 trial. Lancet Respir Med 2023;11:74-86. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36252599.

203. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol 1999;17:658-667. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10080612.

204. Shah C, Ready N, Perry M, et al. A multi-center phase II study of weekly topotecan as second-line therapy for small cell lung cancer. Lung Cancer 2007;57:84-88. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17399850.

205. Shipley DL, Hainsworth JD, Spigel DR, et al. Topotecan: Weekly intravenous (IV) schedule similar to standard 5-day IV schedule as second-line therapy for relapsed small cell lung cancer (SCLC)--A Minnie Pearl Cancer Research Network phase II trial [abstract]. J Clin Oncol 2006;24 (Suppl 18):Abstract 7083. Available at: https://ascopubs.org/doi/abs/10.1200/jco.2006.24.18_suppl.7083.

206. Huber RM, Reck M, Gosse H, et al. Efficacy of a toxicity-adjusted topotecan therapy in recurrent small cell lung cancer. Eur Respir J 2006;27:1183-1189. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16481389.

207. O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. J Clin Oncol 2006;24:5441-5447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17135646.

208. Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 2007;25:2086-2092. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17513814.

209. Spigel DR, Vicente D, Ciuleanu TE, et al. Second-line nivolumab in relapsed small-cell lung cancer: CheckMate 331(☆). Ann Oncol 2021;32:631-641. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33539946.

210. Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. J Clin Oncol 1992;10:1225-1229. Available at: https://www.ncbi.nlm.nih.gov/pubmed/1321891.

211. Edelman MJ, Dvorkin M, Laktionov K, et al. Randomized phase 3 study of the anti-disialoganglioside antibody dinutuximab and irinotecan vs irinotecan or topotecan for second-line treatment of small cell lung cancer. Lung Cancer 2022;166:135-142. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35278766.

212. Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: Results from the CheckMate 032 randomized cohort. J Thorac Oncol 2020;15:426-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31629915.

213. Antonia SJ, Lopez-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. Lancet Oncol 2016;17:883-895. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27269741.

214. Ott PA, Elez E, Hiret S, et al. Pembrolizumab in Patients With Extensive-Stage Small-Cell Lung Cancer: Results From the Phase Ib KEYNOTE-028 Study. J Clin Oncol 2017;35:3823-3829. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28813164.

215. Horn L, Reck M, Spigel DR. The Future of Immunotherapy in the Treatment of Small Cell Lung Cancer. Oncologist 2016;21:910-921. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27354668.

216. Reck M, Vicente D, Ciuleanu T, et al. LBA5: Efficacy and safety of nivolumab (nivo) monotherapy versus chemotherapy (chemo) in recurrent small cell lung cancer (SCLC): Results from CheckMate 331 [abstract]. Ann Oncol 2018;29:43. Available at: https://academic.oup.com/annonc/article/29/suppl_10/mdy511.004/5238042.

217. Keeping ST, Cope S, Chan K, et al. Comparative effectiveness of nivolumab versus standard of care for third-line patients with small-cell lung cancer. J Comp Eff Res 2020;9:1275-1284. Available at: https://pubmed.ncbi.nlm.nih.gov/33140652.

218. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. Pembrolizumab after two or more lines of previous therapy in patients with recurrent or metastatic SCLC: Results from the KEYNOTE-028 and KEYNOTE-158 studies. J Thorac Oncol 2020;15:618-627. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31870883.

219. Chung HC, Piha-Paul SA, Lopez-Martin J, et al. CT073 - Pembrolizumab after two or more lines of prior therapy in patients with advanced small-cell lung cancer (SCLC): Results from the KEYNOTE-028 and KEYNOTE-158 studies [abstract]. AACR Annual Meeting. Atlanta, GA; 2019:Abstract CT073. Available at: https://www.abstractsonline.com/pp8/#!/6812/presentation/9832.

220. Rea F, Rizzardi G, Zuin A, et al. Outcome and surgical strategy in bronchial carcinoid tumors: single institution experience with 252 patients. Eur J Cardiothorac Surg 2007;31:186-191. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17140801.

221. Hellmann MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032 [abstract]. J Clin Oncol 2017;35:Abstract 8503. Available at: http://www.jto.org/article/S1556-0864(16)31687-2/abstract.

222. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. Immunotargets Ther 2017;6:51-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28894725.

223. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of Pneumonitis With Use of Programmed Death 1 and Programmed Death-Ligand 1 Inhibitors in Non-Small Cell Lung Cancer: A Systematic Review and Meta-Analysis of Trials. Chest 2017;152:271-281. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28499515.

224. Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. Anticancer Res 2006;26:777-781. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16739353.

225. Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. Br J Cancer 1998;77:347-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9461009.

