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Small Cell Lung Cancer:

Clinical Practice Guidelines in Oncology

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Abstract

Neuroendocrine tumors account for approximately 20% of lung cancers; most (~15%) are small cell lung cancer (SCLC). These NCCN Clinical Practice Guidelines in Oncology for SCLC focus on extensive-stage SCLC because it occurs more frequently than limited-stage disease. SCLC is highly sensitive to initial therapy; however, most patients eventually die of recurrent disease. In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare. Most cases of SCLC are attributable to cigarette smoking; therefore, smoking cessation should be strongly promoted.

Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (~15%) are small cell lung cancer (SCLC).^{1–3} In 2012, an estimated 33,900 new cases of SCLC will occur in the United States.⁴ Nearly all cases of SCLC are attributable to cigarette smoking.

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

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Disclosures for the Small Cell Lung Cancer Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Small Cell Lung Cancer Panel members can be found on page 98. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

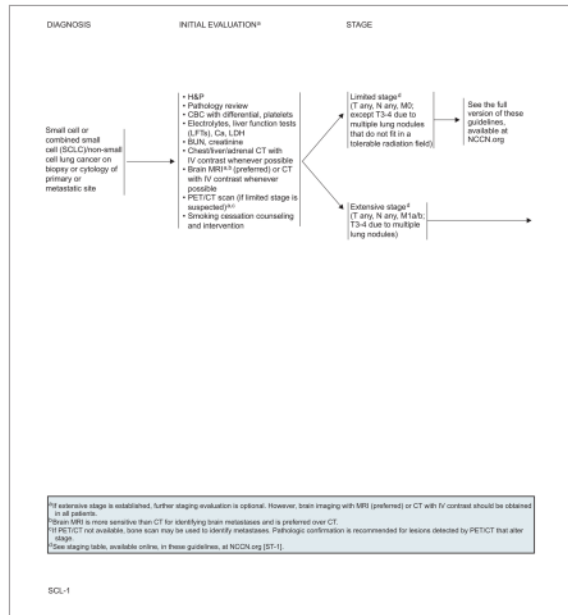
These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

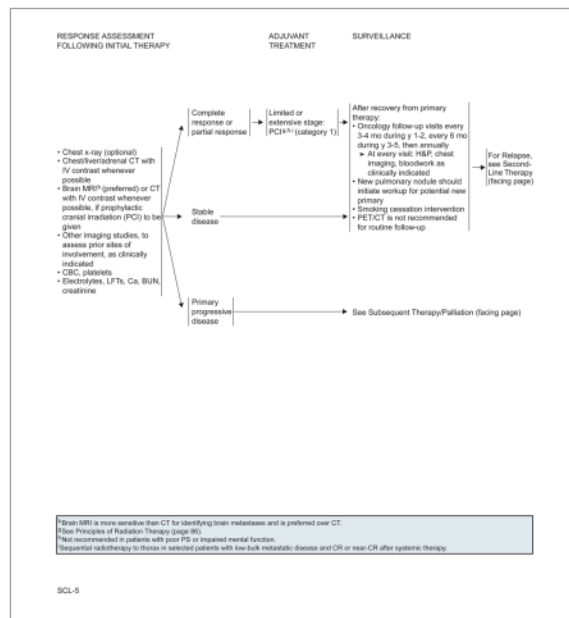
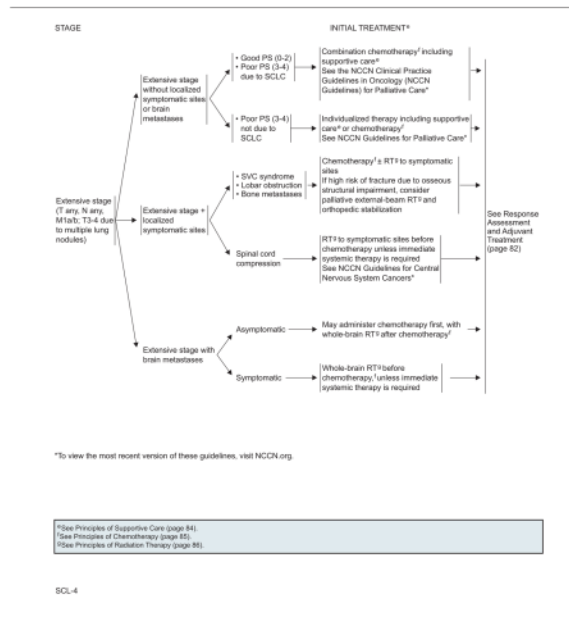
Although the overall incidence of SCLC has been decreasing, in women it is increasing, with the male-to-female incidence ratio now 1:1.² This selection from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for SCLC focuses on extensive-stage SCLC because it occurs more frequently. The complete version of the NCCN Guidelines for SCLC and Lung Neuroendocrine Tumors is available at NCCN.org.

