

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Cell Lung Cancer

Version 2.2018 — January 17, 2018

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Small Cell Lung Cancer

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[NCCN Small Cell Lung Cancer Panel Members](#) [Summary of the Guidelines Updates](#)

Small Cell Lung Cancer:

- [Initial Evaluation and Staging \(SCL-1\)](#)
- [Limited Stage, Workup and Treatment \(SCL-2\)](#)
- [Extensive Stage, Initial Treatment \(SCL-4\)](#)
- [Response Assessment Following Initial Therapy \(SCL-5\)](#)
- [Surveillance \(SCL-5\)](#)
- [Progressive Disease: Subsequent Therapy and Palliative Therapy \(SCL-6\)](#)
- [Signs and Symptoms of Small Cell Lung Cancer \(SCL-A\)](#)
- [Principles of Pathologic Review \(SCL-B\)](#)
- [Principles of Surgical Resection \(SCL-C\)](#)
- [Principles of Supportive Care \(SCL-D\)](#)
- [Principles of Systemic Therapy \(SCL-E\)](#)
- [Principles of Radiation Therapy \(SCL-F\)](#)

[Staging \(ST-1\)](#)

Lung Neuroendocrine Tumors – [See the NCCN Guidelines for Neuroendocrine Tumors](#)

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/physician.html](#).

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

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

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Updates in Version 2.2018 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2018 include:

[MS-1](#)

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

Updates in Version 1.2018 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2017 include:

[General](#)

- For consistency in imaging, statement was revised: “~~CT Chest/liver/adrenal abdomen~~ CT with contrast” as appropriate throughout the guideline.

[SCL-1](#)

• Initial Evaluation

- ▶ Bullet 4 modified: “Electrolytes, liver function tests (LFTs), ~~Ga~~ LDH BUN, creatinine”
- ▶ Bullet 7 modified: “PET/CT scan (*skull base to mid-thigh*), (if limited stage is suspected)”
- ▶ Footnote “b” for H & P was added: “[See Signs and Symptoms of Small Cell Lung Cancer \(SCL-A\)](#)” (Also for SCL-5)
- ▶ Footnote “c” for pathology review was added: “[See Principles of Pathologic Review \(SCL-B\)](#).”

[SCL-2](#)

• Additional Workup

- ▶ Bullet 2 modified: “Pulmonary function tests (PFTs) *during evaluation for surgery (if clinically indicated)*”
- ▶ Bullet 3 modified: “Bone imaging (radiographs or MRI) as appropriate if PET/CT equivocal (*Consider biopsy if bone imaging is equivocal*)”

[SCL-3](#)

• Adjuvant Treatment

- ▶ Clinical stage N+ separated into N1 and N2.
 - ◇ N1 adjuvant treatment option added: “Systemic therapy ± mediastinal RT (sequential or concurrent)”
 - ◇ N2 adjuvant treatment option added: “Systemic therapy + mediastinal RT (sequential or concurrent)”
- Footnote “o” was modified: “For patients receiving adjuvant therapy, response assessment should occur only after completion of *initial adjuvant* therapy ([SCL-5](#)); do not repeat scans to assess response during adjuvant treatment.”

[SCL-4](#)

• Initial Treatment of asymptomatic brain metastases

- ▶ Statement was modified: “May administer systemic therapy first, with whole-brain RT *after completion of systemic therapy*”



Updates in Version 1.2018 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2017 include:

SCL-5

- **Response Assessment Following Initial Therapy**
 - ▶ **Bullet 5 was modified:** “Electrolytes, LFTs, ~~Ga~~, BUN, creatinine”
- **Adjuvant Treatment; Extensive disease:** “PCI ± thoracic RT” revised to “*Consider* PCI ± thoracic RT”
- **Surveillance**
 - ▶ **Footnote “s” was added to heading:** “See NCCN Guidelines for Survivorship”
- **Complete response or partial response**
 - ▶ **Limited stage**
 - ◇ **Statement was revised:** “After ~~completion of initial recovery from primary~~ therapy:”
 - ◇ **Bullet 1 was revised:** “Oncology follow-up visits every 3–4 mo during y 1–2, every 6 mo during y 3–5, then annually”
 - ◇ **Bullet 1 revised:** “At every visit: H&P, CT Chest/*abdomen*; ~~liver/adrenal with contrast~~, bloodwork *only* as clinically indicated”
 - ◇ **Bullet 2 was added:** “If PCI not given, then MRI (preferred) or CT brain with contrast every 3–4 mo during y 1–2”
 - ▶ **Extensive stage**
 - ◇ **Statement was added:** “After completion of initial or subsequent therapy”
 - ◇ **Bullet 1 was added:** “Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during years 4–5, then annually”
 - ◇ **Bullet 1 revised:** “At every visit: H&P, CT Chest/*abdomen*; ~~liver/adrenal with contrast~~, bloodwork *only* as clinically indicated”
 - ◇ **Bullet 2 was added:** “If PCI not given, then MRI (preferred) or CT brain with contrast every 3–4 mo during y 1–2”
 - ◇ **Footnote “u” for thoracic RT was revised:** “Sequential radiotherapy to thorax in selected patients, *especially with residual thoracic disease and low-bulk extrathoracic metastatic disease and complete response that has responded to systemic therapy.*”
- **Stable disease**
 - ▶ **Limited stage and Extensive stage**
 - ◇ **Statement was revised:** “After ~~completion of initial recovery from primary~~ therapy:”
 - ◇ **Bullet 1 was revised:** “Oncology follow-up visits every 3–4 mo during y 1–2, every 6 mo during y 3–5, then annually”
 - ◇ **Statement was added:** “After completion of initial or subsequent therapy”
 - ◇ **Bullet 1 was added:** “Oncology follow-up visits every 2 mo during y 1, every 3–4 mo during y 2–3, then every 6 mo during years 4–5, then annually”

SCL-6

- **Footnote “k,”** “See Principles of Supportive Care (SCL-D)” was added after all “Palliative symptom management” statements.
- **Footnote “v,”** “See Principles of Palliative Care (PAL-1)” was added after all “Palliative symptom management” statements.
- **For “PS 0-2,”** “or” was removed from between “Consider subsequent systemic therapy” and “Palliative symptom management, including localized RT to symptomatic sites”.

(SCL-A) Signs and Symptoms of Small Cell Lung Cancer

- **A new section was added:** “Signs and Symptoms of Small Cell Lung Cancer”

(SCL-B) Principles of Pathologic Review

- **A new section was added:** “Principles of Pathologic Review”

Updates in Version 1.2018 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2017 include:

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

- A footnote was removed: “Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664-672.”

[\(SCL-D\) Principles of Supportive Care](#)

- Syndrome of inappropriate antidiuretic hormone
 - ▶ Sub-bullet 5 was revised: “Vasopressin receptor inhibitors (conivaptan, tolvaptan) *for refractory hyponatremia*”

[\(SCL-E\) Principles of Systemic Therapy \(1 of 3\)](#)

- Extensive stage (maximum of 4–6 cycles)
 - ▶ Bullet 7 was revised: “Cisplatin 30 mg/m² *days 1, 8* and irinotecan 65 mg/m² *days 1, 8*”
 - ▶ Footnote “†” was added: “If not used as original regimen, may be used as therapy for primary progressive disease.”
- Subsequent systemic therapy
 - ▶ Footnote “‡” was added: “Subsequent systemic therapy refers to second-line and beyond therapy.”
- Relapse ≤6 mo, PS 0-2: nivolumab ± ipilimumab
 - ▶ Reference “22” was added: “Hellmann MD, Ott PA, Zugazagoitia J, et al. First report of a randomized expansion cohort from CheckMate 032 [abstract]. *J Clin Oncol* 2017;35: Abstract 8503.”

