



National Comprehensive  
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Small Cell Lung Cancer

Version 1.2019 — April 9, 2019

[NCCN.org](https://www.nccn.org)

[Continue](#)



**\*Gregory P. Kalemkerian, MD/Chair †**  
University of Michigan  
Rogel Cancer Center

**\*Billy W. Loo, Jr., MD, PhD/Vice Chair §**  
Stanford Cancer Institute

**Wallace Akerley, MD †**  
Huntsman Cancer Institute  
at the University of Utah

**Albert Attia, MD §**  
Vanderbilt-Ingram Cancer Center

**Michael Bassetti, MD §**  
University of Wisconsin Carbone Cancer Center

**Collin Blakely, MD, PhD †**  
UCSF Hellen Diller Family  
Comprehensive Cancer Center

**Yanis Bumber, MD, PhD †**  
Fox Chase Cancer Center

**Alberto Chiappori, MD †**  
Moffitt Cancer Center

**Thomas A. D'Amico, MD ¶**  
Duke Cancer Institute

**Roy Decker, MD, PhD §**  
Yale Cancer Center/Smilow Cancer Hospital

**M. Chris Dobelbower, MD, PhD §**  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Afshin Dowlati, MD †**  
Case Comprehensive Cancer Center/University  
Hospitals Seidman Cancer Center and  
Cleveland Clinic Taussig Cancer Institute

**Robert J. Downey, MD ¶**  
Memorial Sloan Kettering Cancer Center

**Anna Farago, MD, PhD †**  
Massachusetts General  
Hospital Cancer Center

**Charles Florsheim**  
Patient Advocate

**Apar Kishor P. Ganti, MD †**  
Fred & Pamela Buffett Cancer Center

**Kathryn A. Gold, MD †**  
UC San Diego Moores Cancer Center

**John C. Grecula, MD §**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Christine L. Hann, MD, PhD †**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

**James A. Hayman, MD, MBA §**  
University of Michigan  
Rogel Cancer Center

**Wade Iams, MD †**  
Vanderbilt-Ingram Cancer Center

**Marianna Koczywas, MD † ‡ P**  
City of Hope  
National Medical Center

**Robert E. Merritt, MD ¶**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

**Nisha Mohindra, MD †**  
Robert H. Lurie Comprehensive Cancer  
Center of Northwestern University

**Julian Molina, MD, PhD ‡ P**  
Mayo Clinic Cancer Center

**Cesar A. Moran, MD ≠**  
The University of Texas  
MD Anderson Cancer Center

**Daniel Morgensztern, MD †**  
Siteman Cancer Center at Barnes-  
Jewish Hospital and Washington  
University School of Medicine

**Saraswati Pokharel, MD ≠**  
Roswell Park Cancer Institute

**David C. Portnoy, MD ‡ †**  
The University of Tennessee  
Health Science Center

**Deborah Rhodes, MD P**  
Mayo Clinic Cancer Center

**Chad Rusthoven, MD §**  
University of Colorado Cancer Center

**Jacob Sands, MD †**  
Dana Farber/Brigham and Women's  
Cancer Center

**Rafael Santana-Davila, MD †**  
Fred Hutchinson Cancer Research Center/  
Seattle Cancer Care Alliance

### NCCN

**Lydia Hammond, MBA**  
**Miranda Hughes, PhD**

† Medical oncology  
¶ Surgery/Surgical oncology  
§ Radiation oncology  
‡ Hematology/Hematology oncology  
P Internal medicine  
≠ Pathology  
\*Discussion Section Writing Committee

**Continue**

[NCCN Guidelines Panel Disclosures](#)



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

- [Initial Evaluation and Staging \(SCL-1\)](#)
- [Limited Stage, Workup and Treatment \(SCL-2\)](#)
- [Extensive Stage, Initial Treatment \(SCL-5\)](#)
- [Response Assessment Following Initial Therapy and Surveillance \(SCL-6\)](#)
- [Progressive Disease: Subsequent Therapy and Palliative Therapy \(SCL-7\)](#)

- [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](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2019.



Updates in Version 1.2019 of the NCCN Guidelines for Small Cell Lung Cancer from Version 2.2018 include:

### SCL-2

- **Additional Workup**
  - ▶ **Bullet 2 was modified to include "or definitive RT."**
  - ▶ **Clinical stage was modified: "T1-2, N0" changed to "I-IIA (T1-2,N0,M0)." (Also for SCL-3)**
  - ▶ **Limited stage was modified: "in excess of T1-T2, N0" changed to "IIB-IIIB (T3-4,N0,M0; T1-4,N1-3,M0)." (Also for SCL-4)**

### SCL-3

- **Testing Results option was split into two different pathways: "Medically inoperable or decision made not to pursue surgical resection" and "Pathologic mediastinal staging positive."**
- **Initial Treatment**
  - ▶ **Medically inoperable or decision made not to pursue surgical resection**
    - ◊ **"SABR or Systemic therapy + concurrent RT (See SCL-4)" was added.**
- **Adjuvant Treatment**
  - ▶ **Medically inoperable or decision made not to pursue surgical resection**
    - ◊ **"Systemic therapy" was added.**

### SCL-6

- **Response Assessment Following Initial Therapy**
  - ▶ **Bullet 2 was revised: "Brain MRI (preferred) or CT with contrast, if prophylactic cranial irradiation (PCI) to be given."**
  - ▶ **"Chest x-ray (optional)" was removed.**
- **Adjuvant Treatment**
  - ▶ **Extensive stage bullet was split into two statements: "Consider PCI or MRI brain surveillance" and "Consider thoracic RT."**
- **Surveillance**
  - ▶ **Bullet 1 was added: "Provide Survivorship Care Plan after completion of initial therapy."**
  - ▶ **Bullet 3 was revised: "If PCI not given, then MRI (preferred) or CT brain with contrast every 3–4 mo during y 1–2" was changed to "MRI (preferred) or CT brain with contrast every 3–4 months during y 1, then every 6 months during y 2 (regardless of PCI status)."**
- **Footnote t was revised by adding the second sentence: "Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close surveillance should be carefully discussed with these patients."**

### SCL-7

- **Progressive Disease**
  - ▶ **Subsequent Therapy/Palliative Therapy statement revised after response: "Continue until *progression* ~~two cycles beyond best response or~~ **Progression** or development of unacceptable toxicity."**



Updates in Version 1.2019 of the NCCN Guidelines for Small Cell Lung Cancer from Version 2.2018 include:

### [SCL-A \(2 of 2\)](#)

- Signs and symptoms of paraneoplastic syndromes

- ▶ Neurologic

- ◊ First sub-bullet was added: "If paraneoplastic neurologic syndrome is suspected, consider obtaining comprehensive paraneoplastic antibody panel."

### [SCL-B](#)

- Pathologic Evaluation

- ▶ Bullet 3 was revised: "...poorly differentiated neuroendocrine ~~tumor~~ carcinoma."

### [SCL-C](#)

- Principles of Surgical Resection

- ▶ Bullet 1 was revised: "Stage I-IIA SCLC..."

- ▶ Bullet 2 was revised from "Patients with disease in excess of T1-2, N0 do not benefit from surgery" to "Patients most likely to benefit from surgery are those with SCLC that is clinical stage I-IIA (T1-2,N0,M0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging)."

- ◊ Sub-bullet 2 was added: "For patients undergoing definitive surgical resection, the preferred operation is lobectomy with mediastinal lymph node dissection."

- ▶ Bullet 3 (and sub-bullets) were condensed from "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." and "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." to: "Patients who undergo complete resection (~~preferably by a lobectomy with either mediastinal nodal dissection or sampling~~) should be treated with postoperative systemic therapy. 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)."

- ▶ Bullet 4 was revised from "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. PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning." to "The benefit of PCI is unknown in patients who have undergone complete resection for pathologic stage I-IIA (T1-2,N0,M0) SCLC. These patients have a lower risk of developing brain metastases than patients with more advanced, limited-stage SCLC, and may not benefit from PCI. However, PCI may have a benefit in patients who are found to have pathologic stage IIB or III SCLC after complete resection; therefore, PCI is recommended in these patients after adjuvant systemic therapy. PCI is not recommended in patients with poor performance status or impaired neurocognitive function."



Updates in Version 1.2019 of the NCCN Guidelines for Small Cell Lung Cancer from Version 2.2018 include:

### **SCL-E (1 of 3)**

- **Systemic therapy as primary or adjuvant therapy**

- ▶ **Limited Stage (maximum of 4-6 cycles):**

- ◊ "Cisplatin 75 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3" was added.
- ◊ "Cisplatin 25 mg/m<sup>2</sup> days 1, 2, 3 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3" was added.
- ◊ "Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3" was removed.

- ▶ **Extended Stage (maximum 4-6 cycles):**

- ◊ "Carboplatin AUC 5 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg (category 1, preferred)" was added.
- ◊ Footnote § was added: "Regimen not recommended for relapsed disease in patients on maintenance atezolizumab at time of relapse. For patients who relapse after > 6 months of atezolizumab maintenance therapy, recommend re-treatment with carboplatin + etoposide alone."

- **Subsequent systemic therapy**

- ▶ Relapse ≤6 mo, PS 0-2: pembrolizumab added as a category 2A recommendation.

### **SCL-F (1 of 3)**

- **Principles of Radiation Therapy**

- ▶ "I. General Treatment Information" section was added.

- ◊ **A. Limited Stage:**

- **Bullet 1 was added:** "Selected patients with stage I-IIA (T1-2,N0,M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative RT (SABR) to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC ([see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C](#))."
- **Bullet 6 was modified and re-formatted to include sub-bullets:** "Dose and schedule: For limited stage SCLC, the optimal dose and schedule of RT have not been established."
  - **Sub-bullet 1 was modified:** "*Based on the randomized phase III trial (INT 0096), ÷ 45 Gy in 3 weeks...*"
  - **Sub-bullet 2 was revised:** "*...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 19 has closed. The European CONVERT trial demonstrated comparable overall survival and toxicity between 45 Gy (BID) and 66 Gy (daily). The randomized, phase III European CONVERT trial did not demonstrate superiority of 66 Gy (once daily) over 45 Gy (BID), but overall survival and toxicity were comparable.~~*"

### **SCL-F (2 of 3)**

- **IV. Prophylactic Cranial Irradiation (PCI)**

- ▶ **Bullet 5 was revised by adding the second sentence:** "The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening."

