National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Cell Lung Cancer

Version 2.2025 — September 5, 2024

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NCCN recognizes the importance of clinical trials and encourages participation when applicable and available. Trials should be designed to maximize inclusiveness and broad representative enrollment.

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NCCN Small Cell Lung Cancer Panel Members
Summary of the Guidelines Updates

Initial Evaluation and Staging (SCL-1)
Limited Stage, Workup and Treatment (SCL-2)
Extensive Stage, Primary Treatment (SCL-5)
Response Assessment Following Primary Treatment and Adjuvant Therapy (SCL-6)
Progressive Disease: Subsequent Therapy and Palliative Therapy (SCL-8)

Signs and Symptoms of Small Cell Lung Cancer (SCL-A)
Principles of Pathologic Review (SCL-B)
Principles of Surgical Resection (SCL-C)
Principles of Supportive Care (SCL-D)
Principles of Systemic Therapy (SCL-E)
Principles of Radiation Therapy (SCL-F)
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Staging (ST-1)

Lung Neuroendocrine Tumors – See NCCN Guidelines for Neuroendocrine and Adrenal Tumors
Abbreviations (ABBR-1)

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.

Updates in Version 2.2025 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2025 include:

MS-1
• The discussion section has been updated to reflect changes within the algorithm

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Updates in Version 1.2025 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2024 include:

SCL-1
• Footnotes modified
  ▸ a: If extensive stage is established, further staging evaluation is optional *and dependent on the clinical situation*. However, brain imaging MRI (preferred), or CT with contrast is recommended ~~in all patients~~.
  ▸ f*:* If FDG-PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for ~~lesions detected by FDG-PET/CT that alter stage~~ *isolated or equivocal lesions if their involvement would change clinical management*.
  ▸ g: Comprehensive molecular profiling *via blood, tissue, or both* can be considered in rare cases—particularly for patients with extensive stage/ relapsed SCLC who do not smoke tobacco, lightly smoke, have remote smoking history, or have a diagnostic or therapeutic dilemma, or at time of relapse—if not previously done, because this may change management.

SCL-2
• Lower pathway modified: Bone marrow biopsy, thoracentesis, or ~~bone studies~~ *any compelling evidence of distant disease* consistent with malignancy

SCL-3
• Footnote o modified: For patients receiving adjuvant systemic therapy ± RT, response assessment is recommended only after completion of adjuvant therapy (SCL-6)~~; do not repeat scans to assess response during adjuvant treatment~~.*Repeating scans to assess response during adjuvant or initial treatment is not recommended in the absence of new symptoms.*
• Footnote p modified: For patients receiving systemic therapy + concurrent RT, response assessment is recommended only after completion of initial therapy (SCL-6)~~; do not repeat scans to assess response during initial treatment~~ *Repeating scans to assess response during adjuvant or initial treatment is not recommended in the absence of new symptoms*. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by C/A/P CT with contrast is recommended after every 2 cycles of systemic therapy and at completion of therapy

SCL-5
• Second column: Extensive stage removed from all 3 pathways.
• Footnote t modified: During systemic therapy, response assessment by C/A/P CT with contrast should occur after every 2–3 cycles of systemic therapy ~~and at completion of therapy~~**.**
• Footnote v modified: Initiate steroids for patients with symptomatic neurologic disease. *Eg, dexamethasone 10 mg loading dose followed by 4–6 mg maintenance dose (IV or PO every 4–6 hours [or as appropriate]). Kumar A, et al. Clin Spine Surg 2017;4:156-163.*

SCL-6, SCL-7, SCL-8
• Pages extensively modified

SCL-A 2 of 2
• Neurologic, all sub-bullets modified:
  ▸ Subacute cerebellar degeneration ~~(anti-Yo antibody)~~ – ataxia, dysarthria
  ▸ Encephalomyelitis ~~(ANNA-1 [anti-Hu] antibody)~~ – confusion, obtundation, dementia
  ▸ Sensory neuropathy ~~(anti-dorsal root ganglion antibody)~~ – pain, sensory loss
  ▸ Lambert-Eaton myasthenic syndrome (LEMS) ~~(anti-voltage-gated calcium channel antibody)~~ – weakness, autonomic dysfunction
  ▸ Cancer-associated retinopathy ~~(anti-recoverin antibody)~~ – visual loss, photosensitivity

Continued
UPDATES

National Comprehensive Cancer Network®

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Updates in Version 1.2025 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2024 include:

SCL-B 1 of 2
- Immunohistochemical Staining, sub-bullet two 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 5% of SCLCs are negative for all neuroendocrine markers. *For cases with suspicious SCLC morphology without expression of neuroendocrine markers, POU2F3 immunohistochemical staining can be considered.*

SCL-B 2 of 2
- References added
  - Wang Y, Jin Y, Shen X, et al. POU2F3: A sensitive and specific diagnostic marker for neuroendocrine-low/negative small cell lung cancer. Am J Surg Pathol 2023;47;1059-1066.
  - Baine MK, Febres-Aldana CA, Chang JC, et al. POU2F3 in SCLC: clinicopathologic and genomic analysis with a focus on its diagnostic utility in neuroendocrine-low SCLC. J Thorac Oncol 2022;17:1109-1121.

SCL-E 1 of 6
- Primary or adjuvant therapy for limited stage SCLC, preferred regimen added: Durvalumab consolidation 1500 mg day 1 every 28 days
- Footnote f added: In those who did not experience disease progression after systemic therapy + concurrent RT: may continue durvalumab until disease progression or intolerable toxicity, or for a maximum of 24 months

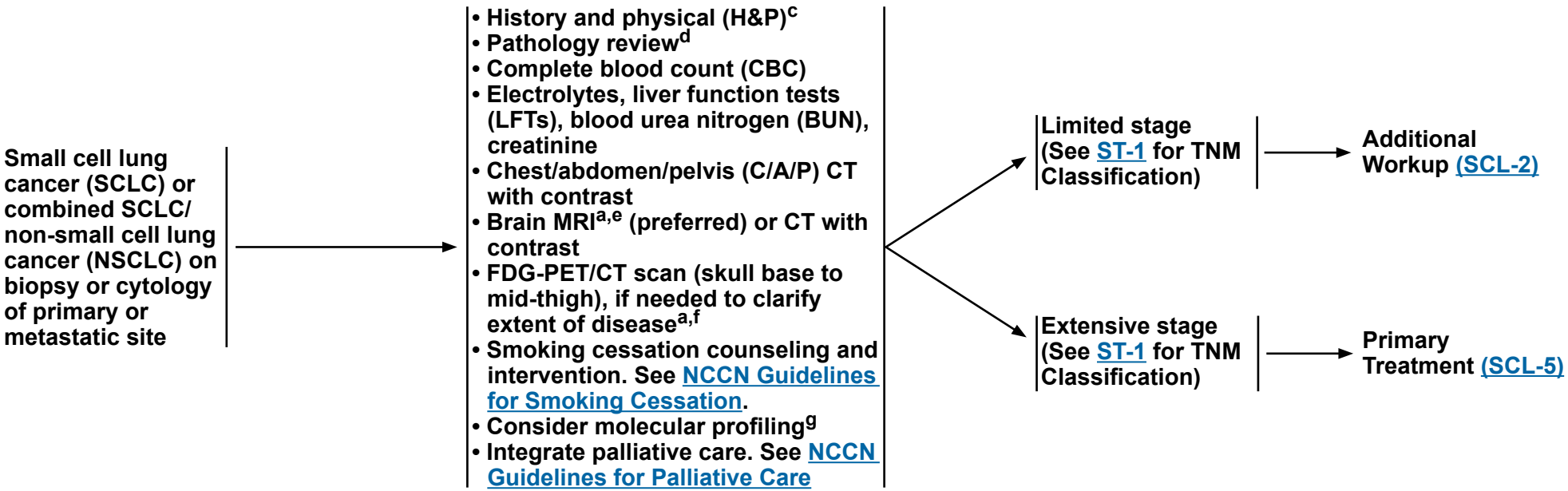
SCL-E 2 of 6
- Footnote b modified: Contraindications for treatment with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. ~~For safety reasons, do not use ICIs in patients who have recently received tyrosine kinase inhibitors (TKIs).~~ *If tyrosine kinase inhibitor (TKI) is continued, ICI should be avoided, due to known toxicity.* (Also for SCL-E 3 of 6)

SCL-F 1 of 7
- Reference added: Zhang C, Zhao G, Wu H, et al. Application of postoperative adjuvant radiotherapy in limited stage small cell lung cancer: A systematic review and meta-analysis. Radiother Oncol 2024;193:110123.

SCL-F 2 of 7
- Sub-bullet 2 modified: Retrospective and randomized phase II studies from *Norway and Canada* 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, *though regional practice between daily and twice daily fractionation has diverged between those countries after subsequent experience*.
- Reference added: Graabak G, Grønberg BH, Sandvei MS, et al. Thoracic Radiotherapy in Limited stage SCLC-a Population-Based Study of Patterns of Care in Norway From 2000 Until 2018. JTO Clin Res Rep 2022;3:100270.

SCL-F 4 of 7
- Reference added: Gondi V, Pugh S, Mehta MP, et al. Primary Endpoint Results of NRG CC003: Phase IIR/ III Trial of Prophylactic Cranial Irradiation (PCI) with or without Hippocampal Avoidance (HA) for Small Cell Lung Cancer (SCLC) [abstract 2023]. Int J Radiat Oncol Biol Phys 2023;117:E3.

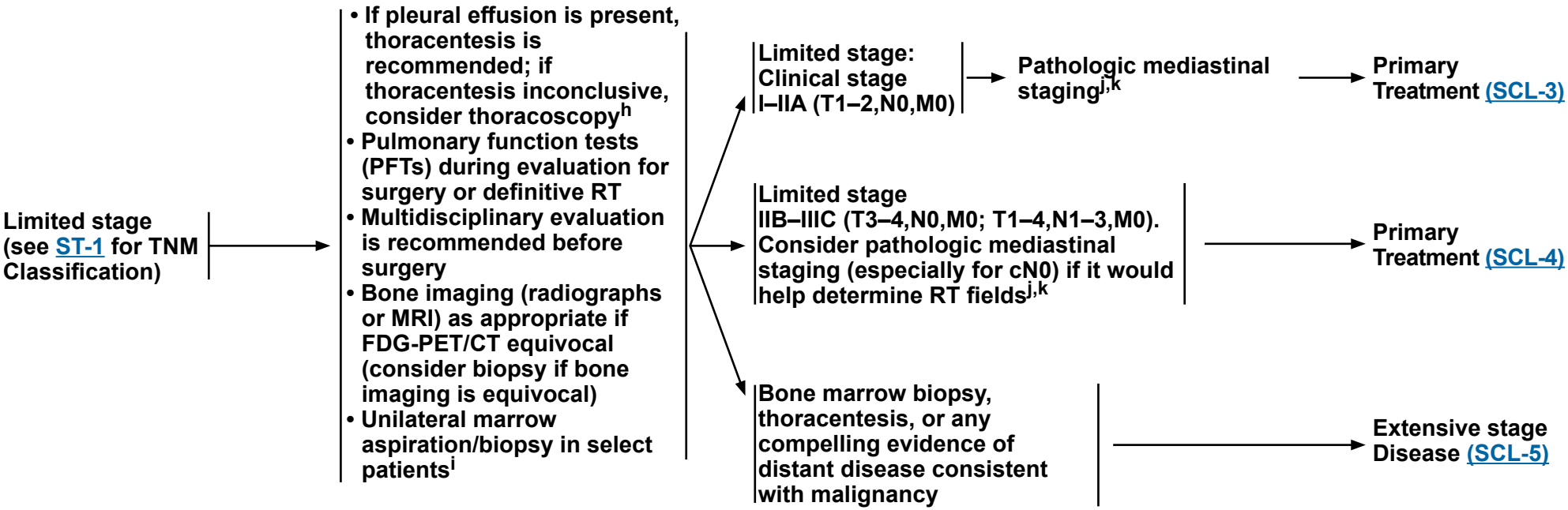
SCL-G
- Principles of Imaging section new to Guidelines



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

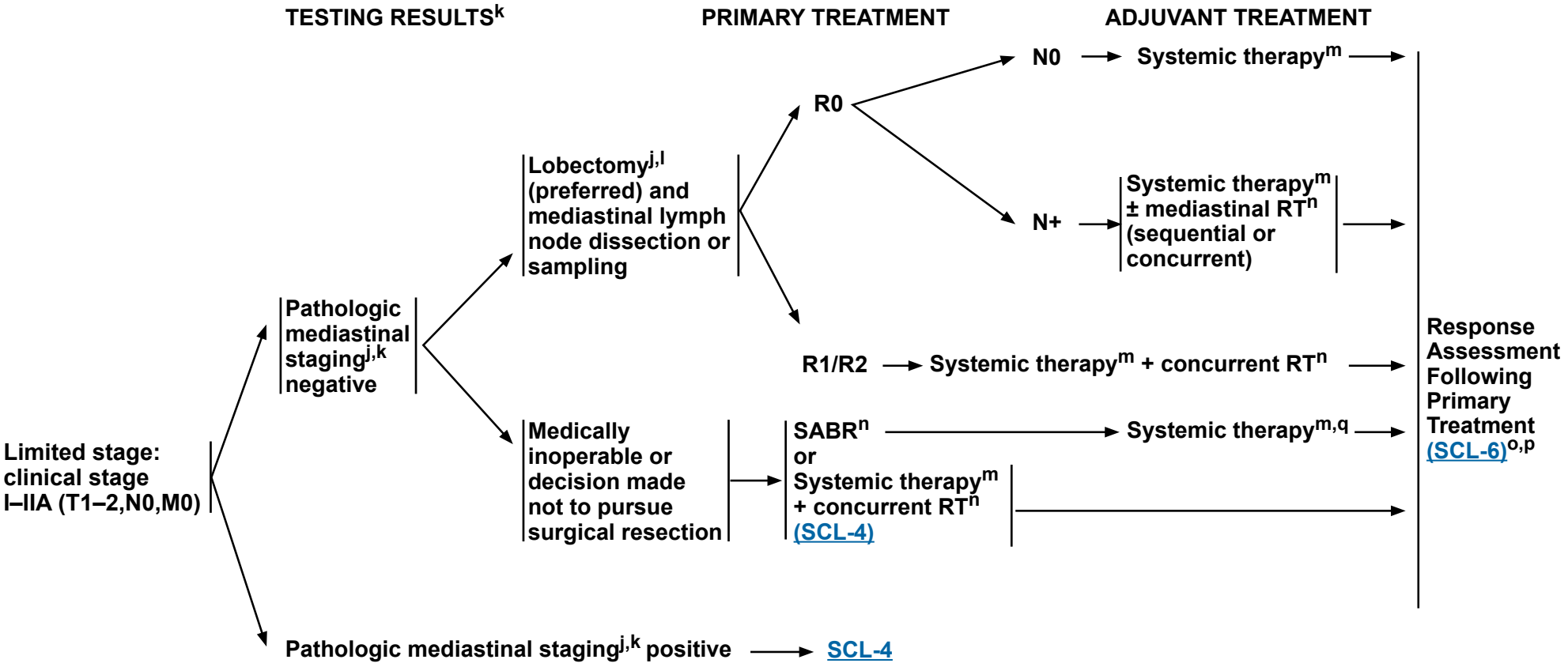
Note: All recommendations are category 2A unless otherwise indicated.

