



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Cell Lung Cancer

Version 3.2021 — March 23, 2021

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NCCN Guidelines Version 3.2021 Small Cell Lung Cancer

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

To find clinical trials online at NCCN Member Institutions, [click here: \[nccn.org/clinical_trials/member_institutions.aspx\]\(http://nccn.org/clinical_trials/member_institutions.aspx\)](#).

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

See [NCCN Categories of Evidence and Consensus](#).

NCCN Categories of Preference: All recommendations are considered appropriate.

See [NCCN Categories of Preference](#).

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Updates in Version 3.2021 of the NCCN Guidelines for Small Cell Lung Cancer from Version 2.2021 include:

[SCL-D](#)

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

[SCL-E 2 of 5](#)

- Pembrolizumab was revised from a category 2A to a category 3 recommendation.

Updates in Version 2.2021 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2021 include:

[SCL-E 2 of 5](#)

- Nivolumab was moved from a category 2A to a category 3 recommendation.

Updates in Version 1.2021 of the NCCN Guidelines for Small Cell Lung Cancer from Version 4.2020 include:

[SCL-5](#)

- **Term revised:** ~~whole-brain RT (WBRT)~~ *brain RT*. Also for [SCL-E 3 of 5](#).
- **Initial Treatment revised for Extensive stage with brain metastases, Asymptomatic:** May administer systemic therapy ~~first, with whole-brain RT (WBRT) before brain RT~~ after completion of induction systemic therapy
- **Footnote r revised:** ~~For patients with asymptomatic brain metastases receiving systemic therapy before WBRT~~ Brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy *until brain RT is initiated or systemic therapy is completed, whichever is first and at completion of therapy* (see [SCL-6](#)). If brain metastases progress while on systemic therapy, ~~then initiate WBRT brain RT should be initiated before completion of systemic therapy.~~ See [Principles of Radiation Therapy \(SCL-F\)](#).

[SCL-6](#)

- Footnote removed: See Principles of Surgical Resection (SCL-C).

[SCL-B 1 of 2](#)

- **Pathologic Evaluation, bullet 6 added:** 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.

[SCL-C](#)

- **Bullet 3 added:** Surgery may be considered for selected patients with T3 (based on size), N0 SCLC, if invasive mediastinal lymph node staging is negative.
- **Bullet 5 revised:** The benefit of PCI is unknown in patients who have undergone complete resection for pathologic stage I–IIA (T1–2,N0,M0) SCLC; *consider PCI or brain MRI surveillance for N0*. These patients...

[SCL-E 1 of 5](#)

- **Primary or Adjuvant Therapy for Limited Stage SCLC, dosing statement revised:** ~~Maximum of 4–6 cycles~~ *Four cycles of systemic therapy are recommended.*
- **Heading revised:** Primary or Adjuvant Therapy for Extensive Stage SCLC
 - **Dosing statement revised:** ~~Maximum of 4–6 cycles~~ *Four cycles of therapy are recommended, but some patients may receive up to 6 cycles based on response and tolerability after 4 cycles.*
- **Footnote removed:** Regimen not recommended for relapsed disease in patients on maintenance atezolizumab or durvalumab at time of relapse. For patients who relapse after >6 months of atezolizumab or durvalumab maintenance therapy, recommend re-treatment with carboplatin + etoposide alone or cisplatin + etoposide alone.



Updates in Version 1.2021 of the NCCN Guidelines for Small Cell Lung Cancer from Version 4.2020 include:

[SCL-E 2 of 5](#)

- **Other Recommended Regimens, regimen revised: Nivolumab ± ipilimumab**
- **Footnote b revised: Regimen not recommended for relapsed disease in patients on maintenance atezolizumab or durvalumab at time of relapse. For patients who relapse after >6 months of atezolizumab or durvalumab maintenance therapy, recommend re-treatment with carboplatin + etoposide alone or cisplatin + etoposide alone.**

[SCL-E 3 of 5](#)

- **Response Assessment, bullet 2 added: Response assessment after adjuvant therapy involves chest/abdomen/pelvic CT with contrast and brain MRI (preferred) with contrast or brain CT with contrast ([see SCL-6](#)).**

[SCL-E 4 of 5](#)

- **Reference 18 revised: Hellmann MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032 [abstract]. *J Clin Oncol* 2017;35: Abstract 8503. *Ready NE, Ott PA, Hellmann MD, et al. Nivolumab monotherapy and nivolumab plus ipilimumab in recurrent small cell lung cancer: results from the CheckMate 032 randomized cohort. *J Thorac Oncol* 2020;15:426-435.***
- **Reference 19 added: Chung HC, Lopez-Martin JA, Kao S, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158. *J Clin Oncol* 2018;36: Abstract 8506.**

[SCL-F 2 of 5](#)

- **Extensive stage, sub-bullet 3 added: Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach, but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are no data on optimal sequencing or safety).**

[SCL-F 3 of 5](#)

- **Prophylactic Cranial Irradiation (cont.)**
 - ▶ **Bullet 5 added: Consider hippocampal-sparing PCI using IMRT.**
 - ▶ **Bullet 6 added: Current randomized trials are evaluating whether MRI surveillance alone is non-inferior to MRI surveillance plus PCI on overall survival and whether hippocampal-sparing PCI reduces memory impairment compared to whole brain PCI in LS-SCLC and ES-SCLC.**
- **Brain Metastases, bullet 1 revised by adding: A current trial is comparing SRS to hippocampal-sparing WBRT plus memantine in this setting.**

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

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

DIAGNOSIS

Small cell lung cancer (SCLC) or combined SCLC/non-small cell lung cancer (NSCLC) on biopsy or cytology of primary or metastatic site

INITIAL EVALUATION^a

- H&P^b
- Pathology review^c
- CBC
- Electrolytes, liver function tests (LFTs), BUN, creatinine
- Chest/abdomen/pelvis CT with contrast
- Brain MRI^{a,d} (preferred) or CT with contrast
- Consider PET/CT scan (skull base to mid-thigh), if limited stage is suspected or if needed to clarify stage^{a,e,f}
- Smoking cessation counseling and intervention. See the [NCCN Guidelines for Smoking Cessation](#).
- Molecular profiling (only for never smokers with extensive stage)^f

STAGE

Limited stage
 (See [ST-1](#) for TNM Classification)

[See Additional Workup \(SCL-2\)](#)

Extensive stage
 (See [ST-1](#) for TNM Classification)

[See Initial Treatment \(SCL-5\)](#)

^a If extensive stage is established, further staging evaluation is optional. However, brain imaging MRI (preferred), or CT with contrast should be obtained in all patients.

^b [See Signs and Symptoms of Small Cell Lung Cancer \(SCL-A\)](#).

^c [See Principles of Pathologic Review \(SCL-B\)](#).

^d Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

^e If PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage.

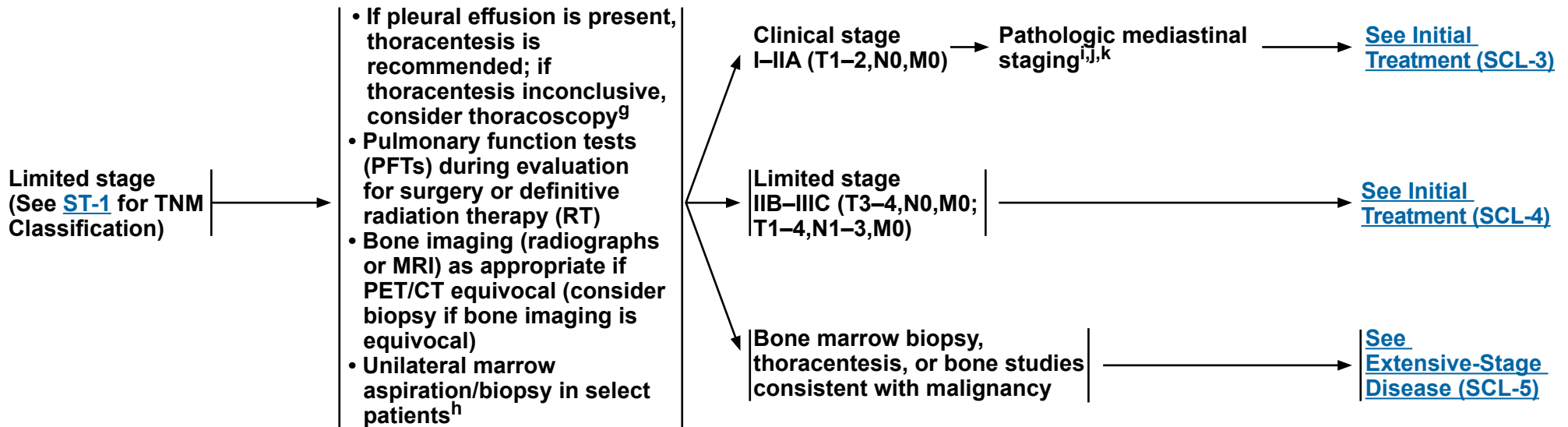
^f Molecular profiling may be considered in never smokers with extensive-stage SCLC to help clarify diagnosis and evaluate for potential targeted treatment options.

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STAGE **ADDITIONAL WORKUP**



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

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

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

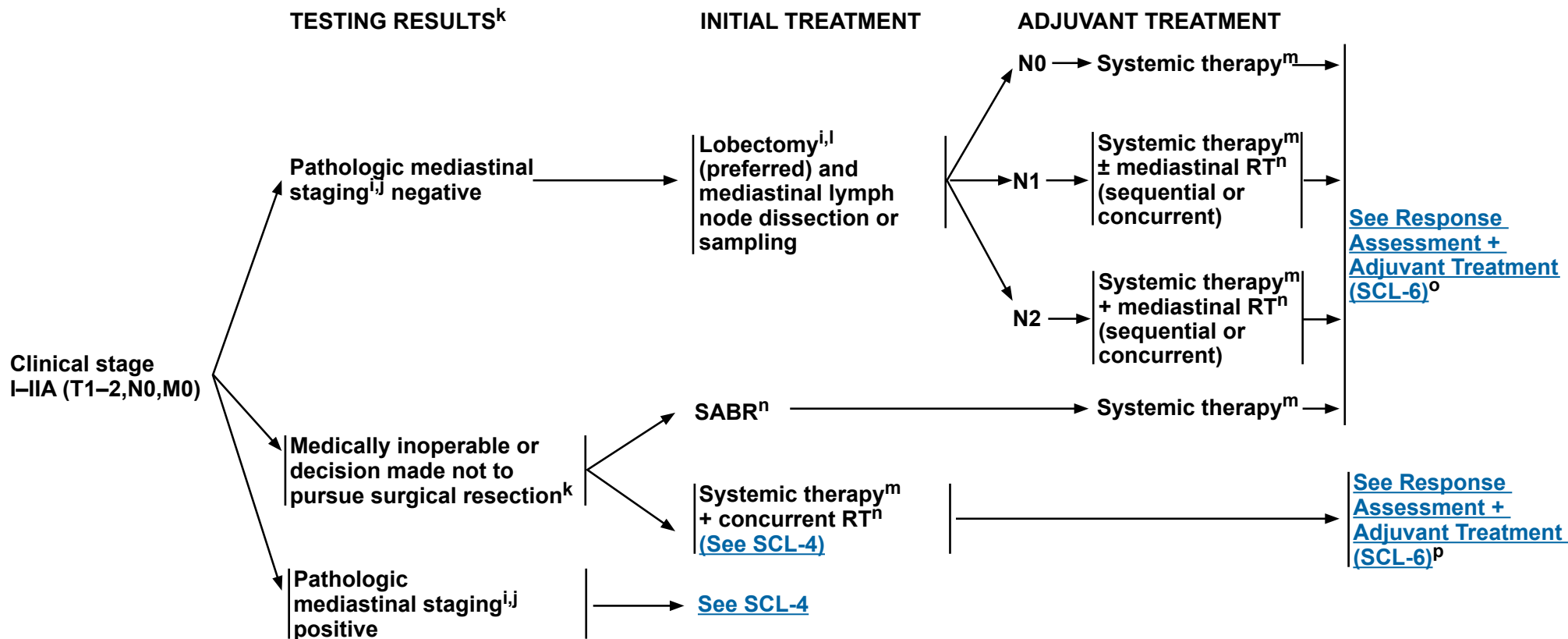
^j Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

