National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Small Cell Lung Cancer

Version 2.2022 — November 24, 2021

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2022
# Small Cell Lung Cancer

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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.

Find an NCCN Member Institution: https://www.nccn.org/home/member-institutions.

**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.

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# NCCN Guidelines Version 2.2022
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Discussion

**Updates in Version 2.2022 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2022 include:**

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

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**Updates in Version 1.2022 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2021 include:**

**SCL-5**
- **Extensive stage with brain metastases; asymptomatic**
  - **May administer systemic therapy before *initiating* brain RT ~~after completion of induction systemic therapy~~**

**SCL-6**
- **Adjuvant RT**
  - **Complete response or partial response; limited stage**
    - ◊ **Prophylactic cranial irradiation**
      **– category 1 changed to category 2A**
  - **Complete response or partial response; extensive stage**
    - ◊ **Consider PCI or MRI brain surveillance changed to MRI brain surveillance ± Consider PCI**
- **Surveillance**
  - **Bullet 2**
    - ◊ **The following removed from the start of the bullet - At every visit**
    - ◊ **CT chest/abdomen/pelvis removed, see bullet 3**
  - **Bullet 3: Surveillance CT added with footnote x**
  - **Footnote x added: Most NCCN Member Institutions use CT chest ± abdomen/pelvis every 2-6 months (more frequently in years 1–2 and less frequently thereafter).**

**SCL-B 1 of 2**
- **Pathologic Evaluation**
  - **Bullet 7 modified: 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.***
- **Immunohistochemical Staining**
  - **Bullet 1; sub-bullet 2 modified: 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 ~~10%~~*5%* of SCLCs are negative for all neuroendocrine markers.**
  - **Bullet 1; sub-bullet 4 added: 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. It should, however, be noted that p40 and p63 can be focally positive in small cell carcinoma.**

**SCL-B 2 of 2**
- **References 11 and 12 added.**

**SCL-C**
- **Last bullet; sentence added: 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**

Continued

**UPDATES**

**Updates in Version 1.2022 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2021 include:**

**SCL-D**

- Bullet 3 modified: Trilaciclib *or G-CSF* may be used as ~~a~~ prophylactic option*s* to decrease the incidence of chemotherapy-induced myelosuppression when administer*ing*~~ed before (or G-CSF may be administered after)~~ platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (ES-SCLC).

**SCL-E 1 of 5**

- Primary Therapy for Extensive-Stage SCLC; Preferred Regimens
  - Regimen added: Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,680 mg day 1, every 28 days

**SCL-E 2 of 5**

- Relapse ≤6 months; Other Recommended Regimens
  - Nivolumab or pembrolizumab: category 3 changed to category 2A
- Relapse >6 months; Other Recommended Regimens
  - The following regimens added as category 2A: topotecan, paclitaxel, docetaxel, irinotecan, temozolomide, cyclophosphamide/doxorubicin/vincristine (CAV), oral etoposide, vinorelbine, gemcitabine, nivolumab, pembrolizumab.
  - The following regimens added as category 2B: bendamustine.
- Footnote d modified: ~~Regimen not recommended for relapsed disease in patients~~ *The use of immune checkpoint inhibitors is discouraged if there is progression* on maintenance atezolizumab or durvalumab at time of relapse.

**SCL-E 5 of 5**

- Reference 38 added.

**SCL-F 2 of 6**

- Limited stage
  - Sub-bullet 3; diamond 2 added: 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.
  - Sub-bullet 3; diamond 3 modified: If using once-daily *conventionally fractionated* RT, higher doses of ~~60~~66–70 Gy should be used. ~~The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks. The randomized, phase III European CONVERT trial did not demonstrate superiority of 66 Gy (once daily) over 45 Gy (BID), but overall survival and toxicity were comparable.~~ *Two randomized phase II 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.*
  - Sub-bullet 3, diamond 4 added: 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.

Continued

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**Updates in Version 1.2022 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2021 include:**

**SCL-F 4 of 6**

- **Prophylactic Cranial Irradiation**
  - **Bullet 3 removed: Consider hippocampal-sparing PCI using IMRT.**
  - **Bullet 3 added: 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 vs. 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 vs. 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 vs. conventional PCI, NRG CC003, is ongoing.**
  - **Bullet 4 removed: Current randomized trials are evaluating whether MRI surveillance alone is non-inferior to MRI surveillance plus PCI on overall survival and whether hippocampal-sparing PCI reduces memory impairment compared to whole brain PCI in LS-SCLC and ES-SCLC.**
  - **Bullet 4 added: 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.**
- **Brain Metastases**
  - **Bullet 1 modified: Brain metastases should typically be treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS). A current *randomized* trial, *NRG CC009*, is comparing SRS to hippocampal-sparing WBRT plus memantine in this setting.**

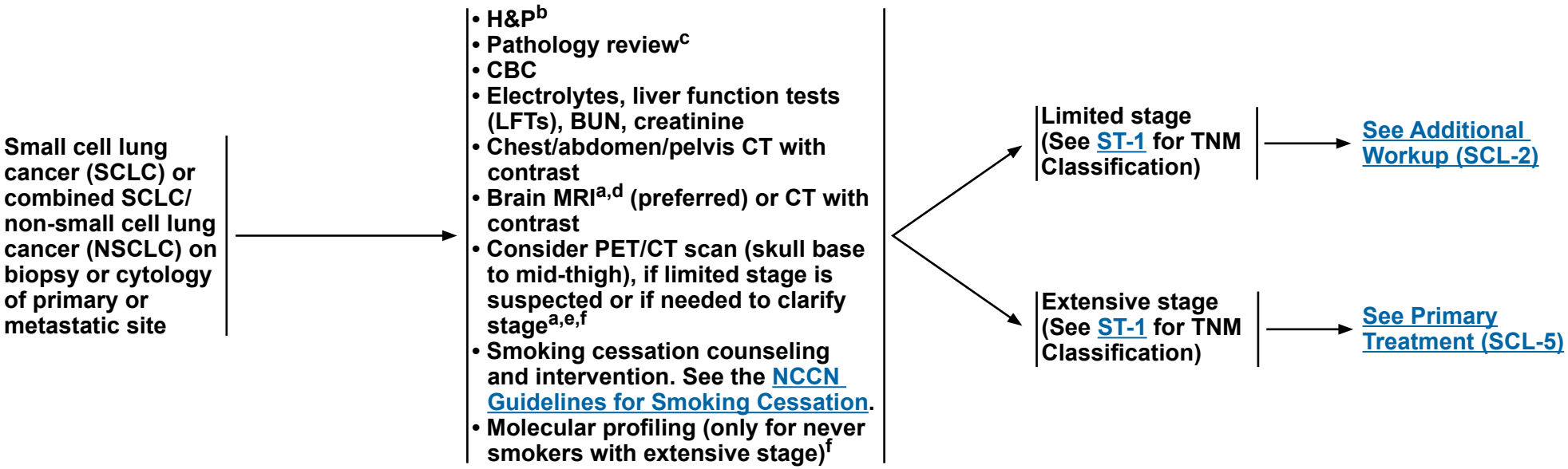
**SCL-F 5 of 6**

- **Reference 11 updated.**
- **References 18, 19, 25, 26 added.**

**SCL-F 6 of 6**

- **References 27, 42–45 added.**




[a] If extensive stage is established, further staging evaluation is optional. However, brain imaging MRI (preferred), or CT with contrast should be obtained in all patients.
[b] See Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[c] See Principles of Pathologic Review (SCL-B).
[d] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[e] If PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage.
[f] Molecular profiling may be considered in never smokers with extensive-stage SCLC to help clarify diagnosis and evaluate for potential targeted treatment options.

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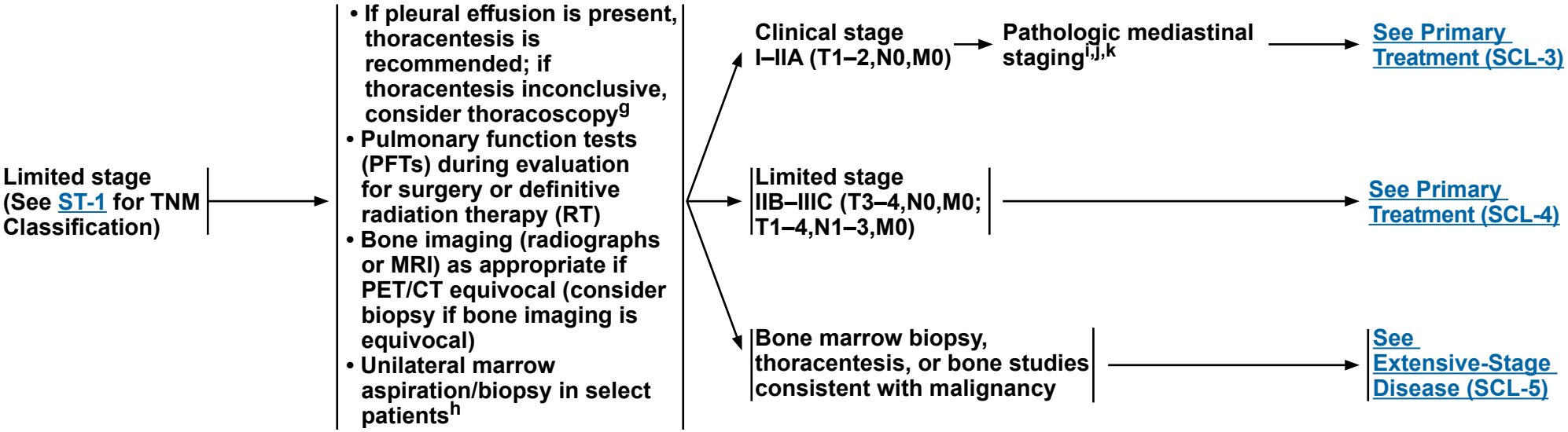


[g] While most pleural effusions in patients with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion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

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

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

[j] 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.

[k] Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.