226. von Eiff D, Bozorgmehr F, Chung I, et al. Paclitaxel for treatment of advanced small cell lung cancer (SCLC): a retrospective study of 185 patients. J Thorac Dis 2020;12:782-793. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32274145.

227. Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. The Early Clinical Trials Group of the EORTC. Eur J Cancer 1994;30A:1058-1060. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7654428.

228. Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. J Clin Oncol 1990;8:1613-1617. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2170589.

229. Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer: a Hoosier Oncology Group study. Semin Oncol 1990;17:32-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/2154857.

230. Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol 2003;21:1550-1555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12697880.

231. van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. Ann Oncol 2001;12:557-561. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11398892.

232. Pietanza MC, Waqar SN, Krug LM, et al. Randomized, Double-Blind, Phase II Study of Temozolomide in Combination With Either Veliparib or Placebo in Patients With Relapsed-Sensitive or Refractory Small-Cell

Lung Cancer. J Clin Oncol 2018;36:2386-2394. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29906251.

233. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. Lung Cancer 2014;86:237-240. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25194640.

234. Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide in patients with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res 2012;18:1138-1145. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22228633.

235. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2016;17:1147-1157. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27312053.

236. Higgins KA, Simone CB, 2nd, Amini A, et al. American Radium Society Appropriate Use Criteria on radiation therapy for extensive-stage SCLC. J Thorac Oncol 2021;16:54-65. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33011389.

237. Chun SG, Simone CB, 2nd, Amini A, et al. American Radium Society Appropriate Use Criteria: Radiation therapy for limited-stage SCLC 2020. J Thorac Oncol 2021;16:66-75. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33166720.

238. Simone CB, 2nd, Bogart JA, Cabrera AR, et al. Radiation therapy for small cell lung cancer: An ASTRO Clinical Practice Guideline. Pract Radiat Oncol 2020;10:158-173. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32222430.

239. Kong FM, Lally BE, Chang JY, et al. ACR Appropriateness Criteria® radiation therapy for small-cell lung cancer. Am J Clin Oncol 2013;36:206-213. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23511336.

240. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol 2004;22:4837-4845. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15570087.

241. Pijls-Johannesma M, De Ruysscher D, Vansteenkiste J, et al. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. Cancer Treat Rev 2007;33:461-473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17513057.

242. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 1993;11:336-344. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8381164.

243. De Ruysscher D, Bremer RH, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. Radiother Oncol 2006;80:307-312. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16949169.

244. De Ruysscher D, Lueza B, Le Pechoux C, et al. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. Ann Oncol 2016;27:1818-1828. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27436850.

245. Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340:265-271. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9920950.

246. Ganti AK, Dueck AC, Fruth B, et al. Comparison of quality of life in patients randomized to high-dose once daily (QD) thoracic radiotherapy (TRT) with standard twice daily (BID) TRT in limited stage small cell lung

cancer (LS-SCLC) on CALGB 30610 (Alliance, Sub-study CALGB 70702) [abstract]. J Clin Oncol 2022;40:Abstract 8504-8504. Available at: https://doi.org/10.1200/JCO.2022.40.16_suppl.8504.

247. Bogart JA, Wang X, Masters GA, et al. Short Communication: Interim toxicity analysis for patients with limited stage small cell lung cancer (LSCLC) treated on CALGB 30610 (Alliance) / RTOG 0538. Lung Cancer 2021;156:68-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33894496.

248. Gronberg BH, Halvorsen TO, Flotten O, et al. Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer. Acta Oncol 2016;55:591-597. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26494411.

249. Turgeon GA, Souhami L, Kopek N, et al. Thoracic irradiation in 3weeks for limited-stage small cell lung cancer: Is twice a day fractionation really needed? Cancer Radiother 2017;21:89-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28325618.

250. Qiu B, Li Q, Liu J, et al. Moderately Hypofractionated Once-Daily Compared With Twice-Daily Thoracic Radiation Therapy Concurrently With Etoposide and Cisplatin in Limited-Stage Small Cell Lung Cancer: A Multicenter, Phase II, Randomized Trial. Int J Radiat Oncol Biol Phys 2021;111:424-435. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33992717.

251. Gronberg BH, Killingberg KT, Flotten O, et al. High-dose versus standard-dose twice-daily thoracic radiotherapy for patients with limited stage small-cell lung cancer: an open-label, randomised, phase 2 trial. Lancet Oncol 2021;22:321-331. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33662285.

252. Bogart J, Wang X, Masters G, et al. High-Dose Once-Daily Thoracic Radiotherapy in Limited-Stage Small-Cell Lung Cancer: CALGB 30610 (Alliance)/RTOG 0538. J Clin Oncol 2023;41:2394-2402. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36623230.

253. Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;56:355-359. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12738309.