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

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

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

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

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

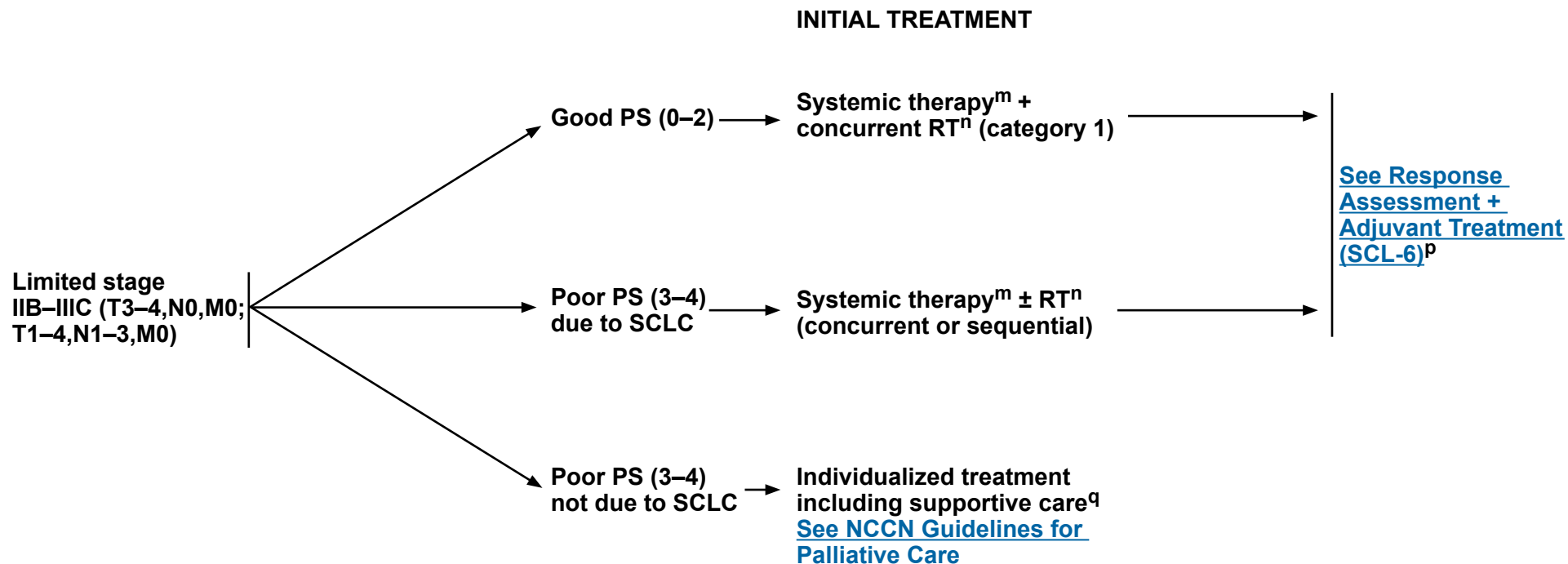
^m See Principles of Systemic Therapy (SCL-E).

ⁿ See Principles of Radiation Therapy (SCL-F).

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

^p For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy (SCL-6); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy (SCL-6).

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^m [See Principles of Systemic Therapy \(SCL-E\).](#)

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

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

^q [See Principles of Supportive Care \(SCL-D\).](#)

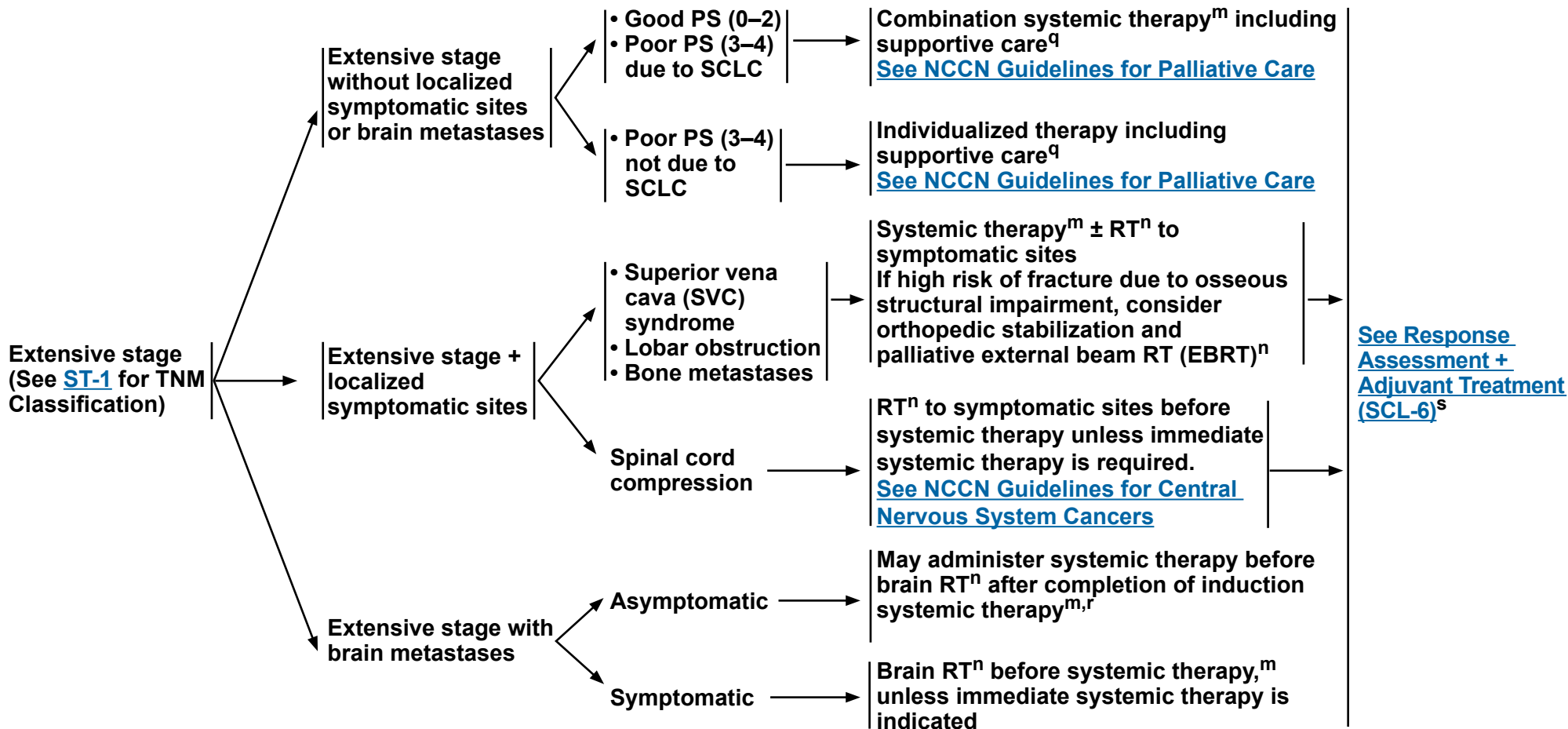
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STAGE



^m See [Principles of Systemic Therapy \(SCL-E\)](#).

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

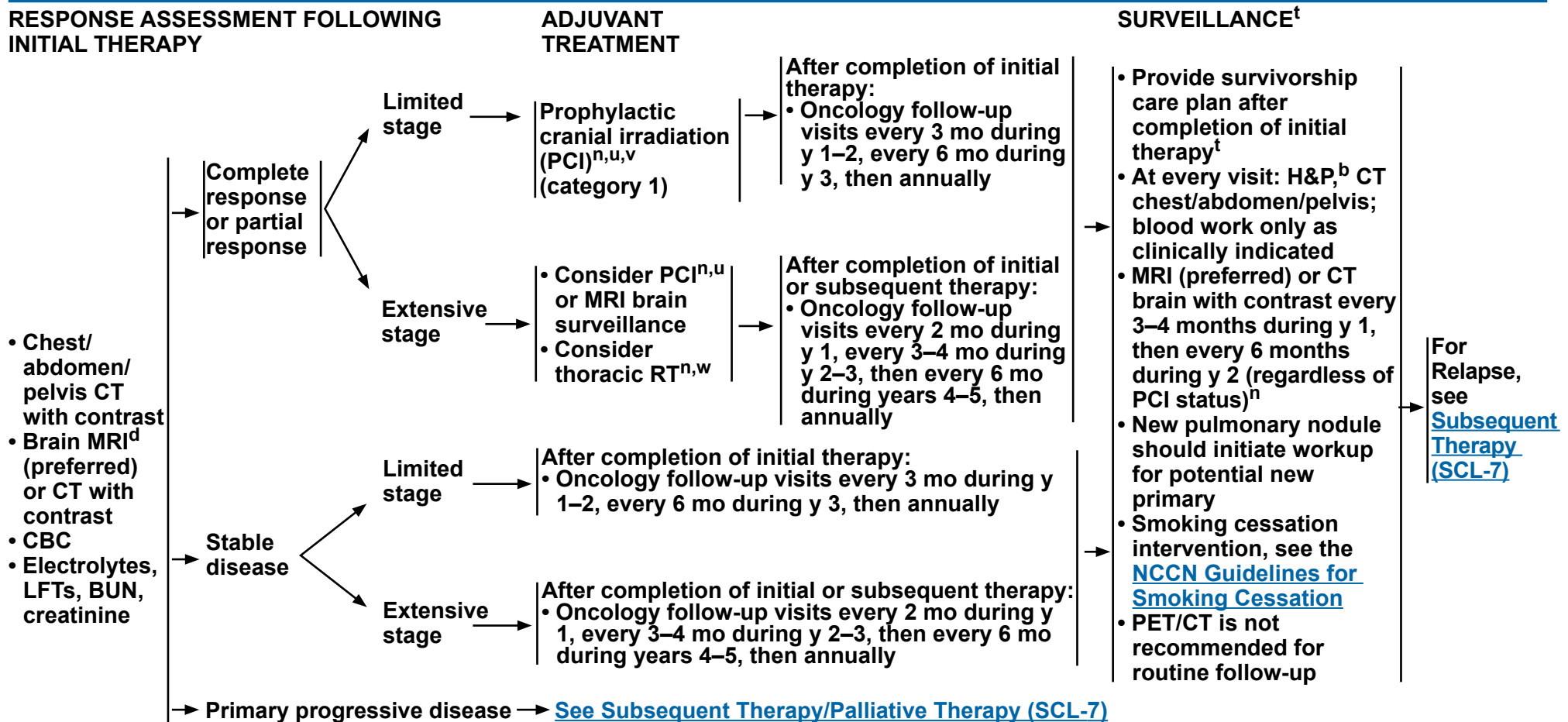
^q See [Principles of Supportive Care \(SCL-D\)](#).

^r Brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy until brain RT is initiated or systemic therapy is completed, whichever is first ([see SCL-6](#)). If brain metastases progress while on systemic therapy, brain RT should be initiated before completion of systemic therapy. [See Principles of Radiation Therapy \(SCL-F\)](#).