- **V. Brain Metastases**

- ▶ **Bullet 1 was revised:** "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.~~"



### DIAGNOSIS

### INITIAL EVALUATION<sup>a</sup>

### STAGE

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

- H&P<sup>b</sup>
- Pathology review<sup>c</sup>
- CBC
- Electrolytes, liver function tests (LFTs), BUN, creatinine
- Chest/abdomen CT with contrast
- Brain MRI<sup>a,d</sup> (preferred) or CT with contrast
- PET/CT scan (skull base to mid-thigh), (if limited stage is suspected)<sup>a,e</sup>
- Smoking cessation counseling and intervention. See the [NCCN Guidelines for Smoking Cessation](#)

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

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

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

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

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

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

<sup>c</sup>See [Principles of Pathologic Review \(SCL-B\)](#).

<sup>d</sup>Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

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

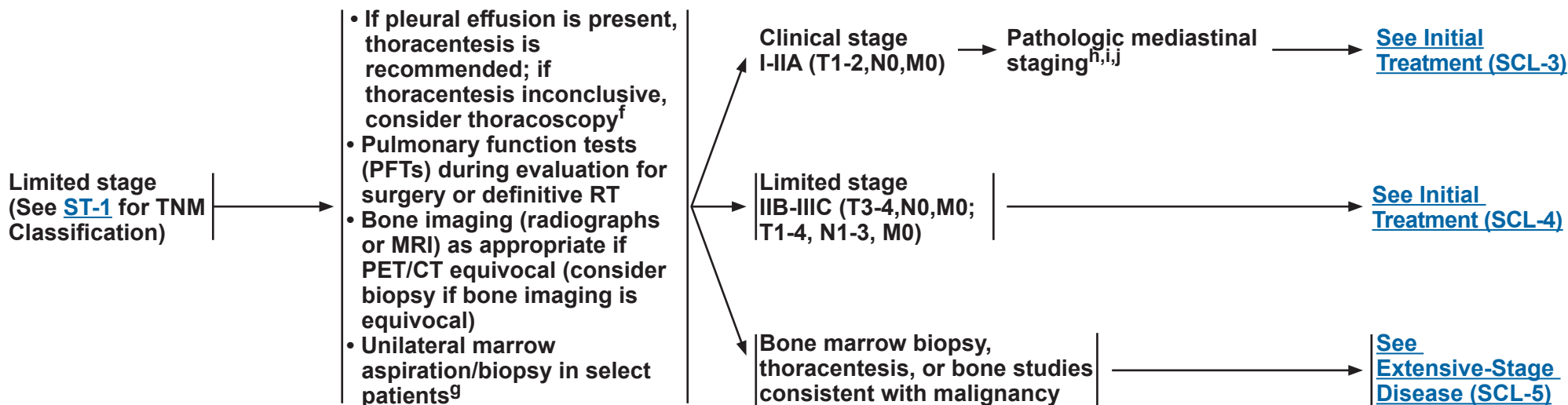
**Note: All recommendations are category 2A unless otherwise indicated.**

**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**



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

<sup>g</sup>Selection criteria include: nucleated red blood cells (RBCs) on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration.

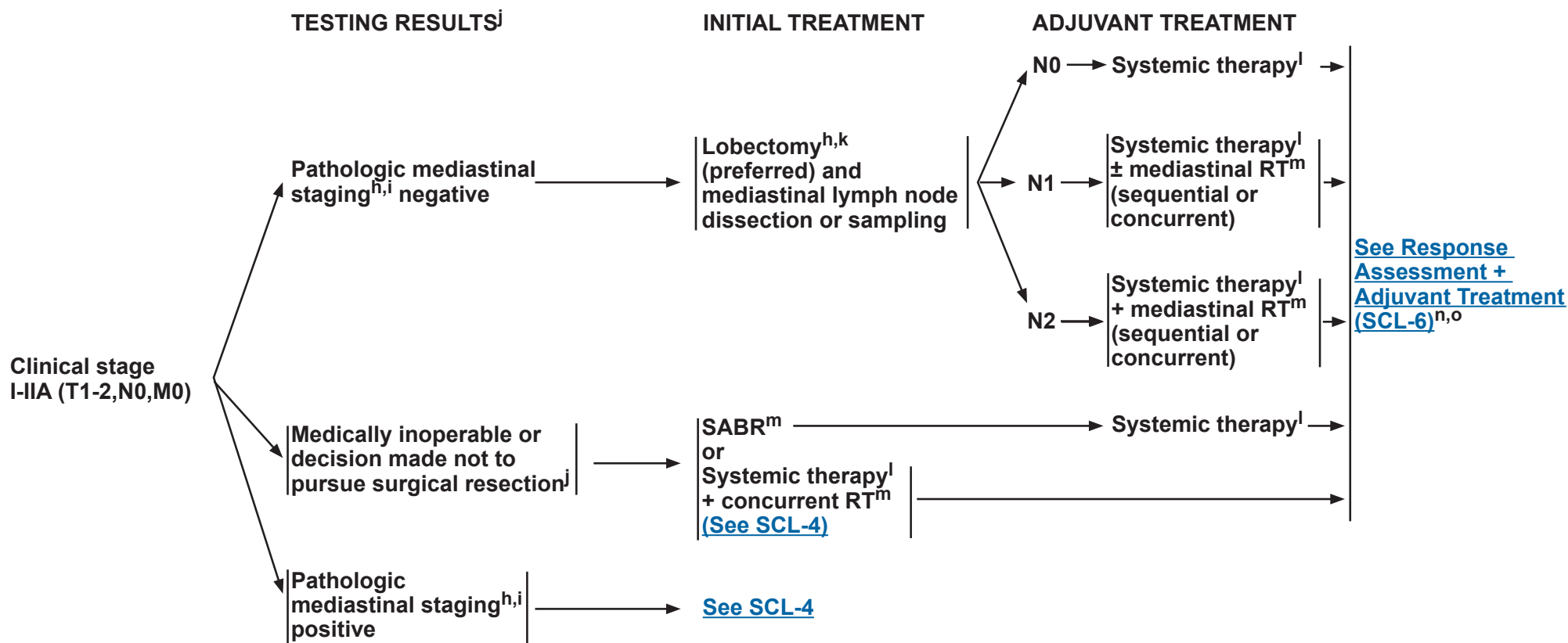
<sup>h</sup>[See Principles of Surgical Resection \(SCL-C\).](#)

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

<sup>j</sup>Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.

**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.**





<sup>h</sup>See Principles of Surgical Resection (SCL-C).

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

<sup>j</sup>Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.

<sup>k</sup>Select patients may be treated with systemic therapy/RT as an alternative to surgical resection.

<sup>l</sup>See Principles of Systemic Therapy (SCL-E).

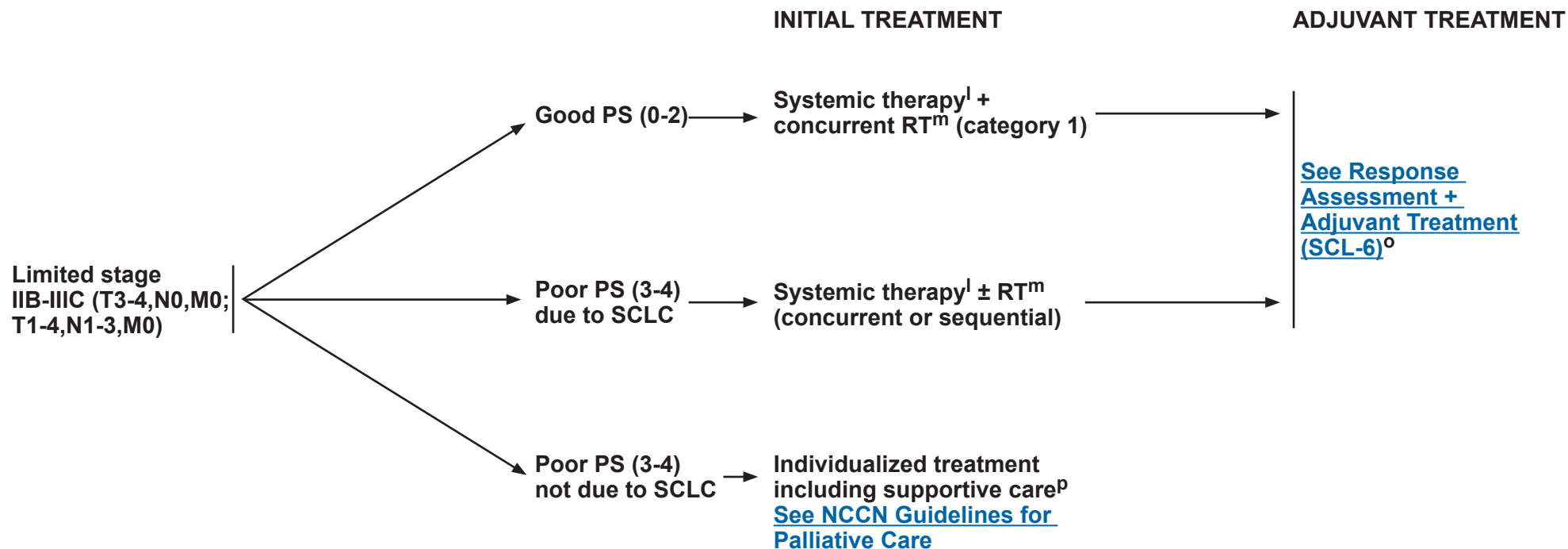
<sup>m</sup>See Principles of Radiation Therapy (SCL-F).