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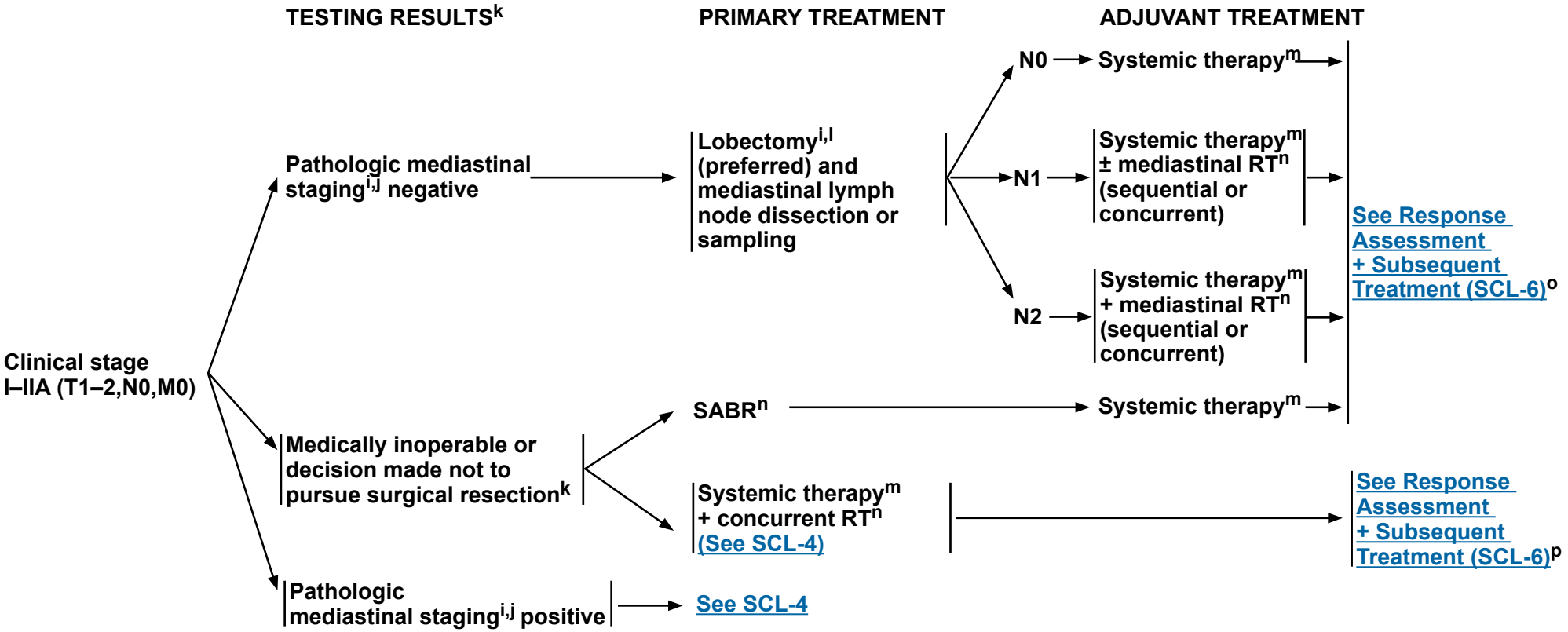


[i] See Principles of Surgical Resection (SCL-C).
[j] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.
[k] Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.
[l] Select patients may be treated with systemic therapy/RT as an alternative to surgical resection.
[m] See Principles of Systemic Therapy (SCL-E).
[n] See Principles of Radiation Therapy (SCL-F).
[o] For patients receiving adjuvant systemic therapy ± RT, response assessment should occur 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 should occur 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 chest/abdomen/pelvis CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy (SCL-6).

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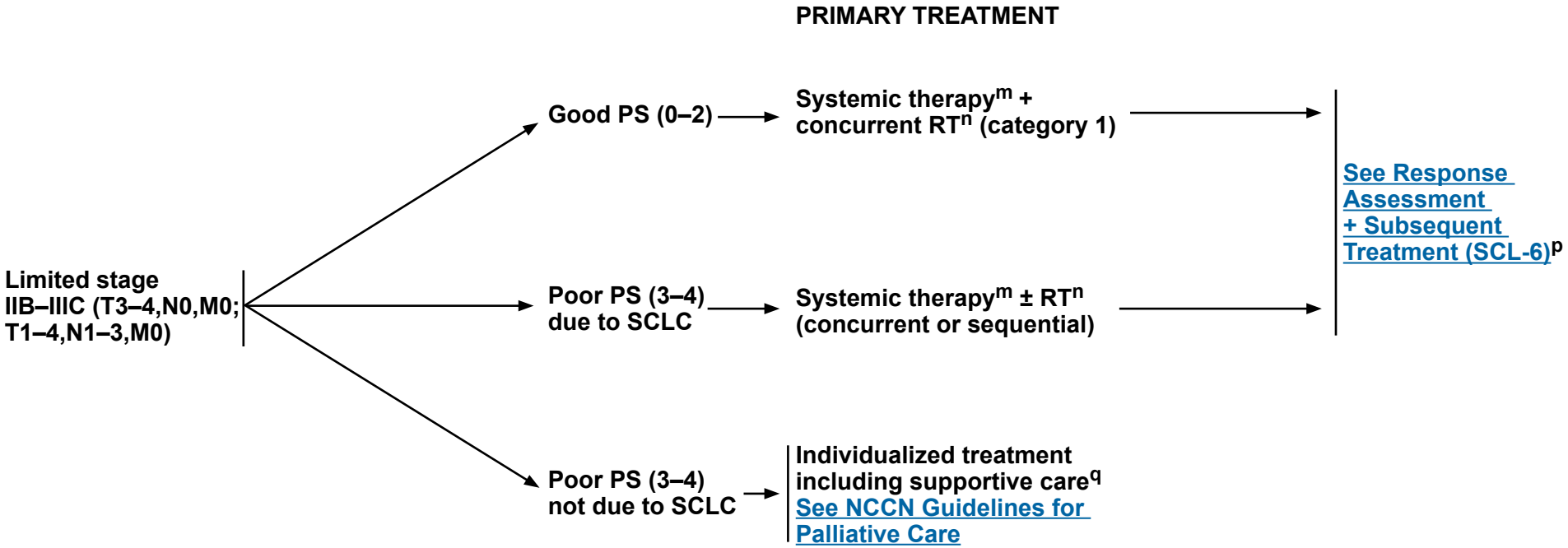


[m] See Principles of Systemic Therapy (SCL-E).
[n] See Principles of Radiation Therapy (SCL-F).
[p] For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy (SCL-6); do not repeat scans to assess response during initial treatment.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

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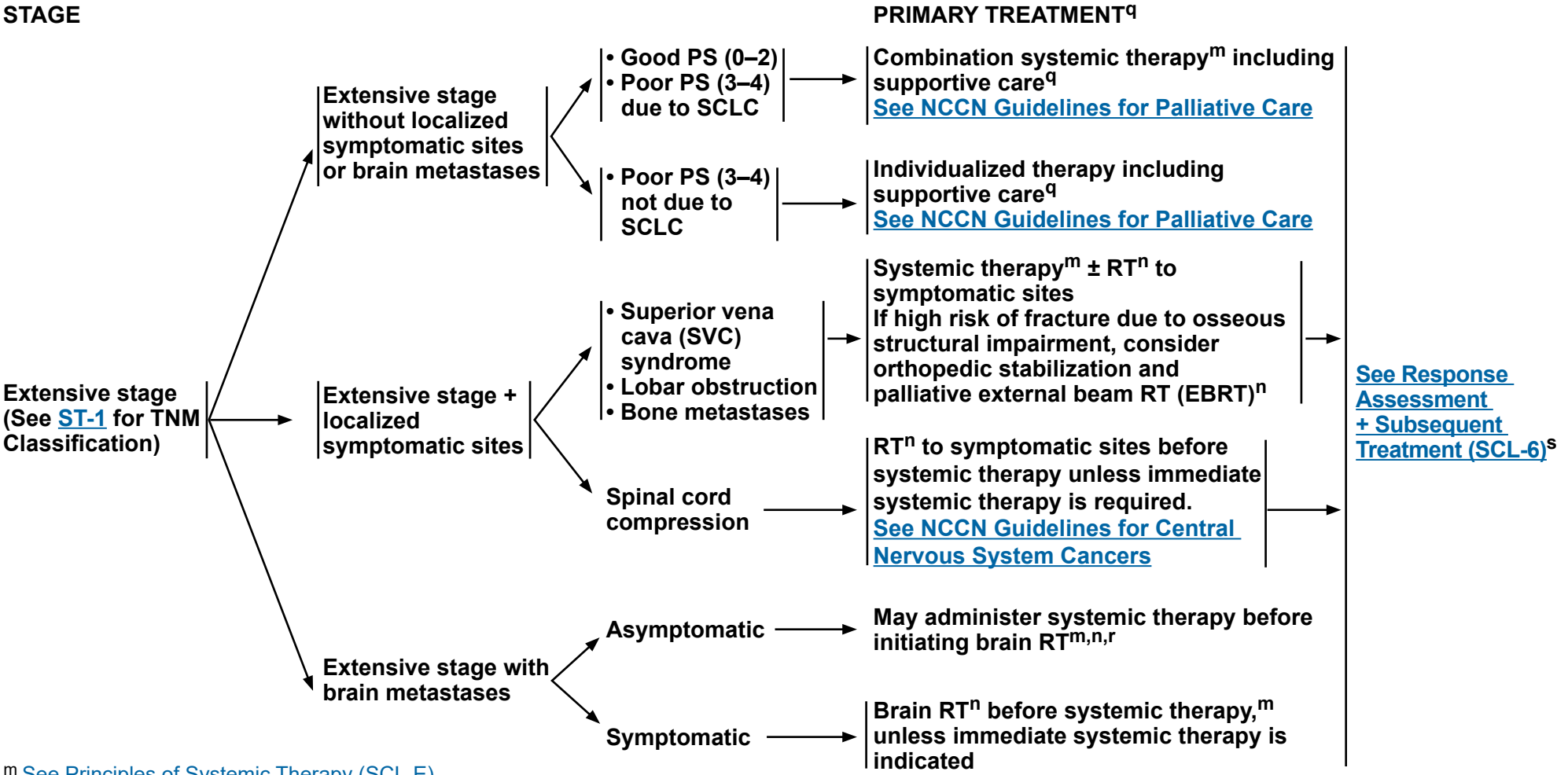


[m] See Principles of Systemic Therapy (SCL-E).
[n] See Principles of Radiation Therapy (SCL-F).
[q] See Principles of Supportive Care (SCL-D).
[r] Brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (see SCL-6). If brain metastases progress while on systemic therapy, brain RT should be initiated before completion of systemic therapy. See Principles of Radiation Therapy (SCL-F).
[s] During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-6).