STAGE | **ADDITIONAL WORKUP[b]**



[b] Workup of SCLC should be expedited, with studies done in parallel whenever possible.
[h] While most pleural effusions in patients with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.
[i] Selection criteria include: nucleated red blood cells (RBCs) on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration.
[j] Principles of Surgical Resection (SCL-C).
[k] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

Note: All recommendations are category 2A unless otherwise indicated.



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

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

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

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

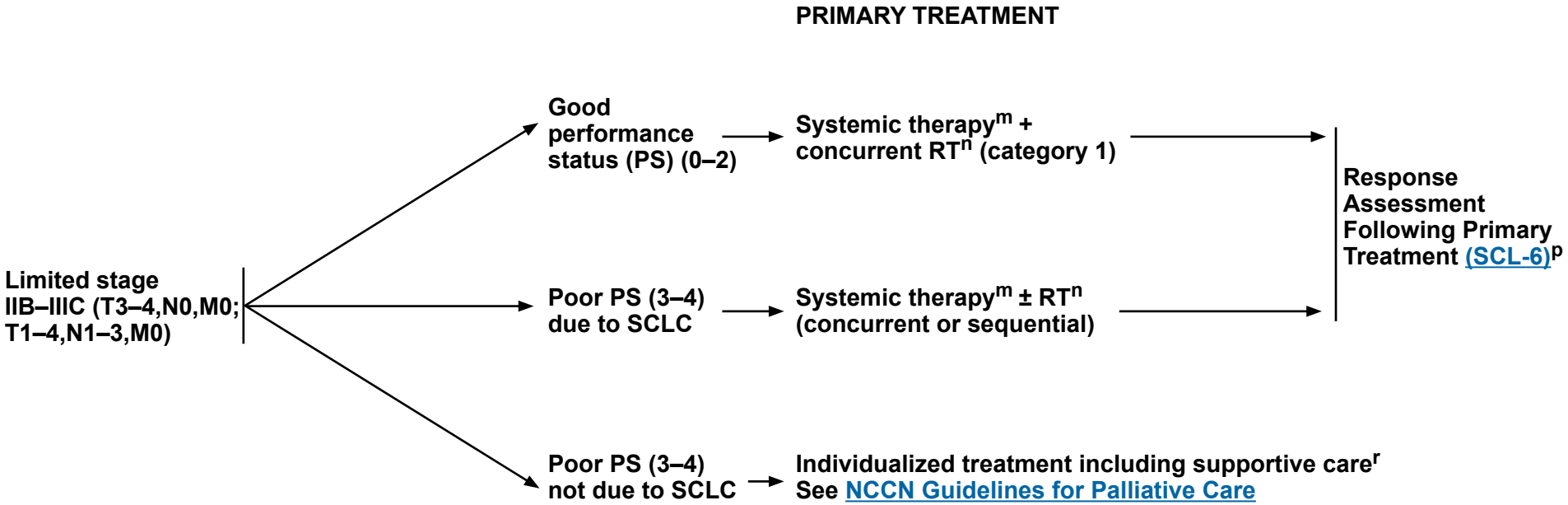
[n] Principles of Radiation Therapy (SCL-F).

[o] For patients receiving adjuvant systemic therapy ± RT, response assessment is recommended only after completion of adjuvant therapy (SCL-6). Repeating scans to assess response during adjuvant or initial treatment is not recommended in the absence of new symptoms.

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

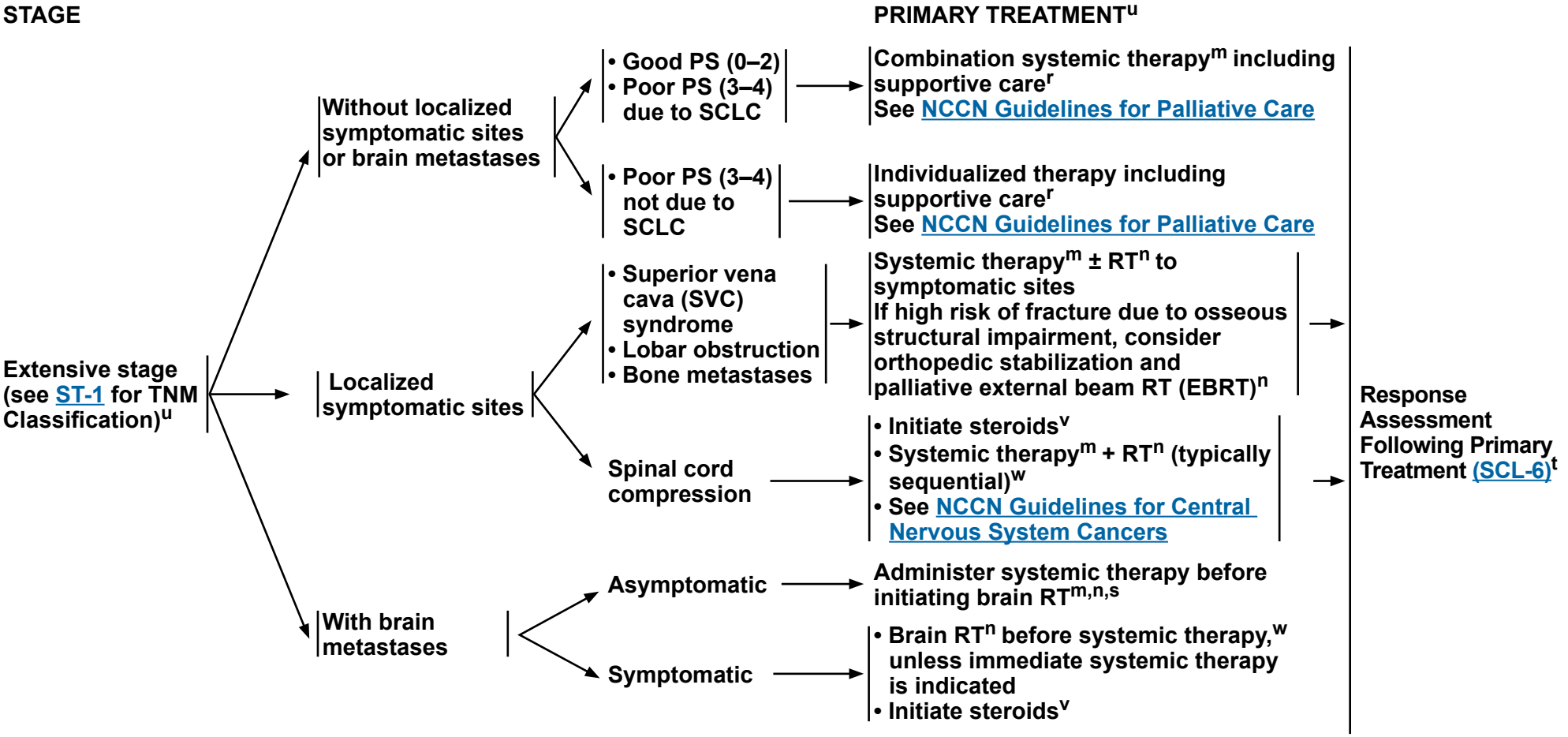
[q] Systemic therapy may be initiated first if time to initiation of stereotactic body radiotherapy (SABR) will be prolonged.

Note: All recommendations are category 2A unless otherwise indicated.



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

Note: All recommendations are category 2A unless otherwise indicated.

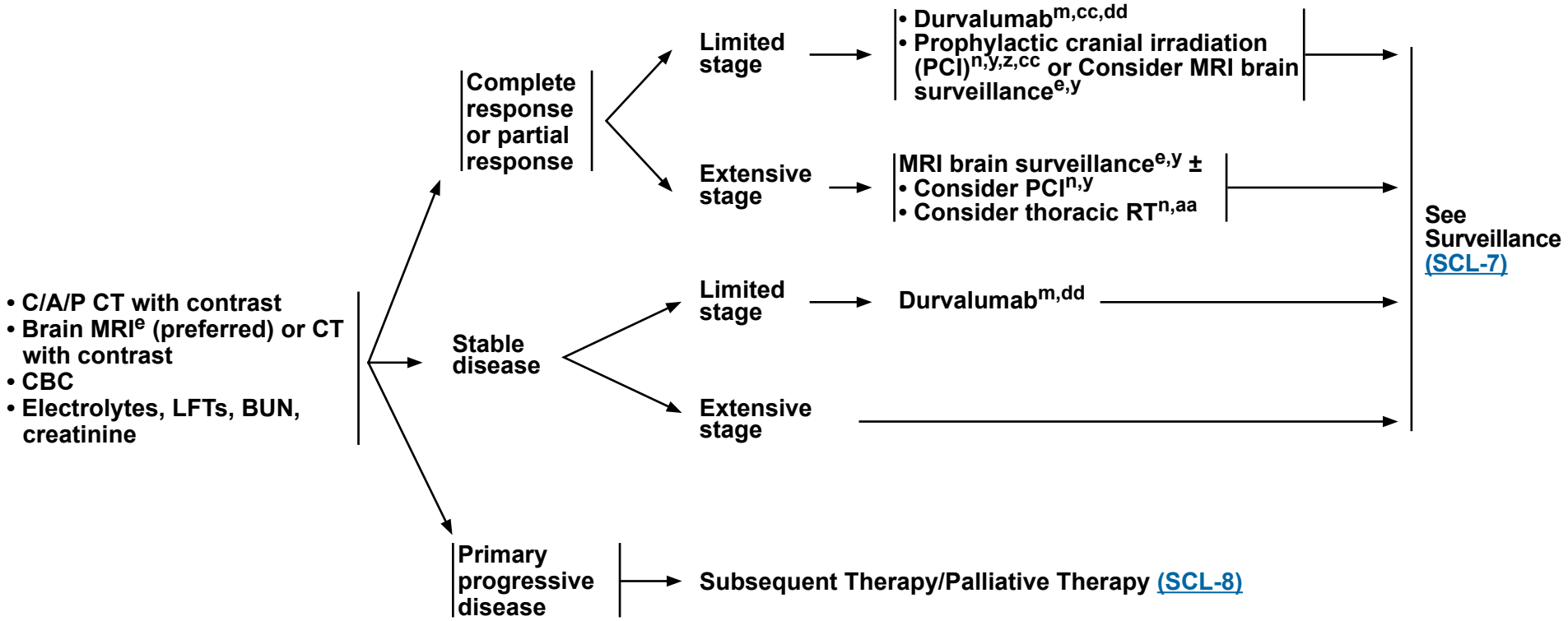


[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[r] Principles of Supportive Care (SCL-D).
[s] Brain MRI (preferred) or CT with contrast is recommended to be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first (SCL-6). If brain metastases progress while on systemic therapy, it is recommended that brain RT is initiated before completion of systemic therapy. See Principles of Radiation Therapy (SCL-F).
[t] During systemic therapy, response assessment by C/A/P CT with contrast should occur after every 2–3 cycles of systemic therapy (SCL-6).
[u] For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).
[v] Initiate steroids for patients with symptomatic neurologic disease. Eg, dexamethasone 10 mg loading dose followed by 4–6 mg maintenance dose (IV or PO every 4–6 hours [or as appropriate]). Kumar A, et al. Clin Spine Surg 2017;4:156-163.
[w] With neurologic symptoms, RT is preferred before systemic therapy. Systemic therapy may start first if RT cannot be started expeditiously or if controlling systemic symptoms is more urgent.

Note: All recommendations are category 2A unless otherwise indicated.

RESPONSE ASSESSMENT FOLLOWING PRIMARY TREATMENT

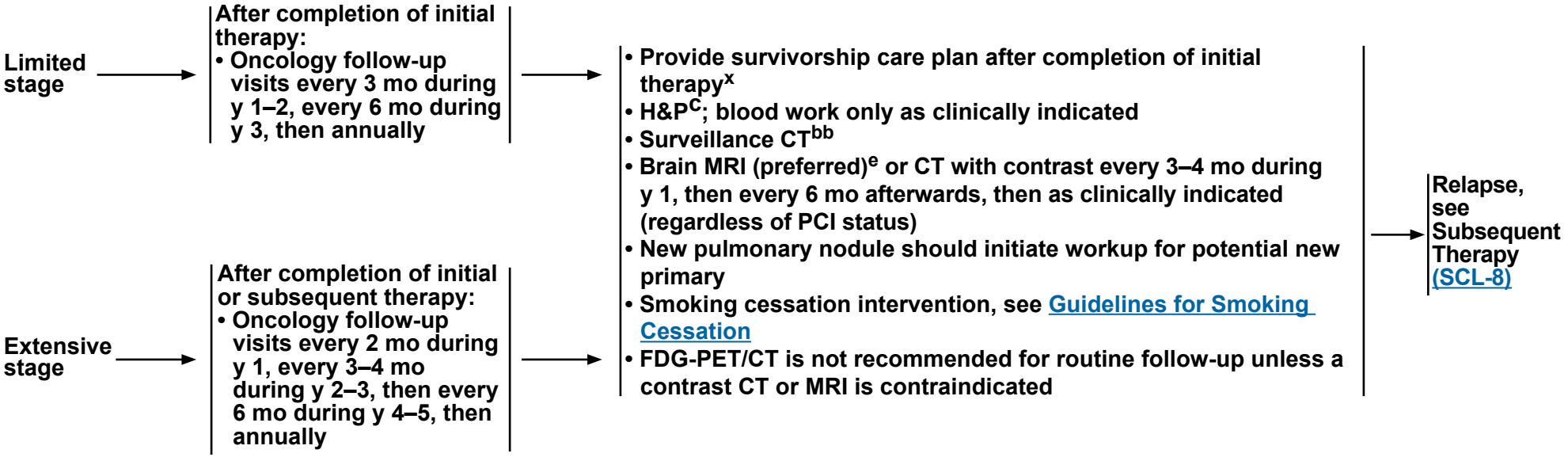
ADJUVANT THERAPY



[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[y] PCI is not recommended in patients with poor PS or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close brain surveillance, MRI (preferred) or CT with contrast, should be carefully discussed with these patients.
[z] The benefit of PCI is unclear in patients who have undergone definitive therapy for pathologic stage I (T1-2a,N0,M0) SCLC. See Principles of Radiation Therapy (SCL-F).
[aa] Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.
[cc] If PCI is considered, it should be given prior to durvalumab
[dd] For those with good PS who are medically inoperable or decision was made not to pursue surgical resection

Note: All recommendations are category 2A unless otherwise indicated.