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

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

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

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



<sup>l</sup>[See Principles of Systemic Therapy \(SCL-E\).](#)

<sup>m</sup>[See Principles of Radiation Therapy \(SCL-F\).](#)

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

<sup>p</sup>[See Principles of Supportive Care \(SCL-D\).](#)

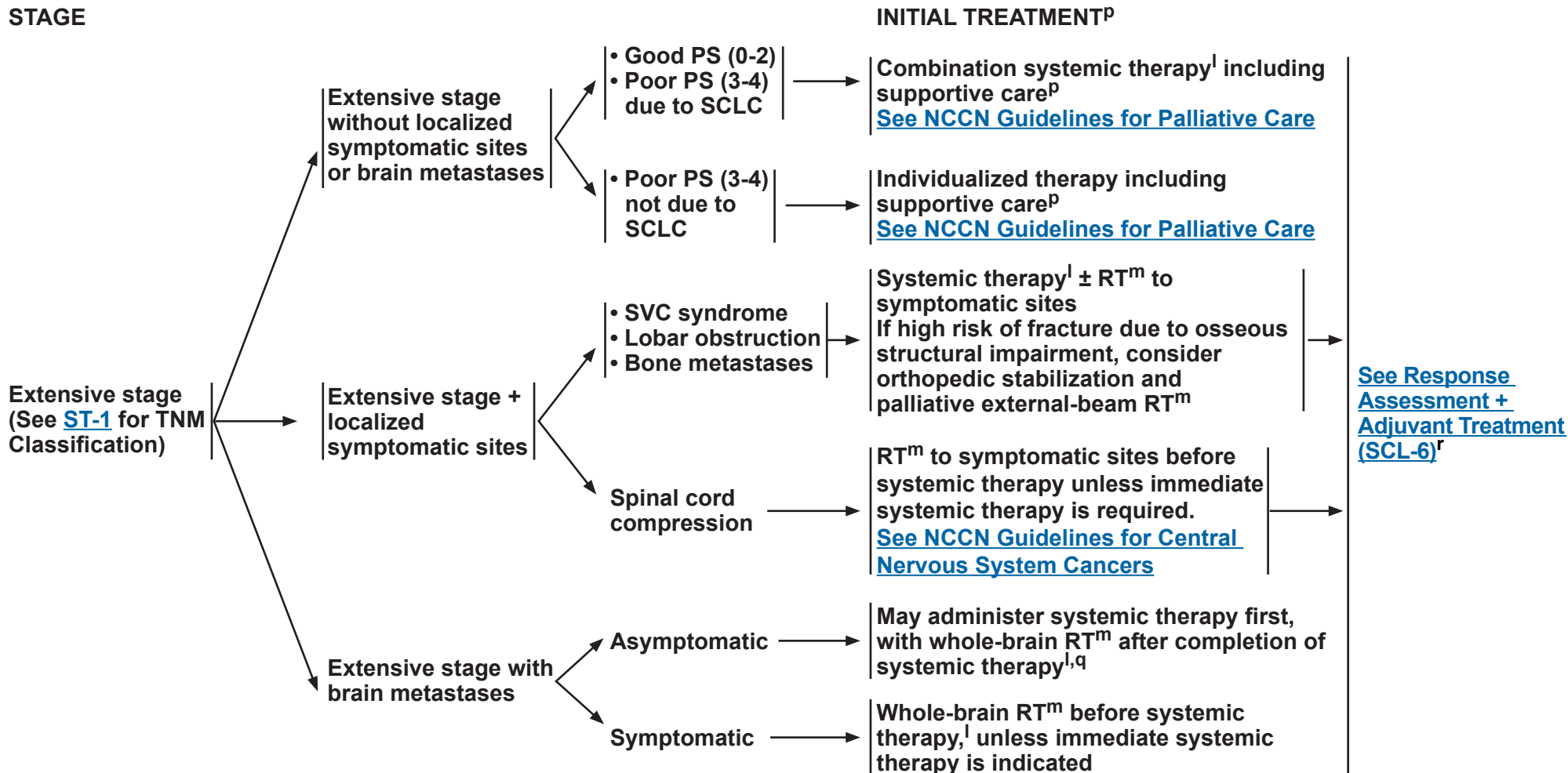
**Note: All recommendations are category 2A unless otherwise indicated.**

**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.**



# NCCN Guidelines Version 1.2019

## Small Cell Lung Cancer



<sup>l</sup>See Principles of Systemic Therapy ([SCL-E](#)).

<sup>m</sup>See Principles of Radiation Therapy ([SCL-F](#)).

<sup>P</sup>See Principles of Supportive Care ([SCL-D](#)).

<sup>q</sup>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 ([SCL-6](#)).

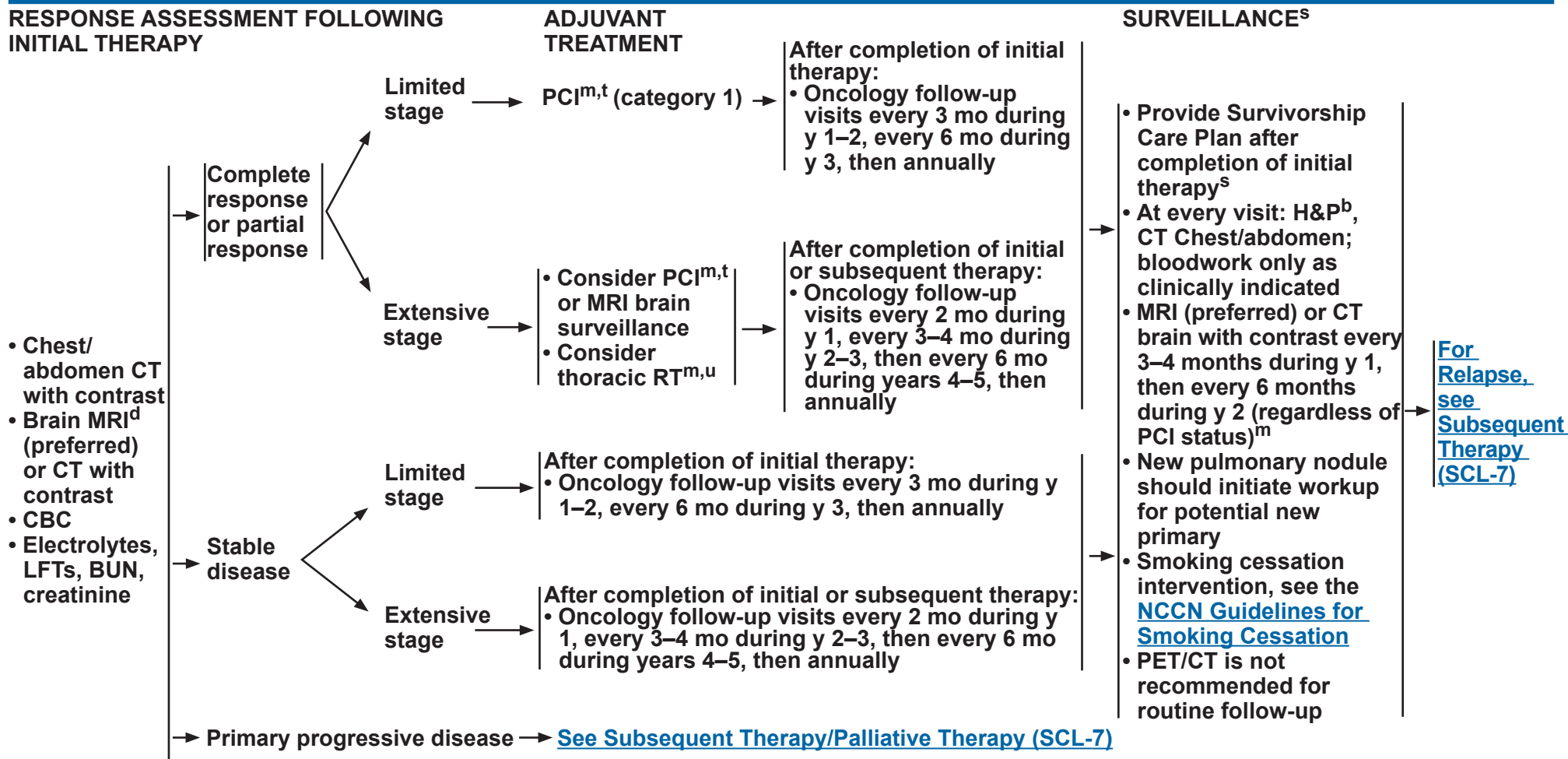
<sup>r</sup>During systemic therapy, response assessment by chest/abdomen CT with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy ([SCL-6](#)).

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



# NCCN Guidelines Version 1.2019

## Small Cell Lung Cancer



[For Relapse, see Subsequent Therapy \(SCL-7\)](#)

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

<sup>d</sup>Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

<sup>m</sup>See [Principles of Radiation Therapy \(SCL-F\)](#).

<sup>s</sup>See [NCCN Guidelines for Survivorship](#).

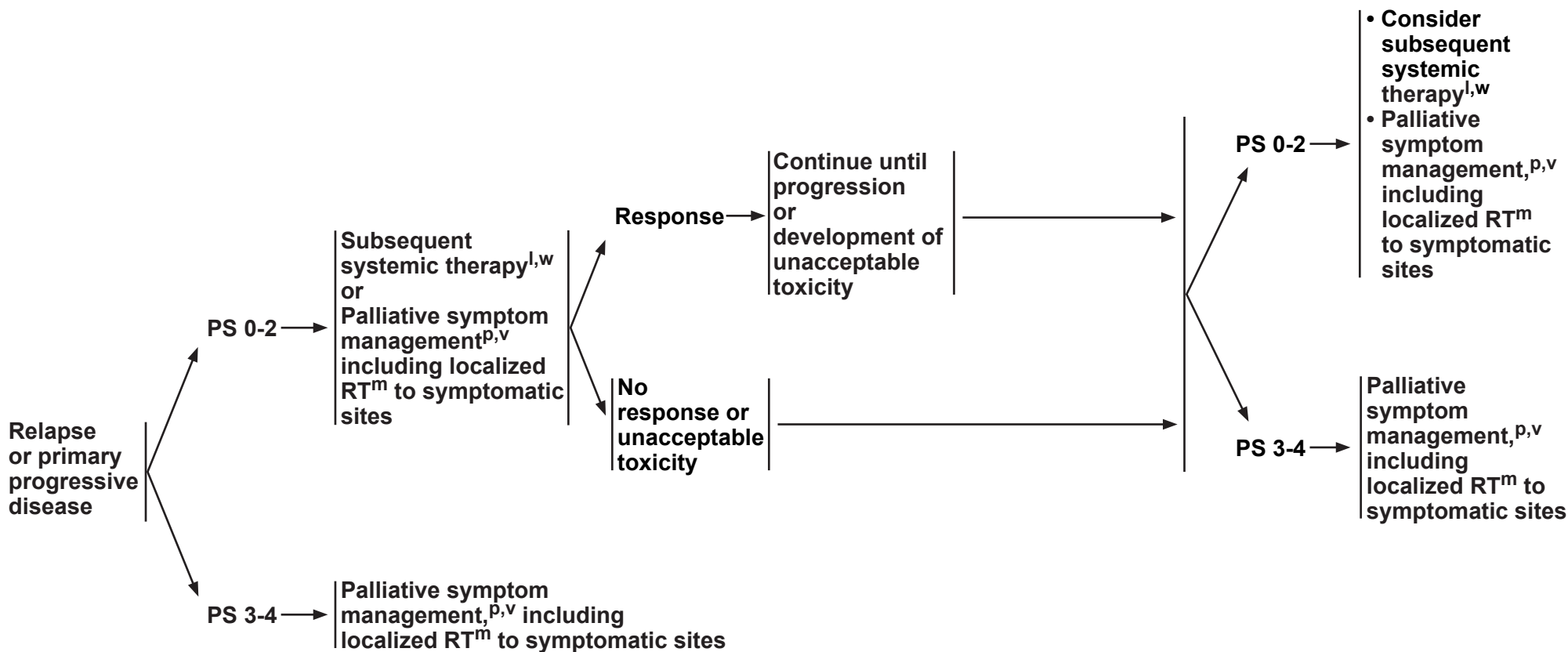
<sup>t</sup>Not recommended in patients with poor performance status or impaired neurocognitive function. Increased cognitive decline after PCI has been observed in older adults (≥60 years) in prospective trials; the risks and benefits of PCI versus close surveillance should be carefully discussed with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

<sup>u</sup>Sequential radiotherapy to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.