^s During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy ([SCL-6](#)).

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^b See [Signs and Symptoms of Small Cell Lung Cancer \(SCL-A\)](#).

^d Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

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

^t See [NCCN Guidelines for Survivorship](#).

^u Not recommended in patients with poor performance status or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close surveillance should be carefully discussed with these patients.

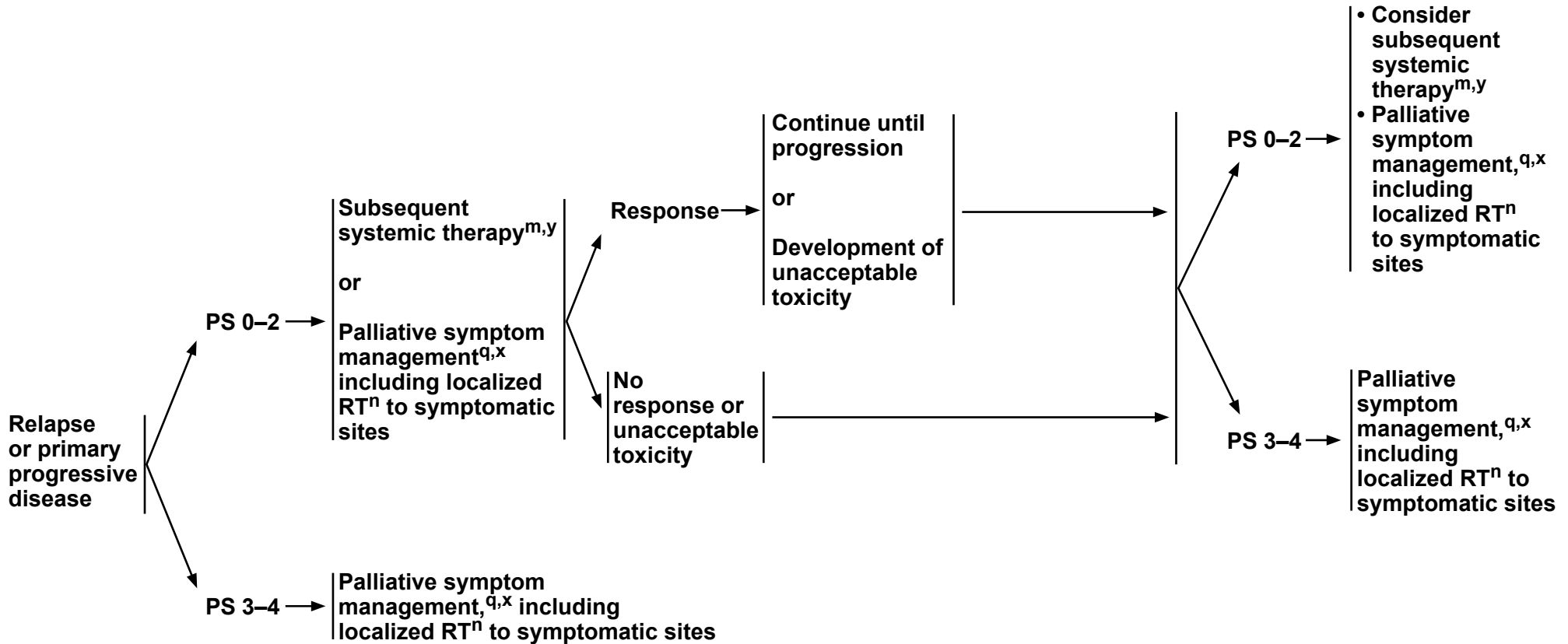
^v The benefit of PCI is unknown in patients who have undergone complete resection for pathologic stage I–IIA (T1–2,N0,M0) SCLC. See [Principles of Surgical Resection \(SCL-C\)](#).

^w Sequential RT to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.

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PROGRESSIVE DISEASE SUBSEQUENT THERAPY/PALLIATIVE THERAPY



^m See Principles of Systemic Therapy (SCL-E).

ⁿ See Principles of Radiation Therapy (SCL-F).

^q See Principles of Supportive Care (SCL-D).

^x See NCCN Guidelines for Palliative Care.

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

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SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and Symptoms Due to Local Primary Tumor Growth

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

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

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

Signs and Symptoms Due to Extrathoracic (Hematogenous) Metastases

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

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[Continued](#)

SCL-A
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SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and Symptoms of Paraneoplastic Syndromes

- Presence does not imply metastases or incurability

- Endocrine:

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

- Neurologic: All specific syndromes are rare

- ▶ If paraneoplastic neurologic syndrome is suspected, consider obtaining comprehensive paraneoplastic antibody panel
- ▶ Subacute cerebellar degeneration (anti-Yo antibody) – ataxia, dysarthria
- ▶ Encephalomyelitis (ANNA-1 [anti-Hu] antibody) – confusion, obtundation, dementia
- ▶ Sensory neuropathy (anti-dorsal root ganglion antibody) – pain, sensory loss
- ▶ Eaton-Lambert syndrome (anti-voltage-gated calcium channel antibody) – weakness, autonomic dysfunction
- ▶ Cancer-associated retinopathy (anti-recoverin antibody) – visual loss, photosensitivity

- Hematologic:

- ▶ Anemia of chronic disease
- ▶ Leukemoid reaction – leukocytosis
- ▶ Trousseau's syndrome – migratory thrombophlebitis

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**PRINCIPLES OF PATHOLOGIC REVIEW****Pathologic Evaluation**

- Pathologic evaluation is performed to determine the histologic classification of lung tumors and relevant staging parameters.
- The World Health Organization (WHO) tumor classification system provides the foundation for the classification of lung tumors, including histologic subtype, staging factors, clinical features, molecular characteristics, genetics, and epidemiology.¹⁻³
- SCLC is a poorly differentiated neuroendocrine carcinoma. Distinguishing SCLC from other neuroendocrine tumors, particularly typical and atypical carcinoids, is important due to significant differences in epidemiology, genetics, treatment, and prognosis.⁴⁻⁶
- SCLC can be diagnosed on good-quality histologic samples via high-quality hematoxylin and eosin (H&E)-stained sections or on well-preserved cytologic samples.
 - ▶ SCLC is characterized by small blue cells with scant cytoplasm, high nuclear-to-cytoplasmic ratio, granular chromatin, and absent or inconspicuous nucleoli.
 - ▶ SCLC cells are round, oval, or spindle-shaped with molding and high mitotic counts.⁷⁻⁹
 - ▶ The most useful characteristics for distinguishing SCLC from large-cell neuroendocrine carcinoma (LCNEC) are the high nuclear-to-cytoplasmic ratio and paucity of nucleoli in SCLC.
- Careful counting of mitoses is essential, because it is the most important histologic criterion for distinguishing SCLC from typical and atypical carcinoids.
 - ▶ SCLC (>10 mitoses/2 mm² field); atypical carcinoid (2–10 mitoses/2 mm² field); typical carcinoid (0–1 mitoses/2 mm² field)
 - ▶ Mitoses should be counted in the areas of highest activity and per 2 mm² field, rather than per 10 high-power fields.
 - ▶ In tumors that are near the defined cutoffs of 2 or 10 mitoses per 2 mm², at least three 2-mm² 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.

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 CD56/NCAM, synaptophysin, and chromogranin A. Fewer than 10% of SCLCs are negative for all neuroendocrine markers.
 - ▶ Thyroid transcription factor-1 (TTF-1) is positive in 85% to 90% of SCLCs.¹¹⁻¹⁴
- Ki-67 immunostaining can be very helpful in distinguishing SCLC from carcinoid tumors, especially in small biopsy samples with crushed or necrotic tumor cells in which counting mitotic figures is difficult.^{4,5}
 - ▶ The Ki-67 proliferative index in SCLC is typically 50% to 100%.¹

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[References on
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**SCL-B
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PRINCIPLES OF PATHOLOGIC REVIEW

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

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

**PRINCIPLES OF SURGICAL RESECTION**

- **Stage I–IIA SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients most likely to benefit from surgery are those with SCLC that is clinical stage I–IIA (T1–2,N0,M0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging).^{1,2}**
 - ▶ **Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.**
 - ▶ **For patients undergoing definitive surgical resection, the preferred operation is lobectomy with mediastinal lymph node dissection.**
- **Surgery may be considered for selected patients with T3 (based on size), N0 SCLC, if invasive mediastinal lymph node staging is negative.**
- **Patients who undergo complete resection should be treated with postoperative systemic therapy.³ Patients without nodal metastases should be treated with systemic therapy alone. Patients with N2 or N3 nodal metastases should be treated with postoperative concurrent or sequential systemic therapy and mediastinal RT. Patients with N1 nodal metastases may be considered for postoperative mediastinal radiation.**
- **The benefit of PCI is unknown in patients who have undergone complete resection for pathologic stage I–IIA (T1–2,N0,M0) SCLC; consider PCI or brain MRI surveillance for N0. These patients have a lower risk of developing brain metastases than patients with more advanced, limited-stage SCLC, and may not benefit from PCI.⁴ However, PCI may have a benefit in patients who are found to have pathologic stage IIB or III SCLC after complete resection; therefore, PCI is recommended in these patients after adjuvant systemic therapy.^{4,5} PCI is not recommended in patients with poor performance status or impaired neurocognitive function.⁶**

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PRINCIPLES OF SUPPORTIVE CARE

- **Smoking cessation advice, counseling, and pharmacotherapy**
 - ▶ Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange (<https://www.ahrq.gov/prevention/guidelines/tobacco/5steps.html>)
 - ▶ [See NCCN Guidelines for Smoking Cessation](#)
- **Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended during concurrent systemic therapy plus RT (category 1 for not using GM-CSF).¹**
- **Trilaciclib may be used as a prophylactic option to decrease the incidence of chemotherapy-induced myelosuppression when administered before (or G-CSF may be administered after) platinum/etoposide ± immune checkpoint inhibitor-containing regimens or a topotecan-containing regimen for extensive-stage small cell lung cancer (ES-SCLC).**
- **SIADH**
 - ▶ Fluid restriction
 - ▶ Saline infusion for symptomatic patients
 - ▶ Antineoplastic therapy
 - ▶ Demeclocycline
 - ▶ Vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) for refractory hyponatremia
- **Cushing's syndrome**
 - ▶ Consider ketoconazole. If not effective, consider metyrapone.
 - ▶ Try to control before initiation of antineoplastic therapy.
- **Leptomeningeal disease:** [See NCCN Guidelines for Central Nervous System Cancers](#)
- **Pain management:** [See NCCN Guidelines for Adult Cancer Pain](#)
- **Nausea/vomiting:** [See NCCN Guidelines for Antiemesis](#)
- **Psychosocial distress:** [See NCCN Guidelines for Distress Management](#)
- [See NCCN Guidelines for Palliative Care](#) as indicated

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

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**PRINCIPLES OF SYSTEMIC THERAPY****PRIMARY OR ADJUVANT THERAPY FOR LIMITED STAGE SCLC:**

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

Preferred Regimens

- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3²
- Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3³

Other Recommended Regimens

- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3²
- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3^{a,4}

PRIMARY THERAPY FOR EXTENSIVE-STAGE SCLC:

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

Preferred Regimens

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

Other Recommended Regimens

- Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3⁷
- Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3⁸
- Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3⁹
- Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3¹⁰

Useful In Certain Circumstances

- Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15¹¹
- Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15¹²
- Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8¹³

^a Cisplatin contraindicated or not tolerated.