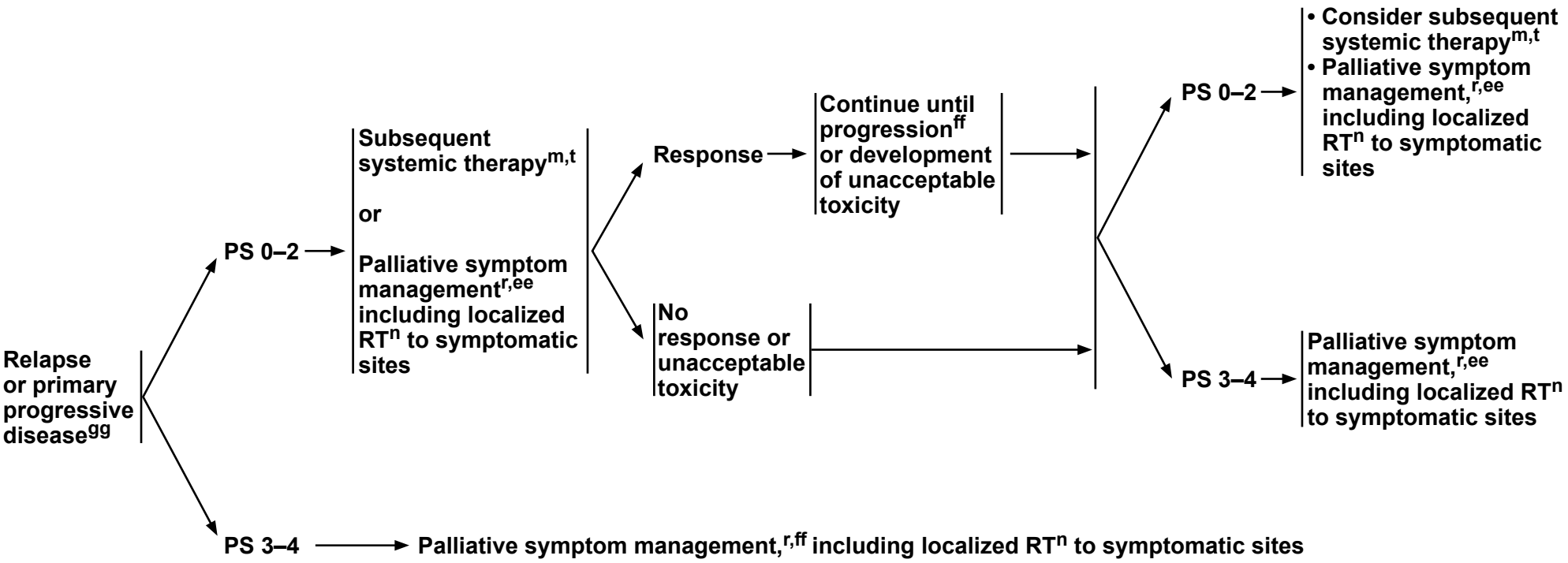
SURVEILLANCE



[c] Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[e] Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[x] See NCCN Guidelines for Survivorship.
[bb] Most NCCN Member Institutions use CT chest ± abdomen/pelvis every 2–6 months (more frequently in years 1–2 and less frequently thereafter).

Note: All recommendations are category 2A unless otherwise indicated.

PROGRESSIVE DISEASE **SUBSEQUENT THERAPY/PALLIATIVE THERAPY**



[m] Principles of Systemic Therapy (SCL-E).
[n] Principles of Radiation Therapy (SCL-F).
[r] Principles of Supportive Care (SCL-D).
[t] During systemic therapy, response assessment by C/A/P CT with contrast should occur after every 2–3 cycles of systemic therapy (SCL-6).
[ee] See NCCN Guidelines for Palliative Care.
[ff] For central nervous system (CNS) progression only, continue systemic therapy and treat the brain metastases with RT (see Principles of Radiation Therapy).
[gg] Consider genomic profiling, if not previously done, to determine clinical trial eligibility.

Note: All recommendations are category 2A unless otherwise indicated.

SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and Symptoms Due to Local Primary Tumor Growth

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

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

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

Signs and Symptoms Due to Extrathoracic (Hematogenous) Metastases

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

Note: All recommendations are category 2A unless otherwise indicated.

Continued

SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and Symptoms of Paraneoplastic Syndromes
- Presence does not imply metastases or incurability

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

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

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

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

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW

Pathologic Evaluation

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

Immunohistochemical Staining

- Immunohistochemistry can be very helpful in diagnosing SCLC in limited samples.[5,7]
  - Nearly all SCLCs are positive for cytokeratin antibody mixtures with broad reactivity, such as AE1/AE3 and CAM5.2.[1,10]
  - The majority of SCLCs are reactive to markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), CD56/NCAM, synaptophysin, and chromogranin A. Fewer than 5% of SCLCs are negative for all neuroendocrine markers.[11,12] For cases with suspicious SCLC morphology without expression of neuroendocrine markers, POU2F3 immunohistochemical staining can be considered.[13,14]
  - Thyroid transcription factor-1 (TTF-1) is positive in 85% to 90% of SCLCs.[15-18]
  - 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]

References on SCL-B 2 of 2

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF PATHOLOGIC REVIEW - REFERENCES

[1] WHO Classification of Tumours Editorial Board. Thoracic Tumours. In: WHO classification or tumours series. 5th ed. Lyon, France. International Agency for Research on Cancer; 2021.
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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SURGICAL RESECTION

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

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SUPPORTIVE CARE

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

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

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

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

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

- **Pain management: See NCCN Guidelines for Adult Cancer Pain**

- **Nausea/vomiting: See NCCN Guidelines for Antiemesis**

- **Psychosocial distress: See NCCN Guidelines for Distress Management**

- **See NCCN Guidelines for Palliative Care as indicated**

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

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY

PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:

Four cycles of cytotoxic chemotherapy are recommended.
Planned cycle length should be every 21–28 days during concurrent RT.
During cytotoxic chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
The use of myeloid growth factors is not recommended during concurrent cytotoxic chemotherapy 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]**
- **Consolidation Therapy**
  - **Durvalumab 1500 mg day 1 every 28 days[a,4]**

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

PRIMARY THERAPY FOR EXTENSIVE STAGE SCLC[c]:

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

Preferred Regimens
- **Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1200 mg day 1, every 21 days (category 1 for all)[d,e,6]**
- **Carboplatin AUC 5 day 1 and etoposide 100 mg/m² days 1, 2, 3 and atezolizumab 1200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1680 mg day 1, every 28 days[d,e]**
- **Carboplatin AUC 5–6 day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]**
- **Cisplatin 75–80 mg/m² day 1 and etoposide 80–100 mg/m² days 1, 2, 3 and durvalumab 1500 mg day 1 every 21 days x 4 cycles followed by maintenance durvalumab 1500 mg day 1 every 28 days (category 1 for all)[d,e,f,7]**

Other Recommended Regimens
- **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[8]**
- **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[9]**
- **Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[10]**
- **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[11]**

Useful in Certain Circumstances
- **Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[12]**
- **Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[13]**
- **Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[14]**

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

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY - FOOTNOTES

[a] Those who did not experience disease progression after systemic therapy + concurrent RT may continue durvalumab until disease progression or intolerable toxicity, or for a maximum of 24 months
[b] Cisplatin contraindicated or not tolerated.
[c] For transformation to SCLC from NSCLC, consider referral to a center with expertise (SCL-E 4 of 6).
[d] Contraindications for treatment with programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1) inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. If tyrosine kinase inhibitor (TKI) is continued, ICI should be avoided, due to known toxicity.
[e] Maintenance immunotherapy with either atezolizumab or durvalumab should continue until progression or intolerable toxicity.
[f] Included patients with asymptomatic untreated brain metastases.

Note: All recommendations are category 2A unless otherwise indicated.

SCLC SUBSEQUENT SYSTEMIC THERAPY (PS 0–2)[g] Consider dose reduction or growth factor support for patients with PS 2
CHEMOTHERAPY-FREE INTERVAL (CTFI) >6 MONTHS
Preferred Regimens • Clinical trial enrollment • Re-treatment with platinum-based doublet[h,15-19] **Other Recommended Regimens** • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[j,28]
CTFI ≤6 MONTHS
Preferred Regimens • Clinical trial enrollment • Lurbinectedin[20,21] • Topotecan oral (PO) or intravenous (IV)[17,22-25] • Irinotecan[i,25,26] • Tarlatamab-dlle[j,28] • Re-treatment with platinum-based doublet may be considered for CTFI 3–6 months[h,17-19] **Other Recommended Regimens** • Nivolumab or pembrolizumab (if not previously treated with an ICI)[d,29-33] • Paclitaxel[34,35] • Temozolomide[36,37] • Cyclophosphamide/doxorubicin/vincristine (CAV)[22] • Docetaxel[38] • Gemcitabine[27,39,40] • Oral etoposide[41,42]

[d] Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. If TKI is continued, ICI should be avoided, due to known toxicity.

[g] Subsequent systemic therapy refers to second-line and beyond therapy..

[h] Rechallenging with the original regimen or similar platinum-based regimen, as shown on SCL-E 1, is recommended if there has been a CTFI of more than 6 months and may be considered if there has been a CTFI of at least 3 to 6 months.

[i] For patients with CNS disease, consider using irinotecan.

[j] For extensive stage with disease progression on or after platinum-based chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

References on (SCL-E 5 of 6)

PRINCIPLES OF SYSTEMIC THERAPY

Response Assessment

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

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

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

- **Transformed SCLC from NSCLC with an Oncogenic Driver**
  - This is a rare population of patients with very limited data to guide treatment.[43-46]
  - Systemic cytotoxic chemotherapy is recommended using the NCCN Guidelines for Small Cell Lung Cancer.[43,44]
  - The role of immunotherapy in this setting is unclear based on limited data.[43-46]
  - If TKI is continued, ICI should be avoided, due to known toxicity.[45,47,48]
  - Consider referral to a center with experience managing transformed SCLC.

References on (SCL-E 5 of 6)

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF SYSTEMIC THERAPY – REFERENCES

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

General Principles:

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

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[5] and may be considered in pathologic N1 stage, either sequentially or concurrently with chemotherapy. Principles of postoperative RT for NSCLC, including target volumes and doses, are recommended.
- Selected patients with stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT), to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC (see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C).[6-8]
- Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[9] RT should start early, with cycle 1 or 2 of systemic therapy (category 1).[10] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[11]
- Target definition: RT target volumes should be defined based on the pretreatment FDG-PET scan and CT scan obtained at the time of RT planning, as well as any positive biopsies. FDG-PET/CT is recommended, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, FDG-PET/CT should be obtained in the treatment position.

Limited Stage (continued), Extensive Stage (SCL-F 2 of 7)
Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation (SCL-F 3 of 7)
Brain Metastasis (SCL-F 4 of 7)

Continued
References
(SCL-F 5 of 7)

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Limited Stage (continued):

- Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Several more modern series, both retrospective and prospective, suggest that omission of elective nodal irradiation (ENI) results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating FDG-PET staging/target definition (1.7%–3%).[12-17] ENI has been omitted in recent prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial). Inclusion of the ipsilateral hilum in the target volume, even if not grossly involved, differs between these trials but may be reasonable.
- In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.[14,18]
- 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).[19,20] 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 from Norway and Canada 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, though regional practice between daily and twice daily fractionation has diverged between those countries after subsequent experience.[21,22,23]
  - If using once-daily conventionally fractionated RT, higher doses of 66–70 Gy are preferred.[24-27] Two randomized phase III trials did not demonstrate superiority of 66 Gy in 6.5 weeks/2 Gy daily (the European CONVERT trial) or 70 Gy in 7 weeks/2 Gy daily (CALGB 30610/RTOG 0538) over 45 Gy in 3 weeks/1.5 Gy BID, but overall survival and toxicity were similar.[28,29,30]
  - 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.[31,32]

Extensive Stage:

- Consolidative thoracic RT is beneficial for selected patients with ES-SCLC with complete response or good response to systemic therapy before immunotherapy, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.[33,34] The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with ES-SCLC that responded to chemotherapy (without immunotherapy) demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.[32] Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.[36]
- Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions up to definitive dosing regimens in patients with a longer life expectancy.

Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation (SCL-F 3 of 7)
Brain Metastasis (SCL-F 4 of 7)

Continued

References (SCL-F 5 of 7)

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Extensive Stage (continued):

- Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach,[37,38] but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are limited data on optimal sequencing or safety). The benefit of thoracic RT in the context of chemo-immunotherapy is under evaluation in the RAPTOR/NRG LU007 trial.

Normal Tissue Dose Constraints:

- Normal tissue dose constraints depend on tumor size and location. For similar RT prescription doses, the normal tissue constraints used for NSCLC are appropriate (see 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 limited stage SCLC (LS-SCLC) who have a good response to initial therapy, PCI decreases brain metastases and increased overall survival[39,40] in meta-analyses of past clinical trials. Of note, none of the past studies that have been used as the basis for PCI recommendations in LS-SCLC employed MRI staging of the brain nor did any utilize FDG-PET scans for overall staging.
- The benefit of PCI is unclear in patients who have undergone definitive therapy for very early LS-SCLC, ie, pathologic stage I–IIA (T1–2,N0,M0).[41] These patients have a lower risk of developing brain metastases than patients with more advanced, LS-SCLC and may not benefit from PCI.[41] Brain MRI surveillance is recommended in patients not receiving PCI.[41] However, PCI may have a benefit in patients who are found to have pathologic stage IIB or III SCLC after complete resection.[40,41] This issue is being evaluated in the ongoing NCI cooperative group trial SWOG S1827/MAVERICK (brain MRI surveillance ± PCI), which includes the population undergoing surgical resection (https://clinicaltrials.gov/ct2/show/NCT04155034).
- In patients with ES-SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the European Organisation for Research and Treatment of Cancer (EORTC) found improved overall survival with PCI.[42] 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.[43] 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.[44,45]
- Neurocognitive function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients >60 years experienced chronic neurotoxicity 12 months after PCI versus 56% of patients <60 years (P = .009).[45] PCI is not recommended in patients with poor PS or impaired neurocognitive function.[44] The role of PCI in MRI and FDG-PET staged SCLC in fit patients with normal neurocognitive function is the subject of ongoing debate, particularly in limited stage, and is being evaluated in the phase III SWOG S1827/MAVERICK trial comparing PCI (active comparator) to MRI surveillance (experimental) in both limited and extensive stage (https://clinicaltrials.gov/ct2/show/NCT04155034).