**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.

**PROGRESSIVE DISEASE      SUBSEQUENT THERAPY/PALLIATIVE THERAPY**



<sup>l</sup>See Principles of Systemic Therapy (SCL-E).

<sup>m</sup>See Principles of Radiation Therapy (SCL-F).

<sup>p</sup>See Principles of Supportive Care (SCL-D).

<sup>v</sup>See NCCN Guidelines for Palliative Care (PAL-1).

<sup>w</sup>Response assessment by chest/abdomen CT with contrast should occur after every 2–3 cycles of systemic therapy.

**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.



### SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

#### Signs and symptoms due to local primary tumor growth

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

#### Signs and symptoms due to primary tumor invasion or regional lymphatic metastases

- Hoarseness – left vocal cord paralysis due to tumor invasion or lymphadenopathy in the 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.

**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.



### SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

#### Signs and symptoms of paraneoplastic syndromes:

- Presence does not imply metastases or incurability

- Endocrine:

- ▶ Due to ectopic peptide hormone production
- ▶ Usually reversible with successful anti-tumor therapy
- ▶ Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH):
  - ◊ Ectopic vasopressin (ADH) secretion
  - ◊ Clinically significant hyponatremia in 5%–10% of SCLC
  - ◊ Malaise, weakness, confusion, obtundation, volume depletion, nausea
  - ◊ Hyponatremia, euolemia, 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

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

- Hematologic:

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

**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****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.<sup>1-3</sup>
- SCLC is a poorly differentiated neuroendocrine carcinoma. Distinguishing SCLC from other neuroendocrine tumors, particularly typical and atypical carcinoids, is important due to significant differences in epidemiology, genetics, treatment, and prognosis.<sup>4-6</sup>
- 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.<sup>7-9</sup>
  - ▶ The most useful characteristics for distinguishing SCLC from large-cell neuroendocrine carcinoma (LCNEC) are the high nuclear-to-cytoplasmic ratio and paucity of nucleoli in SCLC.
- Careful counting of mitoses is essential, because it is the most important histologic criterion for distinguishing SCLC from typical and atypical carcinoids.
  - ▶ SCLC (>10 mitoses/2 mm<sup>2</sup> field); atypical carcinoid (2–10 mitoses/2 mm<sup>2</sup> field); typical carcinoid (0–1 mitoses/2 mm<sup>2</sup> field)
  - ▶ Mitoses should be counted in the areas of highest activity and per 2 mm<sup>2</sup> field, rather than per 10 high-power fields.
  - ▶ In tumors that are near the defined cutoffs of 2 or 10 mitoses per 2 mm<sup>2</sup>, at least three 2-mm<sup>2</sup> fields should be counted and the calculated mean (rather than the single highest mitotic count) should be used to determine the overall mitotic rate.<sup>1,2</sup>

**Immunohistochemical Staining**

- Immunohistochemistry can be very helpful in diagnosing SCLC in limited samples.<sup>5,7</sup>
  - ▶ Nearly all SCLCs are positive for cytokeratin antibody mixtures with broad reactivity, such as AE1/AE3 and CAM5.2.<sup>1,10</sup>
  - ▶ 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.<sup>11-14</sup>
- 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.<sup>4,5</sup>
  - ▶ The Ki-67 proliferative index in SCLC is typically 50% to 100%.<sup>1</sup>

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

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

[References on  
SCL-B 2 of 2](#)

**SCL-B  
1 OF 2**



### PRINCIPLES OF PATHOLOGIC REVIEW

#### References

- <sup>1</sup>Travis WD, Burke AP, Marx A, Nicholson AG. WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. Lyon: IARC Press. 2015.
- <sup>2</sup>Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. *J Thorac Oncol* 2015;10:1240-1242.
- <sup>3</sup>Travis WD, Brambilla E, Nicholson AG, et al and WHO Panel. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol* 2015;10:1243-1260.
- <sup>4</sup>Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. *J Thorac Oncol* 2014;9:273-284.
- <sup>5</sup>Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. *Am J Surg Pathol* 2005;29:179-187.
- <sup>6</sup>Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. *Endocr Relat Cancer* 2014;21:1-16.
- <sup>7</sup>Travis WD. Advances in neuroendocrine lung tumors. *Ann Oncol* 2010;21:vii65-71.
- <sup>8</sup>Zakowski MF. Pathology of small cell carcinoma of the lung. *Semin Oncol* 2003;30:3-8.
- <sup>9</sup>Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol* 2002;26:1184-1197.
- <sup>10</sup>Masai K, Tsuta K, Kawago M, et al. Expression of squamous cell carcinoma markers and adenocarcinoma markers in primary pulmonary neuroendocrine carcinomas. *Appl Immunohistochem Mol Morphol* 2013;21:292-2977.
- <sup>11</sup>Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217-1223.
- <sup>12</sup>Kaufmann O, Dietel M. Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinomas and other neuroendocrine carcinomas of various primary sites. *Histopathology* 2000;36:415-420.
- <sup>13</sup>Lantuejoul S, Moro D, Michalides RJ, et al. Neural cell adhesion molecules (NCAM) and NCAM-PSA expression in neuroendocrine lung tumors. *Am J Surg Pathol* 1998;22:1267-1276.
- <sup>14</sup>Wick MR. Immunohistology of neuroendocrine and neuroectodermal tumors. *Semin Diagn Pathol* 2000;17:194-203.

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

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

**PRINCIPLES OF SURGICAL RESECTION**

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

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

<sup>2</sup>Yang CJ, Chan DY, Shah SA, et al. Long-term survival after surgery compared with concurrent chemoradiation for node-negative small cell lung cancer. *Ann Surg*: 2018;268:1105-1112.

<sup>3</sup>Yang CE, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population based cohort of patients with early-stage small-cell lung cancer. *J Clin Oncol* 2016;34:1057-1064.

<sup>4</sup>Yang Y, Zhang D, Zhou X, et al. Prophylactic cranial irradiation in resected small cell lung cancer: a systematic review with meta-analysis. *J Cancer* 2018;9:433-439.

<sup>5</sup>Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476-484.

<sup>6</sup>Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy. *Lancet Oncol* 2009;10(5):467-474.

**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 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).<sup>1</sup>**
- **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 Central Nervous System Cancers](#)
- **Pain management:** [See NCCN Guidelines for Adult Cancer Pain](#)
- **Nausea/vomiting:** [See NCCN Guidelines for Antiemesis](#)
- **Psychosocial distress:** [See NCCN Guidelines for Distress Management](#)
- [See NCCN Guidelines for Palliative Care](#) as indicated

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

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

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

**PRINCIPLES OF SYSTEMIC THERAPY\*****Systemic therapy as primary or adjuvant therapy:**

- **Limited stage (maximum of 4–6 cycles):**
  - ▶ Cisplatin 75 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>1</sup>
  - ▶ Cisplatin 25 mg/m<sup>2</sup> days 1, 2, 3 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>1</sup>
  - ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and etoposide 120 mg/m<sup>2</sup> days 1, 2, 3<sup>2</sup>
  - ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>3</sup>
  - ▶ 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).<sup>4</sup>
- **Extensive stage (maximum of 4–6 cycles):**
  - ▶ Carboplatin AUC 5 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3 and atezolizumab 1,200 mg day 1 every 21 days x 4 cycles followed by maintenance atezolizumab 1,200 mg (category 1, preferred)<sup>§,5</sup>
  - ▶ Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>†,6</sup>
  - ▶ Cisplatin 75 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>†,7</sup>
  - ▶ Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 80 mg/m<sup>2</sup> days 1, 2, 3<sup>†,8</sup>
  - ▶ Cisplatin 25 mg/m<sup>2</sup> days 1, 2, 3 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>†,9</sup>
  - ▶ Carboplatin AUC 5 day 1 and irinotecan 50 mg/m<sup>2</sup> days 1, 8, 15<sup>†,10</sup>
  - ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and irinotecan 60 mg/m<sup>2</sup> days 1, 8, 15<sup>†,11</sup>
  - ▶ Cisplatin 30 mg/m<sup>2</sup> days 1, 8 and irinotecan 65 mg/m<sup>2</sup> days 1, 8<sup>†,12</sup>

**Subsequent systemic therapy:‡**

- **Clinical trial preferred.**
  - **Relapse ≤6 mo, PS 0-2:**
    - ▶ Topotecan PO or IV<sup>13-15</sup>
    - ▶ Irinotecan<sup>16</sup>
    - ▶ Paclitaxel<sup>17,18</sup>
    - ▶ Docetaxel<sup>19</sup>
    - ▶ Temozolomide<sup>20,21</sup>
    - ▶ Nivolumab ± ipilimumab<sup>22,23</sup>
    - ▶ Pembrolizumab<sup>24</sup>
    - ▶ Vinorelbine<sup>25,26</sup>
    - ▶ Oral etoposide<sup>27,28</sup>
    - ▶ Gemcitabine<sup>29,30</sup>
    - ▶ Cyclophosphamide/doxorubicin/vincristine (CAV)<sup>12</sup>
    - ▶ Bendamustine (category 2B)<sup>31</sup>
  - **Relapse >6 mo: original regimen<sup>32,33§</sup>**
- 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 SCLC. 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.

§Regimen not recommended for relapsed disease in patients on maintenance atezolizumab at time of relapse. For patients who relapse after >6 months of atezolizumab maintenance therapy, recommend re-treatment with carboplatin + etoposide alone.