254. Roof KS, Fidias P, Lynch TJ, et al. Radiation dose escalation in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;57:701-708. Available at: https://www.ncbi.nlm.nih.gov/pubmed/14529774.

255. Bogart JA, Herndon JE, 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys 2004;59:460-468. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15145163.

256. Shirvani SM, Juloori A, Allen PK, et al. Comparison of 2 common radiation therapy techniques for definitive treatment of small cell lung cancer. Int J Radiat Oncol Biol Phys 2013;87:139-147. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23920393.

257. ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements (ICRU); 2010. Available at: https://www.icru.org/report/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrticru-report-83.

258. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21802333.

259. Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) Practice Guidelines for Intensity-Modulated Radiation Therapy (IMRT). Int J Radiat Oncol Biol Phys 2009;73:9-14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19100920.

260. Shirvani SM, Komaki R, Heymach JV, et al. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;82:e91-97. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21489716.

261. Chun SG, Hu C, Choy H, et al. Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial. J Clin Oncol 2017;35:56-62. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28034064.

262. ICRU Report 62: Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50). Bethesda, MD: The International Commission on Radiation Units and Measurement (ICRU); 1999. Available at: https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-62.

263. ICRU Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements (ICRU); 1993. Available at: https://www.icru.org/report/prescribing-recording-and-reporting-photon-beam-therapy-report-50.

264. Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small-cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. J Clin Oncol 1994;12:496-502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/8120547.

265. Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-215. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15703313.

266. Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 2009;91:282-287. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18950881.

267. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442-1457. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20934273.

268. Videtic GM, Stephans KL, Woody NM, et al. Stereotactic body radiation therapy-based treatment model for stage I medically inoperable small cell lung cancer. Pract Radiat Oncol 2013;3:301-306. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24674402.

269. Alongi F, Arcangeli S, De Bari B, et al. Stage-I small cell lung cancer: A new potential option for stereotactic ablative radiation therapy? A review of literature. Crit Rev Oncol Hematol 2017;112:67-71. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28325266.

270. Rathod S, Koul R, Bashir B, et al. Role of Stereotactic Body Radiation Therapy in Early Stage Small Cell Lung Cancer in the Era of Lung Cancer Screening: A Systematic Review. Am J Clin Oncol 2019;42:123-130. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30418179.

271. Shioyama Y, Nakamura K, Sasaki T, et al. Clinical results of stereotactic body radiotherapy for Stage I small-cell lung cancer: a single institutional experience. J Radiat Res 2013;54:108-112. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22923748.

272. Li C, Xiong Y, Zhou Z, et al. Stereotactic body radiotherapy with concurrent chemotherapy extends survival of patients with limited stage small cell lung cancer: a single-center prospective phase II study. Med Oncol 2014;31:369. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25416052.

273. Safavi AH, Mak DY, Boldt RG, et al. Stereotactic ablative radiotherapy in T1-2N0M0 small cell lung cancer: A systematic review and meta-analysis. Lung Cancer 2021;160:179-186. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34330566.

274. Verma V, Simone CB, 2nd, Allen PK, Lin SH. Outcomes of stereotactic body radiotherapy for T1-T2N0 small cell carcinoma according to addition of chemotherapy and prophylactic cranial irradiation: a multicenter analysis. Clin Lung Cancer 2017;18:675-681.e1. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28408183.

275. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol 1999;17:2092-2099. Available at: https://www.ncbi.nlm.nih.gov/pubmed/10561263.

276. Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015;385:36-42. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25230595.

277. Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. Radiother Oncol 2012;102:234-238. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21930323.

278. Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer - Authors' reply. Lancet 2015;385:1292-1293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25890910.

279. Putora PM, Glatzer M, De Ruysscher D, et al. Consolidative thoracic radiotherapy in stage IV small cell lung cancer: Selection of patients amongst European IASLC and ESTRO experts. Radiother Oncol 2019;135:74-77. Available at: https://pubmed.ncbi.nlm.nih.gov/31015173.

280. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 1995;87:183-190. Available at: https://www.ncbi.nlm.nih.gov/pubmed/7707405.

281. Tomassen ML, Pomp J, van der Stap J, et al. The overall survival impact of prophylactic cranial irradiation in limited-stage small-cell lung cancer: A systematic review and meta-analysis. Clin Transl Radiat Oncol 2022;33:145-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35243025.

282. Patel S, Macdonald OK, Suntharalingam M. Evaluation of the use of prophylactic cranial irradiation in small cell lung cancer. Cancer 2009;115:842-850. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19117355.

283. Eze C, Roengvoraphoj O, Niyazi M, et al. Treatment Response and Prophylactic Cranial Irradiation Are Prognostic Factors in a Real-life Limited-disease Small-cell Lung Cancer Patient Cohort Comprehensively Staged With Cranial Magnetic Resonance Imaging. Clin Lung Cancer 2017;18:e243-e249. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28065620.