Brain Metastasis (SCL-F 4 of 7)

Continued
References (SCL-F 5 of 7)

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF RADIATION THERAPY

Prophylactic Cranial Irradiation (continued):

- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor PS or impaired neurocognitive functioning.
- When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases.[46] The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening (see NCCN Guidelines for Central Nervous System Cancers).
- Hippocampal-avoidance (HA) PCI using IMRT may be considered as a potential strategy to improve cognitive preservation. A phase III randomized trial of HA-WBRT versus conventional WBRT demonstrated improved cognitive preservation and patient-reported outcomes with HA-WBRT in patients with brain metastases from mixed histologies.[47] Conflicting data have been reported with HA-PCI versus conventional PCI in SCLC with one trial reporting no differences in cognition[48] and a separate trial reporting improved cognitive preservation with HA-PCI.[49] A larger randomized trial of HA-PCI versus conventional PCI, NRG CC003,[50] has completed accrual with results pending.[51]
- 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.[52]

Brain Metastases:

- Brain metastases have conventionally been treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS).[53] 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).[46]
- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[54,55] SRS is preferred, if feasible.[56,57]
- 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.[47] However, patients with metastases within 5 mm of the hippocampi, leptomeningeal metastases, and other high-risk features were not eligible for hippocampal-sparing WBRT on NRG CC001.[47] Although CC001 did not include patients with brain metastases from SCLC, it is reasonable to extrapolate the findings to SCLC.

Palliative Radiation for Extracranial Metastases:

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

References
(SCL-F 5 of 7)

Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING

General Principles:

- **Both CT and MRI are performed with contrast, unless clinically contraindicated.**
- **Workup of SCLC should be expedited, with studies done in parallel whenever possible.**
- **If extensive stage is established, brain imaging MRI (preferred) or CT with contrast is recommended. Further evaluation is dependent on the clinical situation.**
- **Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.**

Workup:

- **C/A/P CT with contrast**
- **Brain MRI (preferred) or CT with contrast**
- **FDG-PET/CT scan (skull base to mid-thigh), if needed to clarify extent of disease**

Additional workup:

- **Bone imaging (radiographs or MRI) as appropriate, if FDG-PET/CT equivocal**

Note: All recommendations are category 2A unless otherwise indicated.

PRINCIPLES OF IMAGING

Recommendations for scanning are based on patients without altered symptoms or with stable symptoms

Treatment Response Assessment

- **Limited Stage**
  - **For patients receiving adjuvant systemic therapy ± RT, response assessment is recommended only after completion of adjuvant therapy (SCL-6).**
  - **For patients receiving systemic therapy + concurrent RT, response assessment is recommended only after completion of initial therapy (SCL-6).Repeating scans to assess response during adjuvant or initial treatment is not recommended in the absence of new symptoms.**
  - **For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by C/A/P CT with contrast is recommended after every 2 cycles of systemic therapy and at completion of therapy (SCL-6).**

- **Extensive Stage**
  - **In asymptomatic brain metastases, if systemic therapy was initiated prior to brain RT, brain MRI (preferred) or CT with contrast is recommended to be repeated after every 2 cycles of systemic therapy until brain RT is initiated (SCL-6).**
    - **If brain metastases progress while on systemic therapy, it is recommended that brain RT is initiated before completion of systemic therapy.**
  - **During systemic therapy, response assessment by C/A/P CT with contrast is recommended after every 2–3 cycles of systemic therapy.**
  - **For patients with known brain metastases, brain MRI (preferred) or brain CT with contrast should be obtained every 3-4 months, or at a frequency based on clinical indication.**

Follow-up/Surveillance

- **Most NCCN Member Institutions use chest CT ± abdomen/pelvis every 2–6 months (more frequently in years 1–2 and less frequently thereafter).**
- **Brain MRI or CT with contrast every 3–4 months during year 1, then every 6 months in year 2, then after year 2, as clinically indicated (regardless of PCI status).**
  - **Surveillance for all patients consists of:**
    - **CT Chest +/- abdomen/pelvis**
    - **Brain MRI (preferred) or brain CT**
- **Imaging for known metastases (eg, CT neck or MRI spine) should be repeated for follow-up. Other imaging studies may be obtained based on individual clinical scenarios.**
- **New pulmonary nodule should initiate workup for potential new primary.**
- **FDG-PET/CT is not recommended for routine follow-up unless a contrast CT or MRI is contraindicated.**

Note: All recommendations are category 2A unless otherwise indicated.

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Note: All recommendations are category 2A unless otherwise indicated.

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* Squamous cell carcinoma *in situ* (SCIS) 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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National Comprehensive Cancer Network®

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ABBREVIATIONS

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

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence (≥1 randomized phase 3 trials or high-quality, robust meta-analysis), there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus (≥85% support of the Panel) that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus (≥50%, but <85% support of the Panel) that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

Note: All recommendations are category 2A unless otherwise indicated.

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This discussion corresponds to the NCCN Guidelines for Small Cell Lung Cancer. Last updated: September 5, 2024

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Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; of which nearly 14% are small cell lung cancer (SCLC).[1] In 2024, an estimated 33,000 new cases of SCLC will be diagnosed in the United States.[1,2] Although the incidence of SCLC has been decreasing, the frequency in females is increasing and the male-to-female incidence ratio is now close to 1:1.[1] Nearly all cases of SCLC are attributable to cigarette smoking.[3] Patients with SCLC who also continue to smoke tobacco during treatment have increased toxicity and shorter survival.[4] Therefore, tobacco smoking cessation counseling and intervention should be strongly promoted in patients with SCLC and other high-grade neuroendocrine carcinomas (see the NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[5] Patients who previously smoked tobacco should be strongly encouraged to remain abstinent. Programs using behavioral counseling combined with U.S. Food and Drug Administration (FDA)-approved medications that promote smoking cessation can be very useful.

SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present with limited disease confined to the chest. Although 95% of small cell carcinomas originate in the lung, they can also arise from extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract.[6,7] Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior with increased potential for widespread metastases. Management of SCLC is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Small Cell Lung Cancer that includes the algorithm and this supporting Discussion text. Management of other lung neuroendocrine tumors (LNTs) and Non-Small Cell Lung Cancer (NSCLC) are described in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors and Non-Small Cell Lung Cancer, respectively, available at www.NCCN.org.

The definitions for limited-stage and extensive-stage SCLC incorporate TNM staging. The Panel recommends that the workup for SCLC should be expedited and if possible, studies should be performed in parallel. In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiation therapy (RT). However, some patients with resectable tumors (stage I–IIA) are eligible for curative surgery followed by systemic therapy with or without mediastinal RT.[8,9] The Panel recommends multidisciplinary evaluation before any surgery. In other patients with stage I–IIA SCLC, including medically inoperable circumstances or when the decision not to pursue surgical resection is made, stereotactic ablative radiotherapy (SABR) followed by systemic therapy is an option.[10-15] The benefits of prophylactic cranial irradiation (PCI) are unclear in patients with stage I SCLC (T1–2a, N0, M0) who have received definitive therapy. The NCCN Panel recommends that MRI brain surveillance be considered for all patients with limited-stage SCLC who do not receive PCI. In most patients with extensive-stage SCLC, systemic therapy with or without RT can palliate symptoms and prolong survival; however, long-term survival is rare.[16] SCLC is highly sensitive to initial chemotherapy and RT; however, most patients eventually die of recurrent disease.[17] Despite recent advances, the recommended therapy options for SCLC need improvement. Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Thus, participation in clinical trials is strongly encouraged.

Guidelines Update Methodology

The NCCN Guidelines® for Small Cell Lung Cancer were originally published in 1996 and have been subsequently updated at least once every year.[18] The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

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

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

Sensitive/Inclusive Language Usage

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation.[19] NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, instead focusing on organ-specific recommendations. This language is both more accurate and more inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in subsequent analyses.

Diagnosis

Screening

Ideally, a screening test should detect disease at an early stage when it is still curable. The National Lung Screening Trial reported that screening with annual, low-dose, spiral CT scans detected early-stage NSCLC and decreased lung cancer-specific mortality in asymptomatic high-risk individuals (see the NCCN Guidelines for Lung Cancer Screening, available at www.NCCN.org).[20] Low-dose CT is probably not useful for SCLC screening because symptomatic disease can develop between annual scans due to the aggressive nature of the disease; thereby limiting the potential reduction of mortality through screening.[20-23]

Manifestations

Patients with SCLC typically present with a large hilar mass and bulky mediastinal lymphadenopathy that causes cough and dyspnea.[24] Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. 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).[25,26]

Many neurologic and endocrine paraneoplastic syndromes, including Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy, are associated with SCLC.[27-29] Given the occurrence of paraneoplastic neurologic syndromes in individuals with SCLC, the Panel recommends considering early subspecialty consultation for most recent management. Paraneoplastic encephalomyelitis may precede a diagnosis of SCLC.[30] The NCCN SCLC Panel recommends considering a comprehensive paraneoplastic antibody panel and/or neurologic consultation if neurologic paraneoplastic syndrome is suspected.

SCLC tumors sometimes produce polypeptide hormones, including vasopressin and adrenocorticotropic hormone that cause syndrome of inappropriate ADH secretion (SIADH) and Cushing syndrome, respectively.[31,32] In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Primary treatment for SIADH includes fluid restriction (which is difficult for patients because of increased thirst) and demeclocycline. Cancer treatment (e.g., cisplatin) and/or supportive care (e.g., opiates) may also cause hyponatremia.[33] Hyponatremia usually improves after successful treatment of SCLC. However, vasopressin receptor inhibitors (i.e., conivaptan, tolvaptan) can be used for refractory hyponatremia.[33-35]

Pathology

SCLC is a poorly differentiated malignant epithelial tumor that is categorized as a high-grade neuroendocrine carcinoma.[25,36] Up to 30% of tumors from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma).[37] This finding is more common in patients who have received previous treatment. The classic and distinctive histology on hematoxylin and eosin (H&E), including small blue cells with scant cytoplasm, high nuclear/cytoplasmic ratio, fine granular nuclear chromatin, and absent or inconspicuous nucleoli, may be sufficient for identifying SCLC in good-quality histologic samples.[25,38] The mitotic count is high in SCLC compared with the count in atypical and typical carcinoids. However, mitotic figures are difficult to count in small biopsy samples with crushed or necrotic cells. In such samples immunohistochemistry is useful.[39] In cases of diagnostic dilemma, including carcinoids, the Panel strongly recommends getting a second opinion with a pathologist specializing in diagnosis of thoracic malignancies.

Using immunohistochemistry as one of the tools to diagnose and distinguish SCLC from NSCLC or other neuroendocrine tumors is important; especially because these cancer types have different treatment recommendations.[25,39-43] Ki-67 is useful for distinguishing SCLC from carcinoid tumors.[39,43-45] Nearly all SCLCs are immunoreactive for cytokeratin (AE1/Ae3, CAM5.2) and 85% to 90% of SCLCs are positive for thyroid transcription factor-1 (TTF-1).[25,46-48] Most SCLCs (~95%) stain positively for markers of neuroendocrine differentiation, including insulinoma-associated protein 1 (INSM1), chromogranin A, NCAM (CD56), and synaptophysin.[25,49,50] However, at least one of these neuroendocrine markers will be immunoreactive in approximately 10% of NSCLCs and therefore cannot be used alone to distinguish SCLC from NSCLC.[51] For suspicious cases of SCLC morphology without any expression of neuroendocrine markers, POU2F3 IHC staining can be considered.[52,53] Napsin A (adenocarcinoma marker) and p40 (or p63, squamous cell carcinoma marker) are generally negative in SCLC and useful for distinguishing SCLC from poorly differentiated NSCLC and combined SCLC.[54] However, p40 (or p63) can be focally positive in SCLC. For v1.2025, the Panel clarified that comprehensive molecular profiling via blood, tissue, or both may be considered in rare cases, particularly for patients with extensive-stage/relapsed SCLC who have never smoked or lightly smoked, remote smoking history, for diagnostic/pathologic dilemma, or at time of relapse if not done previously because this may change management.[55-60]

The WHO classification recognizes two types of SCLC: pure and combined SCLC.[43,56,61-64] Combined SCLC, which consists of both SCLC and NSCLC histology (squamous cell, adenocarcinoma, spindle/pleomorphic, and/or large cell carcinoma), is more frequent in patients with limited-stage SCLC.[43,56,63,65] Any presence of NSCLC histology (no minimal percentage) results in a classification of combined SCLC. The only exception is combined SCLC and LCNEC where at least 10% of the tumor should show LCNEC morphology.[37,66] Patients with combined SCLC are treated using regimens for SCLC, because it is the more aggressive cancer.[66] Patients with NSCLC can also transform to SCLC after treatment with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors or immune checkpoint inhibitors.[67,68]

Evaluation

Staging Systems

The Veterans Administration (VA) Lung Study Group's 2-stage classification scheme has historically been used to define the extent of disease in patients with SCLC: 1) limited-stage is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage is disease beyond the ipsilateral hemithorax, including malignant pleural/pericardial effusion or hematogenous metastases.[69] Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage SCLC, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial and treatment is individualized.[17,70,71] Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. Most studies use the VA definitions of limited-stage or extensive-stage SCLC, for clinical decision-making. However, the TNM system is useful for selecting patients with T1–2, N0 disease who are eligible for surgery and RT.[70] The American Joint Committee on Cancer (AJCC) revised the TNM staging system (8th edition) for lung cancer in 2017.[72,73] Clinical research studies that include use of the TNM system will allow for more precise assessments of prognosis and specific therapy.[72]

The NCCN SCLC Panel adopted a combined approach of using both the AJCC TNM staging system and the older VA scheme for SCLC staging.[17,70] *Limited-stage* SCLC is defined as stage I–III (T any, N any, M0) that can be safely treated with definitive RT. This excludes T3–4 due to multiple extensive lung nodules or disease with tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan. *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3–4 as previously described.