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

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



### PRINCIPLES OF SYSTEMIC THERAPY

#### 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.

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

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



**PRINCIPLES OF SYSTEMIC THERAPY**  
**References**

- <sup>1</sup>Favre-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.
- <sup>2</sup>Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340(4):265-271.
- <sup>3</sup>Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol* 2001;12(9):1231-1238.
- <sup>4</sup>Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. *J Clin Oncol* 1995;13:1632-1641
- <sup>5</sup>Horn L, Mansfield A, Szczesna A, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018;379:2220-2229.
- <sup>6</sup>Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small cell lung cancer. *J Clin Oncol* 1999;17(11):3540-3545.
- <sup>7</sup>Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. *J Clin Oncol* 2011;29:2215-2222.
- <sup>8</sup>Niell HB, Herndon JE, Miller AA, et al. Randomized phase III Intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte-colony stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B trial 9732. *J Clin Oncol* 2005;23:3752-3759.
- <sup>9</sup>Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985;3(11):1471-1477.
- <sup>10</sup>Schmittl A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Ann Oncol* 2006;17:663-667.
- <sup>11</sup>Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346(2): 85-91.
- <sup>12</sup>Hanna N, Bunn Jr. PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24(13):2038-2043.
- <sup>13</sup>von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17(2):658-667.
- <sup>14</sup>O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006;24(34):5441-5447.
- <sup>15</sup>Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007;25(15):2086-2092.
- <sup>16</sup>Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; 10:1225-1229.
- <sup>17</sup>Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer* 1998; 77:347-351.
- <sup>18</sup>Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Res* 2006; 26:777-781.
- <sup>19</sup>Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. *Eur J Cancer* 1994; 30A:1058-1060.
- <sup>20</sup>Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. *Clin Cancer Res* 2012;18:1138-1145.
- <sup>21</sup>Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer* 2014;86:237-240.
- <sup>22</sup>Antonia SJ, López-Martin JA, Bendell J, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (Checkmate 032): a multicentre, open-label phase 1/2 trial. *Lancet Oncol* 2016;17:883-895.
- <sup>23</sup>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.
- <sup>24</sup>Chung HC, Lopez-Martin JA, Kao S, et al. Phase 2 study of pembrolizumab in advanced small-cell lung cancer (SCLC): KEYNOTE-158 *J Clin Oncol* 2018; 36: Abstract 8506.
- <sup>25</sup>Jassem J, Karnicka-Mlodkowska H, van Pottelsberghe C, et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. *Eur J Cancer* 1993; 29A:1720-1722.
- <sup>26</sup>Furuse K, Kubo K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. *Oncology* 1996;53:169-172.
- <sup>27</sup>Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer. *Semin Oncol* 1990;17:32-35.
- <sup>28</sup>Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990; 8:1613-1617.
- <sup>29</sup>Van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. *Ann Oncol* 2001;12:557-561.
- <sup>30</sup>Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer. *J Clin Oncol* 2003;21:1550-1555.
- <sup>31</sup>Lammers PE, Shyr Y, Li CI, et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. *J Thorac Oncol* 2014;9:559-562.
- <sup>32</sup>Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol* 1987;23:1409-1411.
- <sup>33</sup>Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol* 1987;23:1697-1699.

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



**PRINCIPLES OF RADIATION THERAPY****I. 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 daily.
- Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, intensity-modulated radiation therapy (IMRT)/volumetric-modulated arc therapy (VMAT), image-guided radiation therapy (IGRT), and motion management strategies. IMRT is preferred over 3D conformal EBRT on the basis of reduced toxicity in the setting of concurrent chemotherapy/RT.<sup>1</sup> 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>

**II. General Treatment Information:****A. Limited Stage:**

- ▶ Selected patients with stage I-IIA (T1-2,N0,M0) SCLC who are medically inoperable or in whom a decision is made not to pursue surgery may be candidates for stereotactic ablative RT (SABR) to the primary tumor followed by adjuvant systemic therapy. Principles of SABR for SCLC are similar to those for NSCLC ([see NCCN Guidelines for Non-Small Cell Lung Cancer: NSCL-C](#)).<sup>2-4</sup>
- ▶ Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.<sup>5</sup> RT should start early, with cycle 1 or 2 of systemic therapy (category 1).<sup>6</sup> A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.<sup>7</sup>
- ▶ 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.<sup>8</sup> 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%).<sup>9-14</sup> 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.<sup>11,15</sup>
- ▶ Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established.
  - ◊ Based on the randomized phase III trial, INT 0096, 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).<sup>16,17</sup> When BID fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
  - ◊ If using once-daily RT, higher doses of 60–70 Gy should be used.<sup>18-21</sup> The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks. The randomized, phase III European CONVERT trial did not demonstrate superiority of 66 Gy (once daily) over 45 Gy (BID), but overall survival and toxicity were comparable.<sup>22</sup>

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

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

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

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

**PRINCIPLES OF RADIATION THERAPY****B. 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.<sup>23,24</sup> 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.<sup>25</sup> 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.<sup>26</sup>
- ▶ 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.

**III. Normal Tissue Dose Constraints:**

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

**IV. 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).<sup>27,28</sup> 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.<sup>29</sup> However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection.<sup>30</sup> 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.<sup>31,32</sup>
- 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 ( $P = .009$ ).<sup>32</sup> 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.<sup>33</sup> The dose of memantine used on RTOG 0614 was as follows: week 1 (starting on day 1 of WBRT), 5 mg each morning; week 2, 5 mg each morning and evening; week 3, 10 mg each morning and 5 mg each evening; and weeks 4–24, 10 mg each morning and evening.

**V. Brain Metastases:**

- Brain metastases should be treated with WBRT rather than stereotactic radiotherapy/radiosurgery (SRT/SRS) alone, because these patients tend to develop multiple central nervous system (CNS) metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.<sup>34,35</sup> SRS is preferred, if feasible.<sup>36,37</sup>
- 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](#)**Note:** All recommendations are category 2A unless otherwise indicated.

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

**PRINCIPLES OF RADIATION THERAPY**  
**References**

- <sup>1</sup>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.
- <sup>2</sup>Shiroyama Y, Onishi H, Takayama K, et al. Clinical outcomes of stereotactic body radiotherapy for patients with stage I small-cell lung cancer: Analysis of a subset of the Japanese Radiological Society Multi-Institutional SBRT Study Group Database. *Technol Cancer Res Treat* 2018;17:1533033818783904.
- <sup>3</sup>Verma V, Simone CB 2nd, Allen PK, Lin SH. Outcomes of stereotactic body radiotherapy for T1-T2N0 small cell carcinoma according to addition of chemotherapy and prophylactic cranial irradiation: a multicenter analysis. *Clin Lung Cancer* 2017;18:675-681.e1.
- <sup>4</sup>Verma V, Simone CB 2nd, Allen PK, et al. Multi-institutional experience of stereotactic ablative radiation therapy for stage I small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2017;97:362-371.
- <sup>5</sup>Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054-3060.
- <sup>6</sup>Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004;22:4837-4845.
- <sup>7</sup>De Ruysscher D, Pijls-Johannesma M, Bentzen SM, et al. Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer. *J Clin Oncol* 2006;24:1057-1063.
- <sup>8</sup>Videtic GMM, Belderbos JSA, Kong F-MS, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: small-cell lung cancer (SCLC). *Int J Radiat Oncol Biol Phys* 2008;72:327-334.
- <sup>9</sup>De Ruysscher D, Bremer R-H, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol* 2006;80:307-312.
- <sup>10</sup>van Loon J, De Ruysscher D, Wanders R, et al. Selective nodal irradiation on basis of (18)FDG-PET scans in limited-disease small-cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys* 2010;77:329-336.
- <sup>11</sup>Hu X, Bao Y, Zhang L, et al. Omitting elective nodal irradiation and irradiating postinduction versus preinduction chemotherapy tumor extent for limited-stage small cell lung cancer: interim analysis of a prospective randomized noninferiority trial. *Cancer* 2012;118:278-287.
- <sup>12</sup>Shirvani SM, Komaki R, Heymach JV, et al. Positron emission tomography/computed tomography-guided intensity-modulated radiotherapy for limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;82:e91-97.
- <sup>13</sup>Xia B, Chen G-Y, Cai X-W, et al. Is involved-field radiotherapy based on CT safe for patients with limited-stage small-cell lung cancer? *Radiother Oncol* 2012;102:258-262.
- <sup>14</sup>Colaco R, Sheikh H, Lorigan P, et al. Omitting elective nodal irradiation during thoracic irradiation in limited-stage small cell lung cancer - Evidence from a phase II trial. *Lung Cancer* 2012;76:72-77.
- <sup>15</sup>Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small-cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. *J Clin Oncol* 1994;12:496-502.
- <sup>16</sup>Turrisi AT, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265-271.
- <sup>17</sup>Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:943-951.
- <sup>18</sup>Choi NC, Herndon JE, Rosenman J, et al. Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer. *J Clin Oncol* 1998;16:3528-3536.
- <sup>19</sup>Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;56:355-359.
- <sup>20</sup>Roof KS, Fidias P, Lynch TJ, et al. Radiation dose escalation in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;57:701-708.
- <sup>21</sup>Bogart JA, Herndon JE, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004;59:460-468.
- <sup>22</sup>Favre-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.
- <sup>23</sup>Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. *J Clin Oncol* 1999;17:2092-2099.
- <sup>24</sup>Yee D, Butts C, Reiman A, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer. *Radiother Oncol* 2012;102:234-238.
- <sup>25</sup>Slotman BJ, van Tinteren H, Praag JO, et al. Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. *Lancet* 2015;385:36-42.
- <sup>26</sup>Slotman BJ, van Tinteren H, Praag JO, et al. Radiotherapy for extensive stage small-cell lung cancer-Authors' reply. *Lancet* 2015;385:1292-1293.
- <sup>27</sup>Arriagada R, Le Chevalier T, Rivière A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. *Ann Oncol* 2002;13:748-754.
- <sup>28</sup>Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476-484.
- <sup>29</sup>Slotman B, Favre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664-672.
- <sup>30</sup>Takahashi T, Yamanaka T, Seto T et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2017;18:663-671.
- <sup>31</sup>Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. *Lancet Oncol* 2009;10:467-474.
- <sup>32</sup>Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: Impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:77-84.
- <sup>33</sup>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.
- <sup>34</sup>Sadikov E, Bezjak A, Yi Q-L, et al. Value of whole brain re-irradiation for brain metastases—single centre experience. *Clinical oncology (Royal College of Radiologists (Great Britain))* 2007;19:532-538.
- <sup>35</sup>Son CH, Jimenez R, Niemierko A, et al. Outcomes after whole brain reirradiation in patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2012;82:e167-172.
- <sup>36</sup>Harris S, Chan MD, Lovato JF, et al. Gamma knife stereotactic radiosurgery as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;83:e53-59.
- <sup>37</sup>Wegner RE, Olson AC, Kondziolka D, et al. Stereotactic radiosurgery for patients with brain metastases from small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:e21-27.