[\(SCL-E\) Principles of Systemic Therapy \(2 of 3\)](#)

- Limited-stage
 - ▶ Sub-bullet 1 was revised: “For patients receiving ~~initial~~ *adjuvant* therapy, response assessment should occur only after completion of ~~initial~~ *adjuvant* therapy; do not repeat scans to assess response during adjuvant treatment.”

[\(SCL-F\) Principles of Radiation Therapy \(1 of 3\)](#)

- General Principles
 - ▶ Bullet 4 was revised: “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, IMRT/VMAT, IGRT, and motion management strategies. *IMRT is preferred over 3D conformal external-beam RT (CRT) on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT. Quality assurance measures are essential and are covered in the NSCLC guidelines (see NSCL-C).*”
 - ▶ Reference “1” was added: “Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* 2017;35:56-62.”
- Limited Stage
 - ▶ Bullet 5 was revised: “Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established; 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). When BID fractionation is used, there should be at least a 6-hour inter-fraction interval to allow for repair of normal tissue. If using once-daily RT, higher doses of 60–70 Gy should be used. The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks; accrual to an experimental concomitant boost arm has closed. *The European CONVERT trial demonstrated comparable overall survival and toxicity between 45 Gy (BID) and 66 Gy (daily).*”
 - ▶ Reference 20 was added: “Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol* 2017;18:1116-1125.”

Updates in Version 1.2018 of the NCCN Guidelines for Small Cell Lung Cancer from Version 3.2017 include:

[\(SCL-F\) Principles of Radiation Therapy \(2 of 3\)](#)

• Extensive stage

- ▶ **Bullet 1 modified:** “Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC ~~that responds~~ with CR or good response to systemic therapy. Studies have demonstrated that consolidative thoracic RT *up to definitive doses* is well tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients. The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions), in patients with extensive stage SCLC that responded to systemic therapy demonstrated significantly improved 2-year overall survival and six-month PFS, although the protocol-defined primary endpoint of one-year overall survival was not significantly improved. *Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.*”
- ▶ **Bullet 2 was added:** “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.”
- ▶ **Reference 24 was added:** “Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer– Authors reply. *Lancet* 2015;385:1292-1293.”

• Prophylactic Cranial Irradiation (PCI)

- ▶ **Bullet 1 modified:** “In patients with limited-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1). In patients with extensive-stage SCLC that has responded to systemic therapy, PCI decreases brain metastases. *A randomized trial conducted by the EORTC found improved overall survival with PCI. However, while a Japanese randomized trial conducted by the EORTC found that in patients who had no brain metastases on baseline MRI, improved overall survival with PCI did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection. results from a Japanese randomized trial found no improved overall survival in patients who had MRI to confirm absence of brain metastases at baseline.* In patients not receiving PCI, surveillance for metastases by brain imaging should be ~~considered performed.~~”
- ▶ **Bullet 5 was added:** “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.”
- ▶ **Reference 28 was updated:** “Takahashi T, Yamanaka T, Takashi S et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:663-671.”
- ▶ **Reference 31 was added:** “Brown PD, Pugh S, Laack NN, et al. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* 2013;10:1429-1437.”

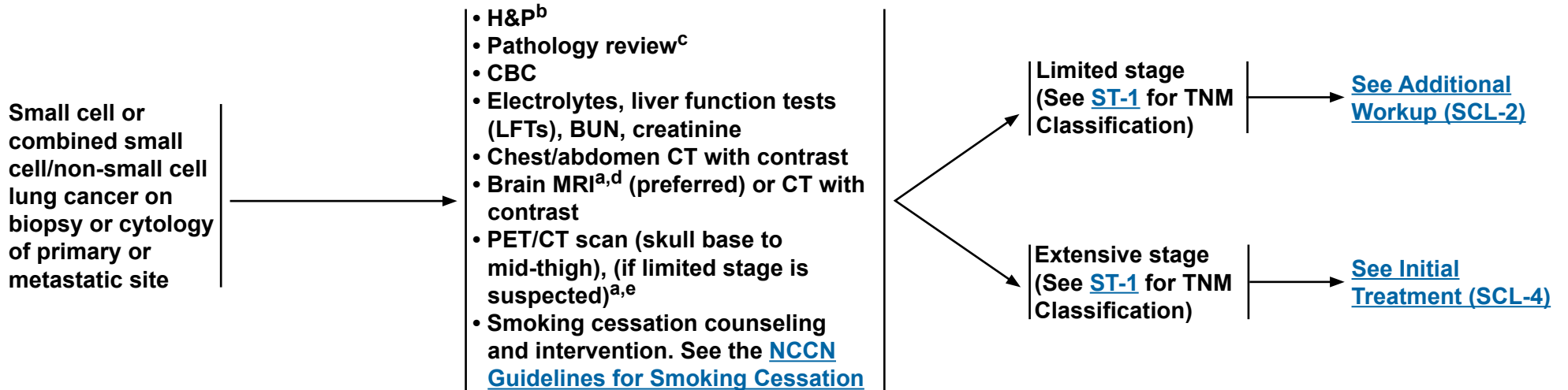
• Brain Metastases

- ▶ **Bullet 1 modified:** “Brain metastases should be treated with WBRT rather than stereotactic radiotherapy/radiosurgery (SRT/SRS) alone, because these patients tend to develop multiple CNS metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients. ~~SRS may also be considered; is preferred if feasible,~~ especially if there has been a long-time interval from initial diagnosis to occurrence of brain metastases and there is no uncontrolled extracranial disease.”

DIAGNOSIS

INITIAL EVALUATION^a

STAGE



^aIf 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 \(SCL-B\).](#)

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

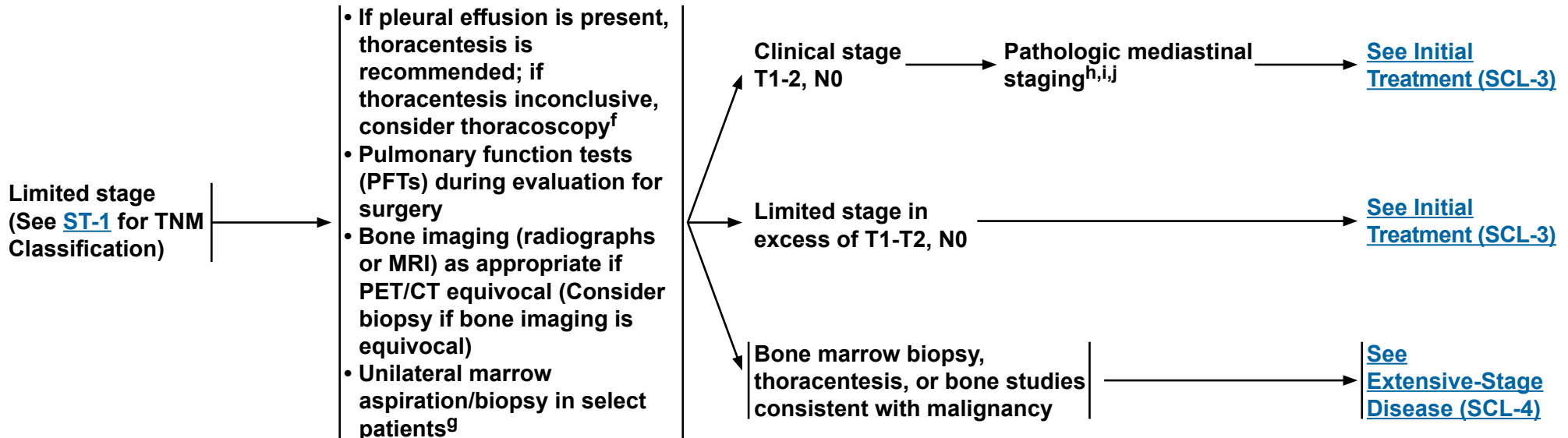
^eIf PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage.