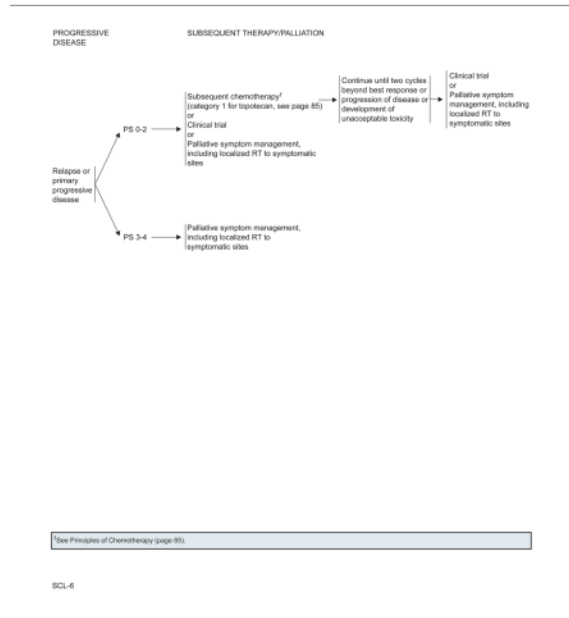
Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (see the NCCN Clinical Practice Guidelines in Oncology for NSCLC at NCCN.org). When compared with NSCLC, SCLC generally has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastases. Most patients with SCLC present with hematogenous metastases (ie, extensive-stage disease), whereas only approximately one-third present with limited-stage disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.^{5,6}

In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients; in chemoresponsive patients, prophylactic cranial irradiation (PCI) can also palliate symptoms and prolong survival. However, long-term survival is rare in patients with extensive-stage disease.^{7,8} Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the standard therapy for SCLC as outlined in these guidelines still needs to be improved. Thus, participation in clinical trials should be strongly encouraged.

Smoking cessation should be strongly promoted (1-800-QUIT-NOW is the national access number to state-based quitline services; www.smokefree.gov); former smokers should be strongly encouraged to remain abstinent. Patients who smoke have increased toxicity during treatment and shorter survival.⁹ Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful (www.ahrq.gov/clinic/tobacco/tobaqr.htm).







- PRINCIPLES OF SUPPORTIVE CARE**
- Smoking cessation counseling and intervention
 - Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) during RT is not recommended (category 1 for GM-CSF).
 - Syndrome of inappropriate antidiuretic hormone
 - Fluid restriction
 - Saline infusion for symptomatic patients
 - Antineoplastic therapy
 - Demeclocycline
 - Vasopressin receptor inhibitors (conivaptan, tolvaptan)
 - Cushing syndrome
 - Consider leflunomide. If not effective, consider metyrapone.
 - Try to control before initiation of antineoplastic therapy
 - Leptomeningeal disease: See NCCN Guidelines for Central Nervous System Cancers: Carcinomatous/Lymphomatous Meningitis*
 - Pain management: See NCCN Guidelines for Adult Cancer Pain*
 - Nausea/vomiting: See NCCN Guidelines for Antiemesis*
 - Psychosocial distress: See NCCN Guidelines for Distress Management*
 - See NCCN Guidelines for Palliative Care* as indicated
- *To view the most recent version of these guidelines, visit NCCN.org.
- SCL-B

PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary therapy:

- Extensive stage (treatment of 4-6 cycles):
 - Cisplatin, 75 mg/m²/day 1 and etoposide, 100 mg/m²/days 1, 2, 3¹
 - Cisplatin, 80 mg/m²/day 1 and etoposide, 80 mg/m²/days 1, 2, 3²
 - Cisplatin, 25 mg/m²/days 1, 2, 3 and etoposide, 100 mg/m²/days 1, 2, 3³
 - Carboplatin, AUC 5-6 day 1 and etoposide, 100 mg/m²/days 1, 2, 3⁴
 - Cisplatin, 60 mg/m²/day 1 and irinotecan, 60 mg/m²/days 1, 8, 15⁵
 - Cisplatin, 30 mg/m²/and irinotecan, 65 mg/m²/days 1, 5, every 21 days⁶
 - Carboplatin, AUC 5 day 1 and irinotecan, 60 mg/m²/days 1, 8, and 15⁷