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

**Table 1 - Definition of small cell lung cancer consists of two stages:**

(1) Limited-stage: Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

(2) Extensive-stage: Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

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

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

[Continued](#)

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





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

<b>N</b>	<b>Regional Lymph Nodes</b>
<b>NX</b>	Regional lymph nodes cannot be assessed
<b>N0</b>	No regional lymph node metastasis
<b>N1</b>	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
<b>N2</b>	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
<b>N3</b>	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
<b>M</b>	<b>Distant Metastasis</b>
<b>MX</b>	Distant metastasis cannot be assessed
<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural or pericardial nodules or malignant pleural or pericardial effusion <sup>a</sup>
M1b	Single extrathoracic metastasis in a single organ (including involvement of a single nonregional node)
M1c	Multiple extrathoracic metastases in a single organ or in multiple organs

**Table 3. AJCC Prognostic Groups**

	<b>T</b>	<b>N</b>	<b>M</b>		<b>T</b>	<b>N</b>	<b>M</b>
<b>Occult Carcinoma</b>	TX	N0	M0	<b>Stage IIIB</b>	T1a	N3	M0
<b>Stage 0</b>	Tis	N0	M0		T1b	N3	M0
<b>Stage IA1</b>	T1mi	N0	M0		T1c	N3	M0
	T1a	N0	M0		T2a	N3	M0
<b>Stage IA2</b>	T1b	N0	M0		T2b	N3	M0
<b>Stage IA3</b>	T1c	N0	M0		T3	N2	M0
<b>Stage IB</b>	T2a	N0	M0	<b>Stage IIIC</b>	T4	N2	M0
<b>Stage IIA</b>	T2b	N0	M0		T3	N3	M0
<b>Stage IIB</b>	T1a	N1	M0		T4	N3	M0
	T1b	N1	M0	<b>Stage IVA</b>	Any T	Any N	M1a
	T1c	N1	M0		Any T	Any N	M1b
	T2a	N1	M0	<b>Stage IVB</b>	Any T	Any N	M1c
	T2b	N1	M0				
	T3	N0	M0				
<b>Stage IIIA</b>	T1a	N2	M0				
	T1b	N2	M0				
	T1c	N2	M0				
	T2a	N2	M0				
	T2b	N2	M0				
	T3	N1	M0				
	T4	N0	M0				
	T4	N1	M0				

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

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



# NCCN Guidelines Version 1.2019 Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

## Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 01/16/18

### 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.**

Systemic Therapy .....	MS-6
Elderly Patients.....	MS-9
Second-Line and Beyond (Subsequent) Systemic Therapy .....	MS-10
Radiotherapy .....	MS-11
Thoracic Radiotherapy.....	MS-12
Prophylactic Cranial Irradiation .....	MS-14
Palliative Radiotherapy .....	MS-15
Surgical Resection of Stage I SCLC.....	MS-15
Surveillance .....	MS-16
Summary .....	MS-16
References .....	MS-18

## Table of Contents

Overview .....	MS-2
Literature Search Criteria and Guidelines Update Methodology .....	MS-2
Diagnosis .....	MS-3
Screening.....	MS-3
Manifestations.....	MS-3
Pathology.....	MS-4
Staging.....	MS-4
Prognostic Factors.....	MS-6
Treatment.....	MS-6

### Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).<sup>1,2</sup> In 2017, an estimated 29,654 new cases of SCLC will occur in the United States.<sup>1,3</sup> Nearly all cases of SCLC are attributable to cigarette smoking.<sup>4</sup> 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.<sup>1,2</sup> 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](http://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](http://www.nccn.org)).<sup>5</sup>

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.<sup>6</sup> In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiotherapy.<sup>7,8</sup> In

patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare.<sup>9</sup> 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.<sup>10</sup> 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](http://www.nccn.org)).<sup>11</sup> Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.<sup>12</sup> 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](http://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).<sup>13</sup> 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](http://www.nccn.org)).<sup>14</sup> 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.<sup>13-15</sup> 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.<sup>13</sup>

### Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea.<sup>16</sup> 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](http://www.nccn.org)).<sup>17,18</sup>

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.<sup>19-21</sup> 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.<sup>22,23</sup> 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.<sup>24</sup>

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.<sup>25,26</sup> In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates).<sup>27</sup> 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).<sup>27-29</sup> 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.<sup>30-32</sup> 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.<sup>17,33</sup> The cells are round, oval, or spindle-shaped; nuclear molding is prominent.<sup>34</sup> 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.<sup>17</sup>

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

### 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.<sup>6,44</sup> 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.<sup>45</sup> 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.<sup>6,44,46</sup> 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 (8<sup>th</sup> edition) and became effective on January 1, 2018 (see *Staging* in the NCCN Guidelines for Small Cell Lung Cancer).<sup>47,48</sup> 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.<sup>44</sup> 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.<sup>47</sup>

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).<sup>46,49</sup> However, once a patient has been found to have extensive-stage disease, further staging is optional, except for brain imaging.<sup>6</sup> 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.<sup>6,44</sup> 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.<sup>50-52</sup> PET/CT is superior to PET alone.<sup>52</sup> 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.<sup>46</sup> 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](http://www.nccn.org)).<sup>53</sup> 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.<sup>46,51,54</sup> 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.<sup>6</sup> 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).<sup>55,56</sup>

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.<sup>57,58</sup>

### 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).<sup>8,59,60</sup> 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](http://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).<sup>9,61</sup> 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).<sup>62</sup> This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.<sup>63-65</sup> EP plus concurrent thoracic radiotherapy is the recommended therapy (category 1) for patients with limited-stage disease in excess of T1-2, N0.<sup>59,60,66,67</sup>

In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.<sup>68</sup> 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.<sup>69</sup> In clinical practice, carboplatin is

frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.<sup>70</sup> However, the use of carboplatin carries a greater risk of myelosuppression.<sup>71</sup> 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.<sup>70,72,73</sup> A meta-analysis of individual patient data from 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.<sup>74</sup> 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 ( $P=.002$ ).<sup>75</sup> In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.<sup>75</sup> 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.<sup>76,77</sup>

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,  $P = .04$ ).<sup>78</sup> 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.<sup>79</sup> 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.<sup>80</sup> Thoracic radiotherapy improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival.<sup>59,60</sup> 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.<sup>81,82</sup>

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.<sup>83,84</sup> 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.<sup>85</sup> 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.<sup>86,87</sup> 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.<sup>88</sup> 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.<sup>89</sup> A meta-analysis reported that maintenance chemotherapy did not prolong overall survival.<sup>90</sup>

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.<sup>91</sup> However, randomized trials have failed to show improved PFS or overall survival with this approach.<sup>92,93</sup>

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.<sup>94,95</sup> Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.<sup>96-99</sup> 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.<sup>100</sup> 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.<sup>101-104</sup> 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.<sup>105</sup>

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,<sup>106</sup> maintenance of dose intensity with growth factors does not prolong disease-free or overall survival.<sup>107,108</sup> 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.<sup>109-112</sup> However, at least 2 randomized trials have demonstrated no survival benefit for the addition of bevacizumab to recommended chemotherapy.<sup>113,114</sup> 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.<sup>115</sup> 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.<sup>116</sup> 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](http://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).<sup>117,118</sup> 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).<sup>119,120</sup> A recent retrospective analysis in 8637 elderly patients with limited-stage disease reported that chemoradiation increased survival when compared



with chemotherapy alone.<sup>117</sup> Several other strategies have been evaluated in elderly patients with SCLC.<sup>73,121-123</sup> 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.<sup>123</sup> However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in this population.<sup>124</sup> 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.<sup>125</sup>

### **Second-Line and Beyond (Subsequent) Systemic Therapy**

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.<sup>126,127</sup> 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.<sup>128</sup> 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.<sup>6,128,129</sup> 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).<sup>130-133</sup> 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.<sup>134</sup> 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).<sup>135</sup> 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.<sup>135,136</sup> Many practicing oncologists have noted excessive toxicity when using 1.5 mg/m<sup>2</sup> of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.<sup>137</sup> Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC.<sup>138,139</sup>

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.<sup>140</sup> 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.<sup>141</sup> 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.<sup>141</sup> 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.<sup>142</sup>

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.<sup>143,144</sup> 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 O<sup>6</sup>-methylguanine-DNA methyltransferase (MGMT).<sup>131,145</sup> 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.<sup>146</sup> Amrubicin is an active drug in patients with relapsed or refractory SCLC.<sup>147-150</sup> However, grade 3 to 4 toxicity, primarily neutropenia, is common.<sup>151,152</sup> 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.<sup>153</sup>

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.<sup>154</sup> 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](http://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.<sup>155,156</sup>

### ***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.<sup>59,60</sup> 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.<sup>68</sup>

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.<sup>157</sup> 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.<sup>158,159</sup> 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]).<sup>160</sup> 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.<sup>161</sup>

### ***Radiation Fractionation***

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.<sup>162</sup> 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.<sup>162</sup> 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.<sup>163</sup> 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.<sup>164</sup> 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).<sup>165-167</sup>

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).<sup>168-173</sup> 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).<sup>174,175</sup> However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.<sup>167,176</sup>

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](http://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).<sup>177-179</sup>

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

Based on the results of a randomized trial by Jeremic et al,<sup>180</sup> 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.<sup>180</sup> 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.<sup>181</sup> A trial in 32 patients who received consolidative thoracic RT reported that only 16% (5/32) of patients had symptomatic chest recurrences.<sup>182</sup> 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.<sup>183</sup>

### **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.<sup>184</sup> 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.<sup>185</sup> 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.<sup>185</sup> 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.<sup>186</sup>

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.<sup>187</sup>

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;  $P = .094$ ).<sup>188</sup> 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.<sup>189,190</sup> Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.<sup>191,192</sup> Older age (>60 years) has also been associated with chronic neurotoxicity.<sup>193</sup> 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.<sup>194</sup> 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.<sup>195</sup> 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.<sup>187,191</sup> 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).<sup>185,187,196</sup> 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.<sup>187</sup> Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with lower doses (25 Gy).<sup>193,196</sup> 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.<sup>193</sup> Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.<sup>192,196</sup> 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.<sup>188</sup>

### **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](http://www.NCCN.org)).<sup>197-199</sup>

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](http://www.NCCN.org)).<sup>200</sup> 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.<sup>189</sup> The recommended dose for whole-brain radiotherapy is 30 Gy in 10 daily fractions.<sup>200</sup> In patients who develop brain metastases after PCI, stereotactic radiosurgery (preferred) or whole-brain radiotherapy may be considered.<sup>201,202</sup>

### **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.<sup>203</sup> Data show that patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery.<sup>204</sup> Note that fewer than 5% of patients with SCLC have true stage I disease.<sup>205</sup>

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.<sup>204</sup> 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.<sup>203,206-210</sup> 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.<sup>211</sup>

Analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.<sup>10,212</sup> 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.<sup>213</sup> 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.<sup>191,208,214,215</sup> 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).<sup>185</sup> 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.<sup>216</sup> 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.<sup>217,218</sup> 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](http://www.NCCN.org)).<sup>219-221</sup> 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](http://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.