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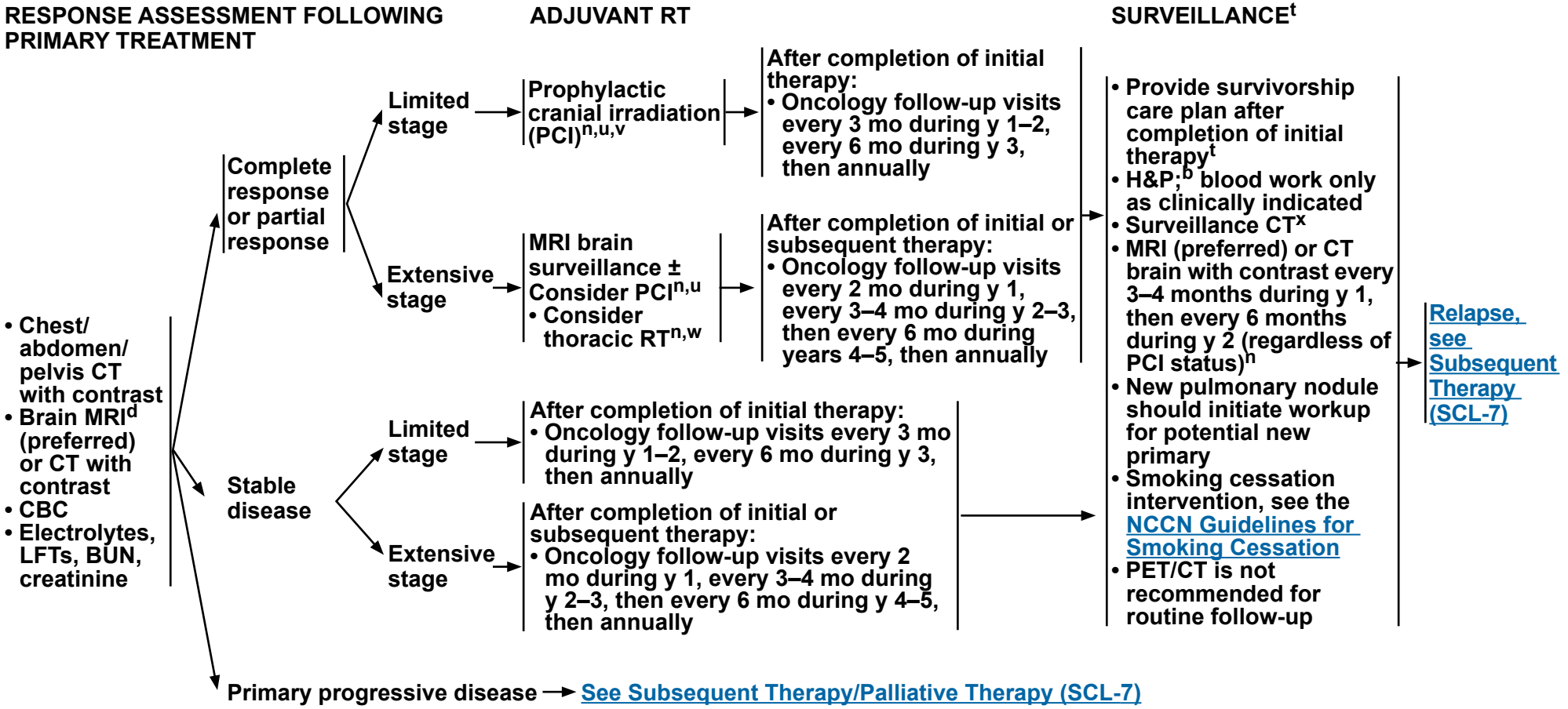


[b] See Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[d] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[n] See Principles of Radiation Therapy (SCL-F).
[t] See NCCN Guidelines for Survivorship.
[u] Not recommended in patients with poor performance status 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 surveillance should be carefully discussed with these patients.
[v] The benefit of PCI is unknown in patients who have undergone complete resection for pathologic stage I–IIA (T1–2,N0,M0) SCLC. See Principles of Surgical Resection (SCL-C).
[w] Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.
[x] 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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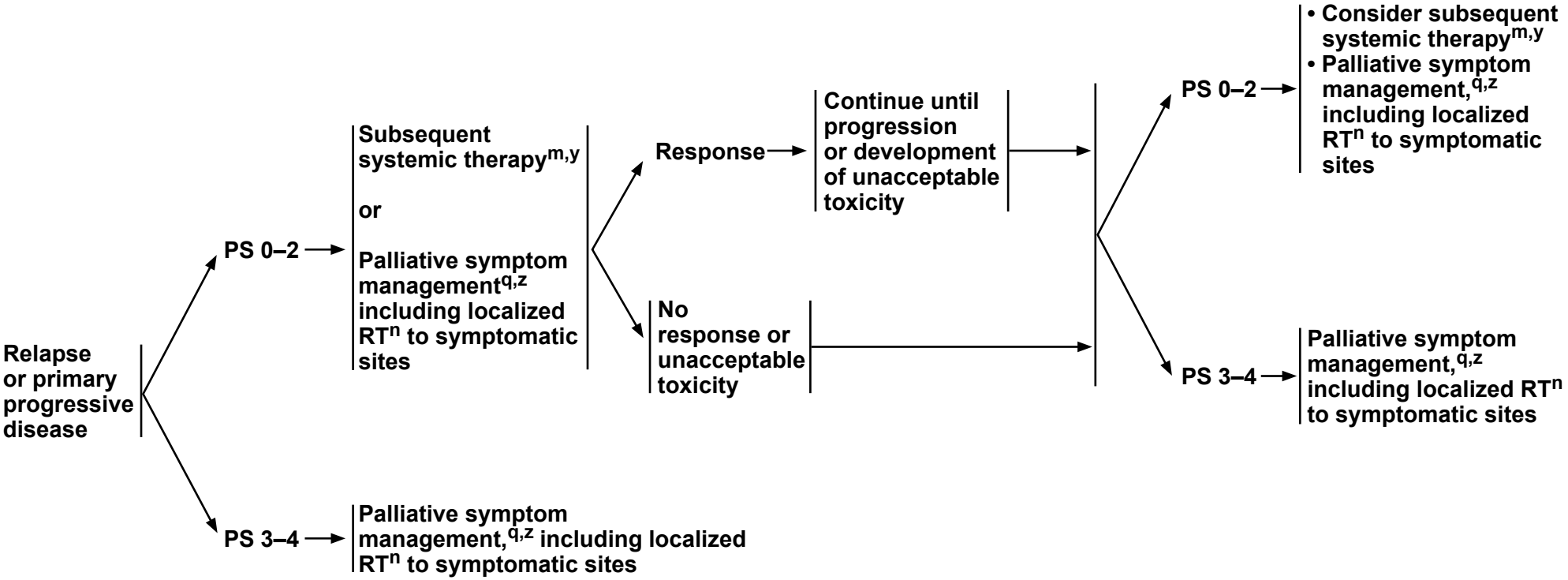
**PROGRESSIVE DISEASE** **SUBSEQUENT THERAPY/PALLIATIVE THERAPY**




[m] See Principles of Systemic Therapy (SCL-E).
[n] See Principles of Radiation Therapy (SCL-F).
[q] See Principles of Supportive Care (SCL-D).
[y] Response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy.
[z] See NCCN Guidelines for Palliative Care.

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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 is 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):**
    - ◊ **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:**
    - ◊ **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**
  - **If paraneoplastic neurologic syndrome is suspected, consider obtaining 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**
  - **Eaton-Lambert syndrome (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**

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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.
  - 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]

### 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

## PRINCIPLES OF PATHOLOGIC REVIEW -- References

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**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 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 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.**
- **Surgery may be considered for selected patients with T3 (based on size), N0 SCLC, if invasive mediastinal lymph node staging is negative.**
- **Patients who undergo complete resection should be treated with postoperative systemic therapy.[3] 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 unknown in patients who have undergone complete resection for pathologic stage I–IIA (T1–2,N0,M0) SCLC; consider PCI or brain MRI surveillance for N0. These patients have a lower risk of developing brain metastases than patients with more advanced, limited-stage SCLC (LS-SCLC), and may not benefit from PCI.[4] However, PCI may have a benefit in patients who are found to have pathologic stage IIB or III SCLC after complete resection; therefore, PCI is recommended in these patients after adjuvant systemic therapy.[4,5] PCI is not recommended in patients with poor performance status or impaired neurocognitive function.[6] 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**

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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 colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).[1]**

- **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-containing regimens or a topotecan-containing regimen for extensive-stage SCLC (ES-SCLC).**

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

- **Cushing syndrome**
  - **Consider ketoconazole. If not effective, consider metyrapone.**
  - **Try to control before initiation of antineoplastic therapy.**

- **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**

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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 AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[a,4]**

### PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

**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 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg day 1, every 21 days (category 1 for all)[b,5]**
- **Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,680 mg day 1, every 28 days[b]**
- **Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,6]**
- **Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1,500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1,500 mg day 1 every 28 days (category 1 for all)[b,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]**

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

[a] Cisplatin contraindicated or not tolerated.
[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.

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## PRINCIPLES OF SYSTEMIC THERAPY

| SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[c]<br>Consider dose reduction or growth factor support for patients with PS 2. | |
|---|---|
| **Relapse ≤6 months** | **Relapse >6 months** |
| **Preferred Regimens**<br>• Topotecan PO or IV[14-16]<br>• Lurbinectedin[17]<br>• Clinical trial<br><br>**Other Recommended Regimens**<br>• Paclitaxel[18,19]<br>• Docetaxel[20]<br>• Irinotecan[21]<br>• Temozolomide[22,23]<br>• Cyclophosphamide/doxorubicin/vincristine (CAV)[14]<br>• Oral etoposide[24,25]<br>• Vinorelbine[26,27]<br>• Gemcitabine[28,29]<br>• Nivolumab[b,d,30,31]<br>• Pembrolizumab[b,d,32-34]<br>• Bendamustine (category 2B)[35] | **Preferred Regimens**<br>• Original regimen[d,36,37]<br><br>**Other Recommended Regimens**<br>• Topotecan PO or IV[14-16]<br>• Paclitaxel[18,19]<br>• Docetaxel[20]<br>• Irinotecan[21]<br>• Temozolomide[22,23]<br>• CAV[14]<br>• Oral etoposide[24,25]<br>• Vinorelbine[26,27]<br>• Gemcitabine[28,29]<br>• Nivolumab[b,d,30,31]<br>• Pembrolizumab[b,d,32-34]<br>• Lurbinectedin[38]<br>• Bendamustine (category 2B)[35] |

Response Assessment (SCL-E 3 of 5)
References (SCL-E 4 of 5)

[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.
[c] Subsequent systemic therapy refers to second-line and beyond therapy.
[d] The use of immune checkpoint inhibitors is discouraged if there is progression on maintenance atezolizumab or durvalumab at time of relapse.

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## PRINCIPLES OF SYSTEMIC THERAPY

**Response Assessment**

- **Limited stage**
  - For patients receiving adjuvant therapy, response assessment should occur only after completion of adjuvant therapy; do not repeat scans to assess response during adjuvant treatment.
  - Response assessment after adjuvant therapy involves chest/abdomen/pelvis CT with contrast and brain MRI (preferred) with contrast or brain CT with contrast (see SCL-6).
  - For patients receiving systemic therapy + concurrent RT, response assessment should occur 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 chest/abdomen/pelvis CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy.

- **Extensive stage**
  - During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur 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, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy.

- **Subsequent systemic therapy**
  - Response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy.