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.

STAGE

ADDITIONAL WORKUP



^fWhile 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.

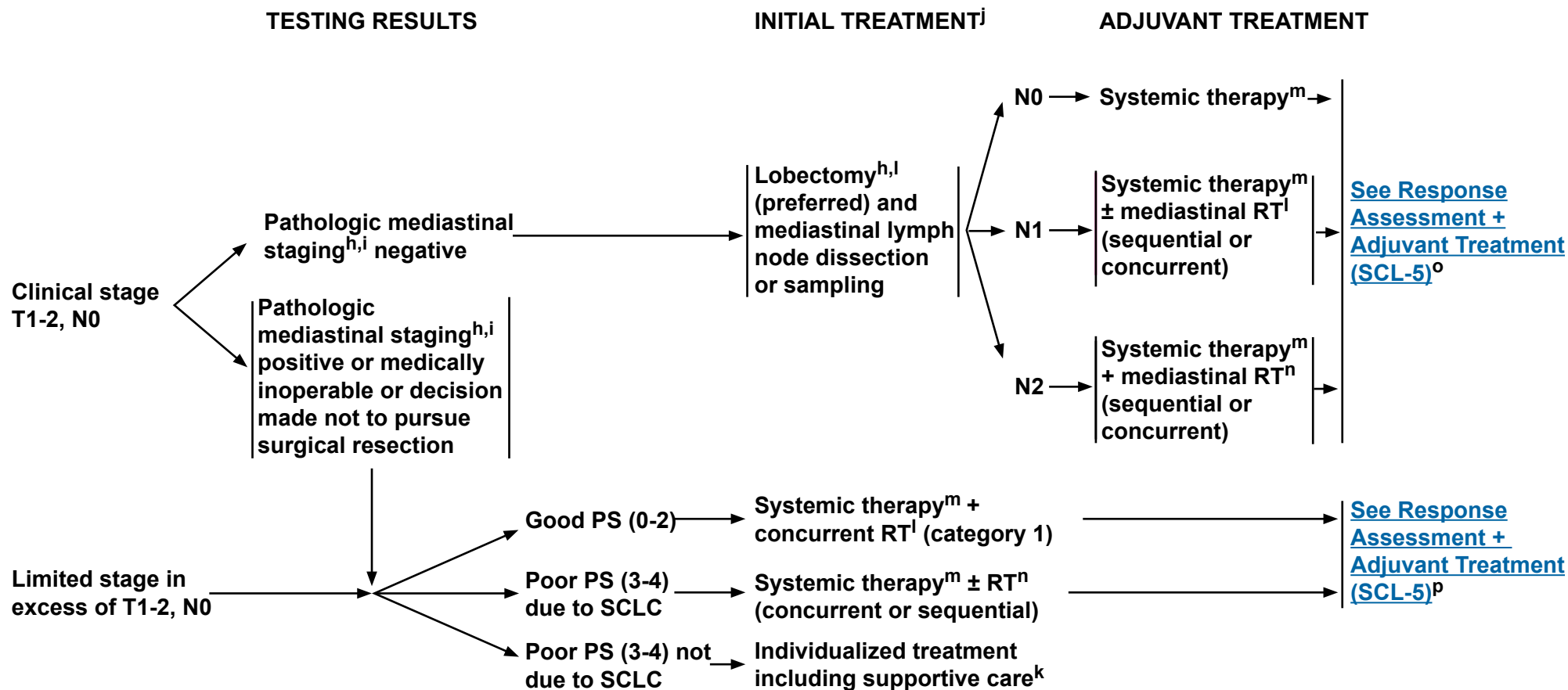
^gSelection criteria include: nucleated red blood cells (RBCs) on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration.

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

ⁱMediastinal 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.

^jPathologic 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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^hSee Principles of Surgical Resection (SCL-C).

ⁱMediastinal 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.

^kSee Principles of Supportive Care (SCL-D).

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

^mSee Principles of Systemic Therapy (SCL-E).

ⁿSee Principles of Radiation Therapy (SCL-F).

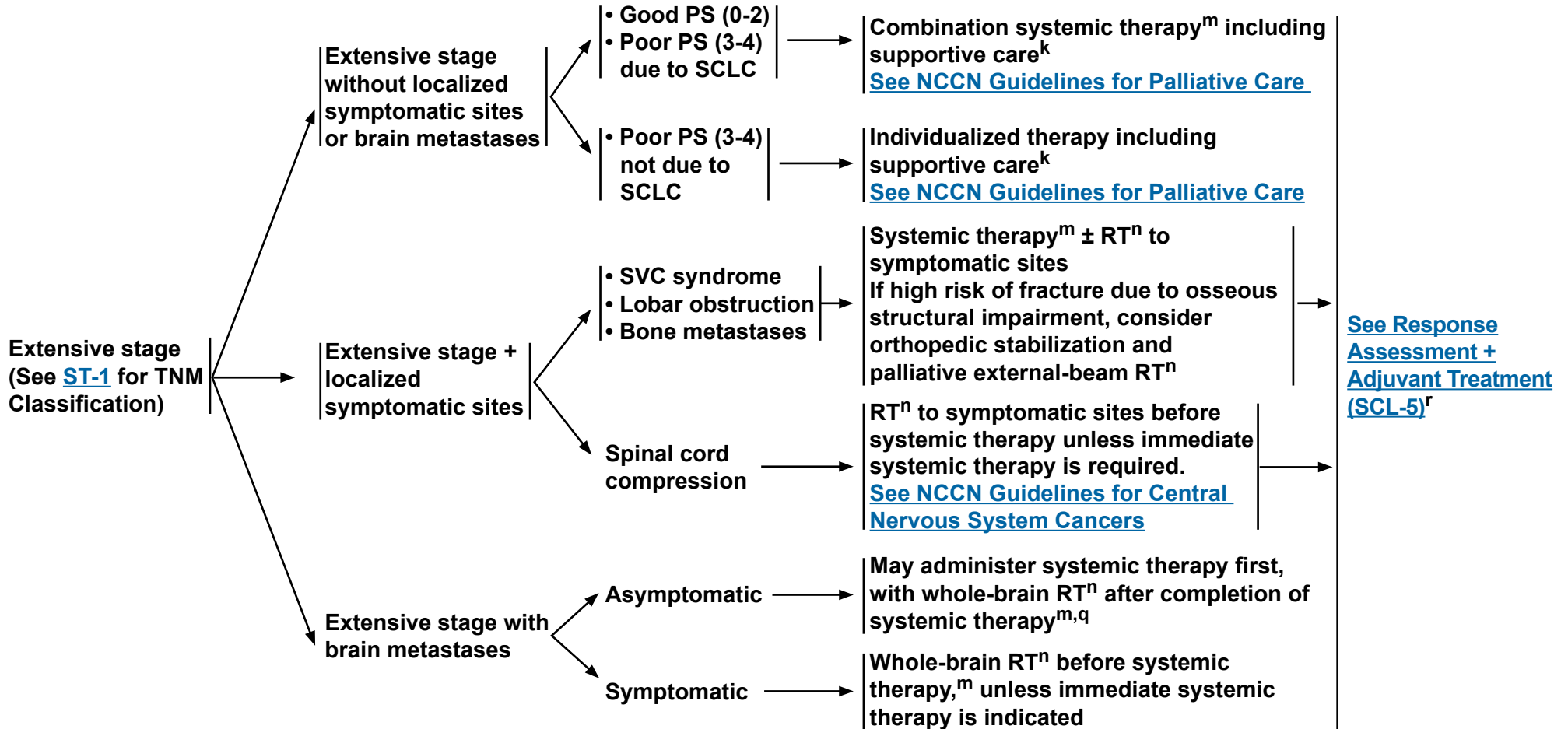
^oFor patients receiving adjuvant therapy, response assessment should occur only after completion of adjuvant therapy (SCL-5); do not repeat scans to assess response during adjuvant treatment.