Initial Evaluation

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

The initial diagnostic evaluation includes a history and physical examination; pathology review; clinical laboratory tests; CT scan with intravenous contrast of the chest/abdomen/pelvis; and MRI (preferred) or CT scan with intravenous contrast for brain imaging.[71,74] An FDG-PET/CT scan (skull base to mid-thigh), which is superior to PET alone, is recommended to clarify the extent of disease if needed.[17,70,75] For most metastatic sites, FDG-PET/CT is superior to CT imaging; however, FDG-PET/CT is inferior to MRI (or contrast-enhanced CT as an alternative when MRI is not possible) for the detection of brain metastases (see the

NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).[76] FDG-PET scans can also increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.[75,77,78] Approximately 19% of patients who undergo FDG-PET are upstaged from limited-stage to extensive-stage SCLC, whereas 8% are down staged from extensive-stage to limited-stage SCLC.[71] Although FDG-PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is recommended for isolated or equivocal lesions if their involvement changes clinical management. FDG-PET staging altered the planned radiation field because of improved detection of intrathoracic disease sites in approximately 27% of patients.[71,78,79]

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

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

Before surgical resection in patients with clinical limited stage I–IIA SCLC (T1–2, N0, M0), pathologic mediastinal staging is recommended to confirm FDG-PET/CT scan results and rule out occult nodal disease.[17] To help determine RT fields, mediastinal staging can be considered for clinical stage IIB–IIIC SCLC (T1–4, N0, M0; T1-4, N1-3, M0), especially for those with clinical N0 disease. Invasive mediastinal staging can be performed either by conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound-guided FNA (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), or video-assisted thoracic surgery (VATS).[80,81] If the endoscopic lymph node biopsy is positive, then additional mediastinal staging is not recommended.

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

Prognostic Factors

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

normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage SCLC.[82,83]

Treatment

Surgical Resection of Stage I–IIA SCLC

Surgery is only recommended for certain patients with stage I–IIA SCLC; with only about 5% of patients eligible for surgery. Concurrent chemoradiation or SABR followed by systemic therapy is recommended for patients with limited-stage I–IIA (T1–2, N0, M0) SCLC who are medically inoperable or do not want to pursue surgical resection. Most of the data regarding the role of surgery in SCLC are from retrospective studies.[84-89] These studies report favorable 5-year survival rates of 40% to 60% in patients with stage I disease. In most series, survival rates decline significantly in patients with advanced disease with lymph node involvement. Therefore, the general recommendation for surgery is restricted to certain patients with stage I–IIA disease (T1–2, N0, M0). Fewer than 5% of patients with SCLC have true stage I–IIA disease.[90] Analyses of the SEER database suggest that surgery is appropriate for some patients with localized disease.[15,91] However, retrospective studies and analyses of the SEER database are limited by the lack of information on chemotherapy. In addition, comparison of the survival of surgical patients to those who did not undergo surgery is inherently flawed by selection bias. Ultimately, the role of surgery in SCLC will not be fully delineated until prospective trials in patients who are rigorously staged compare surgery plus adjuvant chemotherapy versus concurrent chemoradiotherapy.

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[92] Patients with limited-stage SCLC, excluding those with solitary peripheral nodules, that responded to 5 cycles of chemotherapy with cyclophosphamide, doxorubicin, and vincristine (CAV) were randomly assigned to undergo thoracic RT with or without resection. The overall survival rates of patients on the two arms were equivalent, suggesting no benefit to surgery in this setting. However, only 19% of enrolled patients had clinical limited stage I (T1–2, N0, M0) disease. Data show that patients with SCLC who have nodal disease (i.e., T1–3, N1–3, M0–1) do not benefit from surgery.[92]

The NCCN Panel recommends that in patients who do not smoke tobacco, small lesions—that are presumed to be small cell carcinoma on biopsy—should be resected because they are likely carcinoids that have been misdiagnosed (see the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org). The NCCN SCLC Panel also recommends surgery for certain patients with clinical stage I–IIA (T1–2, N0) SCLC with negative mediastinal lymph nodes that have been confirmed by mediastinal staging.[13,84,93] Surgery can include patients with clinical limited stage IIA SCLC based on the staging criteria that includes tumors up to 5 cm in diameter (T2b) without lymph node involvement (N0). The NCCN Panel added recommendations for patients who did not have a preoperative biopsy but have an intraoperative diagnosis of likely SCLC. If resection is performed, the NCCN SCLC Panel recommends lobectomy (preferred) with mediastinal lymph node dissection or systematic lymph node sampling (e.g., ≥3 N2 and ≥1 N1 stations). The Panel does not recommend pneumonectomy if nodal metastatic disease needs to be encompassed or under other circumstances. Chemoradiation is the preferred alternative over any resection requiring pneumonectomy.

Following surgery, adjuvant chemotherapy or chemoradiation is recommended based on the absence or presence of nodal metastases for patients with limited stage I–IIA (T1–2, N0) SCLC with negative margins (R0 resection).[87,94-96] Adjuvant chemotherapy alone is recommended for patients without nodal metastases (N0). Concurrent or sequential chemotherapy and postoperative mediastinal RT are recommended for patients with N+ disease.[97] 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 The benefit of PCI is unclear in patients with pathologic stage I (T1–2a, N0, M0) who have had definitive therapy.[98,99] For patients with limited stage I–IIA (T1–2, N0) SCLC with positive margins (R1/R2 resection), the Panel recommends concurrent chemoradiation following surgery. The NCCN SCLC Panel recommends response assessment following adjuvant therapy to establish new disease baseline.

Systemic Therapy

For all patients with SCLC, systemic therapy is an essential component of appropriate treatment. Adjuvant chemotherapy is recommended for patients with early-stage SCLC who have had surgery or SABR. For patients with limited-stage SCLC who are not eligible for surgery or SABR or have positive mediastinal staging, chemotherapy with concurrent thoracic RT (category 1 for patients with PS 0–2) is the recommended primary treatment.[9,100,101] For patients with extensive-stage SCLC, systemic therapy alone is recommended. RT may be used in select patients with extensive-stage disease for palliation of symptoms (see NCCN Guidelines for Palliative Care, available at www.NCCN.org). These options are rationalized based on studies described in the following sections.

Cisplatin Versus Carboplatin

Randomized trials in a small number of patients with SCLC and retrospective analysis of patients with extensive-stage SCLC suggest similar efficacy between cisplatin and carboplatin regimens.[102-104] In a meta-analysis of 663 patients with limited-stage SCLC (32%) and extensive-stage SCLC (68%), no significant difference was observed in response rate (67% vs. 66%), progression-free survival (PFS) (5.5 vs. 5.3 months), or overall survival (9.6 vs. 9.4 months) between cisplatin- versus carboplatin-containing regimens.[105] Carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.[106] However, the use of carboplatin carries a greater risk of myelosuppression.[106]

Limited-Stage SCLC

Adjuvant chemotherapy alone is recommended for patients who have undergone surgical resection (N0) or SABR for early-stage SCLC. However, most patients with limited-stage SCLC are not eligible for surgery or SABR. Etoposide plus cisplatin is the most commonly used first-line combination chemotherapy regimen for patients with limited-stage SCLC.[107,108] Etoposide plus cisplatin replaced alkylator plus anthracycline-based regimens based on its superiority in both efficacy and toxicity.[109-111] If pathologic lymph node involvement is found at surgery (N1 or N2) for patients with stage I–IIA (T1–2, N0, M0), then thoracic RT can be added concurrently or sequentially to etoposide/cisplatin. Treatment with etoposide/cisplatin plus definitive thoracic RT showed response rates of 70% to 90% with a median overall survival of 25 to 30 months and 5-year overall survival rates of 31% to 34%.[107] Thoracic RT improves local control rates by 25% in patients with limited-stage SCLC and is associated with improved survival.[100,101] Data suggest that chemoradiotherapy may also be indicated for patients with limited-stage SCLC who have cytologically negative or indeterminate pleural effusions but not for those with pericardial effusions.[112,113] Etoposide/cisplatin in combination with thoracic RT increases the risk of esophagitis, pulmonary, and hematologic toxicity.[114]

For patients with limited-stage IIB–IIIC (T3–4, N0, M0; T1–4, N1–3, M0) SCLC, the NCCN Guidelines recommends different etoposide/cisplatin regimens plus concurrent thoracic RT (category 1).[100,101,115,116] The preferred etoposide/cisplatin regimens for limited-stage SCLC are based on the dosing used in the CONVERT trial.[107] Other recommended options for limited-stage SCLC include carboplatin/etoposide and other cisplatin/etoposide doses. The use of myeloid growth factors is not recommended in patients undergoing concurrent chemoradiation

(category 1 for not using granulocyte-macrophage colony-stimulating factor [GM-CSF]).[117] Thus far, there are no data to support the use of immunotherapy in patients with limited-stage SCLC.

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

Durvalumab Consolidation Therapy

The first planned interim analysis of the ADRIATIC trial was presented at ASCO.[126] This trial included patients with stage I–III limited-stage SCLC, PS 0–1 and no disease progression on chemoradiation (total *n* = 730). At this point, median OS was 55.9 months in those patients receiving consolidation therapy compared to 37.2 months in patients receiving placebo. The interim analysis revealed a statistically significant and clinically meaningful OS and PFS improvement in patients receiving consolidation durvalumab. Based on the interim analysis, the Panel recommends durvalumab consolidation therapy in those patients who did not experience disease progression after systemic therapy + concurrent RT (category 2A). Durvalumab may be continued until disease progression or intolerable toxicity, or for a maximum of 24 months. Additionally, the Panel recommends if PCI is being considered in this setting it should be given prior to consolidation durvalumab.

Extensive-Stage SCLC

The NCCN SCLC Panel recommends certain combination chemotherapy plus immunotherapy regimens as preferred options for patients with extensive-stage SCLC.[118-120] In patients with extensive-stage SCLC and brain metastases, systemic therapy can be given either before or after brain RT depending on whether the patient has neurologic symptoms.[16,121] The Panel recommends steroid initiation for patients with spinal cord compression or brain metastasis who have symptomatic neurologic disease. For example: dexamethasone 10 mg loading dose followed by 4 to 6 mg maintenance dose (IV or PO every 4–6 hours [or as appropriate]) can be initiated.[122] If systemic therapy is given first, brain RT is administered after completion of systemic therapy. However, if brain metastases progress while on systemic therapy, it is recommended that brain RT is initiated before completion of systemic therapy. Systemic therapy with or without RT to localized symptomatic sites is recommended for patients with extensive disease, which includes the superior vena cava (SVC), lobar obstruction, and bone metastasis. Prophylactic external beam RT (EBRT) can be considered for patients with high fracture risk due to osseous structural impairment.

During systemic therapy for patients with extensive-stage SCLC, the Panel recommends response assessment using CT with contrast of the chest/abdomen/pelvis after every 2 to 3 cycles of systemic therapy. Serial brain imaging is also recommended for patients with extensive-stage SCLC who have asymptomatic brain metastases and receive systemic therapy before brain RT. Brain MRI (preferred) or CT with contrast is recommended to be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first.

For many years, platinum plus etoposide had been the only recommended therapy for patients with extensive-stage SCLC; however, the preferred regimens now include the programmed death ligand 1 (PD-L1)–targeted immune checkpoint inhibitors, atezolizumab or durvalumab.

Contraindications for treatment with programmed cell death protein 1 (PD-1)/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents. The Panel recommends continuation of maintenance immunotherapy until disease progression or intolerable toxicity. Atezolizumab or durvalumab may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy. Therefore, health care providers should be aware of the spectrum and management of potential immune-mediated adverse events and have a discussion with patients about possible side effects (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org). High-dose corticosteroids are generally recommended for immune-mediated adverse events based on the severity of the reaction. Atezolizumab or durvalumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information)

Atezolizumab Plus Chemotherapy

IMpower133, a phase 3 randomized trial, assessed the addition of atezolizumab (treatment and maintenance) to carboplatin plus etoposide in 403 patients with previously untreated extensive-stage SCLC and compared outcomes to carboplatin plus etoposide alone.[120] The 1-year overall survival rate was 51.9% for the atezolizumab regimen versus 39.0% for chemotherapy alone. The median overall survival was 12.3 months (95% CI, 10.8–15.8) with the addition of atezolizumab versus 10.3 months (95% CI, 9.3–11.3) with chemotherapy alone (hazard ratio [HR], 0.76; 95% CI, 0.6–0.95; *P* = .0154).[118] Response rates were similar in both arms (60% with chemotherapy plus atezolizumab vs. 64% with chemotherapy alone). The rate of grade 3 or 4 adverse events was similar in both groups (67.7% for the atezolizumab regimen vs. 63.3% for chemotherapy alone). There were 4 deaths (2%) in the atezolizumab group versus 11 deaths (5.6%) in the chemotherapy alone group. Different doses for maintenance atezolizumab have been FDA-approved for patients with extensive-stage SCLC. In light of these data and FDA approval, the NCCN SCLC Panel recommends carboplatin plus etoposide plus atezolizumab as a category 1 and preferred first-line systemic therapy option followed by maintenance atezolizumab for patients with extensive-stage SCLC.[118,120] The NCCN Panel recommends either 1200 or 1680 mg of maintenance atezolizumab. The category 1 recommendation is only for 1200 mg of maintenance atezolizumab based on the dose used in the clinical trial.[118,120]

Durvalumab Plus Chemotherapy

CASPIAN, a phase 3 randomized trial, assessed adding durvalumab to etoposide and either carboplatin or cisplatin followed by maintenance durvalumab in 537 patients with previously untreated extensive-stage SCLC and compared response to platinum plus etoposide alone regimens.[119,123] Most patients received carboplatin (78%). A 3-year analysis showed that the median overall survival was 13.0 months (95% CI, 11.5–14.8) in the durvalumab plus chemotherapy group and 10.3 months (95% CI, 9.3–11.2) in the chemotherapy alone group (HR, 0.73; 95% CI, 0.59–0.91; *P* = .0047).[124] The 1-year overall survival rate was 52.8% for the durvalumab regimen versus 39.3% for chemotherapy alone. The rate of serious adverse events was similar in both groups (32% vs. 36%). The death rate from adverse events was also similar (2% vs. 1%). In this trial, adding tremelimumab to durvalumab/etoposide carboplatin (or cisplatin) did not improve overall survival (OS) compared with platinum/etoposide (10.4 vs. 10.5 months; HR, 0.82; 95% CI, 0.68–1.0). Based on the data and FDA approval, the NCCN SCLC Panel recommends durvalumab plus etoposide plus (carboplatin or cisplatin) as a category 1 and preferred first-line systemic therapy option followed by maintenance durvalumab for patients with extensive-stage SCLC, including those with asymptomatic untreated brain metastases.[119,123-125]

Other Primary Systemic Therapies

Other recommended first-line systemic therapy regimens for extensive-stage SCLC include etoposide with either cisplatin or carboplatin. Additional chemotherapy combination regimens evaluated in patients with extensive-stage SCLC show inconsistent evidence of benefit compared with etoposide/cisplatin. For example, the combination of irinotecan and cisplatin initially appeared to be better than etoposide/cisplatin. A phase 3 trial in Japan reported that patients with extensive-stage SCLC treated with irinotecan plus cisplatin had a median survival of 12.8 months compared with 9.4 months for patients treated with etoposide/cisplatin (P = .002).[127] The 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the etoposide/cisplatin group.[127] 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.[128,129] A phase 3 randomized trial of 220 patients with extensive-stage SCLC found that median overall survival slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs. 7.1 months; P = .04).[130] In addition, a meta-analysis suggested an improvement in PFS and overall survival with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.[131] The NCCN SCLC Panel recommends the irinotecan-based regimens as primary therapy options (useful in certain circumstances) for patients with extensive-stage SCLC. However, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens.