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## PRINCIPLES OF SYSTEMIC THERAPY – References

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## PRINCIPLES OF SYSTEMIC THERAPY – References

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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 (see 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 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 (see NSCL-C).
- Useful references include the ACR Appropriateness Criteria at: http://www.acr.org/quality-safety/appropriateness-criteria

**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 RT (SABR) 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).[2-4]
  - Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[5] RT should start early, with cycle 1 or 2 of systemic therapy (category 1).[6] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[7]
  - Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of RT planning. PET/CT should be obtained, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, 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)

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References (SCL-F 4 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. Consensus on elective nodal irradiation (ENI) is evolving.[8] Several more modern series, both retrospective and prospective, suggest that omission of ENI results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating PET staging/target definition (1.7%–3%).[9-14] ENI has been omitted in current 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.[11,15]
  - 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).[16,17] 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.[18,19]
    - ◊ If using once-daily conventionally fractionated RT, higher doses of 66–70 Gy should be used.[20-23] Two randomized phase II 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.[24,25]
    - ◊ 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.[26,27]
- **Extensive stage**:
  - Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy, 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.[28,29] 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 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.[30] 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.[31]

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.
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.

References (SCL-F 4 of 6)

## PRINCIPLES OF RADIATION THERAPY

- **Extensive stage: (continued)**
  - **Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions to 60 Gy in 30 daily fractions, or equivalent regimens in this range.**
  - **Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach,[32,33] 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 data on optimal sequencing or safety).**

**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 NSCL-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 LS-SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival[34,35] In patients with ES-SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI.[36] 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.[37] 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.[38,39]**
- **Neurocognitive function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 56% of patients younger than 60 years of age ($P$ = .009).[39] Concurrent systemic therapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.**

Brain Metastasis (SCL-F 4 of 6)

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References (SCL-F 4 of 6)

## 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 performance status 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.[40] 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.
- 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 vs. conventional WBRT demonstrated improved cognitive preservation and patient-reported outcomes with HA-WBRT in patients with brain metastases from mixed histologies.[41] Conflicting data have been reported with HA-PCI vs. conventional PCI in SCLC with one trial reporting no differences in cognition[42] and a separate trial reporting improved cognitive preservation with HA-PCI.[43] A larger randomized trial of HA-PCI vs. conventional PCI, NRG CC003, is ongoing.[44]
- 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.[45]

**Brain Metastases:**

- Brain metastases should typically be treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS).[46] 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).[40]
- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[47,48] SRS is preferred, if feasible.[49,50]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.[41]

**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).

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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.

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| 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.

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National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2022
# Small Cell Lung Cancer

## Discussion

This discussion corresponds to the NCCN Guidelines for Small Cell Lung Cancer. Last updated: November 24, 2021.

### Table of Contents

## Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).[1,2] In 2021, an estimated 33,000 new cases of SCLC will occur in the United States.[1,3] During the COVID-19 pandemic, the diagnosis and treatment of lung cancer have been hampered; however, this has not been reflected in the 2021 estimates for incidence and mortality because of the typical delays in collecting, calculating, and reporting of data.[3] Nearly all cases of SCLC are attributable to cigarette smoking.[4] Although the incidence of SCLC has been decreasing, the incidence in women is increasing and the male-to-female incidence ratio is now 1:1.[1,2] Management of SCLC is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer, which includes the algorithm and this supporting Discussion text. Management of other lung neuroendocrine tumors (LNTs) is described in a different guideline (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines® for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).

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. SCLC is highly sensitive to initial chemotherapy and radiation therapy (RT); however, most patients eventually die of recurrent disease.[5] In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic RT; some patients are eligible for curative surgery followed by systemic therapy with or without mediastinal RT.[6,7] In most patients with extensive-stage disease, systemic therapy alone can palliate symptoms and prolong survival; however, long-term survival is rare.[8] Note that the definitions for limited-stage and extensive-stage SCLC incorporate TNM staging (see the algorithm and *Staging* in this Discussion). Surgery is only recommended for certain patients with surgically resectable stage I to IIA SCLC; stereotactic ablative radiotherapy (SABR) is an option for certain patients with medically inoperable stage I to IIA SCLC.[9-12] Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the recommended therapy for SCLC as outlined in these NCCN Guidelines still needs to be improved. Thus, participation in clinical trials should be strongly encouraged.

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).[13] Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.[14] Programs using behavioral counseling combined with U.S. Food and Drug Administration (FDA)-approved medications that promote smoking cessation can be very useful.

The NCCN Guidelines for Small Cell Lung Cancer were originally published 20 years ago and have been subsequently updated at least once every year.[15] The *Summary of the Guidelines Updates* section in the SCLC algorithm describes the most recent revisions for the 2022 update, which are described in greater detail in this revised Discussion text; recent references have been added (see *Summary* in this Discussion and the algorithm). For example, new subsequent therapy options have been added for patients with SCLC. Additional supplemental material in the SCLC algorithm includes the *Signs and Symptoms of Small Cell Lung Cancer, Principles of Pathologic Review, Principles of Surgical Resection*, *Principles of Supportive Care, Principles of Systemic Therapy*, *Principles of Radiation Therapy,* and staging tables.

## Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in SCLC using the following search term: *small cell lung cancer*. 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; 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 (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

## Diagnosis

### Screening

Ideally, a screening test should detect disease at an early stage when it is still curable. Currently, no effective screening test is available to detect early-stage SCLC; the disease is typically diagnosed when patients present with symptoms indicative of advanced-stage disease (see *Signs and Symptoms of Small Cell Lung Cancer* in the algorithm).[16] The National Lung Screening Trial (NLST) reported that screening with annual, low-dose, spiral CT scans decreased lung cancer-specific mortality in asymptomatic high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).[17] Although low-dose CT screening can detect early-stage non-small cell lung cancer (NSCLC), it does not seem to be useful for detecting early-stage SCLC.[16-19] Low-dose CT screening is probably not useful for SCLC because of the aggressiveness of the disease, which results in the development of symptomatic disease between annual scans, thereby limiting the potential effect on mortality.[16]

### Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea.[20] Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. The algorithm includes a section describing signs and symptoms of SCLC based on the tumor location and type of metastases (see *Signs and Symptoms of Small Cell Lung Cancer* in the algorithm). 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).[21,22]

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.[23-25] Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. Patients with the Lambert-Eaton myasthenic syndrome present with proximal leg weakness that is caused by antibodies directed against the voltage-gated calcium channels.[26,27] Paraneoplastic encephalomyelitis and sensory neuropathy 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 resulting in multiple neurologic deficits; paraneoplastic encephalomyelitis may precede a tumor diagnosis.[28] The NCCN SCLC Panel recommends that if neurologic paraneoplastic syndrome is suspected, then obtaining a comprehensive paraneoplastic antibody panel should be considered.

SCLC cells sometimes produce polypeptide hormones, including vasopressin (antidiuretic hormone [ADH]) and adrenocorticotropic hormone (ACTH), which cause hyponatremia of malignancy (ie, syndrome of inappropriate ADH secretion [SIADH]) and Cushing syndrome, respectively.[29,30] In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates).[31] Primary treatment for SIADH includes fluid restriction (which is difficult for patients because of increased thirst) and demeclocycline; vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) can be used for refractory hyponatremia (see *Principles of Supportive Care* in the algorithm).[31-33] Hyponatremia usually improves after successful treatment of SCLC.

### Pathology

The NCCN Guidelines for SCLC include a section on pathology (see *Principles of Pathologic Review* in the algorithm). The World Health Organization (WHO) classification system is used to classify lung tumors.[34-39] SCLC is a poorly differentiated malignant epithelial tumor that is categorized as a high-grade neuroendocrine carcinoma.[21,40] The classic and distinctive histology on hematoxylin and eosin (H&E) may be sufficient for identifying SCLC in good-quality histologic samples including small blue cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.[21,41] The cells are round, oval, or spindle-shaped; nuclear molding is prominent.[42] The mitotic count is high in SCLC compared with the count in atypical and typical carcinoids. However, it can be difficult to count mitotic figures in small biopsy samples with crushed or necrotic cells; immunohistochemistry is useful in this setting (see next paragraph).[43] Up to 30% of specimens from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma);[42] this finding is more commonly detected in specimens from previously treated patients and suggests that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along divergent pathways. 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.[44,45] Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases.

Immunohistochemistry is useful for diagnosing SCLC in limited samples and distinguishing SCLC from NSCLC or other neuroendocrine tumors.[21,43,46-48] Nearly all SCLCs are immunoreactive for cytokeratin (AE1/Ae3, CAM5.2); 85% to 90% of SCLCs are positive for thyroid transcription factor-1 (TTF-1).[21,49-51] Napsin A is a marker of adenocarcinoma and p40 (or p63) is a marker of squamous cell carcinoma. Napsin A and p40 (or p63) are generally negative in SCLC and, therefore, useful for distinguishing SCLC from poorly differentiated NSCLC and combined SCLC.[52] However, p40 (or p63) can be focally positive in SCLC. It is important to distinguish SCLC from other neuroendocrine tumors, especially typical and atypical carcinoids, because treatment differs for these tumors (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).[37,43] Most SCLCs also stain positively for markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin.[21,53,54] Fewer than 5% of SCLCs are negative for all neuroendocrine markers. However,

these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs will be immunoreactive for at least one of these neuroendocrine markers.[55] Ki-67 immunostaining is useful for distinguishing SCLC from carcinoid tumors.[37,43,56,57]

The 2015 WHO classification recognizes two types of SCLC: SCLC and combined SCLC.[34,37,39] Combined SCLC consists of both SCLC histology and NSCLC histology (squamous cell, adenocarcinoma, spindle/pleomorphic, and/or large cell carcinoma).[34,37,38] No minimal percentage of NSCLC histologic elements is required for a classification of combined SCLC; if any elements are present along with SCLC, then this can be classified as combined SCLC. The exception is when SCLC is combined with LCNEC. At least 10% of the tumor should show LCNEC morphology to be classified as combined SCLC and LCNEC.[42,58] Patients with combined SCLC are treated using regimens for SCLC, because it is the more aggressive cancer.[58] Combined SCLC is more frequent in patients with limited-stage SCLC. Studies have shown that patients with NSCLC can undergo transformation to SCLC after treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors or immune checkpoint inhibitors.[59,60] Molecular profiling may be considered for patients with extensive-stage SCLC who are never smokers to help clarify the diagnosis and to evaluate for potential targeted treatment options.[34,61-64]

## Staging

The NCCN SCLC Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the older Veterans Administration (VA) scheme for SCLC.[5,65] The 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 disease is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage disease is disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.[66] Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial and treatment is individualized.[5,65,67] Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. The AJCC revised the TNM staging system (8th edition) for lung cancer in 2018 (see *Staging* in the algorithm).[68,69]

The NCCN SCLC Panel will continue to use both the VA and the TNM systems for staging SCLC. In applying the TNM classifications to the VA system, *limited-stage* SCLC is defined as stage I to III (T any, N any, M0) that can be safely treated with definitive RT, excluding 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 (see Table 1 in the algorithm). *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3–4 due to multiple lung nodules as previously described. Because most of the literature on SCLC classifies patients based on the VA's definitions of limited-stage or extensive-stage disease, these definitions are often used 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.[65] Clinical research studies should include use of the TNM system, because it will allow for more precise assessments of prognosis and specific therapy in the future.[68]

All patients with SCLC, even those with radiographically limited-stage disease, require systemic therapy either as primary or adjuvant therapy. Staging provides a therapeutic guideline for thoracic RT, which is indicated primarily for patients with limited-stage disease. Full staging includes a history and physical examination; CT scan with intravenous contrast of the

chest/abdomen/pelvis; and brain imaging using MRI (preferred) or CT scan with intravenous contrast.[67,70] However, once a patient has been found to have extensive-stage disease, further staging is not required, except for brain imaging.[5] Unilateral bone marrow aspirates and biopsies may be indicated in select patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration and with no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in fewer than 5% of patients. If limited-stage disease is suspected, a PET/CT scan (skull base to mid-thigh) can be considered to assess for distant metastases.[5,65] A bone scan can be performed if PET/CT is equivocal or not available; bone biopsy can be considered if bone imaging is equivocal.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.[71-73] PET/CT is superior to PET alone.[73] Approximately 19% of patients who undergo PET are upstaged from limited-stage to extensive-stage disease, whereas only 8% are downstaged from extensive-stage to limited-stage disease.[67] For most metastatic sites, PET/CT is superior to CT imaging; however, PET/CT is inferior to MRI or contrast-enhanced CT for the detection of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[74] Changes in management based on PET staging were reported in approximately 27% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease.[67,72,75] Although PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that would alter the stage.