^b Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

[Subsequent Systemic Therapy \(SCL-E 2 of 4\)](#)
[Response Assessment \(SCL-E 3 of 4\)](#)
[References \(SCL-E 4 of 4\)](#)

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PRINCIPLES OF SYSTEMIC THERAPY

Consider dose reduction or growth factor support for patients with PS 2.

SCLC SUBSEQUENT SYSTEMIC THERAPY: ^c
Relapse ≤6 months PS 0–2
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> • Topotecan PO or IV¹⁴⁻¹⁶ • Lurbinectedin³⁷ • Clinical trial <p><u>Other Recommended Regimens</u></p> <ul style="list-style-type: none"> • Paclitaxel^{22,23} • Docetaxel²⁴ • Irinotecan²⁵ • Temozolomide^{26,27} • Cyclophosphamide/doxorubicin/vincristine (CAV)¹⁴ • Oral etoposide^{28,29} • Vinorelbine^{30,31} • Gemcitabine^{32,33} • Bendamustine (category 2B)³⁴ • Nivolumab^{b,d,17,18} (category 3) • Pembrolizumab^{b,d,19,20,21} (category 3)
Relapse >6 months
<p><u>Preferred Regimens</u></p> <ul style="list-style-type: none"> • Original regimen^{d,35,36} <p><u>Other Recommended Regimen</u></p> <ul style="list-style-type: none"> • Lurbinectedin³⁷

^b Contraindications for treatment with PD-1/PD-L1 inhibitors may include active or previously documented autoimmune disease and/or concurrent use of immunosuppressive agents.

^c Subsequent systemic therapy refers to second-line and beyond therapy.

^d Regimen not recommended for relapsed disease in patients on maintenance atezolizumab or durvalumab at time of relapse.

[Response Assessment \(SCL-E 3 of 4\)](#)

[References \(SCL-E 4 of 4\)](#)

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PRINCIPLES OF SYSTEMIC THERAPY

Response Assessment

• Limited stage

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

• Extensive stage

- ▶ During systemic therapy, response assessment by chest/abdomen/pelvis CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy.
- ▶ For patients with asymptomatic brain metastases receiving systemic therapy before brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy.

• Subsequent systemic therapy

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

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[References](#)
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**PRINCIPLES OF SYSTEMIC THERAPY**
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**PRINCIPLES OF RADIATION THERAPY****General Principles:**

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

General Treatment Information:

- Limited stage:
 - ▶ In patients with clinical stage I–IIA (T1–2,N0,M0) who have undergone lobectomy and are found to have regional nodal involvement on final pathology, postoperative RT is recommended in pathologic N2 and may be considered in pathologic N1 stage, either sequentially or concurrently with chemotherapy. Principles of postoperative RT for NSCLC, including target volumes and doses, are recommended.
 - ▶ Selected patients with stage I–IIA (T1–2,N0,M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative RT (SABR) to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC ([see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C](#)).²⁻⁴
 - ▶ Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.⁵ RT should start early, with cycle 1 or 2 of systemic therapy (category 1).⁶ A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.⁷
 - ▶ Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of RT planning. PET/CT should be obtained, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, PET/CT should be obtained in the treatment position.
 - ▶ Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Consensus on elective nodal irradiation (ENI) is evolving.⁸ Several more modern series, both retrospective and prospective, suggest that omission of ENI results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating PET staging/target definition (1.7%–3%).⁹⁻¹⁴ ENI has been omitted in current prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial). Inclusion of the ipsilateral hilum in the target volume, even if not grossly involved, differs between these trials but may be reasonable.

[See Limited Stage \(cont.\), Extensive Stage, Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation \(SCL-F 2 of 5\)](#)

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

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[References](#)
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**PRINCIPLES OF RADIATION THERAPY****• Limited stage (cont.):**

- ▶ In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.^{11,15}
- ▶ Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established.
 - ◊ Based on the randomized phase III trial, INT 0096, 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).^{16,17} When BID fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
 - ◊ If using once-daily RT, higher doses of 60–70 Gy should be used.^{18–21} The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks. The randomized, phase III European CONVERT trial did not demonstrate superiority of 66 Gy (once daily) over 45 Gy (BID), but overall survival and toxicity were comparable.²²

• Extensive stage:

- ▶ Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC with complete response or good response to systemic therapy, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well-tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.^{23,24} The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with extensive-stage SCLC that responded to systemic therapy demonstrated significantly improved 2-year overall survival and 6-month progression-free survival, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.²⁵ 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.²⁶
- ▶ Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions to 60 Gy in 30 daily fractions, or equivalent regimens in this range.
- ▶ Based on two randomized trials, immunotherapy during and after chemotherapy is a first-line approach,^{27,28} but these studies did not include consolidative thoracic RT. Nevertheless, consolidative thoracic RT after chemoimmunotherapy can be considered for selected patients as above, during or before maintenance immunotherapy (there are no data on optimal sequencing or safety).

Normal Tissue Dose Constraints:

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

Prophylactic Cranial Irradiation:

- In patients with limited-stage SCLC (LS-SCLC) who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).^{29,30} In patients with extensive-stage SCLC (ES-SCLC) that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI.³¹ 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.³² Surveillance imaging for brain metastases is recommended for all patients regardless of PCI status.

[See Prophylactic Cranial Irradiation \(cont.\), Brain Metastases \(SCL-F 3 of 5\)](#)[References](#)
[\(SCL-F 4 of 5\)](#)**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

**PRINCIPLES OF RADIATION THERAPY****Prophylactic Cranial Irradiation (cont.):**

- 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.^{33,34}
- Neurocognitive function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 56% of patients younger than 60 years of age ($P = .009$).³⁴ Concurrent systemic therapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.
- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.
- When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases.³⁵ 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.
- Consider hippocampal-sparing PCI using IMRT.^{36,37,38,39}
- Current randomized trials are evaluating whether MRI surveillance alone is non-inferior to MRI surveillance plus PCI on overall survival and whether hippocampal-sparing PCI reduces memory impairment compared to whole brain PCI in LS-SCLC and ES-SCLC.

Brain Metastases:

- Brain metastases should typically be treated with WBRT; however, selected patients with a small number of metastases may be appropriately treated with stereotactic radiotherapy (SRT)/radiosurgery (SRS).⁴⁰ A current trial 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).³⁵
- In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.^{41,42} SRS is preferred, if feasible.^{43,44}
- 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.³⁹

Palliative Radiation for Extracranial Metastases:

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

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

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

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

**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 <i>in situ</i> Squamous cell carcinoma <i>in situ</i> (SCIS) Adenocarcinoma <i>in situ</i> (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

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

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

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



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Discussion

This discussion corresponds to the NCCN Guidelines for Small Cell Lung Cancer. Last updated on August 5, 2019.

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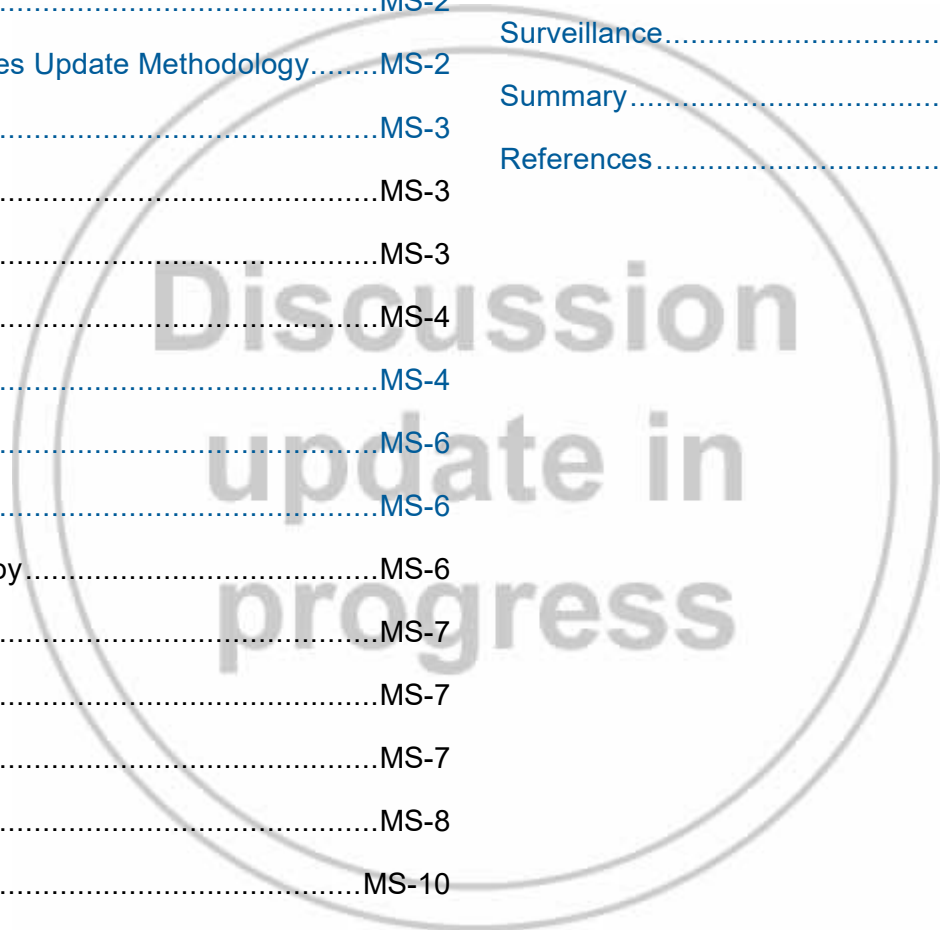
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Small Cell Lung Cancer

Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).^{1,2} In 2019, an estimated 29,660 new cases of SCLC will occur in the United States.^{1,3} Nearly all cases of SCLC are attributable to cigarette smoking.⁴ Although the incidence of SCLC has been decreasing, the incidence in women is increasing and the male-to-female incidence ratio is now 1:1.^{1,2} Management of SCLC is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Small Cell Lung Cancer, which includes the algorithm and this supporting Discussion text. Management of other lung neuroendocrine tumors (LNTs) is described in a different guideline (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines[®] for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).

The NCCN Guidelines for Small Cell Lung Cancer were originally published 20 years ago and have been subsequently updated at least once every year (see www.NCCN.org).⁵ The *Summary of the Guidelines Updates* section in the SCLC algorithm describes the most recent revisions for 2019, which are described in greater detail in this revised Discussion text; recent references have been added (see *Summary* in this Discussion and the algorithm). For example, new immunotherapy options have been added for patients with SCLC. Additional supplemental material in the SCLC algorithm includes the *Signs and Symptoms of Small Cell Lung Cancer*, *Principles of Pathologic Review*, *Principles of Surgical Resection*, *Principles of Supportive Care*, *Principles of Systemic Therapy*, *Principles of Radiation Therapy*, and staging tables.

SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; approximately one third present

with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.⁶ In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiotherapy; some patients are eligible for curative surgery followed by systemic therapy with or without mediastinal radiotherapy.^{7,8} In patients with extensive-stage disease, systemic therapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare.⁹ Note that the definitions for limited-stage and extensive-stage SCLC incorporate TNM staging (see the algorithm and *Staging* in this Discussion). Surgery is only recommended for certain patients with surgically resectable stage I to IIA SCLC; stereotactic ablative radiotherapy (SABR) is an option for certain patients with medically inoperable stage I to IIA SCLC.¹⁰⁻¹³ Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the recommended therapy for SCLC as outlined in these NCCN Guidelines still needs to be improved. Thus, participation in clinical trials should be strongly encouraged.

Smoking cessation 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).¹⁴ Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.¹⁵ Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful.