The use of maintenance or consolidation chemotherapy beyond the recommended 4 to 6 cycles results in a minor increase in the duration of response without improving survival and carries a greater risk of cumulative toxicity.[132,133] The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. Alternating or sequential combination therapies have been designed to overcome drug resistance by exposing the tumor to as many active cytotoxic agents as possible during initial treatment.[134] However, this approach has not improved PFS or overall survival in randomized trials.[135,136] Therefore, the NCCN SCLC Panel recommends 4 cycles of systemic cytotoxic therapy for patients with limited-stage (with concurrent radiation) and extensive-stage (with concurrent immunotherapy) SCLC. However, some patients with extensive-stage SCLC may receive up to 6 cycles based on response and tolerability.

Attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have not shown significant advantages compared to recommended approaches. In two trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to etoposide/cisplatin showed a modest survival advantage.[137,138] 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.[139] Two different phase 3 trials assessing the combination of ifosfamide, etoposide, and epirubicin versus etoposide/cisplatin, and carboplatin plus etoposide with or without palifosfamide confirmed the lack of improvement in survival with three-drug chemotherapy regimens in patients with extensive-stage SCLC.[140,141] 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.[142]

The role of high dose chemotherapy for patients with SCLC remains controversial. Patients receiving high chemotherapy doses compared with

those given conventional doses of the same agents had higher complete and partial response rates, and modestly longer median survival times.[143] However, randomized trials comparing conventional chemotherapy doses to incremental increases in dose intensity (up to 2 times the conventional dose) have not consistently shown an increase in response rate or survival.[144-147] In addition, a meta-analysis of trials that studied dose-intense variations of the CAV and etoposide/cisplatin regimens found that increased relative dose intensity resulted in only a small, clinically insignificant enhancement of median survival in patients with extensive-stage SCLC.[148] Early phase 2 results designed to increase dose intensity by weekly cyclic multidrug chemotherapy were promising, but favorable patient selection was of some concern.[149,150] No survival benefits were documented in randomized trials, and excessive treatment-related mortality were noted with weekly cyclic multidrug chemotherapy regimens.[151-154]

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.[155] Likewise, another phase 3 randomized trial showed no improvement in overall survival in patients with extensive-stage SCLC treated with first-line pembrolizumab plus etoposide/platinum followed by maintenance pembrolizumab compared with chemotherapy alone.[56]

Antiangiogenic therapy has also been evaluated in SCLC. In patients with limited-stage SCLC, a phase 2 study of irinotecan, carboplatin, and bevacizumab with concurrent RT followed by maintenance bevacizumab was terminated early because of an unacceptable incidence of tracheoesophageal fistulae. In extensive-stage SCLC, phase 2 trials of platinum-based chemotherapy plus bevacizumab showed promising response and survival data.[156-159] However, at least two randomized trials have demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.[160,161] Currently, the NCCN SCLC Panel does not recommend use of bevacizumab in patients with SCLC.

Cytokines (e.g., 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,[162] maintenance of dose intensity with growth factors does not prolong disease-free survival or overall survival.[163,164] The Panel does not recommend GM-CSF (category 1 for not using it) or G-CSF for patients with limited-stage SCLC receiving systemic therapy/RT.[117,165] Trilaciclib or G-CSF may be used as prophylactic supportive care options to decrease the incidence of chemotherapy-induced myelosuppression when administering certain regimens for patients with extensive-stage SCLC.[117,165-170] It is important to note that trilaciclib or G-CSF are not treatment options.

Transformed SCLC from NSCLC with an Oncogenic Driver

The Panel recognizes that transformed SCLC from NSCLC is a rare population of patients with limited data including treatment options. The Panel recommends considering referral to a center with expertise in managing transformed SCLC with an oncogenic driver. Oncogenic drivers can be actionable genomic alterations. The Panel recommends systemic cytotoxic chemotherapy using SCLC Guidelines due to lack of data for transformed SCLC. The role of immunotherapy in transformed SCLC is unclear and should be avoided if tyrosine kinase inhibitors are being used. Furthermore, for v1.2025, the Panel clarified that in patients who develop small cell lung cancer as a resistance mechanism to

tyrosine kinase inhibitors used for actionable genomic alteration driven non-small cell lung cancer, if tyrosine kinase inhibitors are continued, immune checkpoint inhibitors (ICI) should be avoided, due to known toxicity that is primarily driven by the long half-life of ICIs.

Older Patients

The incidence of SCLC increases with age with the median age at diagnosis being >70 years.[171] The functional status of an individual patient is more useful than chronological age in guiding clinical decision-making that includes considering treatment tolerance (see the NCCN Guidelines for Older Adult Oncology, available at www.NCCN.org). Greater attention to the needs and support systems of a patient's functional status is recommended to provide optimal care. Patients who are able to perform activities of daily living (ADLs) should be treated with combination systemic therapy and RT, if indicated.[172-174] For example, a subgroup analysis of the CONVERT trial suggests that concurrent chemoradiation yields equivalent median survival in patients <70 years versus patients ≥70 years and limited-stage SCLC (29 vs. 30 months; *P* = .38).[172] However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in patients ≥70 years. Therefore, the study recommended closer surveillance for patients ≥70 years during treatment to avoid excessive risk.[172]

Randomized trials have indicated that less-intense treatment (e.g., single-agent etoposide) is inferior to combination chemotherapy (e.g., platinum plus etoposide) in patients of all ages with good PS (0–2).[175,176] A retrospective analysis in 8637 patients ≥70 years with limited-stage SCLC reported that chemoradiation increased survival compared with chemotherapy alone.[173] Several other strategies have been evaluated in patients ≥65 years with SCLC.[104,177-179] The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve (AUC) dosing of carboplatin takes into account the declining renal function of the patient.[179] However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in the population >70 years.[180] A short 2-week course, full-intensity chemotherapy showed acceptable results in patients (median age, 73 and poor PS); but this approach has not been directly compared with 4 to 6 cycles of therapy.[181]

PCI should be used with caution in patients who are older. A Dutch analysis of more than 5000 patients suggests that median survival is lower in patients ≥70 years compared with patients <70 years treated with PCI, regardless of stage.[182] Patients aged ≥60 years are at increased risk for cognitive decline after PCI; therefore, the risks and benefits of PCI versus close MRI surveillance need to be discussed.[183-186]

Surveillance for Relapse

Although SCLC responds to initial treatment, disease relapse is observed in most patients.[187,188] Therefore, surveillance recommendations to assess for relapse in patients with SCLC are outlined in the algorithm. Most NCCN Member Institutions use chest CT (± abdomen/pelvis) every 2 to 6 months (more frequently in years 1 to 2 and less frequently thereafter). The frequency of surveillance decreases during subsequent years because of the declining risk of recurrence.[189] If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors post-treatment frequently occur in patients with no evidence of SCLC.[190,191] 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 CT with contrast every 3 to 4 months during year 1 for all patients and then every 6 months as clinically indicated, regardless of the PCI status. MRI is more sensitive than CT for identifying brain metastases.[74] The Panel maintains that FDG-PET/CT is not recommended for routine follow-up unless contrast CT chest/abdomen/pelvis is contraindicated. Tobacco smoking cessation intervention is recommended for all patients with SCLC, because second primary tumors occur less commonly in patients who quit smoking (see the

NCCN Guidelines for Smoking Cessation, available at www.NCCN.org).[192-194] Patients who previously smoked tobacco should be encouraged to remain abstinent. The NCCN SCLC Panel also recommends the survivorship guidelines for appropriate patients (see the NCCN Guidelines for Survivorship, available at www.NCCN.org).

Subsequent Systemic Therapy

Patients with disease relapse or with primary progressive disease may be treated with subsequent systemic therapy. Recommended subsequent systemic therapy options are based on chemotherapy-free interval (CTFI) of 1) 6 months or less; or 2) more than 6 months. Clinical trial enrollment is the preferred regimen for both CTFI >6 months and CTFI ≤6 months. The Panel recommends considering genomic profiling of relapsed tumors, if not previously performed, to determine clinical trial eligibility. Subsequent systemic therapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse.[195] If the interval is 6 months or less (refractory or resistant disease), response to most agents or regimens is poor (≤10%). If more than 6 months have elapsed (sensitive disease), expected response rates are approximately 25%. Response rates are higher with newer agents, such as lurbinectedin. Unfortunately, most patients relapse in 6 months or less.[196,197] 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.[198] The NCCN SCLC Panel recommends additional subsequent therapy options for patients with SCLC based on clinical expertise and trial data. Other recommended subsequent therapy options, described in the following sections, include topotecan (oral [PO] or IV), lurbinectedin, CAV, docetaxel, oral etoposide, gemcitabine, irinotecan, nivolumab, paclitaxel, pembrolizumab, and temozolomide (category 2A for all agents). The optimal duration of subsequent systemic therapy has not been fully explored. For cytotoxic chemotherapy agents, the duration of treatment is usually short, and the cumulative toxicity is frequently limiting even in patients who experience response. For these reasons, subsequent systemic therapy should be continued until progression of disease or development of unacceptable toxicity. The Panel recommends response assessment using CT with contrast of the chest/abdomen/pelvis after every 2 to 3 cycles. Dose reduction or growth factor support should be considered for patients with a PS of 2. For CNS progression only, the Panel recommends continuing systemic therapy and treat brain metastases with RT. Additional subsequent systemic therapy (e.g., third line) can be considered if patients are still PS 0 to 2.

Platinum-Based Therapy

A phase 3 randomized trial assessed carboplatin plus etoposide compared with oral topotecan in 162 patients with SCLC relapse after more than 3 months on first-line platinum/etoposide therapy.[199] The median PFS was 4.7 months (90% CI, 3.9–5.5) in the carboplatin/etoposide group versus 2.7 months (90% CI, 2.3–3.2) in the oral topotecan group (HR, 0.57; 90% CI, 0.41–0.73; *P* = .004). Grade 3–4 adverse events included thrombocytopenia, neutropenia, anemia, febrile neutropenia, and asthenia. In the topotecan group, two treatment-related deaths occurred; no deaths occurred in the carboplatin/etoposide group. The NCCN SCLC Panel recommends subsequent therapy with platinum-based regimens based on the clinical trial data.[196,199-202] The NCCN Panel maintains that rechallenging with the original regimen, or similar platinum-based regimen, is recommended for subsequent systemic therapy, if CTFI >6 months and may be considered if there has been a CTFI of at least 3 to 6 months.[196,199-202] The NCCN Panel maintains that platinum-based doublets are the preferred subsequent therapy options for patients with SCLC and a PS of 0 to 2.[196,199,200]

Lurbinectedin

A phase 2 basket trial assessed lurbinectedin (3.2 mg/m^2 every 3 weeks) as second-line therapy in 105 patients with SCLC who previously received

platinum/etoposide; 57% of patients had not received chemotherapy for 3 months or more.[203] The overall response rate with lurbinectedin was 35% (95% CI, 26.2%–45.2%). The response rate was 22% (95% CI, 11.2%–37.1%) if CTFI was less than 3 months. The response rate was 45% (95% CI, 32.1%–58.4%) if CTFI was 3 months or more. Common grade 3–4 adverse events included anemia, leucopenia, neutropenia, and thrombocytopenia. There were no reported treatment-related deaths. In a subset analysis of this trial, lurbinectedin was assessed as second-line therapy in 20 patients with SCLC who had received platinum/etoposide more than 6 months ago.[197] The overall response rate with lurbinectedin was 60% (95% CI, 36.1%–86.9%). The median overall survival was 16.2 months (95% CI, 9.6–upper level not reached). After 1 year, 60.9% of patients were alive and after 2 years, 27.1% were alive. Common grade 3–4 adverse events included neutropenia, anemia, thrombocytopenia, fatigue, and increased liver function tests. The FDA granted approval for lurbinectedin at a dose of 3.2 mg/m^2 every 3 weeks based on clinical trial data.[203]

ATLANTIS, a phase 3 randomized trial, assessed lurbinectedin plus doxorubicin versus control therapy with either CAV or topotecan in 613 patients with relapsed SCLC.[204] Most patients had received first-line platinum-based therapy more than 3 months ago. The median overall survival was 8.6 months (95% CI, 7.1–9.4) with lurbinectedin/doxorubicin versus 7.6 months (95% CI, 6.6–8.2) with CAV or topotecan (HR, 0.97; 95% CI, 0.82–1.15). Grade 3 or higher adverse events occurred in 66% of patients receiving lurbinectedin/doxorubicin versus 86.5% of patients in the control group. Grade 3 or worse adverse events included neutropenia (lurbinectedin/doxorubicin: 37%; control: 69%). Two patients (<1%) died because of treatment-related adverse events in the lurbinectedin/doxorubicin group and 10 (3%) patients died in the control group. The dose of lurbinectedin was 2 mg/m^2 in the ATLANTIS trial, which is less than the dose used in the phase 2 trial discussed earlier.[197,203]

The NCCN SCLC Panel recommends lurbinectedin as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred).[197,203] The NCCN Panel decided to recommend lurbinectedin at the higher dose based on the FDA approval and since the lower dose of lurbinectedin did not perform well in ATLANTIS.[203,204]

Topotecan

Topotecan is also recommended as a subsequent therapy option based on clinical trial data.[199] A randomized phase 3 trial for subsequent treatment for patients with SCLC relapse at least 60 days after therapy compared single-agent IV topotecan with the combination regimen CAV.[205] Both arms had similar response rates (topotecan, 24.3%; CAV, 18.3%) and survival (25.0 vs. 24.7 weeks). Compared to CAV, topotecan caused less grade 4 neutropenia (37.8% vs. 51.4%; $P < .001$) and improved symptoms of dyspnea, anorexia, hoarseness, and fatigue. There is conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.[206,207] Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m^2 of IV topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.[208] In another phase 3 trial, oral topotecan improved overall survival compared with best supportive care (26 vs. 14 weeks).[209] The efficacy and toxicity of oral and IV topotecan seem to be similar and therefore either route may be used.[209,210] The NCCN SCLC Panel recommends oral or IV topotecan as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred).[199,204,205,209,211]

Irinotecan

47% of patients responded (95% CI, 21.4%–71.9%) to irinotecan in a phase 2 study in patients with refractory or relapsed SCLC.[212] Myelosuppression, diarrhea, and pulmonary toxicity were reported in patients receiving irinotecan.[212] Another phase 2/3 trial showed that

irinotecan and topotecan had comparable activity in patients with relapsed or refractory SCLC and metastasis.[213] The NCCN SCLC Panel recommends irinotecan as a subsequent therapy option for patients with SCLC with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred). The Panel added a consideration for irinotecan for patients with CNS disease.