Before surgical resection, pathologic mediastinal staging is required to confirm PET/CT scan results in patients with clinical stage I to IIA SCLC (T1–2,N0,M0) to rule out occult nodal disease.[5] However, mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is planned. 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).[76,77]

Thoracentesis with cytologic analysis is recommended if a 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 would indicate extensive-stage disease. 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 suggests that the effusion is not directly related to the cancer. Pericardial effusions are classified using the same criteria.

Staging should not focus only on sites of symptomatic disease or on sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or without an abnormal alkaline phosphatase level. Bone imaging with radiographs or MRI may be appropriate if PET/CT is equivocal. Brain imaging (MRI preferred 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. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the usefulness of early diagnosis in asymptomatic patients. Because of the aggressive nature of SCLC, staging should not delay the onset of treatment for more than 1 week; otherwise, many patients may become more seriously ill in the interval, with a significant decline in their performance status (PS).

## Prognostic Factors

Poor PS (3–4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease (such as lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis in patients with limited-stage disease. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease.[78,79]

## Treatment

### Surgical Resection of Stage I to IIA SCLC

The *Principles of Surgical Resection* for SCLC are described in the algorithm; studies supporting these recommendations are described in this section. The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[80] Patients with limited-stage disease, excluding those with solitary peripheral nodules, received 5 cycles of chemotherapy with cyclophosphamide, doxorubicin, and vincristine (CAV); those showing a response to chemotherapy 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 stage I (T1–2,N0,M0) disease.

Most of the data regarding the role of surgery in SCLC are from retrospective reviews.[81-86] 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 more advanced disease with lymph node involvement, leading to the general recommendation that surgery should only be considered in those with stage I to IIA disease (T1–2,N0,M0). Interpretation of these results is limited by the selection bias inherent in retrospective reviews and by the variable use of chemotherapy and RT. A meta-analysis describes the evidence from currently available randomized trials in greater detail.[87] Data show that patients with SCLC who have nodal disease (ie, T1–3,N1–3,M0–1) do not benefit from surgery.[80] Note that fewer than 5% of patients with SCLC have true stage I to IIA disease.[88]

Analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.[12,89] However, these studies are limited by the lack of information on chemotherapy use in the database. 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 defined until trials are done to compare surgery plus adjuvant chemotherapy versus concurrent chemoradiotherapy in patients who are rigorously staged.

The NCCN SCLC Panel only recommends surgery for patients with clinical stage I to IIA (T1–2,N0) SCLC with negative mediastinal lymph nodes that have been confirmed by mediastinal staging.[9,81,90] Surgery can include patients with clinical stage IIA SCLC based on the staging criteria that tumors up to 5 cm in diameter (T2b) without lymph node involvement (N0) are classified as IIA. If resection is performed, the NCCN SCLC Panel recommends lobectomy (preferred) with mediastinal lymph node dissection or sampling and does not feel that segmental or wedge resections are appropriate for patients with SCLC. SABR or chemoradiation is recommended for patients with limited-stage disease who are medically inoperable or do not want to pursue surgical resection (see *Systemic Therapy* and *SABR* in this Discussion).

After complete resection or SABR, adjuvant chemotherapy or chemoradiation is recommended (see *Systemic Therapy* in this Discussion).[84,91-93] Adjuvant chemotherapy alone is recommended for patients without nodal metastases. Concurrent or sequential

chemotherapy and postoperative mediastinal RT are recommended for patients with N2 or N3 nodal metastases; postoperative mediastinal RT may be considered for patients with N1 nodal metastases (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 role of prophylactic cranial irradiation (PCI) is unclear in patients with surgically resected early-stage SCLC because they appear to have a lower incidence of brain metastases (see *Prophylactic Cranial Irradiation* in this Discussion and *Adjuvant Treatment* in the algorithm).[94] The NCCN SCLC Panel recommends new baseline disease assessment after adjuvant therapy.

## Systemic Therapy

For all patients with SCLC, systemic therapy is an essential component of appropriate treatment (see *Principles of Systemic Therapy* in the algorithm). Many single-agent and combination systemic therapy regimens have been shown to be active in SCLC. The NCCN SCLC Panel has preference stratified all of the adjuvant, first-line, and subsequent therapy options for patients with SCLC. Certain regimens are recommended as *preferred* interventions, whereas others are designated as either *other recommended interventions* or *useful under certain circumstances*.

Adjuvant chemotherapy is recommended for patients with early-stage disease who have had surgery or SABR (see *Limited-Stage SCLC*, *Surgical Resection of Stage I to IIA SCLC,* and *SABR* in this Discussion). For patients with limited-stage disease who are not eligible for surgery or SABR, recommended primary treatment consists of chemotherapy with concurrent thoracic RT (category 1) (see *Limited-Stage SCLC* and *Radiation Therapy* in this Discussion).[7,95,96] For patients with extensive-stage disease, systemic therapy alone is recommended (see *Extensive-Stage SCLC* in this Discussion). However, RT may be used in select patients for palliation of symptoms (see NCCN Guidelines for Palliative Care, available at www.NCCN.org).

### *Cisplatin Versus Carboplatin*

In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.[97] However, the use of carboplatin carries a greater risk of myelosuppression.[98] Small randomized trials in patients with SCLC have suggested similar efficacy of cisplatin and carboplatin regimens, as did a retrospective analysis in patients with extensive-stage disease.[97,99,100] A meta-analysis of individual patient data from four randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.[101] Of 663 patients included in this meta-analysis, 32% had limited-stage disease and 68% had extensive-stage disease. 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) in patients receiving cisplatin-containing versus carboplatin-containing regimens, suggesting equivalent efficacy in patients with SCLC.

### *Limited-Stage SCLC*

Adjuvant chemotherapy alone is recommended for patients who have undergone surgical resection or SABR for early-stage disease; regimens for limited-stage SCLC are recommended (see *Principles of Systemic Therapy* in the algorithm). Etoposide plus cisplatin is the most commonly used first-line combination chemotherapy regimen for patients with limited-stage SCLC (see *Principles of Systemic Therapy* in the algorithm). [102,103] Etoposide/cisplatin replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity.[104-106]

Most patients with limited-stage disease are not eligible for surgery or SABR. Recommended primary treatment for these patients consists of

chemotherapy with concurrent thoracic RT (category 1) (see *Limited-Stage SCLC* and *Radiation Therapy* in this Discussion).[7,95,96] Treatment with etoposide/cisplatin plus definitive thoracic RT results in 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%.[102] Thoracic RT improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival.[95,96] Data suggest that chemoradiotherapy may be indicated for patients with limited-stage disease who have cytologically negative or indeterminate pleural effusions but not for those with pericardial effusions.[107,108] In combination with thoracic RT, etoposide/cisplatin causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.[109]

If pathologic lymph node involvement is found at surgery, then thoracic RT can be added concurrently or sequentially to etoposide/cisplatin. For patients with limited-stage IIB to IIIC (T3–4,N0,M0; T1–4,N1–3,M0), the NCCN Guidelines recommend etoposide/cisplatin plus concurrent thoracic RT (category 1).[95,96,110,111] The preferred etoposide/cisplatin regimens for limited-stage SCLC are based on the dosing used in the CONVERT trial (see *Principles of Systemic Therapy* in the algorithm and *Radiation Therapy* in this Discussion).[102] 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]).[112] 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 patients with SCLC. After adjuvant chemotherapy alone or chemotherapy with concurrent RT for patients with limited-stage disease, response assessment using CT with contrast should occur only after completion of therapy; repeating CT scans during therapy is not recommended. After adjuvant therapy, response assessment is recommended 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 disease, response assessment using CT with contrast of the chest/abdomen/pelvis should occur after every 2 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.[113-115] In patients with extensive-stage disease 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).[8,116] If systemic therapy is given first, brain RT is administered after completion of systemic therapy.

For many years, platinum plus etoposide had been recommended for patients with extensive-stage SCLC, with a preference for carboplatin over cisplatin due to its equivalent efficacy and more tolerable toxicity profile. However, the preferred regimens for extensive-stage SCLC now include the programmed death ligand 1 (PD-L1)–targeted immune checkpoint inhibitors, atezolizumab or durvalumab, plus platinum plus etoposide. Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. 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 of potential immune-mediated adverse events, know how to manage these adverse events, and educate their patients about possible side effects. High-dose corticosteroids are generally recommended for immune-mediated adverse events based on the severity of the reaction. In addition, 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).

During systemic therapy for patients with extensive-stage disease, response assessment using CT with contrast of the chest/abdomen/pelvis should occur after every 2 to 3 cycles of systemic therapy and again at completion of therapy. Serial brain imaging is also recommended in patients with extensive-stage disease 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 to carboplatin plus etoposide in 403 patients with previously untreated extensive-stage SCLC.[115] In this trial, carboplatin plus etoposide was compared to the same chemotherapy plus atezolizumab followed by maintenance atezolizumab in 403 patients with previously untreated extensive-stage SCLC. Updated data show 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).[113] Similarly, the 1-year overall survival rate was 51.9% for the atezolizumab regimen versus 39.0% for chemotherapy alone. 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. The FDA recently approved different doses for atezolizumab when combined with carboplatin and etoposide for patients with extensive-stage SCLC.