Literature Search Criteria and Guidelines Update Methodology

An electronic search of the PubMed database was performed to obtain key literature in SCLC using the following search term: *small cell lung cancer*. The PubMed database was chosen because it is the most widely



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used resource for medical literature and indexes peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 1; Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The data from key PubMed articles as well as articles from additional sources deemed as relevant to these NCCN Guidelines and discussed by the NCCN SCLC Panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis

Screening

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

symptomatic disease between annual scans, thereby limiting the potential effect on mortality.¹⁶

Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea.²⁰ Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. The NCCN SCLC Panel recently added a new section describing signs and symptoms of SCLC based on the tumor location and type of metastases (see *Signs and Symptoms of Small Cell Lung Cancer* in the algorithm). It is uncommon for patients to present with a solitary peripheral nodule without central adenopathy. In this situation, fine-needle aspiration (FNA) may not adequately differentiate small cell carcinoma (which is a high-grade neuroendocrine carcinoma) from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or large-cell neuroendocrine carcinoma (LCNEC) (which is also a high-grade neuroendocrine carcinoma) (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).^{21,22}

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.²³⁻²⁵ Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. Patients with the Lambert-Eaton myasthenic syndrome present with proximal leg weakness that is caused by antibodies directed against the voltage-gated calcium channels.^{26,27} Paraneoplastic encephalomyelitis and sensory neuropathy are caused by the production of an antibody (anti-*Hu*) that cross-reacts with both small cell carcinoma antigens and human neuronal RNA-binding proteins resulting in multiple neurologic deficits; paraneoplastic encephalomyelitis may precede the diagnosis of a tumor.²⁸ For the 2019 update, the NCCN SCLC Panel now recommends that if neurologic



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paraneoplastic syndrome is suspected, then obtaining a comprehensive paraneoplastic antibody panel should be considered.

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

Pathology

The NCCN Guidelines for SCLC include a section on pathology (see *Principles of Pathologic Review* in the algorithm). The WHO classification system is used to classify lung tumors.³⁴⁻³⁶ SCLC is a poorly differentiated malignant epithelial tumor that is categorized as a high-grade neuroendocrine carcinoma.²¹ The classic and distinctive histology on hematoxylin and eosin (H&E) may be sufficient for identifying SCLC in good-quality histologic samples including small blue cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.^{21,37} The cells are round, oval, or spindle-shaped; nuclear molding is prominent.³⁸ The mitotic count is high in SCLC when compared with the count in atypical and typical carcinoids.

It is important to distinguish SCLC from other neuroendocrine tumors, especially typical and atypical carcinoids, because treatment differs for these tumors (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines

for Neuroendocrine and Adrenal Tumors, available at www.NCCN.org).^{34,39} Up to 30% of specimens from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma);³⁸ this finding is more commonly detected in specimens from previously treated patients and suggests that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along divergent pathways. Although 95% of small cell carcinomas originate in the lung, they can also arise from extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract.^{40,41} Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases.

Immunohistochemistry is useful for diagnosing SCLC in limited samples.^{21,39,42} Nearly all SCLCs are immunoreactive for cytokeratin (AE1/Ae3, CAM5.2); 85% to 90% of SCLCs are positive for thyroid transcription factor-1 (TTF-1).^{21,43-45} Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin.²¹ However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs will be immunoreactive for at least one of these neuroendocrine markers.⁴⁶ Ki-67 immunostaining is useful for distinguishing SCLC from carcinoid tumors.^{34,39,47}

Staging

The NCCN SCLC Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the older Veterans Administration (VA) scheme for SCLC.^{6,48} The VA Lung Study Group's 2-stage classification scheme has historically been used to define the extent of disease in patients with SCLC: 1) limited-stage disease is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage disease is

disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.⁴⁹ Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial and treatment is individualized.^{6,48,50} Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. The AJCC recently revised the TNM staging system for lung cancer; new staging guidelines (8th edition) became effective on January 1, 2018 (see *Staging* in the algorithm).^{51,52} The NCCN SCLC Panel will continue to use both the VA and the TNM systems for staging SCLC.

In applying the TNM classifications to the VA system, *limited-stage* SCLC is defined as stage I to III (T any, N any, M0) that can be safely treated with definitive radiation therapy (RT), excluding T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan (see Table 1 in the algorithm). *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/b/c) or T3-4 due to multiple lung nodules as previously described.

Because most of the literature on SCLC classifies patients based on the VA's definitions of limited-stage or extensive-stage disease, these definitions are often used for clinical decision-making. However, the TNM system is useful for selecting patients with T1-2,N0 disease who are eligible for surgery and for radiation treatment planning.⁴⁸ Clinical research studies should begin to include use of the TNM system, because it will allow for more precise assessments of prognosis and specific therapy in the future.⁵¹

All patients with SCLC, even those with radiographically limited-stage disease, require systemic therapy either as primary or adjuvant therapy. Therefore, staging provides a therapeutic guideline for thoracic

radiotherapy, which is indicated primarily for patients with limited-stage disease. Full staging includes a history and physical examination; CT scan (with intravenous contrast) of the chest/abdomen; and brain imaging using MRI (preferred) or CT scan (with intravenous contrast).^{50,53} However, once a patient has been found to have extensive-stage disease, further staging is not required, except for brain imaging.⁶ Unilateral bone marrow aspirates and biopsies may be indicated in select patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration and with no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in fewer than 5% of patients. If limited-stage disease is suspected, a PET/CT scan (skull base to mid-thigh) can be performed to assess for distant metastases.^{6,48} A bone scan can be performed if PET/CT is equivocal or not available; bone biopsy can be considered if bone imaging is equivocal.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.⁵⁴⁻⁵⁶ PET/CT is superior to PET alone.⁵⁶ Approximately 19% of patients who undergo PET are upstaged from limited-stage to extensive-stage disease, whereas only 8% are downstaged from extensive-stage to limited-stage disease.⁵⁰ For most metastatic sites, PET/CT is superior to CT imaging; however, PET/CT is inferior to MRI or CT for the detection of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).⁵⁷ Changes in management based on PET staging were reported in approximately 27% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease.^{50,55,58} Although PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that would result in upstaging.

Before surgical resection, pathologic mediastinal staging is required to confirm PET/CT scan results in patients with clinical stage I to IIA SCLC (T1–2,N0,M0) to rule out occult nodal disease.⁶ However, mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is planned. Invasive mediastinal staging can be performed either by conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound-guided FNA (EUS-FNA), endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA), or video-assisted thoracic surgery (VATS).^{59,60}

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

Staging should not focus only on sites of symptomatic disease or on sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or without an abnormal alkaline phosphatase level. Bone imaging with radiographs or MRI may be appropriate if PET/CT is equivocal. Brain imaging (MRI preferred or CT with contrast) can identify central nervous system (CNS) metastases in 10% to 15% of patients at diagnosis, of which approximately 30% are asymptomatic. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the usefulness of early diagnosis in asymptomatic patients. Because of the aggressive nature of SCLC, staging should not delay the onset of treatment for more than 1 week; otherwise, many

patients may become more seriously ill in the interval, with a significant decline in their performance status (PS).

Prognostic Factors

Poor PS (3–4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease (such as lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis in patients with limited-stage disease. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease.^{61,62}

Treatment

Primary or Adjuvant Systemic Therapy

For all patients with SCLC, systemic therapy is an essential component of appropriate treatment. Many single-agent and combination chemotherapy regimens have been shown to be active in SCLC. Adjuvant chemotherapy is recommended for patients who have undergone surgical resection or SABR for early-stage disease. For patients with limited-stage IIB to IIIC (T3–4,N0,M0; T1–4,N1–3,M0) and with good PS (0–2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1).^{8,63,64} For patients with extensive-stage disease, systemic therapy alone is the recommended treatment; however, radiotherapy may be used in select patients for palliation of symptoms (*see Initial Treatment and Principles of Systemic Therapy* in the algorithm; see NCCN Guidelines for Palliative Care, available at www.NCCN.org). For the 2019 update (Version 1), the NCCN SCLC Panel added a chemo-immunotherapy regimen as a preferred option for patients with extensive-stage SCLC, which is described in greater detail later in this section.⁶⁵ In patients with extensive-stage disease and brain metastases,



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systemic therapy can be given either before or after whole-brain radiotherapy depending on whether the patient has neurologic symptoms (see *Initial Treatment* in the algorithm).^{9,66} If systemic therapy is given first, whole-brain radiotherapy is administered after completion of systemic therapy.

Response Assessment

Response assessment is an important aspect of the management of patients with SCLC. After adjuvant chemotherapy alone or chemotherapy with concurrent RT for patients with limited-stage disease, response assessment using CT with contrast of the chest/abdomen should occur only after completion of therapy; repeating CT scans during therapy is not recommended. For systemic therapy alone or sequential systemic therapy followed by RT in patients with limited-stage disease, response assessment using CT with contrast of the chest/abdomen should occur after every 2 cycles of systemic therapy and again at completion of therapy. During systemic therapy for patients with extensive-stage disease, response assessment using CT with contrast of the chest/abdomen should occur after every 2 to 3 cycles of systemic therapy and again at completion of therapy. Serial brain imaging is also recommended in patients with extensive-stage disease who have asymptomatic brain metastases and are receiving systemic therapy before whole-brain RT; brain MRI (preferred) or brain CT with contrast is recommended after every 2 cycles of systemic therapy and again at completion of therapy.

Limited-Stage SCLC

Etoposide plus cisplatin (EP) is the most commonly used initial combination chemotherapy regimen for patients with limited-stage SCLC (see *Principles of Systemic Therapy* in the algorithm).⁶⁷ This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity.⁶⁸⁻⁷⁰ EP alone is recommended as adjuvant

therapy for patients who have undergone resection of stage IA to IIA SCLC. If pathologic lymph node involvement is found at surgery, then thoracic radiotherapy can be added concurrently or sequentially to EP. For patients with limited-stage IIB to IIIC (T3–4,N0,M0; T1–4,N1–3,M0), EP plus concurrent thoracic radiotherapy is the recommended therapy (category 1).^{63,64,71,72} For the 2019 update, the NCCN SCLC Panel slightly revised the recommended EP regimens for limited-stage SCLC based on the dosing used in the CONVERT trial (see *Principles of Systemic Therapy* in the algorithm).⁷³ Thus far, there are no data to support the use of immunotherapy in patients with limited-stage SCLC.

Thoracic radiotherapy improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival.^{63,64} Data suggest that chemoradiotherapy may be indicated for patients with limited-stage disease who have cytologically negative or indeterminate pleural effusions but not for those with pericardial effusions.^{74,75} In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.⁷⁶ The use of myeloid growth factors is not recommended (category 1 for not using granulocyte-macrophage colony-stimulating factor [GM-CSF]) in patients undergoing concurrent chemoradiation.⁷⁷ In patients with limited-stage disease, treatment with EP plus definitive thoracic radiotherapy results in response rates of 70% to 90% with a median overall survival of only 24 to 30 months and 5-year overall survival rates of 25% to 30%.⁷³

Cisplatin versus Carboplatin

In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.⁷⁸ However, the use of carboplatin carries a greater risk of myelosuppression.⁷⁹ Small randomized trials in patients with SCLC have suggested similar efficacy of cisplatin and carboplatin regimens, as did a retrospective analysis in patients with extensive-stage disease.^{78,80,81} A meta-analysis of individual



patient data from 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.⁸² Of 663 patients included in this meta-analysis, 32% had limited-stage disease and 68% had extensive-stage disease. No significant difference was observed in response rate (67% vs. 66%), progression-free survival (PFS) (5.5 vs. 5.3 months), or overall survival (9.6 vs. 9.4 months) in patients receiving cisplatin-containing versus carboplatin-containing regimens, suggesting equivalent efficacy in patients with SCLC.