Tarlatamab-dlle

A phase 1 trial in patients heavily pretreated for relapsed/refractory SCLC showed promising durability and acceptable safety profile with tarlatamab, a bispecific T-cell engager antibody that targets delta-like ligand 3 (DLL-3) and CD3.[214] DLL3 is abnormally expressed on the surface of the majority of SCLC cells (85-94%) and inhibits Notch A phase 2 trial evaluated the activity and safety of two doses (10 mg and 100 mg) of IV tarlatamab-dlle in patients with SCLC that had relapsed or was refractory to one platinum-based treatment and at least one other regimen (n = 176).[215] The median PFS in patients who received 10 mg of was 4.9 months compared to 3.9 months in patients who received 100 mg of tarlatamab-dlle. Although the overall survival data have not matured, the percentage of patients alive at last follow-up (~10 months in both groups) was 57% and 51% in patients who received 10 mg and 100 mg, respectively. Because of the favorable benefit to risk ratio in patients who received 10 mg versus 100 mg, the lower dose has been chosen for subsequent studies. Based on this trial, the Panel recommends tarlatamab-dlle (10 mg dosing schedule) as a category 2A, subsequent therapy option for patients with CTFI >6 months (other recommended regimens) and CTFI ≤6 months (preferred regimens).

Nivolumab and Pembrolizumab

ICIs have been evaluated in patients with relapsed SCLC.[216-219] CheckMate 032, a phase 1/2 trial, assessed nivolumab alone (n = 147) or various doses of nivolumab plus ipilimumab (n = 96) for relapsed SCLC.[216,217] Response rates were 11.6% for nivolumab and 21.9% for nivolumab plus ipilimumab.[216] The 12- and 24-month overall survival rates were similar (nivolumab, 30.5% and 17.9%; nivolumab plus ipilimumab, 30.2% and 16.9%, respectively). Grade 3–4 adverse events were 12.9% for nivolumab alone and 37.5% for nivolumab plus ipilimumab. In patients receiving nivolumab alone, the most common grade 3 or 4 treatment-related adverse events were pneumonitis and increased levels of lipase and aspartate aminotransferase.

CheckMate 331, a randomized phase 3 trial, assessed nivolumab monotherapy versus topotecan or amrubicin in 569 patients with relapsed SCLC.[211,220] 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).[211] Overall survival was similar regardless of PD-L1 levels. Response rates were 13.7% for nivolumab compared with 16.5% for chemotherapy. Treatment-related deaths occurred in two patients receiving nivolumab and in three patients receiving chemotherapy. Fewer grade 3–4 adverse events occurred in patients receiving nivolumab compared with chemotherapy (14% vs. 73%, respectively). A study reported that third-line therapy with nivolumab was associated with longer survival (5.7 months; 95% CI, 3.5–8.0) compared with other treatments such as paclitaxel or topotecan (3.8 months; 95% CI, 2.8–4.9; HR, 0.63; 95% CI, 0.44–0.90).[221] The 1-year overall survival rate is 28% with nivolumab versus 4% with the other treatments.

A combined analysis of two trials, phase Ib (KEYNOTE-028) and phase 2 (KEYNOTE-158), evaluated the activity of pembrolizumab in 83 patients with relapsed SCLC who had received two or more lines of therapy. 56% of patients were positive for PD-L1 (≥1%) and 84% patients did not have brain metastases.[222,223] This analysis reported a response rate of 19.3% (95% CI, 11.4%–29.4%). The median overall survival was 7.7 months (95% CI, 5.2–10.1); the estimated 12-month overall survival rate was 34%. Both overall survival and response rate were higher in those who were

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

The FDA has withdrawn the subsequent therapy indications for nivolumab or pembrolizumab for patients with relapsed SCLC, because phase 3 randomized trial data did not show an improvement in overall survival.[211,217,218,220,222-225] However, the NCCN SCLC Panel lists these agents as subsequent systemic therapy options (other recommended regimens) for patients with CTFI ≤6 months. The Panel decided that nivolumab or pembrolizumab are just as effective as (sometimes better than) and less toxic than the other subsequent therapy options.[211,221] In addition, many agents recommended as subsequent therapy options for patients with SCLC do not have an FDA indication in this setting but data show that they are effective. Patients with limited-stage SCLC who relapse and have not previously received immune checkpoint inhibitors may benefit from subsequent therapy with nivolumab or pembrolizumab. However, the use of nivolumab and pembrolizumab is discouraged in patients whose disease progresses while on maintenance atezolizumab or durvalumab as part of first-line therapy. There are no data to suggest that giving patients subsequent immune checkpoint inhibitors is effective if their disease previously progressed on other immune checkpoint inhibitors.

Health care providers should be aware of the spectrum of potential immune-mediated adverse events unique to immunotherapeutic agents, such as nivolumab and pembrolizumab, know how to manage these events, and discuss possible side effects with patients (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at www.NCCN.org).[226,227] For patients with immune-mediated adverse events, high-dose corticosteroids are generally recommended based on the severity of the reaction. Nivolumab or pembrolizumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

Other Subsequent Therapy Options

Paclitaxel and docetaxel that belong to the taxane class of drugs have been assessed in patients with refractory or relapsed SCLC. In a phase 2 study in patients with refractory or relapsed SCLC; 24% of patients responded to paclitaxel.[228] Grade 3–4 toxicity included neutropenia, infection, rash, neuropathy, and pulmonary toxicity. Another phase 2 study of paclitaxel in patients with refractory SCLC yielded a response rate of 29% (95% CI, 12%–51%).[229] A retrospective study in 185 patients showed a response rate of 17% during third-line or fourth-line therapy with paclitaxel. Toxicity rates were similar in patients with PS 2 compared with PS 0 to 1 (63% vs. 62%).[230] 25% of patients responded to docetaxel in a phase 2 trial in patients with previously treated SCLC. Reported toxicities included neutropenia and asthenia.[231]

Oral etoposide was assessed in a phase 2 trial in 22 patients with recurrent SCLC.[232] Ten patients (45%; 95% CI, 27%–65%) had a complete or partial response. Median survival was 3.5 or more months (range, 1 to 15+). Five patients were hospitalized because of neutropenia and fever. Two patients died from sepsis. Another phase 2 trial assessed oral etoposide in 26 patients with refractory SCLC.[233] The overall response rate was 23%; there was one complete response and five partial responses.

Gemcitabine was assessed in a phase 2 trial in 42 patients with sensitive or refractory SCLC.[234] The median survival was 7.1 months. The overall objective response rate was 11.9%. One patient with refractory SCLC and four patients with sensitive SCLC responded. Grade 3–4 toxicities included neutropenia (27%), thrombocytopenia (27%), neurologic toxicity (14%), and pulmonary (9%). Another phase 2 trial assessed gemcitabine

in 38 patients with resistant SCLC that progressed within 3 months of last therapy.[235] The median survival was 17 weeks (range, 4–84). The response rate was 13% (95% CI, 6%–27%); there were five partial responses and no complete responses. Grade 3 toxicities included thrombocytopenia (29%) and leukopenia (18%).

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O^6-methylguanine-DNA methyltransferase (MGMT).[236-238] Temozolomide was assessed in a phase 2 trial in patients with relapsed or refractory SCLC. In patients with sensitive SCLC, the overall response rate was 23% (95% CI, 12%–37%). The response rate improved for patients with methylated MGMT compared to those with unmethylated MGMT (38% vs. 7%; *P* = .08).

A phase 3 trial (JCOG0605) from Japan in patients with sensitive, relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival compared with topotecan (median survival, 18.2 vs. 12.5 months; HR, 0.67; 90% CI, 0.51–0.88; *P* = .0079). However, the toxicity of this regimen was significant and it is not recommended for subsequent therapy.[239] The NCCN Panel recommends CAV as a subsequent therapy options based on clinical trial data.[205]

Radiation Therapy

RT is not recommended as primary treatment for patients with extensive-stage SCLC, however consolidative or palliative RT is an option for these patients. The American Radium Society appropriate use criteria and the American Society for Radiation Oncology (ASTRO) guidelines are useful resources.[240-243] The *Principles of Radiation Therapy* section in the NSCLC algorithm may also be useful (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).

Thoracic Radiation Therapy

Achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge. The addition of thoracic RT has improved survival for patients with limited-stage SCLC. Meta-analyses that include more than 2000 patients show that thoracic radiation for limited-stage SCLC yields a 25% to 30% reduction in local progression, and a corresponding 5% to 7% improvement in 2-year overall survival compared with chemotherapy alone.[100,101] A phase 3 trial has reported 5-year overall survival of more than 30%, which is close to outcomes of locally advanced NSCLC of similar stage.[107]

Timing of Radiation with Chemotherapy

Optimal thoracic RT is impacted by several factors, including the timing of chemotherapy and RT (concurrent vs. sequential), timing of RT (early vs. late), the RT target volume (original tumor volume vs. shrinking field as the tumor responds), dose of radiation, and fractionation of RT. Early concurrent chemoradiotherapy is recommended for patients with limited-stage SCLC based on randomized trials. A randomized phase 3 trial by the Japanese Cooperative Oncology Group (9104) assessed sequential versus concurrent thoracic RT combined with etoposide/cisplatin for 231 patients with limited-stage SCLC. Overall survival was 27.2 months for those receiving concurrent chemoradiation versus 19.7 months for those receiving sequential chemoradiation (*P* = .097).[114] Patients receiving concurrent chemoradiation had more severe hematologic toxicity. Severe esophagitis occurred in 9% of patients receiving concurrent chemoradiation and 4% receiving sequential chemoradiation.

Several systematic reviews and meta-analyses on the timing of thoracic RT in limited-stage SCLC have reported that early concurrent chemoradiation results in a small, but significant improvement in overall survival compared with late concurrent or sequential chemoradiation.[244,245] A randomized phase 3 trial (by the National Cancer Institute of Canada)

compared RT beginning with either cycle 2 or cycle 6 of chemotherapy and showed that early RT was associated with improved local and systemic control and longer survival.[246] Another meta-analysis in patients with limited-stage SCLC showed that survival improved with rapid completion of the chemoradiotherapy regimen (start of any chemotherapy until the end of RT [SER]).[247] A meta-analysis of individual patient data from 12 trials (2668 patients) reported that early concurrent chemoradiation, associated with increase in acute esophagitis, had higher 5-year overall survival (HR, 0.79; 95% CI, 0.69–0.91) compared with late concurrent chemoradiation.[248]

Radiation Fractionation

The Eastern Cooperative Oncology Group (ECOG)/Radiation Therapy Oncology Group (RTOG) compared accelerated to conventionally fractionated RT with etoposide/cisplatin.[249] In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiation using a total dose of 45 Gy delivered either twice daily over 3 weeks (accelerated) or once daily over 5 weeks (conventional). Median overall survival was 23 versus 19 months (P = .04), and 5-year survival rates were 26% versus 16% in the accelerated and conventional RT arms, respectively.[249] A higher incidence of grade 3–4 esophagitis was seen with the accelerated regimen compared with the conventional regimen.[249] A significant criticism of this trial is that the 45 Gy conventional regimen provided suboptimal dose intensity compared to modern conventionally fractionated regimens using higher total doses.

CONVERT, a phase 3 randomized trial, compared accelerated 45 Gy (given twice daily over 3 weeks) with higher dose conventionally fractionated 66 Gy (given once daily over 6.5 weeks) in 547 patients with limited-stage SCLC.[107] Median overall survival was similar between the 2 groups (30 vs. 25 months). However, the CONVERT trial was not powered to show equivalence. Although toxicity was generally similar between the arms, patients receiving accelerated 45 Gy had more grade 4 neutropenia compared with those receiving conventional 66 Gy (49% vs. 38%; P = .05).

CALGB 30610 (Alliance)/RTOG 0538, a randomized phase 3 trial, compared high-dose conventional 70 Gy (once daily over 7 weeks) with accelerated 45 Gy (twice daily over 3 weeks) in 638 patients with limited-stage SCLC.[250] Originally, there was a 61.2 Gy concomitant boost group in this trial, but it was removed based on a planned interim toxicity analysis.[251] Median overall survival was 30.5 months in the conventional 70 Gy arm versus 28.5 months in the accelerated 45 Gy arm (HR, 0.94; 95% CI, 0.75–1.17; P = .591). There were 5 deaths in the conventional 70 Gy arm and 2 deaths in the accelerated 45 Gy arm. Overall survival and toxicity were similar. The conventional 70 Gy arm had better quality-of-life scores at 3 weeks with patients reporting it to be more convenient. The study was not designed to assess whether the conventional 70 Gy arm was superior to the accelerated 45 Gy arm.

A randomized phase 2 trial assessed concurrent chemoradiation with two similarly accelerated regimens, 42 Gy given as once-daily fractions over 3 weeks compared with 45 Gy given as twice-daily fractions also over 3 weeks in 157 patients with limited-stage SCLC.[252] 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.[253] The median survival was 28 months which is comparable to outcomes of similarly accelerated twice-daily fractionation.

Two randomized phase 2 trials compared high-dose accelerated RT with standard-dose accelerated RT. One trial in 182 patients with limited-stage SCLC compared concurrent chemoradiation with high-dose accelerated 65 Gy given as once-daily fractions over approximately 5 weeks with

standard-dose accelerated 45 Gy given as twice-daily fractions over 3 weeks.[254] Estimated PFS was 17.2 months in the high-dose group versus 13.4 months in the standard-dose group (*P* = .031). Overall survival was 39.3 months in the high-dose group versus 33.6 months in the standard-dose group (*P* = .137). Grade 3 or higher esophagitis (high-dose, 17.4% vs. standard-dose, 15.3%), grade 3 or higher pneumonitis (high-dose, 3.3% vs. standard-dose, 2.4%), and treatment-related deaths (high-dose, 2.2% vs. standard-dose, 1.2%) were similar in each group. The second trial in 176 patients with limited-stage SCLC compared concurrent chemoradiation using high-dose accelerated RT with 60 Gy given as twice-daily fractions over 4 weeks with accelerated standard-dose 45 Gy given as twice-daily fractions over 3 weeks.[255] After 2 years, 74.2% (95% CI, 63.8%–82.9%) of patients were alive in the 60 Gy group versus 48.1% (95% CI, 36.9%–59.5%) in the 45 Gy group. Three treatment-related deaths occurred in each group.