Subsequent chemotherapy:

- Clinical trial preferred.
- Relapse < 2-3 mo. PS 0-2:
 - Platinol®¹¹
 - Docetaxel¹¹
 - Irinotecan¹¹
- Relapse > 2-3 mo up to 8 mo:
 - Topotecan PO or IV (category 1)^{11,12,18}
 - Platinol®¹¹
 - Docetaxel¹¹
 - Irinotecan¹¹
 - Gemtuzumab^{15,16}
 - Vinorelbine^{16,20}
 - Oral etoposide^{11,22}
- Relapse > 8 mo. original regimen^{23,24}
- Topotecan, 75 mg/m²/d x 21 days¹⁴
- Cyclophosphamide/irinotecan (CAI)¹¹
- Relapse > 6 mo. original regimen^{23,24}

Consider dose reductions versus growth factors in patients with poor performance status.

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

Footnotes:

¹Tomassetti B, Brambilla B, Kjaer S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and irinotecan regimen in limited-stage small-cell lung cancer: results from a randomized phase III trial. *J Clin Oncol* 2012;30:409-415.

²Paul DC, Blaskin A, Kjaer S, et al. Prospective randomized comparison of high-dose and biweekly-dose epirubicin-based chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12:2022-2024.

³Evans R, Blaskin A, Kjaer S, et al. Irinotecan and etoposide versus etoposide and irinotecan in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1998;16:3433-3437.

⁴Chen H, Wu Y, Wang C, et al. Randomized phase III study comparing carboplatin and etoposide versus cisplatin and etoposide in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2004;22:2528-2534.

⁵Wang C, Wu Y, Wang C, et al. Randomized phase III study comparing carboplatin and irinotecan versus cisplatin and irinotecan in patients with extensive-stage small-cell lung cancer. *Ann Oncol* 2006;17:1420-1426.

⁶Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

⁷Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

⁸Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

⁹Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁰Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹¹Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹²Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹³Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁴Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁵Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁶Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁷Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁸Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

¹⁹Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

²⁰Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

²¹Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

²²Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

²³Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

²⁴Wang C, Wu Y, Wang C, et al. A phase III study of irinotecan in heavily pretreated patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 2007;25:300-305.

SCLC

PRINCIPLES OF RADIATION THERAPY

General Principles:

- General principles of radiation therapy (RT) for lung cancer—including commonly used abbreviations, standards for clinical and technological expertise and quality assurance, and principles of RT simulation, planning, and delivery—are provided in the NCCN Guidelines for NSCLC (available online at NCCN.org [NSCLC-8]) 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 (4-6, ideally more) should be used, with all fields treated each day.
- Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4DCT and/or PET/CT simulation, IMRT/AMAT, IGRT, and motion management strategies. Quality assurance measures are essential and are covered in the NCCN Guidelines for NSCLC (available online at NCCN.org [NSCLC-8]).

Extensive Stage:

- Concomitant thoracic RT may be beneficial for selected patients with extensive-stage SCLC who respond to chemotherapy. Studies have demonstrated that concomitant thoracic RT is well tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.^{1,2} This approach is currently being evaluated in prospective clinical trials (RTOG 0937, Dutch CREST trial NTR1527).

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 the NCCN Guidelines for NSCLC, available online at NCCN.org [NSCLC-8]).
- 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/FTOC 0538 protocol should be used as a guide; 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.
- In patients with limited- or extensive-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1³).
- Recommended doses for PCI in the whole brain are 25 Gy in 10 daily fractions, 30 Gy in 10-15 daily fractions, or 24 Gy in 8 daily fractions. In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared with patients treated with 25 Gy.⁴
- Neurocognitive Function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RT02-0212, 82% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 58% of patients younger than 60 years of age (P=0.09).⁵ Concurrent chemotherapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.

Brain Metastases:

- Brain metastases should be treated with whole-brain RT (WBRT) rather than stereotactic RT/neurosurgery (SRS) alone, because these patients tend to develop multiple CMO metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.^{6,7} SRS may also be considered, especially if there has been a long interval from initial diagnosis to occurrence of brain metastases and there is no extracranial disease.^{8,9,11}

Footnotes:

¹Jensen D, Shibamoto Y, Nishi N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive-stage small-cell lung cancer: a randomized study. *J Clin Oncol* 1999;17:2050-2056.