Extensive-Stage SCLC

For many years, platinum plus etoposide had been the standard treatment for patients with extensive-stage SCLC, with a preference for carboplatin over cisplatin due to its equivalent efficacy and more tolerable toxicity profile. Recently, this standard has changed due to a randomized phase 3 trial (IMpower133) demonstrating improved survival with the addition of atezolizumab, a PD-L1–targeted immune checkpoint inhibitor, to carboplatin plus etoposide.⁶⁵ In this study, standard carboplatin plus etoposide was compared to the same chemotherapy plus atezolizumab followed by maintenance atezolizumab in 403 patients with previously untreated extensive-stage SCLC. Response rates were similar in both arms (60% with chemotherapy plus atezolizumab versus 64% with chemotherapy alone), but the median overall survival was significantly longer with the addition of atezolizumab (12.3 months [95% CI, 10.8–15.9] vs. 10.3 months [95% CI, 9.3–11.3]). Similarly, the 1-year overall survival rate was 51.7% versus 38.2%, favoring the atezolizumab-containing regimen (hazard ratio [HR] for death, 0.7 [95% CI, 0.54–0.91; $P = .007$]). The rate of grade 3 or 4 adverse events was similar in both groups (56%). For the 2019 update (Version 1), the NCCN SCLC Panel now recommends (category 1) carboplatin/etoposide/atezolizumab as the preferred first-line systemic therapy option followed by maintenance atezolizumab for patients with extensive-stage SCLC.⁶⁵

Atezolizumab may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage these adverse events, and educate their patients about possible side effects. High-dose corticosteroids are generally recommended for immune-mediated adverse events based on the severity of the reaction. In addition, atezolizumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

Other Primary Systemic Therapies

Prior to the recent favorable data on immunotherapy, many other chemotherapy combination regimens had been evaluated in patients with extensive-stage disease with little consistent evidence of benefit when compared with EP. For example, the combination of irinotecan and cisplatin initially appeared to be better than EP. A small phase 3 Japanese trial reported that patients with extensive-stage SCLC who were treated with irinotecan plus cisplatin had a median survival of 12.8 months compared with 9.4 months for patients treated with EP ($P = .002$).⁸³ In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.⁸³ However, two subsequent large phase 3 trials performed in the United States comparing irinotecan plus cisplatin with EP failed to show a significant difference in response rate or overall survival between the regimens.^{84,85} A phase 3 randomized trial of 220 patients with extensive-stage SCLC found that median overall survival was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs. 7.1 months, $P = .04$).⁸⁶ Based on these studies, the cisplatin or carboplatin plus irinotecan regimens are included as options in the NCCN Guidelines for patients with extensive-stage disease. In addition, a meta-analysis suggested an improvement in PFS and overall survival with irinotecan plus platinum



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regimens compared with etoposide plus platinum regimens.⁸⁷ However, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN SCLC Panel continues to recommend etoposide plus platinum regimens for patients with either limited-stage or extensive-stage SCLC.

Many other strategies have been evaluated in an effort to improve on the recommended treatment for extensive-stage SCLC, including the addition of a third agent. In two trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP showed a modest survival advantage.^{88,89} 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 EP alone.⁹⁰ Two phase 3 randomized trials have confirmed the lack of improvement in survival with three-drug systemic therapy regimens compared to platinum plus etoposide in patients with extensive-stage SCLC. One of these studies assessed the combination of ifosfamide, etoposide, and epirubicin versus EP, while the other evaluated carboplatin plus etoposide with or without palifosfamide.^{91,92} Similarly, the addition of paclitaxel to either cisplatin or carboplatin plus etoposide yielded promising results in phase 2 trials, but did not improve survival and was associated with unacceptable toxicity in a phase 3 study.⁹³

The use of maintenance or consolidation chemotherapy beyond 4 to 6 cycles of recommended treatment produces a minor prolongation of duration of response without improving survival and carries a greater risk of cumulative toxicity.⁹⁴ A meta-analysis reported that maintenance chemotherapy did not prolong overall survival.⁹⁵ The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. To overcome drug resistance, alternating or sequential combination therapies have been designed to expose the tumor to as

many active cytotoxic agents as possible during initial treatment.⁹⁶ However, randomized trials have failed to show improved PFS or overall survival with this approach.^{97,98}

Multidrug cyclic weekly chemotherapy was designed to increase dose intensity. Early phase 2 results of this approach were promising, although favorable patient selection was of some concern.^{99,100} Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly chemotherapy regimens.¹⁰¹⁻¹⁰⁴ The role of higher-dose chemotherapy for patients with SCLC remains controversial. Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high chemotherapy doses when compared with those given conventional doses of the same agents.¹⁰⁵ In general, however, randomized trials comparing conventional chemotherapy doses to an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival.¹⁰⁶⁻¹⁰⁹ In addition, a meta-analysis of trials that compared recommended versus dose-intense variations of the cyclophosphamide, doxorubicin, and vincristine (CAV) and EP regimens found that increased relative dose intensity resulted in only a small, clinically insignificant enhancement of median survival in patients with extensive-stage disease.¹¹⁰

Currently available cytokines (eg, GM-CSF, 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,¹¹¹ maintenance of dose intensity with growth factors does not prolong disease-free or overall survival.^{112,113} Thus, the routine use of growth factors at the initiation of systemic therapy is not recommended. Despite

the recent success with atezolizumab, other immunotherapy-based strategies have not been as favorable. A phase 3 randomized trial 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 in patients with extensive-stage SCLC.¹¹⁴

The benefits of antiangiogenic therapy have also been evaluated in SCLC. In patients with limited-stage SCLC, a phase 2 study of irinotecan, carboplatin, and bevacizumab with concurrent radiotherapy followed by maintenance bevacizumab was terminated early because of an unacceptable incidence of tracheoesophageal fistulae. In extensive-stage SCLC, phase 2 trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.¹¹⁵⁻¹¹⁸ However, at least two randomized trials have demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.^{119,120} Currently, the NCCN SCLC Panel does not recommend use of bevacizumab in patients with SCLC. Overall, attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy regimens, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have failed to yield significant advantages when compared to recommended approaches.

Elderly Patients

The incidence of SCLC increases with age. Although the median age at diagnosis is older than 70 years, elderly patients are underrepresented in clinical trials.¹²¹ While advanced chronologic age does adversely affect tolerance to treatment, the functional status of an individual patient is much more useful than age in guiding clinical decision-making (see the NCCN Guidelines for Older Adult Oncology, available at www.NCCN.org). Older patients who are able to perform activities of daily living should be treated with combination systemic therapy (and radiotherapy, if indicated).¹²²⁻¹²⁴ For example, a subgroup analysis of the CONVERT trial

suggests that concurrent chemoradiation yields equivalent median survival in older versus younger patients with limited-stage SCLC (29 vs. 30 months; $P = .38$).¹²² However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in elderly patients; therefore, they must be watched carefully during treatment to avoid excessive risk.¹²² Greater attention to the needs and support systems of elderly patients is recommended to provide optimal care. Overall, elderly patients have a similar prognosis as stage-matched younger patients.

Randomized trials have indicated that less-intensive treatment (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in elderly patients with good PS (0–2).^{125,126} A retrospective analysis in 8637 elderly patients with limited-stage disease reported that chemoradiation increased survival when compared with chemotherapy alone.¹²³ Several other strategies have been evaluated in elderly patients with SCLC.^{81,127-129} The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve (AUC) dosing of carboplatin takes into account the declining renal function of the aging patient.¹²⁹ However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in this population.¹³⁰ The usefulness of short-course, full-intensity chemotherapy has also been explored in elderly or infirm patients, and the results with only 2 cycles of chemotherapy seem to be acceptable, although this approach has not been directly compared with 4 to 6 cycles of therapy.¹³¹ Prophylactic cranial irradiation (PCI) should be used with caution in elderly patients. Elderly patients (≥ 60 years) are at increased risk for cognitive decline after PCI; therefore, the risks and benefits of PCI versus close surveillance need to be discussed in detail with elderly patients.¹³²⁻¹³⁵ A Dutch analysis in more than 5000 patients suggests that median survival is decreased in older patients treated with PCI when compared with younger patients regardless of stage.¹³⁶

Subsequent Systemic Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.^{137,138} These patients have a median survival of only 4 to 5 months when treated with further systemic therapy. 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.¹³⁹ If this interval is less than 3 months (refractory or resistant disease), response to most agents or regimens is poor ($\leq 10\%$). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25%. If patients relapse more than 6 months after first-line treatment, then treatment with their original regimen is recommended. However, the NCCN SCLC Panel added a caveat that patients who relapse after 6 months while on maintenance atezolizumab should receive carboplatin plus etoposide (without atezolizumab).^{6,139,140} For patients on subsequent systemic therapy, response assessment should occur after every 2 to 3 cycles using CT with contrast of the chest/abdomen. Dose reduction or growth factor support should be considered for patients with a PS of 2 who are receiving subsequent systemic therapy.

Based on phase 2 trials, recommended subsequent systemic therapy agents for patients who have relapsed 6 months or less after primary therapy include topotecan, irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab with or without ipilimumab, pembrolizumab, vinorelbine, oral etoposide, gemcitabine, CAV, and bendamustine (category 2A for all agents except for bendamustine, which is a category 2B recommendation) (see *Principles of Systemic Therapy* in the algorithm).¹⁴¹⁻¹⁴⁴ A randomized phase 3 trial compared single-agent intravenous topotecan with the combination regimen CAV.¹⁴⁵ Both arms had similar response rates (topotecan: 24.3% [26/107]; CAV: 18.3% [19/104]) and survival (25 weeks), but intravenous topotecan caused less grade 4 neutropenia (37.8% vs. 51.4%; $P < .001$). When compared with CAV, topotecan also

improved symptoms of dyspnea, anorexia, hoarseness, and fatigue. In another phase 3 trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).¹⁴⁶ Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who relapse after initial response to systemic therapy. Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.^{146,147} Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m² of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.¹⁴⁸ Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.^{149,150}

Irinotecan was assessed in a phase 2 study in patients with refractory or relapsed SCLC; 47% of patients responded (7/15; [95% CI, 21.4%–71.9%]); myelosuppression, diarrhea, and pulmonary toxicity were reported.¹⁵¹ Paclitaxel was assessed in a phase 2 study in patients with refractory or relapsed SCLC; 24% of patients responded (5/21).¹⁵² Grade 3 to 4 toxicity included neutropenia, infection, rash, neuropathy, and pulmonary toxicity. Another phase 2 study of paclitaxel in patients with refractory SCLC yielded a response rate of 29% (7/24; 95% CI, 12%–51%).¹⁵³ Docetaxel was assessed in a phase 2 trial in patients with previously treated SCLC; 25% of patients responded (7/28). Reported toxicities included neutropenia and asthenia.¹⁵⁴

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O⁶-methylguanine-DNA methyltransferase (MGMT).^{142,155,156} A phase 2 study assessed temozolomide in patients with relapsed or refractory SCLC. In patients with sensitive SCLC, the overall response rate was 23% (95% CI, 12%–37%). The response rate was improved for patients with methylated MGMT compared to those with unmethylated MGMT (38% vs.