^pFor patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy (SCL-5); 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 CT with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy (SCL-5).

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STAGE

INITIAL TREATMENT^k



^kSee Principles of Supportive Care (SCL-D).

^mSee Principles of Systemic Therapy (SCL-E).

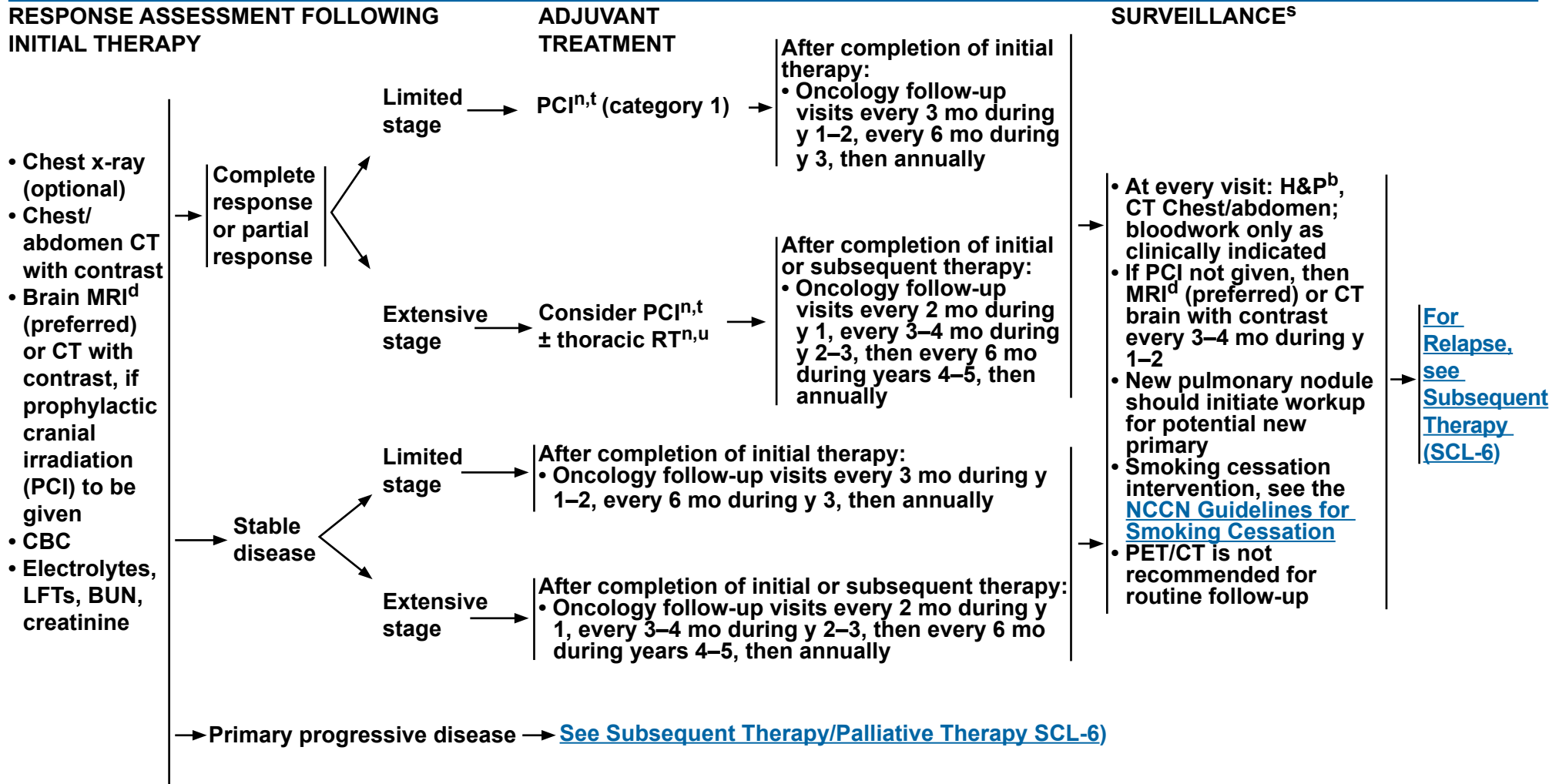
ⁿSee Principles of Radiation Therapy (SCL-F).

^qFor patients with asymptomatic brain metastases receiving systemic therapy before whole-brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy (SCL-5).

^rDuring systemic therapy, response assessment by chest/abdomen CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-5).

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

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

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

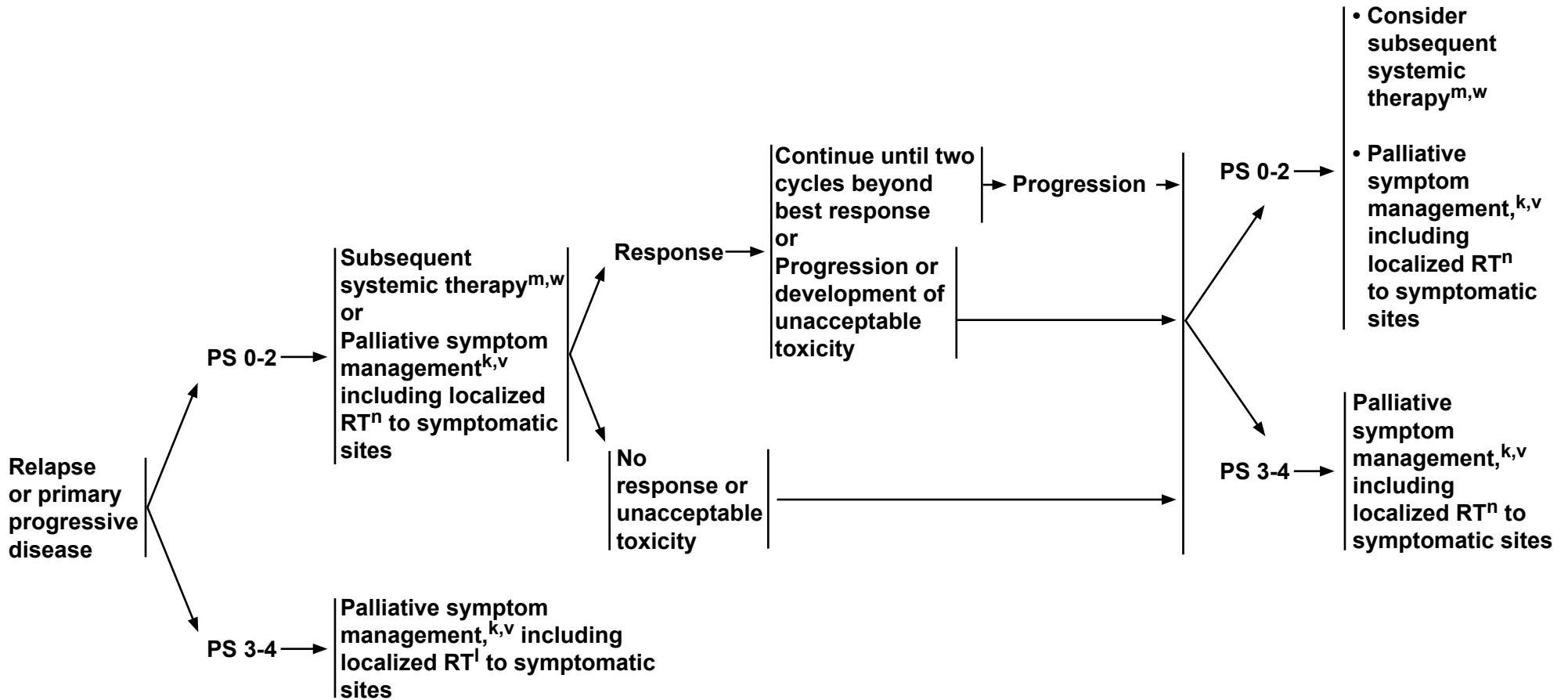
^sSee [NCCN Guidelines for Survivorship](#).