Discussion  
update in  
progress

### References

- Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2014, based on November 2016 SEER data submission, posted to the SEER web site, April 2017. Bethesda, MD: National Cancer Institute; 2017. Available at: [https://seer.cancer.gov/csr/1975\\_2014/](https://seer.cancer.gov/csr/1975_2014/).
- Govindan R, Page N, Morgensztern D, et al. Changing epidemiology of small-cell lung cancer in the United States over the last 30 years: analysis of the surveillance, epidemiologic, and end results database. *J Clin Oncol* 2006;24:4539-4544. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17008692>.
- Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7-30 Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29313949>.
- Pesch B, Kendzia B, Gustavsson P, et al. Cigarette smoking and lung cancer--relative risk estimates for the major histological types from a pooled analysis of case-control studies. *Int J Cancer* 2012;131:1210-1219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22052329>.
- Demetri G, Elias A, Gershenson D, et al. NCCN small-cell lung cancer practice guidelines. *The National Comprehensive Cancer Network. Oncology (Williston Park)* 1996;10:179-194. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8953602>.
- Jett JR, Schild SE, Kesler KA, Kalemkerian GP. Treatment of small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e400S-419S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649448>.
- Kalemkerian GP. Advances in the treatment of small-cell lung cancer. *Semin Respir Crit Care Med* 2011;32:94-101. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21500128>.
- Stinchcombe TE, Gore EM. Limited-stage small cell lung cancer: current chemoradiotherapy treatment paradigms. *Oncologist* 2010;15:187-195. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20145192>.
- Demedts IK, Vermaelen KY, van Meerbeeck JP. Treatment of extensive-stage small cell lung carcinoma: current status and future prospects. *Eur Respir J* 2010;35:202-215. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20044461>.
- Yu JB, Decker RH, Detterbeck FC, Wilson LD. Surveillance epidemiology and end results evaluation of the role of surgery for stage I small cell lung cancer. *J Thorac Oncol* 2010;5:215-219. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20101146>.
- Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e61S-77S. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23649454>.
- Videtic GMM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. *J Clin Oncol* 2003;21:1544-1549. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12697879>.
- Cuffe S, Moua T, Summerfield R, et al. Characteristics and outcomes of small cell lung cancer patients diagnosed during two lung cancer computed tomographic screening programs in heavy smokers. *J Thorac Oncol* 2011;6:818-822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21623258>.
- Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21714641>.
- Kondo R, Yoshida K, Kawakami S, et al. Different efficacy of CT screening for lung cancer according to histological type: analysis of Japanese-smoker cases detected using a low-dose CT screen. *Lung*



Cancer 2011;74:433-440. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21663995>.

16. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e142S-165S. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/23649436>.

<https://www.ncbi.nlm.nih.gov/pubmed/23649436>.

17. Travis WD. Advances in neuroendocrine lung tumors. Ann Oncol 2010;21 Suppl 7:vii65-71. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/20943645>.

18. Renshaw AA, Haja J, Lozano RL, Wilbur DC. Distinguishing carcinoid tumor from small cell carcinoma of the lung: correlating cytologic features and performance in the College of American Pathologists

Non-Gynecologic Cytology Program. Arch Pathol Lab Med 2005;129:614-618. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/15859631>.

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

20. Kazarian M, Laird-Offringa IA. Small-cell lung cancer-associated autoantibodies: potential applications to cancer diagnosis, early detection, and therapy. Mol Cancer 2011;10:33. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21450098>.

21. Marchioli CC, Graziano SL. Paraneoplastic syndromes associated with small cell lung cancer. Chest Surg Clin N Am 1997;7:65-80. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9001756>.

22. Titulaer MJ, Wirtz PW, Willems LN, et al. Screening for small-cell lung cancer: a follow-up study of patients with Lambert-Eaton myasthenic syndrome. J Clin Oncol 2008;26:4276-4281. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18779614>.

23. Meriney SD, Hulsizer SC, Lennon VA, Grinnell AD. Lambert-Eaton myasthenic syndrome immunoglobulins react with multiple types of calcium channels in small-cell lung carcinoma. Ann Neurol 1996;40:739-749. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8957015>.

24. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain 2001;124:1138-1148. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/11353730>.

25. Delisle L, Boyer MJ, Warr D, et al. Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. Arch Intern Med 1993;153:746-752. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/8383484>.

26. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. Am J Respir Crit Care Med 1997;156:1669-1678. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/9372692>.

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

28. Schrier RW, Gross P, Gheorghiu M, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 2006;355:2099-2112. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17105757>.

29. Verbalis JG, Zeltser D, Smith N, et al. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvolaemic hyponatraemia: subgroup analysis of a randomized, controlled study. Clin Endocrinol (Oxf) 2008;69:159-168. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/18034777>.

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



# NCCN Guidelines Version 1.2019

## Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

31. Travis WD, Brambilla E, Burke AP, et al. Introduction to The 2015 World Health Organization Classification of Tumors of the Lung, Pleura, Thymus, and Heart. *J Thorac Oncol* 2015;10:1240-1242. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26291007>.
32. Travis WD, Brambilla E, Nicholson AG, et al. The 2015 World Health Organization classification of lung tumors: impact of genetic, clinical and radiologic advances since the 2004 classification. *J Thorac Oncol* 2015;10:1243-1260. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26291008>.
33. Zakowski MF. Pathology of small cell carcinoma of the lung. *Semin Oncol* 2003;30:3-8. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12635085>.
34. Nicholson SA, Beasley MB, Brambilla E, et al. Small cell lung carcinoma (SCLC): a clinicopathologic study of 100 cases with surgical specimens. *Am J Surg Pathol* 2002;26:1184-1197. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12218575>.
35. Pelosi G, Rodriguez J, Viale G, Rosai J. Typical and atypical pulmonary carcinoid tumor overdiagnosed as small-cell carcinoma on biopsy specimens: a major pitfall in the management of lung cancer patients. *Am J Surg Pathol* 2005;29:179-187. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15644774>.
36. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol* 2004;22:2730-2739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15226341>.
37. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997;79:1729-1736. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9128989>.
38. Rindi G, Klersy C, Inzani F, et al. Grading the neuroendocrine tumors of the lung: an evidence-based proposal. *Endocr Relat Cancer* 2014;21:1-16. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24344249>.
39. Masai K, Tsuta K, Kawago M, et al. Expression of squamous cell carcinoma markers and adenocarcinoma markers in primary pulmonary neuroendocrine carcinomas. *Appl Immunohistochem Mol Morphol* 2013;21:292-297. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23060301>.
40. Ordonez NG. Value of thyroid transcription factor-1 immunostaining in distinguishing small cell lung carcinomas from other small cell carcinomas. *Am J Surg Pathol* 2000;24:1217-1223. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10976695>.
41. Kaufmann O, Dietel M. Expression of thyroid transcription factor-1 in pulmonary and extrapulmonary small cell carcinomas and other neuroendocrine carcinomas of various primary sites. *Histopathology* 2000;36:415-420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10792482>.
42. Guinee DG, Jr., Fishback NF, Koss MN, et al. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. *Am J Clin Pathol* 1994;102:406-414. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7524299>.
43. Pelosi G, Rindi G, Travis WD, Papotti M. Ki-67 antigen in lung neuroendocrine tumors: unraveling a role in clinical practice. *J Thorac Oncol* 2014;9:273-284. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24518085>.
44. Kalemkerian GP, Gadgeel SM. Modern staging of small cell lung cancer. *J Natl Compr Canc Netw* 2013;11:99-104. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23307985>.
45. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? *Lung Cancer* 2002;37:271-276. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12234695>.

46. Kalemkerian GP. Staging and imaging of small cell lung cancer. *Cancer Imaging* 2011;11:253-258. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22245990>.
47. Amin MB, Greene FL, Byrd DR, et al. *AJCC Cancer Staging Manual*, 8th edition: Springer International Publishing; 2016:1-1024.
48. Nicholson AG, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals for the revision of the clinical and pathologic staging of small cell lung cancer in the forthcoming eighth edition of the TNM classification for lung cancer. *J Thorac Oncol* 2016;11:300-311. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26723244>.
49. Seute T, Leffers P, ten Velde GP, Twijnstra A. Detection of brain metastases from small cell lung cancer: consequences of changing imaging techniques (CT versus MRI). *Cancer* 2008;112:1827-1834. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18311784>.
50. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. *J Natl Compr Canc Netw* 2009;7 Suppl 2:S1-26. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19555588>.
51. Bradley JD, Dehdashti F, Mintun MA, et al. Positron emission tomography in limited-stage small-cell lung cancer: a prospective study. *J Clin Oncol* 2004;22:3248-3254. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15310768>.
52. Fischer BM, Mortensen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. *Ann Oncol* 2007;18:338-345. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17060487>.
53. Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET on the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging* 2004;31:1614-1620. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15258700>.
54. Kamel EM, Zwahlen D, Wyss MT, et al. Whole-body (18)F-FDG PET improves the management of patients with small cell lung cancer. *J Nucl Med* 2003;44:1911-1917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14660716>.
55. Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. *J Thorac Oncol* 2009;4:44-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19096305>.
56. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. *Curr Opin Pulm Med* 2009;15:334-342. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19395972>.
57. Foster NR, Mandrekar SJ, Schild SE, et al. Prognostic factors differ by tumor stage for small cell lung cancer: a pooled analysis of North Central Cancer Treatment Group trials. *Cancer* 2009;115:2721-2731. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19402175>.
58. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 1990;8:1563-1574. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2167954>.
59. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618-1624. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1331787>.
60. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992;10:890-895. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1316951>.
61. Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain-only metastases of small cell lung cancer; efficacy of whole brain radiotherapy.



An EORTC phase II study. *Radiother Oncol* 1998;46:29-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9488124>.

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

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

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

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

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

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

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

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

70. Hatfield LA, Huskamp HA, Lamont EB. Survival and toxicity after cisplatin plus etoposide versus carboplatin plus etoposide for extensive-stage small-cell lung cancer in elderly patients. *J Oncol Pract* 2016;12:666-673. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27352949>.

71. Bishop JF, Raghavan D, Stuart-Harris R, et al. Carboplatin (CBDCA, JM-8) and VP-16-213 in previously untreated patients with small-cell lung cancer. *J Clin Oncol* 1987;5:1574-1578. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2821197>.

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

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

74. Rossi A, Di Maio M, Chiodini P, et al. Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS

meta-analysis of individual patient data. *J Clin Oncol* 2012;30:1692-1698. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22473169>.

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

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

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

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

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

80. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794-1801. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10561217>.

81. Niho S, Kubota K, Yoh K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with

ipsilateral pleural effusion. *J Thorac Oncol* 2008;3:723-727. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18594317>.

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

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

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

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

86. Berghmans T, Scherpereel A, Meert AP, et al. A phase III randomized study comparing a chemotherapy with cisplatin and etoposide to a etoposide regimen without cisplatin for patients with extensive small-cell lung cancer. *Front Oncol* 2017;7:217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28975084>.

87. Jalal SI, Lavin P, Lo G, et al. Carboplatin and etoposide with or without palifosfamide in untreated extensive-stage small-cell lung cancer: a multicenter, adaptive, randomized phase III study (MATISSE). *J Clin Oncol* 2017;35:2619-2623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28605291>.