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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 when compared with topotecan (median survival, 18.2 vs. 12.5 months; HR, 0.67 [90% CI, 0.51–0.88]; $P = .0079$). However, the toxicity of this approach was significant and it is not recommended for subsequent therapy.¹⁵⁷

Amrubicin is an active drug in patients with relapsed or refractory SCLC.¹⁵⁸⁻¹⁶¹ However, grade 3 to 4 toxicity, primarily neutropenia, is common.^{162,163} A phase 3 trial reported that amrubicin did not improve overall survival as second-line treatment for SCLC when compared to topotecan, except in a subset of patients with refractory disease.¹⁶⁴

Immune checkpoint inhibitors have also been evaluated in patients with relapsed SCLC.¹⁶⁵ A phase 1/2 trial (CheckMate 032) assessed nivolumab alone or various doses of nivolumab plus ipilimumab for relapsed SCLC.¹⁶⁶ Response rates were 10% (10/98) for nivolumab 3 mg/kg, 23% (14/61) for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 19% (10/54) for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. The responses did not correlate with PD-L1 expression; studies indicate that SCLC has a lower rate of PD-L1 expression than NSCLC.¹⁶⁶ Diarrhea was the most common grade 3 or 4 treatment-related adverse event. The overall frequency of grade 3 or 4 adverse events was about 20%, and fewer than 10% of patients discontinued treatment because of treatment-related adverse events. Updated preliminary data from an expansion cohort of this trial reported a 1-year overall survival of 42% in patients receiving nivolumab/ipilimumab and 30% in those receiving nivolumab alone.¹⁶⁷ Further data suggest that tumor mutational burden may be a useful biomarker for assessing whether patients will respond to nivolumab with or without ipilimumab.¹⁶⁸

A recent phase 3 trial (CheckMate 331) assessed nivolumab monotherapy versus topotecan or amrubicin in 569 patients with relapsed SCLC.¹⁶⁹

Preliminary data show that overall survival was similar between the groups (nivolumab: 7.5 months vs. chemotherapy: 8.4 months; HR, 0.86 [95% CI, 0.72–1.04]; $P = .11$). Treatment-related deaths occurred in two patients receiving nivolumab and in three patients receiving chemotherapy. Fewer grade 3 to 4 adverse events occurred in patients receiving nivolumab compared with chemotherapy (14% vs. 73%, respectively). The NCCN SCLC Panel recommends nivolumab or nivolumab plus ipilimumab (both are category 2A) as subsequent therapy options for patients who have relapsed 6 months or less after primary therapy.^{166,167,169} However, patients whose disease progresses while on atezolizumab as part of first-line therapy should not be treated with other immune checkpoint inhibitors.

A recent combined analysis of two studies, one phase 1b (KEYNOTE-028) and one phase 2 (KEYNOTE-158), evaluated the activity of pembrolizumab in 83 evaluable patients with relapsed SCLC.¹⁷⁰ This analysis reported a response rate of 19.3% and a median overall survival of 7.7 months (95% CI, 5.2–10.1). Both overall survival and response rate were higher in those who were PD-L1 positive. Grade 3 or 4 adverse events occurred in 12% of patients and two patients died from treatment-related adverse events (pneumonitis and encephalitis). For the 2019 update, the NCCN SCLC Panel added pembrolizumab as a new subsequent therapy option for patients with SCLC regardless of PD-L1 levels based on phase 1 and 2 data.^{170,171}

Immunotherapeutic agents, such as nivolumab, ipilimumab, and pembrolizumab may cause unique immune-mediated adverse events that are not seen with traditional cytotoxic chemotherapy; therefore, health care providers should be aware of the spectrum of potential immune-mediated adverse events, know how to manage these adverse events, and educate their patients about possible side effects.^{172,173} For patients with immune-mediated adverse events, high-dose corticosteroids



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are generally recommended based on the severity of the reaction. Nivolumab, ipilimumab, or pembrolizumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

The optimal duration of subsequent systemic therapy has not been fully explored. For cytotoxic chemotherapy agents, the duration of treatment is usually short and the cumulative toxicity is frequently limiting even in patients who experience response. For these reasons, subsequent systemic therapy should be continued until 2 cycles beyond best response (for chemotherapy), progression of disease, or development of unacceptable toxicity. Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0 to 2.

Radiotherapy

The *Principles of Radiation Therapy* section in the algorithm describes the radiation doses, target volumes, and normal tissue dose-volume constraints for limited-stage SCLC, and includes references to support the recommendations; PCI and treatment of brain metastases are also discussed (see the algorithm). The American College of Radiology (ACR) Appropriateness Criteria® are a useful resource.¹⁷⁴ The *Principles of Radiation Therapy* section in the NSCLC algorithm may also be useful (eg, general principles of radiotherapy, palliative radiotherapy) (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). This section describes the studies supporting the NCCN RT recommendations for SCLC.

Thoracic Radiotherapy

The addition of thoracic radiotherapy has improved survival for patients with limited-stage SCLC. Meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease yields a 25% to 30% reduction in local failure, and a corresponding 5% to 7%

improvement in 2-year overall survival when compared with chemotherapy alone.^{63,64} However, achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge.

Timing of Radiation with Chemotherapy

The administration of thoracic radiotherapy requires the assessment of several factors, including the timing of chemotherapy and radiotherapy (concurrent vs. sequential), timing of radiotherapy (early vs. late), volume of the radiation port (original tumor volume vs. shrinking field as the tumor responds), dose of radiation, and fractionation of radiotherapy. 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 assessed sequential versus concurrent thoracic radiotherapy combined with EP for patients with limited-stage disease. They reported that patients treated with concurrent radiotherapy lived longer than those treated with sequential radiotherapy.⁷⁶

Another randomized phase 3 trial (by the National Cancer Institute of Canada) comparing radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy showed that early radiotherapy was associated with improved local and systemic control and longer survival.¹⁷⁵ Several systematic reviews and meta-analyses on the timing of thoracic radiotherapy in limited-stage SCLC have reported that early concurrent radiotherapy results in a small, but significant improvement in overall survival when compared with late concurrent or sequential radiotherapy.^{176,177} Another meta-analysis in patients with limited-stage SCLC showed that survival was improved with more rapid completion of the chemoradiotherapy regimen (start of any chemotherapy until the end of radiotherapy).¹⁷⁸ A meta-analysis of individual patient data from 12 trials (2668 patients) reported that early concurrent chemoradiotherapy



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increased 5-year overall survival (HR, 0.79; 95% CI, 0.69–0.91), although severe acute esophagitis was also increased, when compared with late concurrent therapy.¹⁷⁹

Radiation Fractionation

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.¹⁸⁰ In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiotherapy using a total dose of 45 Gy delivered either twice daily over 3 weeks or once daily over 5 weeks. The twice-daily schedule produced a survival advantage, but a higher incidence of grade 3 to 4 esophagitis was seen when compared with the once-daily regimen. Median overall survivals were 23 versus 19 months ($P = .04$), and 5-year survival rates were 26% versus 16% in the twice-daily and once-daily radiotherapy arms, respectively.¹⁸⁰ A significant criticism of this trial is that the doses of radiation in the 2 arms were not biologically equivalent, with the 45 Gy once-daily regimen providing suboptimal therapy.

Another randomized phase 3 trial showed no survival difference between once-daily thoracic radiotherapy to 50.4 Gy with concurrent EP and a split course of twice-daily thoracic radiotherapy to 48 Gy with concurrent EP.¹⁸¹ However, split-course radiotherapy may be less efficacious because of interval tumor regrowth between courses. The CONVERT randomized phase 3 trial assessed 45 Gy twice daily compared with 66 Gy once daily in 547 patients with limited-stage SCLC.⁷³ Median overall survival was similar between the 2 arms (30 vs. 25 months; HR for death in the once-daily group, 1.18 [95% CI, 0.95–1.45]; $P = .14$). Although toxicity was generally similar between the arms, patients receiving 45 Gy twice daily had more grade 4 neutropenia when compared with those receiving 66 Gy once daily (49% vs. 38%; $P = .05$).

Based on the data from these randomized trials, the optimal dose and fractionation of thoracic radiotherapy for SCLC remain unresolved. The

NCCN SCLC Panel recommends that either 45 Gy with twice-daily fractionation or 60 to 70 Gy with once-daily fractionation are acceptable options depending on individual patient characteristics. For example, twice-daily thoracic radiation is technically challenging for patients with bilateral mediastinal adenopathy, and logistically challenging for many patients and radiotherapy centers. Overall, patients selected for combined modality treatment that incorporates twice-daily radiotherapy must have an excellent PS and good baseline pulmonary function.

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 radiotherapy should be used concurrently with chemotherapy and that radiotherapy should start with the first or second cycle (category 1). The optimal dose and schedule of radiotherapy have not been established. For twice-daily radiotherapy, the recommended schedule is 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks. For once-daily radiotherapy, the recommended schedule is 2.0 Gy once daily to a total dose of 60 to 70 Gy (see *Principles of Radiation Therapy* in the algorithm).¹⁸²⁻¹⁸⁴

The minimum technical requirement for thoracic irradiation is CT-planned 3-D conformal radiotherapy. For concurrent chemoradiation, intensity-modulated radiation therapy (IMRT) is preferred over 3D-conformal external-beam RT because IMRT is less toxic (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).¹⁸⁵⁻¹⁹⁰ More advanced technologies may also be used when needed (eg, 4D-CT) (see *Principles of Radiation Therapy* in the algorithm). The radiation target volumes can be defined on the PET/CT scan obtained at the time of radiotherapy planning using definitions in reports 50 and 62 from the International Commission on Radiation Units & Measurements



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(ICRU).^{191,192} However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.^{184,193}

The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar radiotherapy doses (see the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org). When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALCB 30610/RTOG 0538 protocol can be used as a guide (see *Principles of Radiation Therapy* in the algorithm).¹⁹⁴⁻¹⁹⁶

SABR

Emerging data suggest that SABR (also known as stereotactic body radiation therapy [SBRT]) may be useful for patients with clinical stage I to IIA (T1–2,N0) SCLC who are medically inoperable or refuse surgery.^{11,197-201} One study of 43 patients with clinical stage I SCLC who received SABR found that 31 patients were stage IA and 79% were medically inoperable.¹¹ Patients typically received 48 to 50 Gy (4–5 fractions), and only 8 patients received chemotherapy and PCI. The 2-year overall survival was 72.3% and 2-year PFS was 44.6%. Distant metastasis occurred in 47% of patients. A multicenter analysis of 74 patients suggested that the addition of chemotherapy typically after SABR improves survival for patients with clinical limited-stage SCLC.^{12,202} Most of these patients had PET staging, although they did not have pathologic nodal staging. Patients who received chemotherapy after SABR had a median overall survival of 31.4 months versus 14.3 months for those receiving SABR alone ($P = .02$). For the 2019 update, the NCCN SCLC Panel now recommends (category 2A) SABR followed by systemic therapy as an option for select patients with clinical stage I to IIA (T1–2, N0) who are medically inoperable or decline surgery. 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).