^tNot recommended in patients with poor performance status or impaired neurocognitive function.

^uSequential radiotherapy 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



^kSee Principles of Supportive Care (SCL-D).

^mSee Principles of Systemic Therapy (SCL-E).

ⁿSee Principles of Radiation Therapy (SCL-F).

^vSee Principles of Palliative Care (PAL-1).

^wResponse assessment by chest/abdomen 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 (1 of 2)

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—post-obstructive 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 aorto-pulmonary 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
- Superior vena cava 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

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

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SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER (2 of 2)

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
 - ▶ SIADH:
 - ◇ Ectopic vasopressin (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 ACTH secretion
 - ◇ Weight gain, moon facies, hypertension, hyperglycemia, generalized weakness
 - ◇ High serum cortisol and ACTH, hypernatremia, hypokalemia, alkalosis
- Neurologic: All specific syndromes are rare
 - ▶ Subacute cerebellar degeneration [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

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

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 2)

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
- Small cell lung cancer (SCLC) is a poorly differentiated neuroendocrine tumor. 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}

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 (TTF1) 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

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 PATHOLOGIC REVIEW (2 of 2) - References

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PRINCIPLES OF SURGICAL RESECTION

- **Stage I SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients with disease in excess of T1-2, N0 do not benefit from surgery.¹**
- **Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging) may be considered for surgical resection.**
 - ▶ **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.**
 - ▶ **Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative systemic therapy.² Patients without nodal metastases should be treated with systemic therapy alone. Patients with nodal metastases should be treated with postoperative concurrent systemic therapy and mediastinal radiation therapy (RT).**
- **Because PCI can improve both disease-free and overall survival in patients with SCLC who have complete or partial response, PCI is recommended after adjuvant systemic therapy in patients who have undergone a complete resection.³ PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.⁴**

¹Lad T, Piantadosi S, Thomas P, et al. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. *Chest* 1994;106:320S-3S.

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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 (<http://www.ahrq.gov/clinic/tobacco/5steps.htm>)
 - ▶ [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 radiotherapy (category 1 for not using GM-CSF).¹**
- **Syndrome of inappropriate antidiuretic hormone**
 - ▶ Fluid restriction
 - ▶ Saline infusion for symptomatic patients
 - ▶ Antineoplastic therapy
 - ▶ Demeclocycline
 - ▶ Vasopressin receptor inhibitors (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 Carcinomatous/Lymphomatous Meningitis](#)
- **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* (1 of 3)

Systemic therapy as primary or adjuvant therapy:

- **Limited stage (maximum of 4–6 cycles):**
 - ▶ Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3¹
 - ▶ Cisplatin 80 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3²
 - ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3³
 - ▶ During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).
 - ▶ The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).⁴
- **Extensive stage (maximum of 4–6 cycles):[†]**
 - ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3⁵
 - ▶ Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3⁶
 - ▶ Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3⁷
 - ▶ Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3⁸
 - ▶ Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15⁹
 - ▶ Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15¹⁰
 - ▶ Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8¹¹

Subsequent systemic therapy:[‡]

- **Clinical trial preferred.**
 - **Relapse ≤6 mo, PS 0-2:**
 - ▶ Topotecan PO or IV¹²⁻¹⁴
 - ▶ Irinotecan¹⁵
 - ▶ Paclitaxel^{16,17}
 - ▶ Docetaxel¹⁸
 - ▶ Temozolomide^{19,20}
 - ▶ Nivolumab ± ipilimumab^{21,22}
 - ▶ Vinorelbine^{23,24}
 - ▶ Oral etoposide^{25,26}
 - ▶ Gemcitabine^{27,28}
 - ▶ Cyclophosphamide/doxorubicin/vincristine (CAV)¹²
 - ▶ Bendamustine (category 2B)²⁹
 - **Relapse >6 mo: original regimen^{30,31}**
- Consider dose reduction or growth factor support for patients with PS 2

[Response Assessment SCL-E 2 of 3](#)

[References on SCL-E 3 of 3](#)

*The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.

[†]If not used as original regimen, may be used as therapy for primary progressive disease.

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

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PRINCIPLES OF SYSTEMIC THERAPY (2 of 3)

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.
- ▶ 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 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 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 whole-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 CT with contrast should occur after every 2–3 cycles of systemic therapy.

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PRINCIPLES OF SYSTEMIC THERAPY (3 of 3)

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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 planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3D conformal RT. Multiple fields should be used, with all fields treated each day.
- 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, IMRT/VMAT, IGRT, and motion management strategies. IMRT is preferred over 3D conformal external-beam RT (CRT) on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.¹ Quality assurance measures are essential and are covered in the NSCLC guidelines ([see NSCL-C](#)).
- Useful references include the ACR Appropriateness Criteria at: <http://www.acr.org/quality-safety/appropriateness-criteria>

Limited Stage:

- Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.² RT should start early, with cycle 1 or 2 of systemic therapy (category 1).³ A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.⁴
- Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of radiotherapy 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.⁵ 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%).⁶⁻¹¹ ENI has been omitted in current prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial).
- 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.^{8,12}
- Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established; 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).^{13,14} When BID fractionation is used, there should be at least a 6-hour inter-fraction interval to allow for repair of normal tissue. If using once-daily RT, higher doses of 60–70 Gy should be used.¹⁵⁻¹⁸ 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; accrual to an experimental concomitant boost arm¹⁹ has closed. The European CONVERT trial demonstrated comparable overall survival and toxicity between 45 Gy (BID) and 66 Gy (daily).²⁰

[See Extensive Stage, Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation, Brain Metastases on SCL-F 2 of 3](#)

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

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PRINCIPLES OF RADIATION THERAPY

Extensive Stage:

- Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC with CR or good response to systemic therapy. 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.^{21,22} 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 PFS, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.²³ 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.²⁴
- 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.

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 longer 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 (PCI):

- In patients with limited-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).^{25,26} In patients with extensive-stage SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI. However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI²⁷ did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection.²⁸ In patients not receiving PCI, surveillance for metastases by brain imaging should be performed.
- 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.^{29,30}
- 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 ($P = .009$).³⁰ 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.³¹

Brain Metastases:

- Brain metastases should be treated with WBRT rather than stereotactic radiotherapy/radiosurgery (SRT/SRS) alone, because these patients tend to develop multiple CNS metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.^{32,33} SRS is preferred if feasible, especially if there has been a long-time interval from initial diagnosis to occurrence of brain metastases and there is no uncontrolled extracranial disease.^{34,35}
- Recommended dose for WBRT is 30 Gy in 10 daily fractions.