²Yee D, Bala C, Reaman N, et al. Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small-cell lung cancer. *Radiation Oncol* 2012;10:234-238.

³Arriaga R, La Chaux T, Rivlin A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 335 reirradiated patients. *Ann Oncol* 2002;13:748-754.

⁴Auguin A, Arriaga R, Popon JF, 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;341:474-484.

⁵La Rouchon C, Dreyer S, Sessa 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 2003-09034, RTOG 0212, and ICR 99-01): a randomized clinical trial. *Lancet Oncol* 2008;9:407-414.

⁶Solomon B, Fainwiler C, Kramer D, et al. Prophylactic cranial irradiation in extensive-stage small-cell lung cancer. *N Engl J Med* 2007;357:664-672.

⁷Wolfson AH, Bao 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-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:77-84.

⁸Radakov E, Sogun A, Li Q, et al. Value of whole brain re-irradiation for brain metastases—single centre experience. *Clin Oncol (R Coll Radiol)* 2007;18:932-938.

⁹Shin CH, Jernese R, Neebawit A, et al. Outcomes after whole brain irradiation in patients with brain metastases. *Int J Radiat Oncol Biol Phys* 2012;82:1761-1772.

¹⁰Yokoyama S, Chan M, Liaw JF, et al. Gamma knife stereotactic radiotherapy as salvage therapy after failure of whole-brain radiotherapy in patients with small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;82:653-659.

¹¹Wagner RE, Olson AC, Kozlowski D, et al. Stereotactic radiotherapy for patients with brain metastases from small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:w21-w27.

SCLC

Pathology

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.¹⁰ The cells are round, oval, or spindle-shaped; nuclear molding is prominent. The mitotic count is high. Up to 30% of autopsies in patients with SCLC reveal areas of non-small cell carcinoma differentiation; 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.^{11–13} Both pulmonary and extrapulmonary small cell carcinomas have similar clinical and biologic behaviors, leading to high potential for widespread metastases. However, unlike SCLC, malignant cells from patients with extrapulmonary small cell carcinoma do not exhibit macromolecular 3p deletions, a finding that suggests a different pathogenesis.¹⁴

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor-1 (TTF-1). Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLC cancers will be immunoreactive for at least 1 of these neuroendocrine markers.¹⁵

Clinical Manifestations, Staging, and Prognostic Factors

Clinical Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea. Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. It is uncommon for patients to present with a solitary peripheral nodule without central adenopathy. In this situation, fine-needle aspiration may not adequately differentiate small cell carcinoma from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or high-grade (large-cell) neuroendocrine carcinoma (see the complete version of the NCCN Guidelines for SCLC and Lung Neuroendocrine Tumors at NCCN.org).^{16–18}

The National Lung Screening Trial reported that screening with annual, low-dose, spiral CT scans decreased lung cancer–specific mortality and all-cause mortality in asymptomatic high-risk individuals (www.cancer.gov/newscenter/qa/2002/nlstqaQA; see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).¹⁹ Although CT screening can detect early-stage NSCLC, it does not seem to be useful for detecting early-stage SCLC.¹⁹ This is probably because of the aggressiveness of SCLC, which results in the development of symptomatic disease between annual scans, thereby limiting the potential effect on mortality.²⁰

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.^{21–23} Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. Patients with Lambert-Eaton syndrome present with proximal leg weakness caused by antibodies directed against the voltage-gated calcium channels.^{24,25} 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.²⁶

SCLC cells sometimes produce polypeptide hormones, including vasopressin (antidiuretic hormone [ADH]) and adrenocorticotropic hormone, which cause hyponatremia of malignancy (ie, syndrome of inappropriate ADH secretion [SIADH]) and Cushing syndrome, respectively.^{27,28} In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care (eg, cisplatin, opiates) may also cause hyponatremia.^{29,30} Treatment for SIADH includes fluid restriction (which is difficult for patients because of increased thirst), demeclocycline, or vasopressin receptor inhibitors (ie, conivaptan, tolvaptan; see page 84).^{29,31,32} ADH levels and hyponatremia usually improve after successful treatment of SCLC.³⁰

Staging

The Veteran's Administration Lung Group's 2-stage classification scheme has been routinely used to define the extent of disease in patients with SCLC (see Table 1 in the complete version of these guidelines at NCCN.org [ST-1]): 1) *extensive-stage disease* is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases; and 2) *limited-stage disease* is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field.³³ 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.³⁴ Approximately two-thirds of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow.