Despite multiple trials, the optimal dose and fractionation of thoracic RT for SCLC remains unresolved. Higher dose accelerated RT may be advantageous, and this remains to be confirmed in larger studies. Two randomized trials have not shown superiority of high dose without acceleration (66 Gy or 70 Gy over 6.5–7 weeks) over moderate dose accelerated fractionation (45 Gy over 3 weeks); however, survival and toxicity are similar.[107,250,256] Overall, accelerated RT (whether given once or twice daily) is superior to similar doses of conventionally fractionated RT and comparable to higher dose conventionally fractionated RT. The NCCN SCLC Panel recommends that either accelerated 45 Gy given as twice-daily fractions over 3 weeks (category 1) or conventionally fractionated 66 to 70 Gy given as once-daily fractions over 6.5 to 7 weeks are acceptable options depending on individual patient circumstances.[107,250,256] The NCCN SCLC Panel maintains that higher doses of 66 to 70 Gy are preferred if using once-daily fractionation,[256] since the twice-daily thoracic radiation is logistically challenging for many patients and RT centers.

Radiation for Limited-Stage SCLC

External-Beam RT

For limited-stage IIB to IIIC disease (T3–4, N0, M0; T1–4, N1–3, M0), the NCCN Guidelines recommend that RT should be used concurrently with chemotherapy and that RT should start with the first or second cycle (category 1 for patients with PS 0–2).[241,244] The optimal dose and schedule of RT have not been established. For accelerated RT, the recommended schedule is 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks. For conventionally fractionated RT, the recommended schedule is 2.0 Gy once daily to a total dose of 66 to 70 Gy.[107,256-259]

The minimum technical requirement for thoracic irradiation is CT-planned 3D-conformal RT. Intensity-modulated RT (IMRT) is preferred over 3D-conformal external-beam RT (EBRT) because of lower toxicity. The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar RT doses (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).[260-265] More advanced technologies, such as 4D-CT and proton therapy, may also be appropriate to limit normal tissue toxicity. The radiation target volumes can be defined on the FDG-PET/CT scan obtained at the time of RT planning, as well as any positive biopsies, using definitions in Reports 50 and 62 from the International Commission on Radiation Units & Measurements (ICRU).[266,267] However, the pre-chemotherapy FDG-PET/CT scan should be reviewed to include the original involved lymph node regions in the treatment fields if chemotherapy begins before RT.[259,268] When using accelerated schedules (e.g., 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol can be used as a guide.[256,269-271]

SABR

Emerging data suggest that SABR (also known as stereotactic body RT [SBRT]) is effective for patients with clinical limited-stage I–IIA (T1–2, N0) SCLC, especially for medically inoperable circumstances or in those refuse surgery.[12,272-277] A meta-analysis of 7 studies (399 patients) summarized outcomes in patients with early-stage SCLC who received SABR; 94% of the patients in this study were deemed inoperable.[277] 44% of patients received chemotherapy and 13.8% of patients received PCI. Overall survival was 86% (95% CI, 74%–95%) and 64% (95% CI, 46%–80%) at 1 year and 2 years, respectively. The nodal and distal recurrence rates were 18% (95% CI, 7.5%–31%) and 27% (95% CI, 7.4%–53%), respectively. Grade 3 toxicity was observed in 1.4% of patients (95% CI, 0%–5.3%). A multicenter analysis of 74 patients suggested that the addition of chemotherapy typically after SABR improves survival for patients with clinical limited-stage SCLC.[14,278] Most of these patients had FDG-PET staging but not pathologic nodal staging. Patients who received chemotherapy after SABR had a median overall survival of 31.4 months versus 14.3 months for those who received SABR alone (P = .02).

An analysis of 2107 patients with histologically confirmed T1–T2, N0, M0 from the National Cancer Database found that 7.1% had upfront SABR followed by adjuvant chemotherapy and 92.9% had concurrent chemoradiation.[10] Compared with patients receiving upfront concurrent chemoradiation, those receiving SABR were often older, had T1 disease, and treated recently in academic medical settings. Median survival was 29.2 months in those receiving SABR/chemotherapy versus 31.2 months in those receiving chemoradiation (P = .77). Both ASTRO and the American Radium Society recommend SABR followed by adjuvant chemotherapy as an option for medically inoperable patients with clinical limited stage I–IIA SCLC (T1–2, N0).[241,242]

The NCCN SCLC Panel recommends (category 2A) SABR followed by systemic therapy as an option for select patients with clinical limited stage I–IIA (T1–2, N0) who are medically inoperable or decline surgery.[12,278] The NCCN SCLC Panel added a caveat that systemic therapy may be initiated first, if time to initiation of SABR will be prolonged. The NCCN Guidelines for NSCLC provide detailed recommendations for SABR that may be useful for SCLC (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC, available at www.NCCN.org).

Radiation for Extensive-Stage SCLC

Sequential Thoracic Radiation for Extensive-Stage SCLC

A randomized trial by Jeremic et al[279] 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 (i.e., 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide.[279] The addition of RT resulted in improved median overall survival (17 vs. 11 months). The Dutch CREST trial, a phase 3 randomized trial in patients with extensive-stage SCLC, reported that the addition of consolidative thoracic RT (30 Gy in 10 fractions) did not improve the primary endpoint of 1-year overall survival (33% vs. 28%; P = .066). A secondary analysis found improvement in 2-year overall survival (13% vs. 3%; P = .004) and 6-month PFS compared with patients who did not receive consolidative thoracic RT.[280] A trial involving 32 patients who received consolidative thoracic RT reported that only 16% of patients had symptomatic chest recurrences.[281] Consolidative thoracic RT appears to mainly benefit patients with residual thoracic disease after chemotherapy (without immunotherapy) and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.[282] The American Radium Society recommends that consolidative thoracic RT be considered for select patients with extensive-stage SCLC based on the limited data.[240] European experts (International Association for the Study of Lung Cancer [IASLC] and European Society Radiation Oncology [ESTRO]) recommend

consolidative thoracic RT in select patients with stage IV SCLC who have responded to first-line chemotherapy and have limited extrathoracic tumor burden.[283]

The NCCN SCLC Panel recommends that consolidative thoracic RT be considered in select patients with low bulk extra thoracic metastatic extensive stage disease who have a complete or near complete response after initial systemic therapy before maintenance immunotherapy.[240,279,280] Sequential thoracic RT can be considered for selected patients, during or before maintenance immunotherapy; however, there are limited data on optimal sequencing. The benefit of thoracic RT in the context of chemoimmunotherapy is under evaluation in the RAPTOR/NRG LU007 trial (NCT04402788).

Prophylactic Cranial Irradiation

Intracranial metastases occur in greater than 50% of patients with SCLC. Randomized studies show that PCI is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to show a meaningful survival advantage.[284] Several meta-analyses suggest that PCI after complete resection may benefit patients with pathologic stage IIB or stage III SCLC.[98,99,285] A meta-analysis of all randomized PCI trials reported a reduction in the 3-year incidence of brain metastases, from 58.6% in the control group to 33.3% in the PCI-treated group.[99] Thus, PCI seems to prevent, and not simply delay, the emergence of brain metastases. This meta-analysis also reported an increase in 3-year overall survival from 15.3% in the control group to 20.7% in the PCI group.[99] Although the number of patients with extensive-stage SCLC was small, the observed benefit was similar in patients with both limited-stage and extensive-stage SCLC. A retrospective study of patients with limited-stage SCLC also found that PCI increased survival at 2, 5, and 10 years compared with those who did not receive PCI.[286] A study of 184 patients with limited-stage SCLC assessed PCI versus no PCI in patients who responded to chemoradiotherapy, and who had no brain metastases on MRI imaging before and after primary treatment.[287] In patients receiving PCI, median overall survival was 26 months (range, 19.4–32.6 months) versus 14 months for those without PCI (range, 11.4–16.6 months; $P < .0001$).

None of the abovementioned studies in limited-stage SCLC used MRI staging of the brain or FDG-PET scans for overall staging. A retrospective study included 49 patients with limited-stage SCLC who were staged with brain MRI before treatment.[288] The median overall survival was 55 months in patients with limited-stage SCLC who received PCI versus 24 months in those who did not receive PCI ($P < .05$). At 1 year, the probability of developing symptomatic brain metastases was 4% in patients with limited-stage SCLC who received PCI versus 22% in those who did not receive PCI ($P < .05$). For patients with extensive-stage SCLC, but without brain metastases, a large retrospective analysis of 4257 patients showed that PCI improved median overall survival compared with no PCI (13.9 vs. 11.1 months; $P < .0001$).[289] 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 brain imaging surveillance.[290]

The EORTC performed a randomized trial that assessed PCI versus no PCI in 286 patients with extensive-stage SCLC that had responded to initial chemotherapy. PCI decreased symptomatic brain metastases (14.6% vs. 40.4%) and increased the 1-year survival rate (27.1% vs. 13.3%) compared with controls.[291] However, the study did not require brain imaging prior to PCI and did not standardize the PCI dose or fractionation. Conflicting data from a randomized phase 3 trial in Japan found that median overall survival is not improved in patients receiving PCI compared with MRI surveillance (11.6 months; 95% CI, 9.5–13 vs. 13.7 months; 95% CI, 10.2–16.4) (HR, 1.27; 95% CI, 0.96–1.68; $P = .094$).[292] In

this trial, patients were required to have an MRI to confirm that they did not have brain metastases prior to PCI, and the PCI regimen was standardized at 25 Gy in 10 fractions. In addition, the study required close MRI surveillance imaging in patients to allow for the early treatment of brain metastases. The American Radium Society recommends either PCI or brain MRI surveillance for patients with extensive-stage SCLC and without brain metastases based on the limited data.[240] A randomized trial (SWOG S1827/MAVERICK) is currently assessing brain MRI surveillance alone compared to brain MRI surveillance plus PCI for patients with late-stage SCLC and early-stage SCLC. Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrently with chemotherapy.[184,293,294] Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.[96,295] PCI has also been associated with chronic neurotoxicity in patients who are aged ≥60 years.[183,185]

The NCCN SCLC Panel has gradually revised the adjuvant recommendations for patients whose disease showed a complete or partial response after primary treatment based on conflicting clinical trial data and concerns about using PCI. Before a decision is made to administer PCI, a balanced discussion is necessary between the patient and physician.[184,296] The NCCN Panel recommends considering PCI for patients with limited-stage SCLC that have achieved a complete or partial response.[96,99,291] PCI should be administered prior to consolidation durvalumab therapy. The NCCN Panel maintains that the benefit of PCI is unclear in patients with very early-stage SCLC (pathologic limited-stage I [T1–2a, N0, M0]) who have had definitive therapy (i.e., surgery, SABR). These patients have a lower risk of developing brain metastases than patients with more advanced limited-stage SCLC and may not benefit from PCI.[98,278,297] The NCCN Panel recommends MRI brain surveillance for all patients with limited-stage SCLC who do not receive PCI. In patients with extensive-stage SCLC, the NCCN Panel recommends MRI brain surveillance with or without consideration of PCI based on the conflicting trial results from Japan and the EORTC.[291,292] Brain imaging surveillance for metastases is recommended using either MRI (preferred) or CT with contrast in patients who are unable to undergo MRI.[292]

Higher PCI doses (e.g., 36 Gy) increased mortality and toxicity compared with lower doses (25 Gy).[183,298] Therefore, the preferred dose for PCI is 25 Gy in 10 daily fractions (2.5 Gy/fraction).[99,291,298] A shorter course of PCI may be appropriate (e.g., 20 Gy in 5 fractions) for selected patients with extensive-stage SCLC.[291] 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.[183] 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.[295,298]

The NCCN SCLC Panel recommends that memantine be considered for patients receiving PCI or therapeutic whole-brain irradiation. Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist that may delay cognitive dysfunction in patients receiving brain RT.[299] Patients receiving memantine have a longer time before cognitive decline (HR, 0.78; 95% CI, 0.62–0.99; *P* = .01). NRG Oncology CC001, a phase 3 randomized trial, assessed hippocampal-avoidance (HA) whole-brain IMRT plus memantine compared with conventional whole-brain RT plus memantine in patients with brain metastases who were not diagnosed with SCLC.[300] Cognitive preservation and patient-reported outcomes were improved with HA-IMRT (HR, 0.74; 95% CI, 0.58–0.95; *P* =.02). However, conflicting data have been reported with HA-PCI versus conventional PCI. PREMER, a phase 3 randomized trial, reported improved cognitive preservation with HA-PCI.[301] However, another phase 3 randomized trial (NCT01780675) reported no

differences in cognition with HA PCI.[302] A large randomized trial (NRG CC003) is assessing HA-PCI versus conventional PCI.[303]

Palliative Radiation Therapy

For patients with localized symptomatic sites of disease (i.e., 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).[304-306] 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. Brain metastases have conventionally been treated with whole brain RT in patients with SCLC due to the frequent occurrence of multiple metastases. The recommended dose for whole-brain RT is 30 Gy in 10 daily fractions.[307] Also, see the NCCN Guidelines for NSCLC, available at www.NCCN.org). IMRT, SABR, or stereotactic radiosurgery (SRS) may be appropriate for select patients (e.g., those whose tumors are in close proximity to organs at risk).

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).[308] A meta-analysis of nine observational studies (1638 patients) also reported favorable lesion control and survival outcomes with SRS versus whole-brain RT.[309] A randomized trial (NRG CC009) is comparing SRS to HA whole-brain IMRT plus memantine in this setting. The NCCN Panel decided that SRS may be used for selected patients with a small number of brain metastases based on available data, pending outcomes of the ongoing trials.[308] In patients who develop brain metastases after PCI, SRS (preferred) or repeat whole-brain RT (in carefully selected patients) may be considered.[310,311] For patients with a better prognosis (e.g., ≥4 months), HA whole-brain IMRT plus memantine is preferred because it produces less of a decrease in cognitive function than conventional whole-brain RT plus memantine. However, patients with metastases within 5 mm of the hippocampi, leptomeningeal metastases, and other high-risk features were not eligible for HA whole-brain IMRT in the phase 3 NRG CC001 trial.[300]

Summary

In summary, the NCCN Guidelines for SCLC v1.2025 has recommendations for diagnosis, evaluation, therapy options and surveillance for both limited-stage and extensive-stage SCLC. These recommendations are based on data from clinical trials and Panel expertise.

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