[See General Principles, Limited Stage \(SCL-F 1 of 3\)](#)

[References on
SCL-F 3 of 3](#)

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PRINCIPLES OF RADIATION THERAPY

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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: AJCC (7th edition) 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: AJCC (7th edition) Stage IV (T any, N any, M 1a/b), 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., 2016

Definitions of TNM

T Primary Tumor

- TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumor
Tis Carcinoma in situ:
Tis (AIS): adenocarcinoma
Tis (SCIS): squamous cell carcinoma
T1 Tumor 3 cm or less 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); the uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified as T1a
T1mi Minimally invasive adenocarcinoma
T1a Tumor 1 cm or less in greatest dimension
T1b Tumor more than 1 cm but not more than 2 cm in greatest dimension
T1c Tumor more than 2 cm but not more than 3 cm in greatest dimension
T2 Tumor more than 3 cm but not more than 5 cm; or tumor with any of the following features (T2 tumors with these features are classified T2a if 4 cm or less or if size cannot be determined and as T2b if greater than 4 cm but not larger than 5 cm):
• Involves main bronchus regardless of distance to the carina, but without involving the carina
• Invades visceral pleura
• Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, either involving part of the lung or the entire lung
T2a Tumor more than 3 cm but not more than 4 cm in greatest dimension
T2b Tumor more than 4 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm but not more than 7 cm in greatest dimension or one that directly invades any of the following: parietal pleura (PL3), chest wall (including superior sulcus tumors), phrenic nerve, parietal pericardium; or associated separate tumor nodule(s) in the same lobe as the primary
T4 Tumors more than 7 cm or one that invades any of the following: diaphragm, mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe to that of the primary

N Regional Lymph Nodes

- NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Metastasis to 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

- M0 No distant metastasis
M1 Distant metastasis
M1a Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural or pericardial effusion; most pleural (pericardial) effusions with lung cancer are due to tumor; in a few patients, however, multiple microscopic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate; where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging descriptor
M1b Single extrathoracic metastasis in a single organ and involvement of a single distant (nonregional) node
M1c Multiple extrathoracic metastases in one or several organs

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Anatomic Stage/Prognostic Groups

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,b,c	N1	M0
	T2a,b	N1	M0
	T3	N0	M0
Stage IIIA	T1a,b,c	N2	M0
	T2a,b	N2	M0
	T3	N1	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a,b,c	N3	M0
	T2a,b	N3	M0
	T3	N2	M0
	T4	N2	M0
Stage IIIC	T3	N3	M0
	T4	N3	M0
Stage IVA	Any T	Any N	M1a
	Any T	Any N	M1b
Stage IVB	Any T	Any N	M1c

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Discussion

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.

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Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).^{1,2} In 2017, an estimated 29,654 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 algorithms 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 Tumors, available at www.nccn.org).

The *Summary of the Guidelines Updates* section in the SCLC algorithm describes the most recent revisions, which have been incorporated into this revised Discussion (see *Summary* in this Discussion and the NCCN Guidelines for Small Cell Lung Cancer). For the 2018 update, 2 new sections were added to the NCCN Guidelines for Small Cell Lung Cancer: 1) *Principles of Pathologic Review*; and 2) *Signs and Symptoms of Small Cell Lung Cancer*. Other changes for the 2018 update are outlined in the summary updates. 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

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.^{7,8} In patients with extensive-stage disease, chemotherapy 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 NCCN Guidelines for Small Cell Lung Cancer and *Staging* in this Discussion). Surgery is only appropriate for few patients (2%–5%) with surgically resectable stage I SCLC.¹⁰ 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).¹¹ Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.¹² 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 used resource for medical literature and indexes only 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 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 on the NCCN webpage (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 NCCN Guidelines for Small Cell Lung Cancer).¹³ 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).¹⁴ 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.¹³⁻¹⁵ 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.¹³

Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea.¹⁶ Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. For the 2018 update, the NCCN Panel 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 NCCN Guidelines for Small Cell Lung Cancer). 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 Tumors, available at www.nccn.org).^{17,18}

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.¹⁹⁻²¹ 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.^{22,23} 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.²⁴

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.^{25,26} In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates).²⁷ 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 NCCN Guidelines for Small Cell Lung Cancer).²⁷⁻²⁹ Hyponatremia usually improves after successful treatment for SCLC.

Pathology

For the 2018 update, the NCCN Panel added a new section on pathology to the SCLC Guidelines (see *Principles of Pathologic Review* in the NCCN Guidelines for Small Cell Lung Cancer). The WHO classification system is used to classify lung tumors.³⁰⁻³² SCLC is a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.^{17,33} The cells are round, oval, or spindle-shaped; nuclear molding is prominent.³⁴ The mitotic count is high in SCLC when compared with the count in atypical and typical carcinoids. The classic and distinctive histology on hematoxylin and eosin (H&E) may be sufficient for identifying SCLC in good-quality histologic samples; it is a poorly differentiated tumor that is categorized as a high-grade neuroendocrine carcinoma.¹⁷

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 Tumors, available at www.nccn.org).^{30,35} Up to 30% of specimens from patients with SCLC reveal areas of NSCLC differentiation (mainly large cell carcinoma);³⁴ 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.^{36,37} 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.^{17,35,38} 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).^{17,39-41} Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin.¹⁷ 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.⁴² Ki-67 immunostaining is useful for distinguishing SCLC from carcinoid tumors.^{30,35,43}

Staging

The NCCN Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the older Veterans Administration (VA) scheme for SCLC.^{6,44} 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.⁴⁵ 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.^{6,44,46} 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 were published in late 2016 (8th edition) and became effective on January 1, 2018 (see *Staging* in the NCCN Guidelines for Small Cell Lung Cancer).^{47,48} The SCLC panel will continue to use both the VA and the TNM systems for staging SCLC after January 1, 2018.

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, 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 NCCN Guidelines for Small Cell Lung Cancer). *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/b) 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.

Since 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.⁴⁴ 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.⁴⁷

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).^{46,49} However, once a patient has been found to have extensive-stage disease, further staging is optional, 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.^{6,44} 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.⁵⁰⁻⁵² PET/CT is superior to PET alone.⁵² 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.⁴⁶ 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).⁵³ 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.^{46,51,54} 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 who seem to have clinical stage T1-2, N0 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 thoracoscopy (VATS).^{55,56}

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 scan) 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.^{57,58}

Treatment

Systemic Therapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment. Adjuvant chemotherapy is recommended for those who have undergone surgical resection. For patients with limited-stage SCLC in excess of T1-2, N0 and with good PS (0–2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1).^{8,59,60} For patients with extensive-stage disease, chemotherapy alone is the recommended treatment, although radiotherapy may be used in select patients for

palliation of symptoms (see *Initial Treatment* and *Principles of Systemic Therapy* in the NCCN Guidelines for Small Cell Lung Cancer; see NCCN Guidelines for Palliative Care, available at www.nccn.org). In patients with extensive-stage disease and brain metastases, chemotherapy can be given either before or after whole-brain radiotherapy depending on whether the patient has neurologic symptoms (see *Initial Treatment* in the NCCN Guidelines for Small Cell Lung Cancer).^{9,61} If systemic therapy is given first, whole-brain radiotherapy is administered after completion of systemic therapy.

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 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 chemotherapy and again at completion of therapy. Scanning for brain metastases 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 should occur after every 2 cycles of chemotherapy and again at completion of therapy.

Many single-agent and combination chemotherapy regimens have been shown to be active in SCLC. Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see

Principles of Systemic Therapy in the NCCN Guidelines for Small Cell Lung Cancer).⁶² This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.⁶³⁻⁶⁵ EP plus concurrent thoracic radiotherapy is the recommended therapy (category 1) for patients with limited-stage disease in excess of T1-2, N0.^{59,60,66,67}

In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.⁶⁸ 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.⁶⁹ In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.⁷⁰ However, the use of carboplatin carries a greater risk of myelosuppression.⁷¹ Small randomized trials in patients with SCLC have suggested similar efficacy of cisplatin and carboplatin as did a retrospective analysis in patients with extensive-stage disease.^{70,72,73} A meta-analysis of individual patient data from 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.⁷⁴ 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.

Many other combinations have been evaluated in patients with extensive-stage disease, with little consistent evidence of benefit when compared with EP. The combination of irinotecan and a platinum agent initially appeared to be better than EP. A small phase 3 trial performed in Japan reported that patients with extensive-stage SCLC who were

treated with irinotecan plus cisplatin experienced a median survival of 12.8 months compared with 9.4 months for patients treated with EP ($P=.002$).⁷⁵ In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.⁷⁵ However, 2 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.^{76,77}

A phase 3 randomized trial ($n = 220$) found that median overall survival was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs. 7.1 months, $P = .04$).⁷⁸ Based on these findings, the carboplatin and irinotecan regimen is an option in the NCCN Guidelines for patients with extensive-stage disease. A meta-analysis suggested an improvement in PFS and overall survival with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.⁷⁹ However, this meta-analysis was not performed using data from individual patients. In addition, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN Panel continues to recommend etoposide plus platinum regimens for patients with either limited-stage or extensive-stage SCLC.