A lung cancer TNM staging system was developed by the International Association of the Study of Lung Cancer (IASLC) and adopted by the AJCC Cancer Staging Manual 7th edition (see Tables 2 and 3 in the complete version of these guidelines at NCCN.org [ST-1 and ST-2]).³⁵⁻³⁹ This staging system is applicable to both NSCLC and SCLC based on studies by the IASLC that showed the prognostic significance of the various stage designations in both diseases.^{35,39} Using the TNM staging system, extensive-stage SCLC is T_{any},N_{any},M1a/b, and T3-4 because of multiple lung nodules (see Table 1, available at NCCN.org [ST-1]).

Because most of the literature on SCLC classifies patients based on limited- or extensive-stage disease, these definitions are still most relevant for clinical decision making. For now, application of the TNM system will not change how patients are treated; however, clinical research studies should begin to use the TNM system, because it will allow for more precise assessments of prognosis and specific therapy in the future. Therefore, the SCLC algorithm was revised to include the TNM staging information (see Table 2, at NCCN.org [ST-1]).

Full staging includes a history and physical examination; CT scan (with intravenous contrast) of the chest, liver, and adrenal glands; and brain imaging using MRI (preferred) or CT scan (with intravenous contrast).³⁴ However, once a patient has been found to have extensive-stage disease, further staging is optional, except for brain imaging. 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). Unilateral bone marrow aspirates and biopsies may be indicated in select patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia and no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in fewer than 5% of patients.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.⁴⁰⁻⁴⁴ PET/CT is superior to PET alone.⁴⁴ Approximately 19% of patients who undergo PET are upstaged from limited- to extensive-stage disease, whereas only 8% are downstaged from extensive- to limited-stage disease.³⁴ For most metastatic sites, PET/CT is superior to standard imaging; however, PET/CT is inferior to MRI or CT for the detection of brain metastases (see the NCCN Clinical Practice Guidelines in Oncology for Central Nervous System Cancers; to view the most recent version of these guidelines, visit NCCN.org).⁴⁵ 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.^{34,41,46,47} Although PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that result in upstaging.

Mediastinal staging is typically not required for patients with extensive-stage disease because they are not candidates for surgical resection, and non-surgical treatment is usually planned. Thoracentesis with cytological 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.

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 an abnormal alkaline phosphatase level. Brain imaging (MRI preferred or CT scan) can identify central nervous system 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.

Prognostic Factors

Extensive-stage disease, poor PS (3–4), weight loss, and markers associated with excessive bulk of disease (eg, lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease.^{48–50}

Chemotherapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment.⁷ Adjuvant chemotherapy is recommended for those who have undergone surgical resection. 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 pages 81 and 85 for recommended regimens). In patients with extensive disease and brain metastases, chemotherapy can be given either before or after whole-brain radiotherapy, depending on whether the patient has neurologic symptoms (see page 81).^{8,51}

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.^{52–54} Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see page 85).^{7,55,56} This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.⁵⁷

In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin carries a greater risk of myelosuppression.⁵⁸ Small randomized trials have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC.^{59,60} A meta-analysis of 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.⁶¹ Of 663 patients included in this meta-analysis, 32% had limited-stage and 68% had extensive-stage disease. No significant difference was observed in response rate (67% vs. 66%), progression-free survival (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 panel recommends etoposide plus platinum as the standard regimen for patients with SCLC. Recently, the combination of irinotecan and a platinum agent has provided the greatest challenge to EP.

Initially, a small phase III 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 ($P=.002$).⁶² In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.⁶² However, 2 subsequent large phase III trials performed in the United States comparing irinotecan plus cisplatin versus EP failed to show a significant difference in response rate or overall survival between the regimens.^{63,64}

A randomized phase II trial (n=70) comparing carboplatin and irinotecan versus carboplatin and etoposide showed a modest improvement in progression-free survival with the irinotecan combination.⁶⁵ A phase III 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; $P=.04$).⁶⁶ Based on these findings, the carboplatin and irinotecan regimen has been added to these guidelines as an option for patients with extensive-stage disease. A recent meta-analysis suggests an improvement in progression-free survival and overall survival with irinotecan plus platinum regimens compared with etoposide plus platinum regimens.⁶⁷ However, this meta-analysis was not performed using individual patient data. In addition, the relatively small absolute survival benefit must be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the panel continues to recommend etoposide plus platinum as the standard regimen for patients with SCLC.