284. Held MK, Hansen O, Schytte T, et al. Outcomes of prophylactic cranial irradiation in patients with small cell lung cancer in the modern era of baseline magnetic resonance imaging of the brain. Acta Oncol 2022;61:185-192. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34583620.

285. Sharma S, McMillan MT, Doucette A, et al. Effect of Prophylactic Cranial Irradiation on Overall Survival in Metastatic Small-Cell Lung Cancer: A Propensity Score-Matched Analysis. Clin Lung Cancer 2018;19:260-269.e3. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29358031.

286. Bang A, Kendal WS, Laurie SA, et al. Prophylactic Cranial Irradiation in Extensive Stage Small Cell Lung Cancer: Outcomes at a Comprehensive Cancer Centre. Int J Radiat Oncol Biol Phys 2018;101:1133-1140. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29908788.

287. Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-672. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17699816.

288. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncol 2017;18:663-671. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28343976.

289. Lee JS, Umsawasdi T, Lee YY, et al. Neurotoxicity in long-term survivors of small cell lung cancer. Int J Radiat Oncol Biol Phys 1986;12:313-321. Available at: https://www.ncbi.nlm.nih.gov/pubmed/3007407.

290. Slotman BJ, Senan S. Radiotherapy in small-cell lung cancer: lessons learned and future directions. Int J Radiat Oncol Biol Phys 2011;79:998-1003. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21353159.

291. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol 2009;27:78-84. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19047288.

292. Pechoux CL, Sun A, Slotman BJ, et al. Prophylactic cranial irradiation for patients with lung cancer. Lancet Oncol 2016;17:e277-e293. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27396646.

293. Eze C, Roengvoraphoj O, Manapov F. Prophylactic cranial irradiation in resected early-stage small cell lung cancer. Int J Radiat Oncol Biol Phys 2017;98:612-614. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28581402.

294. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 2009;10:467-474. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19386548.

295. Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. Neuro Oncol 2013;15:1429-1437. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23956241.

296. Brown PD, Gondi V, Pugh S, et al. Hippocampal Avoidance During Whole-Brain Radiotherapy Plus Memantine for Patients With Brain Metastases: Phase III Trial NRG Oncology CC001. J Clin Oncol 2020;38:1019-1029. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32058845.

297. Rodriguez de Dios N, Counago F, Murcia-Mejia M, et al. Randomized Phase III Trial of Prophylactic Cranial Irradiation With or Without Hippocampal Avoidance for Small-Cell Lung Cancer (PREMER): A GICOR-GOECP-SEOR Study. J Clin Oncol 2021;39:3118-3127. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34379442.

298. Belderbos JSA, De Ruysscher DKM, De Jaeger K, et al. Phase 3 Randomized Trial of Prophylactic Cranial Irradiation With or Without Hippocampus Avoidance in SCLC (NCT01780675). J Thorac Oncol 2021;16:840-849. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33545387.

299. Gondi V, Pugh SL, Mehta MP, et al. NRG Oncology CC003: A randomized phase II/III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small cell lung cancer [abstract]. J Clin Oncol 2019;37:TPS8578-TPS8578. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.TPS8578.

300. Maranzano E, Trippa F, Casale M, et al. 8Gy single-dose radiotherapy is effective in metastatic spinal cord compression: results of a phase III randomized multicentre Italian trial. Radiother Oncol 2009;93:174-179. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19520448.

301. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol

Phys 2011;79:965-976. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21277118.

302. Ferrell B, Koczywas M, Grannis F, Harrington A. Palliative care in lung cancer. Surg Clin North Am 2011;91:403-417, ix. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21419260.

303. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev 2012;4:CD003869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22513917.

304. Rusthoven CG, Yamamoto M, Bernhardt D, et al. Evaluation of First-line Radiosurgery vs Whole-Brain Radiotherapy for Small Cell Lung Cancer Brain Metastases: The FIRE-SCLC Cohort Study. JAMA Oncol 2020;6:1028-1037. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32496550.

305. Viani GA, Gouveia AG, Louie AV, Moraes FY. Stereotactic radiosurgery for brain metastases from small cell lung cancer without prior whole-brain radiotherapy: A meta-analysis. Radiother Oncol 2021;162:45-51. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34171453.

306. Bernhardt D, Bozorgmehr F, Adeberg S, et al. Outcome in patients with small cell lung cancer re-irradiated for brain metastases after prior prophylactic cranial irradiation. Lung Cancer 2016;101:76-81. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27794411.

307. Wegner RE, Olson AC, Kondziolka D, et al. Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:e21-27. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21345622.