Thoracic Radiation for Extensive-Stage SCLC

The addition of sequential (consolidative) thoracic radiotherapy may be considered in select patients with low-bulk metastatic extensive-stage disease who have a complete or near complete response after initial systemic therapy. This recommendation was initially based on the results of a randomized trial by Jeremic et al,²⁰³ in which patients experiencing a complete response at distant metastatic sites after 3 cycles of EP were randomized to receive either 1) further EP; or 2) accelerated hyperfractionated radiotherapy (ie, 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide.²⁰³ The investigators found that the addition of radiotherapy resulted in improved median overall survival (17 vs. 11 months). Another phase 3 randomized trial in patients with extensive-stage SCLC (Dutch CREST trial) reported that the addition of consolidative thoracic radiotherapy (30 Gy in 10 fractions) did not improve the primary endpoint of 1-year overall survival (33% vs. 28%, $P = .066$), but a secondary analysis did find improvement in 2-year overall survival (13% vs. 3%, $P = .004$) and 6-month PFS when compared with patients who did not receive consolidative thoracic radiotherapy.²⁰⁴ A trial involving 32 patients who received consolidative thoracic RT reported that only 16% (5/32) of patients had symptomatic chest recurrences.²⁰⁵ Consolidative thoracic RT appears to mainly benefit patients with residual thoracic disease after systemic therapy, but with low-bulk extrathoracic metastatic disease that has responded to systemic therapy.²⁰⁶

Prophylactic Cranial Irradiation

Intracranial metastases occur in more than 50% of patients with SCLC. Randomized studies have shown that PCI is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to show a meaningful survival advantage.²⁰⁷ A



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meta-analysis of all randomized PCI trials (using data from individual patients) reported a nearly 50% reduction in the 3-year incidence of brain metastases, from 58.6% in the control group to 33.3% in the PCI-treated group.²⁰⁸ Thus, PCI seems to prevent (and not simply delay) the emergence of brain metastases. This meta-analysis also reported a 5.4% increase in 3-year overall survival in patients treated with PCI, from 15.3% in the control group to 20.7% in the PCI group.²⁰⁸ Although the number of patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in patients with both limited-stage and extensive-stage disease. A retrospective study of patients with limited-stage disease also found that PCI increased survival at 2, 5, and 10 years compared with those who did not receive PCI.²⁰⁹ A study in 184 patients with limited-stage SCLC assessed PCI versus no PCI in patients who responded to chemoradiotherapy and had no brain metastases on brain MRI imaging before and after primary treatment.²¹⁰ In patients receiving PCI, median overall survival was 26 months (range, 19.4–32.6 months) versus 14 months (range, 11.4–16.6 months; $P < .0001$) for those without PCI.

For patients (4257) 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; $P < .0001$).²¹¹ Another analysis of patients with extensive-stage SCLC ($n = 397$) reported that PCI improved overall survival compared with no PCI (13.5 vs. 8.5 months, respectively; HR, 0.55; 95% CI, 0.39–0.77; $P = .0005$); however, these patients did not receive routine surveillance brain imaging.²¹²

In light of the paucity of data on the benefits of PCI in patients with extensive-stage SCLC, the EORTC performed a randomized trial that assessed PCI versus no PCI in 286 patients with extensive-stage SCLC whose disease had responded to initial chemotherapy; PCI decreased

symptomatic brain metastases (14.6% vs. 40.4%) and increased the 1-year survival rate (27.1% vs. 13.3%) compared with controls.²¹³ However, the study did not require brain imaging prior to PCI and did not standardize the PCI dose or fractionation. Conflicting data come from a randomized phase 3 trial from Japan, which found that median overall survival was not improved in patients receiving PCI when compared with observation (11.6 months [95% CI, 9.5–13.3] versus 13.7 months [95% CI, 10.2–16.4]) (HR, 1.27; 95% CI, 0.96–1.68; $P = .094$).²¹⁴ 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.

Based on the conflicting trial results from Japan and the EORTC, the NCCN SCLC Panel recently softened the recommendation for PCI in patients with extensive-stage disease to *consider* either PCI or close surveillance brain imaging. The NCCN SCLC Panel also added detailed imaging recommendations for patients regardless of PCI (see *Surveillance* in this Discussion). Therefore, depending on individual patient factors, either PCI or close brain surveillance imaging (MRI preferred or CT with contrast) appear to be reasonable options for patients with extensive-stage SCLC and good response to initial systemic therapy. For the 2019 update, the NCCN SCLC Panel added a caveat that the risks and benefits of PCI versus brain surveillance imaging should be discussed with patients.

Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrently with chemotherapy.^{133,215,216} Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.^{217,218} Older age (>60 years) has also been associated with chronic

neurotoxicity.^{132,134} When given after the completion of chemotherapy and at a low dose per fraction, PCI may cause less neurologic toxicity.

Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist that may delay cognitive dysfunction in patients receiving whole-brain RT.²¹⁹

Patients receiving memantine had a longer time before cognitive decline (HR, 0.78; 95% CI, 0.62–0.99, $P = .01$). The NCCN SCLC Panel recommends that memantine be considered for patients receiving PCI or therapeutic whole-brain irradiation. For the 2019 update, the panel added memantine dosing to the algorithm based on clinical trial data (RTOG 0614).²¹⁹

Before the decision is made to administer PCI, a balanced discussion between the patient and physician is necessary.^{133,220} The NCCN SCLC Panel recommends PCI (category 1) for patients with limited-stage disease who attain a complete or partial response; PCI can be considered (category 2A) for patients with extensive-stage disease.^{213,217} For the 2019 update, the NCCN SCLC Panel added a caveat that it is not clear whether patients who have had surgical resection for stage I to IIA SCLC will benefit from PCI because these patients have a lower risk of developing brain metastases.^{202,221,222} The preferred dose for PCI is 25 Gy in 10 daily fractions (2.5 Gy/fraction) (see *Principles of Radiation Therapy* in the algorithm).^{208,213,223} The NCCN SCLC Panel feels that a shorter course of PCI may be appropriate (eg, 20 Gy in 5 fractions) for selected patients with extensive-stage disease.²¹³ Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with lower doses (25 Gy).^{132,223} PCI should not be given concurrently with chemotherapy, and high total radiotherapy dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity.¹³² Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.^{218,223} After the acute toxicities of initial systemic therapy have resolved, PCI can be administered. For patients not receiving PCI, surveillance for metastases with brain imaging

is recommended using either MRI (preferred) or CT with contrast. Detailed brain imaging recommendations are provided in the algorithm.²¹⁴

Palliative Radiotherapy

For patients with localized symptomatic sites of disease (ie, painful bony lesions, spinal cord compression, obstructive atelectasis) or with brain metastases, radiotherapy can provide excellent palliation (see the algorithm and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).²²⁴⁻²²⁶ 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. Whole-brain radiotherapy is recommended for brain metastases in patients with SCLC due to the frequent occurrence of multiple metastases (see *Principles of Radiation Therapy* in the algorithm and the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org).²²⁷ Although late complications, such as neurocognitive impairment, may occur with whole-brain radiotherapy, this is less of an issue in patients with SCLC because long-term survival is rare.¹³³ The recommended dose for whole-brain radiotherapy is 30 Gy in 10 daily fractions.²²⁷ In patients who develop brain metastases after PCI, stereotactic radiosurgery (preferred) or whole-brain radiotherapy may be considered.^{228,229}

Surgical Resection of Stage I to IIA SCLC

The *Principles of Surgical Resection* for SCLC are described in the NCCN algorithm; studies supporting these recommendations are described in this section. Briefly, the NCCN Guidelines state that surgery is only recommended for patients with stage I to IIA (T1–2,N0) SCLC in whom mediastinal staging has confirmed that mediastinal lymph nodes are not involved.^{10,230} Data show that patients with nodal disease (ie, T1–3,N1–3,



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M0–1) do not benefit from surgery.²³¹ Note that fewer than 5% of patients with SCLC have true stage I to IIA disease.²³²

For the 2019 update, the NCCN SCLC Panel expanded the indication for surgery to include patients with clinical stage IIA SCLC based on the change in staging criteria such that tumors up to 5 cm in diameter (T2b) without lymph node involvement (N0) are now classified as IIA. The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.²³¹ Patients with limited-stage disease, excluding those with solitary peripheral nodules, received 5 cycles of chemotherapy with CAV; those showing a response to chemotherapy were randomly assigned to undergo resection plus thoracic radiotherapy or thoracic radiotherapy alone. The overall survival rates of patients on the two arms were equivalent, suggesting no benefit to surgery in this setting. However, only 19% of enrolled patients had clinical stage I (T1–2,N0,M0) disease.

Most of the data regarding the role of surgery in SCLC are from retrospective reviews.^{230,233–237} These studies report favorable 5-year survival rates of 40% to 60% in patients with stage I disease. In most series, survival rates decline significantly in patients with more advanced disease with lymph node involvement, leading to the general recommendation that surgery should only be considered in those with stage I to IIA disease (T1–2,N0,M0). Interpretation of these results is limited by the selection bias inherent in retrospective reviews and by the variable use of chemotherapy and radiotherapy. A meta-analysis describes the evidence from currently available randomized trials in greater detail.²³⁸

Analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.^{13,239} However, these studies are limited by the lack of information on chemotherapy use in the database. In addition, comparison of the survival of surgical patients to all

those who did not undergo surgery is inherently flawed by selection bias. Ultimately, the role of surgery in SCLC will not be fully defined until trials are done to compare surgery plus adjuvant chemotherapy to concurrent chemoradiotherapy in patients who are rigorously staged.

In patients with clinical stage I to IIA (T1–2,N0) SCLC who are being considered for surgical resection, occult nodal disease should be ruled out through mediastinal staging before resection.²⁴⁰ If resection is performed, the NCCN SCLC Panel recommends lobectomy with mediastinal lymph node dissection as the preferred operation and does not feel that segmental or wedge resections are appropriate for patients with SCLC. After complete resection, adjuvant chemotherapy or chemoradiation is recommended.^{217,235,241,242} Adjuvant chemotherapy alone is recommended for patients without nodal metastases, whereas concurrent chemotherapy and postoperative mediastinal radiotherapy are recommended for patients with nodal metastases (see *Adjuvant Treatment* in the algorithm). Although panel members agree that postoperative mediastinal radiotherapy is recommended in this setting, it should be based on the extent of nodal sampling/dissection and extent of nodal positivity; however, there are no data to support this recommendation. The role of PCI is unclear in surgically resected early-stage patients, because they appear to have a lower incidence of brain metastases (see *Prophylactic Cranial Irradiation* in this Discussion and *Adjuvant Treatment* in the algorithm).²⁰⁸ The NCCN SCLC Panel recommends new baseline disease assessment after adjuvant therapy.

Surveillance

The surveillance recommendations for patients with SCLC are outlined in the algorithm. The frequency of surveillance decreases during subsequent years because of the declining risk of recurrence.²⁴³ If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors are a frequent occurrence in



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patients who are cured of SCLC.^{244,245} It is important to monitor for brain metastases, which allows for early treatment prior to the development of potentially debilitating neurologic symptoms. The NCCN SCLC Panel recommends brain MRI (preferred) or brain CT with contrast every 3 to 4 months during year 1 for all patients. For the 2019 update, the panel revised these imaging recommendations to every 6 months during year 2, regardless of the PCI status. PET/CT is not recommended for routine follow-up. Smoking cessation should be encouraged 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).²⁴⁶⁻²⁴⁸ Former smokers should be encouraged to remain abstinent. The NCCN SCLC Panel also recommends the survivorship guidelines for appropriate patients (see the NCCN Guidelines for Survivorship, available at www.NCCN.org).

Summary

SCLC is a poorly differentiated high-grade neuroendocrine carcinoma.²¹ Most cases of SCLC are caused by cigarette smoking.⁴ Management of SCLC is described in the NCCN Guidelines for SCLC, which include the algorithm and this supporting Discussion text. Revisions for the 2019 update of the NCCN Guidelines for SCLC are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates* in the algorithm). For the 2019 update (Version 1), the NCCN SCLC Panel now recommends atezolizumab/carboplatin/etoposide as a preferred first-line systemic therapy option (category 1) for extensive-stage SCLC based on clinical trial data and the FDA approval.⁶⁵ The panel also added pembrolizumab as a new subsequent therapy option for patients with SCLC regardless of PD-L1 levels based on phase 1 and 2 data.^{170,171} In addition, the panel added a new recommendation for SABR followed by systemic therapy for select patients with clinical stage I to IIA SCLC (T1–2, N0,M0) who are medically inoperable or decline surgery.^{11,12,197,202}

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