In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with EP plus thoracic radiotherapy, whereas in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone. Unfortunately, median survival rates are only 14 to 20 months and 9 to 11 months for patients with limited-stage and extensive-stage disease, respectively. After appropriate treatment, the 2-year survival rate is approximately 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease.⁸⁰ Thoracic radiotherapy improves local control rates by 25% in patients with limited-stage disease and is

associated with improved survival.^{59,60} 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.^{81,82}

Many 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 2 trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP showed a modest survival advantage for patients with extensive-stage disease.^{83,84} 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.⁸⁵ Two recent phase 3 randomized trials have confirmed the lack of improvement in survival with 3-drug chemotherapy regimens compared to platinum plus etoposide in patients with extensive-stage SCLC. One of these studies assessed the combination of ifosfamide, etoposide, and epirubicin versus EP, while the other evaluated carboplatin plus etoposide with or without palifosfamide.^{86,87} 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.⁸⁸ 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.⁸⁹ A meta-analysis reported that maintenance chemotherapy did not prolong overall survival.⁹⁰

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.⁹¹ However, randomized trials have failed to show improved PFS or overall survival with this approach.^{92,93}

Multidrug cyclic weekly therapy was designed to increase dose intensity. Early phase 2 results of this approach were promising, although favorable patient selection was of some concern.^{94,95} Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.⁹⁶⁻⁹⁹ The role of higher-dose therapy 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 doses when compared with those given conventional doses of the same agents.¹⁰⁰ In general, however, randomized trials comparing conventional 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.¹⁰¹⁻¹⁰⁴ 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.¹⁰⁵

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,¹⁰⁶ maintenance of dose intensity with growth factors does not prolong disease-free or overall survival.^{107,108} Thus, the routine use of growth factors at the initiation of systemic therapy is not recommended.

The benefits of antiangiogenic therapy are being 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.¹⁰⁹⁻¹¹² However, at least 2 randomized trials have demonstrated no survival benefit for the addition of bevacizumab to recommended chemotherapy.^{113,114} Currently, the NCCN Panel does not recommend use of bevacizumab in patients with SCLC.

Although immune checkpoint inhibitors have demonstrated activity in a variety of cancers, including SCLC, a recent phase 3 randomized trial reported that the addition of ipilimumab to etoposide with either cisplatin or carboplatin for first-line therapy did not improve either overall survival or PFS in patients with extensive-stage SCLC.¹¹⁵ However, immune checkpoint inhibitors are an option for subsequent systemic therapy (see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion). 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 lung cancer increases with age. Although the median age at diagnosis is 70 years, elderly patients are under-represented in clinical trials.¹¹⁶ Although advanced chronologic age adversely affects tolerance to treatment, the functional status of an individual patient is much more useful than age in guiding clinical decision making (see the

NCCN Guidelines for Older Adult Oncology, available at www.nccn.org). Older patients who are functional in terms of the ability to perform activities of daily living should be treated with combination chemotherapy (and radiotherapy, if indicated).^{117,118} 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. 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).^{119,120} A recent retrospective analysis in 8637 elderly patients with limited-stage disease reported that chemoradiation increased survival when compared with chemotherapy alone.¹¹⁷ Several other strategies have been evaluated in elderly patients with SCLC.^{73,121–123} 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.¹²³ However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in this population.¹²⁴ 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.¹²⁵

Second-Line and Beyond (Subsequent) Systemic Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.^{126,127} 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.¹²⁸ 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.^{6,128,129} Response assessment should occur after every 2 to 3 cycles of subsequent systemic therapy 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, 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 NCCN Guidelines for Small Cell Lung Cancer).^{130–133} These agents are listed in order of preference in the NCCN Guidelines. Ifosfamide was recently deleted, because panel members no longer use this agent.

A randomized phase 3 trial compared single-agent intravenous topotecan with the combination regimen CAV.¹³⁴ Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase 3 trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).¹³⁵ Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who relapse after initial response to chemotherapy. Either oral or intravenous topotecan may be used,

because efficacy and toxicity seem to be similar with either route.^{135,136} 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.¹³⁷ Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.^{138,139}

The NCCN Panel recently added recommendations for nivolumab and nivolumab plus ipilimumab (both are category 2A) as options for subsequent therapy for patients who have relapsed 6 months or less after primary therapy. Nivolumab and ipilimumab are novel immunotherapeutic agents that stimulate the immune system and thus have different mechanisms of action when compared with recommended cytotoxic chemotherapy.¹⁴⁰ These recommendations are based on a recent phase 1/2 trial in which patients received either nivolumab alone or various doses of nivolumab with ipilimumab for relapsed SCLC.¹⁴¹ 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 the SCLC has a lower rate of PD-L1 expression than NSCLC.¹⁴¹ 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.¹⁴²

Immunotherapeutic agents, such as nivolumab and ipilimumab, are associated with 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.^{143,144} For patients with immune-mediated adverse events, high-dose corticosteroids are generally recommended based on the severity of the reaction. Nivolumab and ipilimumab should be withheld or discontinued for severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O⁶-methylguanine-DNA methyltransferase (MGMT).^{131,145} A recent phase 3 trial (JCOG0605) from Japan in patients with sensitive relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival (median, 18.2 months; 95% CI, 15.7–20.6) when compared with topotecan (12.5 months, 10.8–14.9; hazard ratio [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.¹⁴⁶ Amrubicin is an active drug in patients with relapsed or refractory SCLC.¹⁴⁷⁻¹⁵⁰ However, grade 3 to 4 toxicity, primarily neutropenia, is common.^{151,152} 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.¹⁵³

The optimal duration of subsequent systemic therapy has not been fully explored, although its duration 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, progression of disease, or development of unacceptable toxicity. Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0-2.

Radiotherapy

The *Principles of Radiation Therapy* in the algorithm describe the radiation doses, target volumes, and normal tissue dose volume constraints for mainly limited-stage SCLC, and include references to support the recommendations; prophylactic cranial irradiation (PCI) and treatment of brain metastases are also discussed (see the NCCN Guidelines for Small Cell Lung Cancer). The American College of Radiology (ACR) Appropriateness Criteria® are a useful resource.¹⁵⁴

The *Principles of Radiation Therapy* 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. A few reports have suggested that stereotactic ablative radiotherapy (SBRT) might be useful for select patients with limited-stage SCLC; however, there are insufficient data to make a recommendation.^{155,156}

Thoracic Radiotherapy

The addition of thoracic radiotherapy has improved survival for patients with limited-stage disease. 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 survival when compared with chemotherapy alone.^{59,60} 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.⁶⁸

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 with longer survival.¹⁵⁷ 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.^{158,159} Another meta-analysis in patients with limited-stage SCLC showed that survival was improved with more rapid completion of the chemo/RT regimen (start of any chemotherapy until the end of radiotherapy [SER]).¹⁶⁰ A recent meta-analysis of individual patient data from 12 trials (2668 patients) reported that early concurrent chemo/RT 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.¹⁶¹

Radiation Fractionation

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.¹⁶² In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiotherapy using a total dose of 45 Gy delivered either twice a day over 3 weeks or

once a day 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 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.¹⁶² A significant criticism of this trial is that the doses of radiation in the 2 arms were not biologically equivalent.