The NCCN SCLC Panel recommends (category 1) carboplatin plus etoposide plus atezolizumab as a preferred first-line systemic therapy option followed by maintenance atezolizumab for patients with extensive-stage SCLC based on clinical trial data and the FDA approval.[113,115] For the 2022 update (Version 1), the NCCN Panel now recommends two different carboplatin/etoposide/atezolizumab regimens with slightly different doses for the maintenance atezolizumab; either 1200 or 1680 mg of maintenance atezolizumab is recommended. However, the category 1 recommendation is only for the regimen with 1200 mg of maintenance atezolizumab because that dose was used in the clinical trial.[113,115]

*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.[114,117] In this trial, carboplatin (or cisplatin) plus etoposide was compared to the same chemotherapy plus durvalumab followed by maintenance durvalumab. Most patients received the carboplatin regimen (78%). Updated data from 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).[118] Similarly, 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).

The NCCN SCLC Panel recommends (category 1) durvalumab plus etoposide plus (carboplatin or cisplatin) as a preferred first-line systemic therapy option followed by maintenance durvalumab for patients with extensive-stage SCLC based on clinical trial data and the FDA approval.[114,117-119]

*Other Primary Systemic Therapies*

Other recommended regimens for extensive-stage SCLC include etoposide with either cisplatin or carboplatin. Prior to the recent favorable data on immunotherapy, many other chemotherapy combination regimens had been evaluated in patients with extensive-stage disease with little consistent evidence of benefit compared with etoposide/cisplatin. For example, the combination of irinotecan and cisplatin initially appeared to be better than etoposide/cisplatin. A small phase 3 Japanese trial reported that patients with extensive-stage SCLC who were 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).[120] In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the etoposide/cisplatin group.[120] However, 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 between the regimens.[121,122] A phase 3 randomized trial of 220 patients with extensive-stage SCLC found that median overall survival was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs. 7.1 months; $P$ = .04).[123] Based on these studies, the cisplatin or carboplatin plus irinotecan regimens are included as options in the NCCN Guidelines for patients with extensive-stage disease. In addition, a meta-analysis suggested an improvement in PFS and overall survival with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.[124] However, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN SCLC Panel recommends the irinotecan-based regimens as useful in certain circumstances for patients with extensive-stage SCLC.

Many other strategies have been evaluated in an effort to improve on the recommended treatment for extensive-stage SCLC, including the addition of a third agent. As previously mentioned, the addition of atezolizumab or durvalumab improves overall survival compared with chemotherapy alone.[113-115,117,118] 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.[125] Likewise, another phase 3 randomized trial reported that first-line therapy with pembrolizumab plus etoposide and either carboplatin or cisplatin followed by maintenance pembrolizumab did not improve overall survival compared with chemotherapy alone in patients with extensive-stage SCLC.[34]

The benefits of antiangiogenic therapy have 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 have yielded promising response and survival data.[126-129] However, at least two randomized trials have demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.[130,131] Currently, the

NCCN SCLC Panel does not recommend use of bevacizumab in patients with SCLC.

Overall, attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy regimens, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have yielded no 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.[132,133] 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.[134] Two phase 3 randomized trials have confirmed the lack of improvement in survival with three-drug chemotherapy regimens compared to platinum plus etoposide in patients with extensive-stage SCLC. One of these studies assessed the combination of ifosfamide, etoposide, and epirubicin versus etoposide/cisplatin, while the other evaluated carboplatin plus etoposide with or without palifosfamide.[135,136] 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.[137]

The use of maintenance or consolidation chemotherapy beyond 4 to 6 cycles of recommended treatment produces a minor prolongation of duration of response without improving survival and carries a greater risk of cumulative toxicity.[138] A meta-analysis reported that maintenance chemotherapy did not prolong overall survival.[139] 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. To overcome drug resistance, alternating or sequential combination therapies have been designed to expose the tumor to as many active cytotoxic agents as possible during initial treatment.[140] However, randomized trials have not shown improved PFS or overall survival with this approach.[141,142] The NCCN SCLC Panel recommends 4 cycles of systemic therapy (with or without RT) for patients with limited-stage disease. Four cycles of systemic therapy are also recommended for patients with extensive-stage disease; however, some patients may receive up to 6 cycles based on the response and tolerability after 4 cycles.

Multidrug cyclic weekly chemotherapy was designed to increase dose intensity. Early phase 2 results of this approach were promising, although favorable patient selection was of some concern.[143,144] Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly chemotherapy regimens.[145-148] The role of higher-dose chemotherapy for patients with SCLC remains controversial. Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high chemotherapy doses compared with those given conventional doses of the same agents.[149] In general, however, randomized trials comparing conventional chemotherapy doses to an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival.[150-153] In addition, a meta-analysis of trials that compared recommended versus 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 disease.[154]

Currently available 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,[155] maintenance of dose intensity with growth factors does not prolong disease-free survival or overall survival.[156,157] Thus, the routine use of growth factors at the initiation of systemic therapy/RT is not recommended for patients with limited-stage SCLC. Trilaciclib or G-CSF may be used as prophylactic 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).[158-161]

### Older Patients

The incidence of SCLC increases with age. Although the median age at diagnosis is older than 70 years, older patients are underrepresented in clinical trials.[162] While advanced chronologic age adversely affects tolerance to treatment, the functional status of an individual patient is much more useful than age in guiding clinical decision-making (see the NCCN Guidelines for Older Adult Oncology, available at www.NCCN.org). Older patients who are able to perform activities of daily living (ADLs) should be treated with combination systemic therapy and RT, if indicated.[163-165] For example, a subgroup analysis of the CONVERT trial suggests that concurrent chemoradiation yields equivalent median survival in older versus younger patients with limited-stage SCLC (29 vs. 30 months; $P = .38$).[163] However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in older patients; therefore, they must be watched carefully during treatment to avoid excessive risk.[163] Greater attention to the needs and support systems of older patients is recommended to provide optimal care. Overall, older patients have a similar prognosis as stage-matched younger patients.

Randomized trials have indicated that less-intensive treatment (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in older patients with good PS (0–2).[166,167] A retrospective analysis in 8637 older patients with limited-stage disease reported that chemoradiation increased survival compared with chemotherapy alone.[164] Several other strategies have been evaluated in older patients with SCLC.[100,168-170] 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 aging patient.[170] However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in this population.[171] The usefulness of short-course, full-intensity chemotherapy has also been explored in older or infirm patients, and the results with only 2 cycles of chemotherapy seem to be acceptable, although this approach has not been directly compared with 4 to 6 cycles of therapy.[172] PCI should be used with caution in older patients. Older patients (≥60 years) are at increased risk for cognitive decline after PCI; therefore, the risks and benefits of PCI versus close surveillance need to be discussed in detail with older patients.[173-176] A Dutch analysis of more than 5000 patients suggests that median survival is decreased in older patients treated with PCI compared with younger patients regardless of stage.[177]

### Surveillance for Relapse

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease (see also *Surveillance* in this Discussion).[178,179] The surveillance recommendations to assess for relapse in patients with SCLC are outlined in the algorithm. For the 2022 update (Version 1), the algorithm now states that 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.[180] If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors are a frequent occurrence in patients who are cured of SCLC.[181,182] It is important to monitor for brain metastases, which allows for early treatment

prior to the development of potentially debilitating neurologic symptoms. The NCCN SCLC Panel recommends brain MRI (preferred) or brain CT with contrast every 3 to 4 months during year 1 for all patients and then every 6 months during year 2, regardless of the PCI status. MRI is more sensitive than CT for identifying brain metastases and, therefore, is preferred over CT. PET/CT is not recommended for routine follow-up. 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).[183-185] Former smokers 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 who relapse or those with primary progressive disease may be treated with subsequent systemic therapy regimens. These patients have a median survival of only 4 to 5 months when treated with older regimens; some of the newer regimens are associated with longer survival. 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.[186] If this 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%. 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.[187] Response rates are higher with newer agents, such as lurbinectedin. For patients on subsequent systemic therapy, response assessment should occur after every 2 to 3 cycles using CT with contrast of the chest/abdomen/pelvis. Dose reduction or growth factor support should be considered for patients with a PS of 2 who are receiving subsequent systemic therapy. Recommended subsequent systemic therapy options for patients who have relapsed after primary therapy are listed in the algorithm and described here (see *Principles of Systemic Therapy* in the algorithm).[188-193]

#### *Lurbinectedin*

Lurbinectedin inhibits oncogenic transcription, leading to tumor cell apoptosis. A phase 2 basket trial assessed lurbinectedin as second-line therapy in 105 patients with SCLC who had received first-line platinum/etoposide; only 8% of patients had received immunotherapy.[188] Most patients (57%) had not received chemotherapy for 3 months or more. 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 the chemotherapy-free interval was less than 90 days. The response rate was 45% (95% CI, 32.1%–58.4%) if the chemotherapy-free interval was 90 days or more. Common grade 3 to 4 adverse events included anemia, leucopenia, neutropenia, and thrombocytopenia. There were no reported treatment-related deaths. The NCCN SCLC Panel recommends lurbinectedin as a preferred subsequent therapy option for patients with SCLC who have relapsed 6 months or less after therapy based on this trial and the FDA approval.[188]

In a subset analysis of the phase 2 trial previously discussed, lurbinectedin was assessed as second-line therapy in 20 patients with SCLC who had received first-line platinum/etoposide more than 6 months ago.[189] 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; after 2 years, 27.1% were alive. Common grade 3 to 4 adverse events included neutropenia, anemia, thrombocytopenia, fatigue, and increased liver function tests. The NCCN SCLC Panel recommends lurbinectedin as a subsequent therapy option (one of many “other recommended regimens”) for patients with

SCLC who have relapsed more than 6 months after therapy based on this study and the FDA approval.[189]

***Topotecan***

A randomized phase 3 trial compared single-agent intravenous topotecan with the combination regimen CAV as subsequent therapy for patients with SCLC who had relapsed at least 60 days after therapy.[194] Both arms had similar response rates (topotecan, 24.3% [26/107]; CAV, 18.3% [19/104]) and survival (25.0 vs. 24.7 weeks), but intravenous topotecan caused less grade 4 neutropenia (37.8% vs. 51.4%; $P < .001$). Compared with CAV, topotecan also improved symptoms of dyspnea, anorexia, hoarseness, and fatigue. In another phase 3 trial, oral topotecan improved overall survival compared with best supportive care (26 vs. 14 weeks).[195] Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who relapse after initial response to systemic therapy. Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.[195,196] Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m$^2$ of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.[197] Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.[198,199] The NCCN SCLC Panel recommends topotecan as a preferred subsequent therapy option for patients with SCLC who have relapsed 6 months or less after therapy based on these trials and the FDA approval (See *Principles of Systemic Therapy* in the algorithm).[194,195]

***Nivolumab and Pembrolizumab***

Immune checkpoint inhibitors have been evaluated in patients with relapsed SCLC.[200-203] CheckMate 032, a phase 1/2 trial, assessed nivolumab alone (n = 147) or various doses of nivolumab plus ipilimumab (n = 96) for relapsed SCLC.[200,201] Updated data showed response rates were 11.6% for nivolumab and 21.9% for nivolumab plus ipilimumab. 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 to 4 adverse events were 12.9% (19/147) for nivolumab alone and 37.5% (36/96) for nivolumab plus ipilimumab. In patients receiving nivolumab alone, the most common grade 3 or 4 treatment-related adverse events were increased levels of lipase and aspartate aminotransferase and pneumonitis.