88. Niell HB, Herndon JE, 2nd, Miller AA, et al. Randomized phase III intergroup trial of etoposide and cisplatin with or without paclitaxel and



granulocyte colony-stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B Trial 9732. *J Clin Oncol* 2005;23:3752-3759. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15923572>.

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

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

108. Sculier JP, Paesmans M, Lecomte J, et al. A three-arm phase III randomised trial assessing, in patients with extensive-disease small-cell

lung cancer, accelerated chemotherapy with support of haematological growth factor or oral antibiotics. *Br J Cancer* 2001;85:1444-1451. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11720426>.

109. Petrioli R, Roviello G, Laera L, et al. Cisplatin, etoposide, and bevacizumab regimen followed by oral etoposide and bevacizumab maintenance treatment in patients with extensive-stage small cell lung cancer: a single-institution experience. *Clin Lung Cancer* 2015;16:e229-234. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26072097>.

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

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

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

113. Tiseo M, Boni L, Ambrosio F, et al. Italian, multicenter, phase III, randomized study of cisplatin plus etoposide with or without bevacizumab as first-line treatment in extensive-disease small-cell lung cancer: The GOIRC-AIFA FARM6PMFJM trial. *J Clin Oncol* 2017;35:1281-1287. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28135143>.

114. Pujol JL, Lavole A, Quoix E, et al. Randomized phase II-III study of bevacizumab in combination with chemotherapy in previously untreated extensive small-cell lung cancer: results from the IFCT-0802 trial. *Ann Oncol* 2015;26:908-914. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25688059>.

115. Reck M, Luft A, Szczesna A, et al. Phase III randomized trial of ipilimumab plus etoposide and platinum versus placebo plus etoposide and platinum in extensive-stage small-cell lung cancer. *J Clin Oncol* 2016;34:3740-3748. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27458307>.

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

117. Corso CD, Rutter CE, Park HS, et al. Role of chemoradiotherapy in elderly patients with limited-stage small-cell lung cancer. *J Clin Oncol* 2015;33:4240-4246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26481366>.

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

119. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. *Lancet* 1996;348:563-566. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8774567>.

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

121. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with eastern cooperative oncology group performance status of 2, or age  $\geq$  70 years. *J Clin Oncol* 2004;22:1872-1877. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15143079>.

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

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

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

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

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

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

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

129. Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol*

1987;23:1409-1411. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/2824211>.

130. Lammers PE, Shyr Y, Li CI, et al. Phase II study of bendamustine in relapsed chemotherapy sensitive or resistant small-cell lung cancer. *J Thorac Oncol* 2014;9:559-562. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24736081>.

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

<https://www.ncbi.nlm.nih.gov/pubmed/22228633>.

132. Cheng S, Evans WK, Stys-Norman D, Shepherd FA. Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline. *J Thorac Oncol* 2007;2:348-354. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17409809>.

133. Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. *J Clin Oncol* 2003;21:1550-1555. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/12697880>.

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

<https://www.ncbi.nlm.nih.gov/pubmed/10080612>.

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

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17135646>.

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

<https://www.ncbi.nlm.nih.gov/pubmed/17513814>.

137. Huber RM, Reck M, Gosse H, et al. Efficacy of a toxicity-adjusted topotecan therapy in recurrent small cell lung cancer. *Eur Respir J* 2006;27:1183-1189. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/16481389>.

138. Shah C, Ready N, Perry M, et al. A multi-center phase II study of weekly topotecan as second-line therapy for small cell lung cancer. *Lung Cancer* 2007;57:84-88. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17399850>.

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

[https://meeting.ascopubs.org/cgi/content/abstract/24/18\\_suppl/7083](https://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7083).

140. Horn L, Reck M, Spigel DR. The future of immunotherapy in the treatment of small cell lung cancer. *Oncologist* 2016;21:910-921. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27354668>.

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

<https://www.ncbi.nlm.nih.gov/pubmed/27269741>.

142. Hellmann MD, Ott PA, Zugazagoitia J, et al. Nivolumab (nivo) ± ipilimumab (ipi) in advanced small-cell lung cancer (SCLC): First report of a randomized expansion cohort from CheckMate 032 [abstract]. *J Clin Oncol* 2017;35:Abstract 8503. Available at:

[https://www.jco.org/article/S1556-0864\(16\)31687-2/abstract](https://www.jco.org/article/S1556-0864(16)31687-2/abstract).

143. Davies M, Duffield EA. Safety of checkpoint inhibitors for cancer treatment: strategies for patient monitoring and management of immune-mediated adverse events. *Immunotargets Ther* 2017;6:51-71.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28894725>.



144. Khunger M, Rakshit S, Pasupuleti V, et al. Incidence of pneumonitis with use of programmed death 1 and programmed death-ligand 1 inhibitors in non-small cell lung cancer: a systematic review and meta-analysis of trials. *Chest* 2017;152:271-281. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28499515>.
145. Zauderer MG, Drilon A, Kadota K, et al. Trial of a 5-day dosing regimen of temozolomide in patients with relapsed small cell lung cancers with assessment of methylguanine-DNA methyltransferase. *Lung Cancer* 2014;86:237-240. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25194640>.
146. Goto K, Ohe Y, Shibata T, et al. Combined chemotherapy with cisplatin, etoposide, and irinotecan versus topotecan alone as second-line treatment for patients with sensitive relapsed small-cell lung cancer (JCOG0605): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2016;17:1147-1157. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27312053>.
147. Asai N, Ohkuni Y, Matsunuma R, et al. Efficacy and safety of amurubicin for the elderly patients with refractory relapsed small cell lung cancer as third-line chemotherapy. *J Cancer Res Ther* 2012;8:266-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22842373>.
148. Ettinger DS, Jotte R, Lorigan P, et al. Phase II study of amrubicin as second-line therapy in patients with platinum-refractory small-cell lung cancer. *J Clin Oncol* 2010;28:2598-2603. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20385980>.
149. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. *J Clin Oncol* 2008;26:5401-5406. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18854562>.
150. Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. *J Clin Oncol* 2006;24:5448-5453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17135647>.
151. Shimokawa T, Shibuya M, Kitamura K, et al. Retrospective analysis of efficacy and safety of amrubicin in refractory and relapsed small-cell lung cancer. *Int J Clin Oncol* 2009;14:63-69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19225927>.
152. Jotte R, Conkling P, Reynolds C, et al. Randomized phase II trial of single-agent amrubicin or topotecan as second-line treatment in patients with small-cell lung cancer sensitive to first-line platinum-based chemotherapy. *J Clin Oncol* 2011;29:287-293. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21135284>.
153. von Pawel J, Jotte R, Spigel DR, et al. Randomized phase III trial of amrubicin versus topotecan as second-line treatment for patients with small-cell lung cancer. *J Clin Oncol* 2014;32:4012-4019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25385727>.
154. Kong FM, Lally BE, Chang JY, et al. ACR Appropriateness Criteria(R) radiation therapy for small-cell lung cancer. *Am J Clin Oncol* 2013;36:206-213. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23511336>.
155. Shioyama Y, Nakamura K, Sasaki T, et al. Clinical results of stereotactic body radiotherapy for Stage I small-cell lung cancer: a single institutional experience. *J Radiat Res* 2013;54:108-112. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22923748>.
156. Li C, Xiong Y, Zhou Z, et al. Stereotactic body radiotherapy with concurrent chemotherapy extends survival of patients with limited stage small cell lung cancer: a single-center prospective phase II study. *Med Oncol* 2014;31:369. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25416052>.
157. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993;11:336-344. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8381164>.

158. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. *J Clin Oncol* 2004;22:4837-4845. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15570087>.
159. Pijls-Johannesma M, De Ruyscher D, Vansteenkiste J, et al. Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials. *Cancer Treat Rev* 2007;33:461-473. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17513057>.
160. De Ruyscher D, Bremer RH, Koppe F, et al. Omission of elective node irradiation on basis of CT-scans in patients with limited disease small cell lung cancer: a phase II trial. *Radiother Oncol* 2006;80:307-312. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16949169>.
161. De Ruyscher D, Lueza B, Le Pechoux C, et al. Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis. *Ann Oncol* 2016;27:1818-1828. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27436850>.
162. Turrisi AT, 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340:265-271. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9920950>.
163. Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59:943-951. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15234027>.
164. Faivre-Finn C, Snee M, Ashcroft L, et al. Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial. *Lancet Oncol* 2017;18:1116-1125. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28642008>.
165. Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;56:355-359. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12738309>.
166. Roof KS, Fidias P, Lynch TJ, et al. Radiation dose escalation in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;57:701-708. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14529774>.
167. Bogart JA, Herndon JE, 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004;59:460-468. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15145163>.
168. Shirvani SM, Juloori A, Allen PK, et al. Comparison of 2 common radiation therapy techniques for definitive treatment of small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2013;87:139-147. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23920393>.
169. ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements (ICRU); 2010. Available at: <https://www.icru.org/testing/reports/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrt-icru-report-83>.
170. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in intensity-modulated radiation therapy (ICRU report No. 83). *Cancer Radiother* 2011;15:555-559. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21802333>.
171. Hartford AC, Palisca MG, Eichler TJ, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guidelines for intensity-modulated radiation therapy (IMRT). *Int J Radiat Oncol Biol Phys* 2009;73:9-14. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19100920>.

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

173. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG Oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* 2017;35:56-62. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28034064>.

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

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

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

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

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

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

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

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

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

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

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

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



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

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

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

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

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

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

192. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms--Results of an international phase III randomized controlled trial by the EORTC radiation

oncology and lung cancer groups. *J Clin Oncol* 2009;27:78-84. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19047288>.

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

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

195. Pechoux CL, Sun A, Slotman BJ, et al. Prophylactic cranial irradiation for patients with lung cancer. *Lancet Oncol* 2016;17:e277-293. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27396646>.

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

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

198. Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965-976. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21277118>.





# NCCN Guidelines Version 1.2019

## Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[Table of Contents](#)  
[Discussion](#)

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

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

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

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

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

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

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

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

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

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

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

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

211. Barnes H, See K, Barnett S, Manser R. Surgery for limited-stage small-cell lung cancer. *Cochrane Database Syst Rev* 2017;4:CD011917. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28429473>.

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

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

214. Shepherd FA, Evans WK, Feld R, et al. Adjuvant chemotherapy following surgical resection for small-cell carcinoma of the lung. *J Clin*

Oncol 1988;6:832-838. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/2835443>.

2010;340:b5569. Available at:  
<https://www.ncbi.nlm.nih.gov/pubmed/20093278>.

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

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

217. Johnson BE, Linnoila RI, Williams JP, et al. Risk of second aerodigestive cancers increases in patients who survive free of small-cell lung cancer for more than 2 years. J Clin Oncol 1995;13:101-111. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7799009>.

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

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

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

221. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. BMJ