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.¹⁶³ However, split-course radiotherapy may be less efficacious because of interval tumor regrowth between courses. Overall, patients selected for combined modality treatment that incorporates twice-daily radiotherapy must have an excellent PS and good baseline pulmonary function. A recent randomized phase 3 trial (CONVERT) assessed 45 Gy twice daily compared with 66 Gy once daily in patients with limited-stage SCLC.¹⁶⁴ 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% [129/266] vs. 38% [101/263]; $P = .05$).

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

Radiation for Limited-Stage SCLC

For limited-stage disease in excess of T1-2, N0, 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 (category 1). 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 NCCN Guidelines for Small Cell Lung Cancer).¹⁶⁵⁻¹⁶⁷

The minimum 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 it is less toxic (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Non-Small Cell Lung Cancer).¹⁶⁸⁻¹⁷³ More advanced technologies may also be used when needed (eg, 4D-CT) (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer). 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 (ICRU).^{174,175} However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.^{167,176}

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 NCCN Guidelines for Small Cell Lung Cancer).¹⁷⁷⁻¹⁷⁹

Thoracic Radiation for Extensive-Stage SCLC

Based on the results of a randomized trial by Jeremic et al,¹⁸⁰ 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 chemotherapy. In this trial, 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.¹⁸⁰ The investigators found that the addition of radiotherapy resulted in improved median overall survival (17 vs. 11 months). In patients with extensive-stage SCLC who responded to chemotherapy, a phase 3 trial by Slotman et al (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.¹⁸¹ A trial in 32 patients who received consolidative thoracic RT reported that only 16% (5/32) of patients had symptomatic chest recurrences.¹⁸² 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.¹⁸³

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.¹⁸⁴ A meta-analysis of all randomized PCI trials (using data from individual patients) reported a 25% decrease in the 3-year incidence of brain metastases, from 58.6% in the control group to 33.3% in the PCI-treated group.¹⁸⁵ 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 survival in patients treated with PCI, from 15.3% in the control group to 20.7% in the PCI group.¹⁸⁵ 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.¹⁸⁶

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.¹⁸⁷ 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 recent randomized phase 3 trial from Japan, which found that median overall survival was not improved in patients receiving PCI (11.6 months [95% CI, 9.5–13.3]) when compared with observation (13.7 months [95% CI, 10.2–16.4]) (HR, 1.27; 95% CI, 0.96–1.68; $P = .094$).¹⁸⁸ 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 these conflicting trial results, the NCCN Panel softened the recommendation for PCI in patients with extensive-stage disease to *consider* PCI for the 2018 update. The NCCN Panel also added detailed imaging recommendations for patients who do not have PCI (see *Surveillance* in this Discussion). Therefore, depending on individual patient factors, either PCI or close MRI surveillance appear to be reasonable options for patients with extensive-stage SCLC and good response to initial chemotherapy.

Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrently with chemotherapy.^{189,190} Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.^{191,192} Older age (>60 years) has also been associated with chronic neurotoxicity.¹⁹³ 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.¹⁹⁴ Patients receiving memantine had a longer time to cognitive decline (HR, 0.78; 95% CI, 0.62–0.99, $P = .01$). For the 2018 update, the NCCN Panel recommends that memantine be considered for patients receiving PCI.

Before the decision is made to administer PCI, a balanced discussion between the patient and physician is necessary.¹⁹⁵ PCI is a category 1 recommendation 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.^{187,191} PCI is also recommended for all patients who have had a complete resection (see *Principles of*

Surgical Resection in the NCCN Guidelines for Small Cell Lung Cancer). The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions (2.5 Gy/fraction) (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer).^{185,187,196} The NCCN Panel feels that a shorter course of PCI may be appropriate (eg, 20 Gy in 5 fractions) for selected patients with extensive-stage disease.¹⁸⁷ Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with lower doses (25 Gy).^{193,196} PCI should not be given concurrently with systemic therapy, and high total radiotherapy dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity.¹⁹³ Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.^{192,196} After the acute toxicities of initial 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. For the 2018 update, the NCCN Panel added detailed brain imaging recommendations to the algorithm based on the recent Japanese trial.¹⁸⁸

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 NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Non-Small Cell Lung Cancer, available at www.NCCN.org).¹⁹⁷⁻¹⁹⁹ 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 NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Central Nervous System Cancers, available at www.NCCN.org.²⁰⁰ 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.¹⁸⁹ The recommended dose for whole-brain radiotherapy is 30 Gy in 10 daily fractions.²⁰⁰ In patients who develop brain metastases after PCI, stereotactic radiosurgery (preferred) or whole-brain radiotherapy may be considered.^{201,202}

Surgical Resection of Stage I 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 should only be considered for patients with stage I (T1-2, N0) SCLC in whom mediastinal staging has confirmed that mediastinal lymph nodes are not involved.²⁰³ Data show that patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery.²⁰⁴ Note that fewer than 5% of patients with SCLC have true stage I disease.²⁰⁵

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.²⁰⁴ 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 2 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 data regarding the benefit of surgery are from retrospective reviews.^{203,206-210} 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, leading to the general recommendation that surgery should only be considered in those with stage I disease. Interpretation of these results is limited by the selection bias inherent in retrospective reviews and by the variable use of chemotherapy and radiotherapy. A recent meta-analysis describes the evidence from currently available randomized trials in greater detail.²¹¹

Analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.^{10,212} 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 all patients with clinical stage I (T1-2, N0) SCLC who are being considered for surgical resection, occult nodal disease should be ruled out through mediastinal staging before resection.²¹³ If resection is performed, the NCCN Panel favors lobectomy and does not feel that segmental or wedge resections are appropriate for patients with SCLC. After complete resection, adjuvant chemotherapy or chemoradiation is recommended.^{191,208,214,215} 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 NCCN Guidelines for Small Cell Lung Cancer).

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. PCI should be considered after adjuvant therapy in select patients, because it may improve survival (see *Prophylactic Cranial Irradiation* in this Discussion and *Adjuvant Treatment* in the NCCN Guidelines for Small Cell Lung Cancer).¹⁸⁵ The NCCN Panel recommends new baseline disease assessment after adjuvant therapy.

Surveillance

For the 2018 update, the NCCN Panel revised the schedule for follow-up examinations (see *Surveillance* in the NCCN Guidelines for Small Cell Lung Cancer); the frequency of surveillance decreases during subsequent years because of the declining risk of recurrence.²¹⁶ The NCCN Panel also added a recommendation for brain MRI (preferred) or CT with contrast every 3 to 4 months for 2 years for patients who do not receive PCI. PET/CT is not recommended for routine follow-up. If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors are a frequent occurrence in patients who are cured of SCLC.^{217,218} 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).²¹⁹⁻²²¹ Former smokers should be encouraged to remain abstinent. For the 2018 update, the NCCN Panel also recommends the survivorship guidelines for appropriate patients (see the NCCN Guidelines for Survivorship, available at www.NCCN.org).

Summary

Revisions for the 2018 update are described in this Discussion and outlined in the algorithm (see *Summary of the Guidelines Updates* in the NCCN Guidelines for Small Cell Lung Cancer). For example, 2 new sections were added to the NCCN Guidelines: 1) *Principles of Pathologic Review*; and 2) *Signs and Symptoms of Small Cell Lung Cancer*. The section on *Principles of Radiation Therapy* was revised. The NCCN Panel prefers IMRT over 3-D conformal external-beam RT for concurrent chemotherapy/RT. For patients with limited-stage SCLC, the optimal dose and schedule of RT have not been established. However, a recent trial (CONVERT) reported that overall survival and toxicity are comparable when using either 45 Gy (twice daily) or 66 Gy (daily). Panel members softened the recommendation for adjuvant PCI in patients with extensive-stage disease to *consider* PCI based on a recent Japanese trial. For patients who do not have adjuvant PCI, the NCCN Panel added detailed imaging recommendations for surveillance based on this trial.

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