CheckMate 331, a randomized phase 3 trial, assessed nivolumab monotherapy versus topotecan or amrubicin in 569 patients with relapsed SCLC.[204,205] 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; $P = .11$).[204] 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 2 patients receiving nivolumab and in 3 patients receiving chemotherapy. Fewer grade 3 to 4 adverse events occurred in patients receiving nivolumab compared with chemotherapy (14% vs. 73%, respectively). A recent comparative effectiveness 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).[206] The 1-year overall survival rate was 28% with nivolumab versus 4% with the other treatments.

The NCCN SCLC Panel recommends nivolumab as a subsequent therapy option for patients who have relapsed 6 months or less after primary therapy based on clinical trial data, although the FDA has withdrawn the indication (see subsequent paragraph in this section for further details).[200,201,204,205,207] However, the use of nivolumab 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 if patients have progressed on immune checkpoint inhibitors, then giving them as subsequent therapy will be effective. Previously, the panel had recommended nivolumab plus ipilimumab as an option, but this regimen was removed for Version 1.2021 because the combined regimen is more toxic and the overall survival is the same.

A combined analysis of two studies, one phase Ib (KEYNOTE-028) and one phase 2 (KEYNOTE-158), evaluated the activity of pembrolizumab in 83 evaluable patients with relapsed SCLC.[208] This analysis reported a response rate of 19.3% and a median overall survival of 7.7 months (95% CI, 5.2–10.1). Both overall survival and response rate were higher in those who were PD-L1 positive. Grade 3 or 4 adverse events occurred in 12% of patients and two patients died from treatment-related adverse events (pneumonitis and encephalitis). The NCCN SCLC Panel recommends pembrolizumab as a subsequent therapy option for patients with SCLC, regardless of PD-L1 levels, based on phase 1 and 2 data.[202,208]

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.[204] However, the NCCN SCLC Panel still recommends these agents for certain patients. The panel feels that nivolumab or pembrolizumab are just as effective as, and sometimes better than, the other subsequent therapy options; nivolumab or pembrolizumab are also less toxic.[204,206,209] In addition, a significant proportion of 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. For the 2022 update (Version 1), the NCCN SCLC Panel revised the recommendations for nivolumab or pembrolizumab to category 2A from category 3.

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 adverse events, and educate their patients about possible side effects (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[210,211] 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).

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. Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0 to 2.

***Other Subsequent Therapy Options***

Paclitaxel was assessed in a phase 2 study in patients with refractory or relapsed SCLC; 24% of patients responded (5/21).[212] Grade 3 to 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% (7/24; 95% CI, 12%–51%).[213] A retrospective study in 185 patients showed that third- or fourth-line therapy with paclitaxel was associated with a response rate of 17%. Toxicity was similar in patients with PS 2 compared with PS 0 to 1 (63% vs. 62%).[214]

Docetaxel was assessed in a phase 2 trial in patients with previously treated SCLC; 25% of patients responded (7/28). Reported toxicities included neutropenia and asthenia.[215] Irinotecan was assessed in a phase 2 study in patients with refractory or relapsed SCLC; 47% of patients responded (7/15; 95% CI, 21.4%–71.9%); myelosuppression, diarrhea, and pulmonary toxicity were reported.[216]

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated $O^6$-methylguanine-DNA methyltransferase (MGMT).[191,217,218] A phase 2 study assessed temozolomide 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 was 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 approach was significant and it is not recommended for subsequent therapy.[219] Amrubicin is an active drug in patients with relapsed or refractory SCLC.[220-223] However, grade 3 to 4 toxicity, primarily neutropenia, is common.[224,225] A phase 3 trial reported that amrubicin did not improve overall survival as second-line treatment for SCLC when compared to topotecan, except in a subset of patients with refractory disease.[226] Amrubicin is not approved by the FDA for patients with SCLC.

Another phase 3 randomized trial assessed carboplatin plus etoposide compared with oral topotecan in 162 patients with SCLC who had relapsed more than 3 months after therapy.[227] The median PFS was 4.7 months (90% CI, 3.9–5.5) in the chemotherapy 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). Grade 3 to 4 adverse events included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and asthenia. In the topotecan group, 2 treatment-related deaths occurred; no deaths occurred in the chemotherapy group. The NCCN SCLC Panel recommends the original platinum regimen, as preferred for patients with SCLC who have relapsed more than 6 months after therapy, based on this trial.[227] The panel added a caveat that the use of immune checkpoint inhibitors is discouraged if patients have progressed on maintenance atezolizumab or durvalumab.[5,186,228] Since topotecan is also effective in this setting, it is a recommended option (other recommended regimen) based on this trial.

***NCCN Recommendations***

The NCCN SCLC Panel recommends the following subsequent therapies for patients with SCLC based on clinical expertise and trial data. For relapse of 6 months or less, the preferred regimens are topotecan (oral [PO] or intravenous), lurbinectedin, or a clinical trial; other recommended regimens include paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, and pembrolizumab (category 2A for all agents). Bendamustine is also recommended (category 2B). For the 2022 update (Version 1), the panel voted to recommend all of these subsequent therapy options regardless of the time since relapse.[229] Previously, most of these agents were only recommended for relapse of 6 months or less. For relapse more than 6 months, the preferred regimen is the original regimen.[227,228,230,231] However, the NCCN SCLC Panel added a caveat that the use of immune checkpoint inhibitors is discouraged in patients who relapse after 6 months while on maintenance atezolizumab or durvalumab.[5,186,228] Other recommended options for relapse greater than 6 months include: topotecan, paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, pembrolizumab, and lurbinectedin (category 2A for all agents). Bendamustine is also recommended (category 2B).

## Radiation Therapy

The *Principles of Radiation Therapy* section in the algorithm describes the radiation doses, target volumes, and normal tissue dose-volume constraints for limited-stage SCLC, and includes references to support the recommendations; PCI and treatment of brain metastases are also discussed (see the algorithm). The American College of Radiology (ACR) Appropriateness Criteria®, American Radium Society appropriate use criteria, and American Society for Radiation Oncology (ASTRO) guidelines are useful resources.[232-235] The *Principles of Radiation Therapy* section in the NSCLC algorithm may also be useful (eg, general principles of RT, palliative RT) (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). This section describes the studies supporting the NCCN RT recommendations for SCLC.

### *Thoracic Radiation Therapy*

The addition of thoracic RT has improved survival for patients with limited-stage SCLC. Older meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease yields a 25% to 30% reduction in local failure, and a corresponding 5% to 7% improvement in 2-year overall survival compared with chemotherapy alone.[95,96] Achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge. However, more modern series have reported 5-year overall survival of more than 30%, approaching outcomes of locally advanced NSCLC of similar stage.[102]

#### *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 disease. Overall survival was 27.2 months for those receiving concurrent chemoradiation versus 19.7 months for those receiving sequential chemoradiation ($P$ = .097).[109] Patients receiving concurrent chemoradiation had more severe hematologic toxicity. Severe esophagitis occurred in 9% of patients receiving concurrent chemoradiation and 4% receiving sequential chemoradiation.

Another 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 with longer survival.[236] 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.[237,238] Another meta-analysis in patients with limited-stage SCLC showed that survival was improved with more rapid completion of the chemoradiotherapy regimen (start of any chemotherapy until the end of RT).[239] A meta-analysis of individual patient data from 12 trials (2668 patients) reported that early concurrent chemoradiation increased 5-year overall survival (HR, 0.79; 95% CI, 0.69–0.91), although severe acute esophagitis was also increased, compared with late concurrent chemoradiation.[240]

#### *Radiation Fractionation*

The Eastern Cooperative Oncology Group (ECOG)/Radiation Therapy Oncology Group compared once-daily to twice-daily RT with etoposide/cisplatin.[241] 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 fractionation) or once daily over 5 weeks (conventional fractionation). 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.[241] A higher incidence of grade 3 to 4 esophagitis was seen with the accelerated regimen compared with the conventional regimen.[241] A significant criticism of this trial in retrospect 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, assessed 45 Gy twice daily over 3 weeks (accelerated fractionation) compared with higher dose 66 Gy once daily over 6.5 weeks (conventional fractionation) in 547 patients with limited-stage SCLC.[102] Median overall survival was similar between the 2 arms (30 vs. 25 months; HR for death in the 66 Gy conventional group, 1.18; 95% CI, 0.95–1.45; $P$ = .14]). 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). Of note, while outcomes were similar between arms, the CONVERT trial was not powered to show equivalence. Another randomized phase 3 trial assessed high-dose conventional 70 Gy once daily over 7 weeks compared with accelerated 45 Gy twice daily over 3 weeks in 638 patients with limited-stage SCLC.[242] Preliminary data suggest that overall survival and toxicity are similar.

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.[243] 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.[244] The median survival was 28 months, 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 assessed concurrent chemoradiation with 65 Gy given as once-daily fractions over approximately 5 weeks (high-dose accelerated) compared with standard-dose accelerated 45 Gy given as twice-daily fractions over 3 weeks in 182 patients with limited-stage SCLC.[245] Estimated PFS (the primary endpoint) 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 was similar in each group (high-dose: 17.4% vs. standard-dose: 15.3%). Grade 3 or higher pneumonitis was also similar in each group (high-dose: 3.3% vs. standard-dose: 2.4%). Treatment-related deaths were similar in each group (high-dose: 2.2% vs. standard-dose: 1.2%).

Another randomized phase 2 trial assessed concurrent chemoradiation using high-dose accelerated RT with 60 Gy given as twice-daily fractions over 4 weeks versus standard-dose accelerated 45 Gy given as twice-daily fractions over 3 weeks in 176 patients with limited-stage SCLC.[246] After 2 years, 74.2% (95% CI, 63.8%–82.9%) of patients were alive in the 60 Gy group versus 48.1% (36.9%–59.5%) in the 45 Gy group. Three treatment-related deaths occurred in each group.

Based on the data from these trials, the optimal dose and fractionation of thoracic RT for SCLC remain unresolved. 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. Higher dose accelerated RT may be advantageous, and this remains to be confirmed in larger studies. 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.[102,242] However, 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).[233,237] The optimal dose and schedule of RT have not been established. For twice-daily RT, the recommended schedule is 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks. For once-daily RT, the recommended schedule is 2.0 Gy once daily to a total dose of 66 to 70 Gy (see *Principles of Radiation Therapy* in the algorithm).[242,247-249] For the 2022 update (Version 2), the NCCN SCLC Panel revised the once-daily dosing to 66 to 70 Gy based on clinical trial data.[102,242]

The minimum technical requirement for thoracic irradiation is CT-planned 3D-conformal RT. For concurrent chemoradiation, intensity-modulated RT (IMRT) is preferred over 3D-conformal external-beam RT (EBRT) because IMRT is less toxic (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).[250-255] More advanced technologies may also be appropriate to limit normal tissue toxicity (eg, 4D-CT and proton therapy) (see *Principles of Radiation Therapy* in the algorithm). The radiation target volumes can be defined on the PET/CT scan obtained at the time of RT planning using definitions in Reports 50 and 62 from the International Commission on Radiation Units & Measurements (ICRU).[256,257] However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.[249,258]

The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar RT doses (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALCB 30610/RTOG 0538 protocol can be used as a guide (see *Principles of Radiation Therapy* in the algorithm).[259-261]

**SABR**

Emerging data suggest that SABR (also known as stereotactic body RT [SBRT]) is effective for patients with clinical stage I to IIA (T1–2,N0) SCLC, especially those who are medically inoperable or refuse surgery.[10,262-266] One study of 43 patients with clinical stage I SCLC who received SABR found that 31 patients were stage IA and 79% were medically inoperable.[10] Patients typically received 48 to 50 Gy (4–5 fractions), and only 8 patients received chemotherapy and PCI. The 2-year overall survival was 72.3% and 2-year PFS was 44.6%. Distant metastasis occurred in 47% of patients. A multicenter analysis of 74 patients suggested that the addition of chemotherapy typically after SABR improves survival for patients with clinical limited-stage SCLC.[11,267] Most of these patients had PET staging, although they did not have pathologic nodal staging. Patients who received chemotherapy after SABR had a median overall survival of 31.4 months versus 14.3 months for those receiving SABR alone ($P$ = .02).

An analysis of 2107 patients from the National Cancer Database in patients with histologically confirmed T1–T2,N0,M0 found that 7.1% had upfront SABR followed by adjuvant chemotherapy and 92.9% had concurrent chemoradiation.[268] Compared with patients receiving upfront concurrent chemoradiation, those receiving SABR were often older, had T1 disease, and had been treated more recently in academic medical

settings. Median survival was 29.2 months in those receiving SABR/chemotherapy and 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 stage I to IIA (T1–2,N0) SCLC.[233,234]

The NCCN SCLC Panel recommends (category 2A) SABR followed by systemic therapy as an option for select patients with clinical stage I to IIA (T1–2,N0) who are medically inoperable or decline surgery.[10,267] 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).

*Sequential Thoracic Radiation for Extensive-Stage SCLC*

A randomized trial by Jeremic et al[269] 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.[269] 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), but 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.[270] A trial involving 32 patients who received consolidative thoracic RT reported that only 16% (5/32) of patients had symptomatic chest recurrences.[271] Consolidative thoracic RT appears to mainly benefit patients with residual thoracic disease after systemic therapy, but with low-bulk extrathoracic metastatic disease that has responded to systemic therapy.[272] The American Radium Society recommends that consolidative thoracic RT can be considered for select patients with extensive-stage SCLC based on the limited data.[232] European experts (International Association for the Study of Lung Cancer [IASLC] and European Society Radiation Oncology [ESTRO]) recommend consolidation thoracic RT in select patients with stage IV SCLC who have responded to first-line chemotherapy and have limited extrathoracic tumor burden.[273]

The NCCN SCLC Panel recommends that sequential thoracic RT be considered in select patients with low-bulk extrathoracic metastatic extensive-stage disease who have a complete or near complete response after initial systemic therapy.[232,269,270] Immunotherapy/chemotherapy regimens are now the preferred first-line regimens for patients with extensive-stage SCLC; the clinical trials did not include sequential thoracic RT (see *Atezolizumab Plus Chemotherapy* and *Durvalumab Plus Chemotherapy* in this Discussion).[113-115] The NCCN SCLC Panel feels that sequential thoracic RT can be considered for selected patients, during or before maintenance immunotherapy; however, there are no data on optimal sequencing.

*Prophylactic Cranial Irradiation*

Intracranial metastases occur in more than 50% of patients with SCLC. Randomized studies have shown 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.[274] A meta-analysis of all randomized PCI trials (using data from individual patients) 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.[94] Thus, PCI seems to prevent (and not simply delay) the emergence of brain metastases. This meta-analysis also reported a 5.4% increase in 3-year overall survival in patients treated with PCI, from 15.3% in the control group to 20.7% in the PCI group.[94] Although the number of

patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in patients with both limited-stage and extensive-stage disease. A retrospective study of patients with limited-stage disease also found that PCI increased survival at 2, 5, and 10 years compared with those who did not receive PCI.[275] A study in 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.[276] 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.

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; $P < .0001$).[277] 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.[278]

In light of the paucity of data on the benefits of PCI in patients with extensive-stage SCLC, the EORTC performed a randomized trial that assessed PCI versus no PCI in 286 patients with extensive-stage SCLC whose disease 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.[279] However, the study did not require brain imaging prior to PCI and did not standardize the PCI dose or fractionation. Conflicting data come from a randomized phase 3 trial from Japan, which found that median overall survival was 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; $P = .094$).[280] 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 but without brain metastases based on the limited data.[232] A randomized trial (SWOG S1827/MAVERICK) is currently assessing whether brain MRI surveillance alone is non-inferior 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.[174,281,282] Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.[93,283] Older age (>60 years) has also been associated with chronic neurotoxicity.[173,175] The NCCN SCLC Panel has gradually revised the adjuvant recommendations for patients with 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.[174,284]

The NCCN SCLC Panel recommends PCI (category 2A) for patients with limited-stage disease who attain a complete or partial response.[93,94,279] For patients with limited-stage SCLC, the panel revised the PCI recommendation to category 2A from category 1 for the 2022 update (Version 1) because brain imaging was not done with MRI in the older meta-analysis used to support PCI.[94] It is not clear whether patients who have had surgical resection for stage I to IIA SCLC will benefit from PCI, because these patients have a lower risk of developing brain metastases.[267,285,286] For the 2022 update (Version 1), the NCCN SCLC Panel revised the adjuvant recommendations in patients with

extensive-stage disease to MRI brain surveillance with or without consideration of PCI based on the conflicting trial results from Japan and the EORTC.[279,280] Surveillance for metastases with brain imaging is recommended using either MRI (preferred) or CT with contrast in patients who are unable to undergo MRI.[280]

Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist that may delay cognitive dysfunction in patients receiving brain RT.[287] Patients receiving memantine had a longer time before cognitive decline (HR, 0.78; 95% CI, 0.62–0.99, *P* = .01). The NCCN SCLC Panel recommends that memantine be considered for patients receiving PCI or therapeutic whole-brain irradiation. Higher PCI doses (eg, 36 Gy) increased mortality and toxicity compared with lower doses (25 Gy).[173,288] Therefore, the preferred dose for PCI is 25 Gy in 10 daily fractions (2.5 Gy/fraction) (see *Principles of Radiation Therapy* in the algorithm).[94,279,288] The NCCN SCLC Panel feels that a shorter course of PCI may be appropriate (eg, 20 Gy in 5 fractions) for selected patients with extensive-stage disease.[279] 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.[173] 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.[283,288]

A phase 3 randomized trial assessed hippocampal-avoidance (HA) brain RT compared with conventional brain RT in patients with brain metastases.[289] Cognitive preservation and patient-reported outcomes were improved. 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.[290] However, another phase 3 randomized trial (NCT01780675) reported no differences in cognition.[291] A large randomized trial (NRG CC003) is assessing HA-PCI versus conventional PCI.[292] For the 2022 update (Version 1), the NCCN Panel feels that HA PCI using IMRT may be considered to improve cognitive preservation based on the conflicting data.[290,291]

***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).[293-295] 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).

Whole-brain RT is recommended for brain metastases 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).[296] The recommended dose for whole-brain RT is 30 Gy in 10 daily fractions.[296]

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]).[297] A randomized trial (NRG CC009) is comparing SRS to hippocampal sparing whole-brain RT plus memantine in this setting. The NCCN Panel

feels 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.[297] In patients who develop brain metastases after PCI, SRS (preferred) or repeat whole-brain RT (in carefully selected patients) may be considered.[298,299]

## Summary

SCLC is a poorly differentiated high-grade neuroendocrine carcinoma.[21] Most cases of SCLC are caused by cigarette smoking.[4] Management of SCLC is described in the NCCN Guidelines for SCLC, which include the algorithm and this supporting Discussion text. Revisions for the 2022 update of the NCCN Guidelines for SCLC are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates* in the algorithm). For the 2022 update (Version 1), the NCCN SCLC Panel now recommends the following subsequent therapy agents for patients who have relapsed more than 6 months after therapy: topotecan, paclitaxel, docetaxel, irinotecan, temozolomide, CAV, oral etoposide, vinorelbine, gemcitabine, nivolumab, pembrolizumab, and lurbinectedin (category 2A for all); bendamustine is a category 2B recommendation in this setting.[229] However, the original regimen is the preferred regimen for patients who have relapsed more than 6 months after therapy.[227,228,230,231] The FDA has removed the subsequent therapy indications for nivolumab or pembrolizumab, because phase 3 randomized trial data did not show an improvement in overall survival.[204] However, the NCCN SCLC Panel still recommends these agents in certain settings. Patients with limited-stage SCLC who relapse and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. The panel feels that nivolumab or pembrolizumab are as effective as, sometimes better than, and less toxic than the other subsequent therapy options.[204,209] For the 2022 update (Version 1), the NCCN SCLC Panel revised the recommendations for nivolumab or pembrolizumab to category 2A from category 3, regardless of the time since relapse.

The FDA recently approved different doses for atezolizumab when combined with carboplatin and etoposide as primary therapy for patients with extensive-stage SCLC. For the 2022 update (Version 1), the NCCN Panel now recommends a new carboplatin/etoposide/atezolizumab regimen with slightly different dosing for the maintenance atezolizumab; 1680 mg of maintenance atezolizumab is recommended. However, the category 1 recommendation is only for the regimen with 1200 mg of maintenance atezolizumab since that dose was used in the clinical trial.[113,115]

The NCCN SCLC Panel recommends adjuvant PCI (category 2A) for patients with limited-stage disease who attain a complete or partial response.[93,94,279] For patients with limited-stage SCLC, the panel revised the PCI recommendation to category 2A from category 1 for the 2022 update (Version 1) because brain imaging was not done with MRI in the older meta-analysis used to support PCI.[94] For the 2022 update (Version 1), the NCCN SCLC Panel revised the adjuvant recommendations for patients with extensive-stage SCLC to MRI brain surveillance with or without consideration of PCI based on the conflicting results from Japan and the EORTC trials.[279,280] Surveillance for brain metastases is recommended using either MRI (preferred) or CT with contrast in patients who are unable to undergo MRI.[280]

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