In patients with extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.⁵² Unfortunately, median survival rates are only 9 to 11 months for patients with extensive-stage disease. After appropriate treatment, the 2-year survival rate is less than 5% in those with extensive-stage disease.⁶⁸

Many strategies have been evaluated in an effort to improve on the results that have been achieved with standard treatment for extensive-stage SCLC, including the addition of a third agent to standard 2-drug regimens. In 2 trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP showed a modest survival advantage for patients with extensive disease.^{69,70} However, these findings have not been uniformly observed, and the addition of an alkylating agent, with or without an anthracycline, significantly increases hematologic toxicity compared with EP alone.⁷¹ Similarly, the addition of paclitaxel to either cisplatin or carboplatin plus etoposide yielded promising results in phase II trials but did not improve survival, and was associated with unacceptable toxicity in a subsequent phase III study.⁷² The use of maintenance or consolidation chemotherapy beyond 4 to 6 cycles of standard treatment produces a minor prolongation of duration of response without improving survival and carries a greater risk of cumulative toxicity.⁷³

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.⁷⁴ However, randomized trials have failed to show improved progression-free or overall survival with this approach.^{75,76}

Multidrug cyclic weekly therapy was designed to increase dose intensity. Early phase II results of this approach were promising, although favorable patient selection was of some concern.^{77,78} Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.^{79–82}

The role of higher-dose therapy for patients with SCLC remains controversial.⁸³ Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high doses compared with those given conventional doses of the same agents.⁸⁴ In general, however, randomized trials comparing conventional doses with an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival.^{85–88} In addition, a meta-analysis of trials that compared standard versus dose-intense variations of the CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine) 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.⁸⁹

Currently available cytokines (eg, granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor) 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,⁹⁰ little evidence suggests that maintenance of dose intensity with growth factors prolongs disease-free or overall survival, and the routine use of growth factors at the initiation of chemotherapy is not recommended.

The potential benefits of antiangiogenic therapy have begun to be evaluated in SCLC. In extensive-stage SCLC, 2 phase II trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.^{91–93} Randomized phase III trials are ongoing to determine if the addition of bevacizumab to chemotherapy improves survival in patients with extensive-stage SCLC. Currently, the panel does not recommend use of bevacizumab in patients with SCLC.

Overall, attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy regimens, maintenance therapy, or alternating non-cross-resistant chemotherapy regimens have failed to yield significant advantages compared with standard approaches.

Elderly Patients

The incidence of lung cancer increases with age. Although the median age at diagnosis is 70 years, elderly patients are underrepresented in clinical trials.⁹⁴ Although advanced chronologic age adversely affects tolerance to treatment, an individual patient's functional status is much more useful than age in guiding clinical decision-making (see the NCCN Clinical Practice Guidelines in Oncology for Senior Adult Oncology; to view the most recent version of these guidelines, visit NCCN.org). Older patients who are functional in terms of their ability to perform activities of daily living should be treated with standard combination chemotherapy (and radiotherapy, if indicated). 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).^{95,96} Several other strategies have been evaluated in elderly patients with SCLC.^{60,97–99} 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.⁹⁹ However, targeting carboplatin to an AUC of 5, rather than 6, may be more reasonable in this population.¹⁰⁰

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 standard therapy.¹⁰¹

Second-Line (Subsequent) Therapy

Although SCLC is very responsive to initial treatment, most patients experience relapse with relatively resistant disease.^{102,103} These patients have a median survival of only 4 to 5 months when treated with further chemotherapy. Second-line (ie, subsequent) chemotherapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse. If this interval is less than 3 months (refractory or resistant disease), response to most agents or regimens is poor (10%). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25%.

Subsequent chemotherapy generally involves single-agent therapy. Based on phase II trials, active subsequent agents include paclitaxel, docetaxel, topotecan, irinotecan, vinorelbine, gemcitabine, ifosfamide, temozolomide, and oral etoposide (see page 85).^{56,104–108} Recent data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated methyguanine-DNA methyltransferase.¹⁰⁴

A randomized phase III trial compared single-agent intravenous topotecan with the combination regimen CAV.¹⁰⁹ Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase III trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).¹¹⁰ Single-agent topotecan is FDA-approved as subsequent therapy for patients with SCLC who experience initial response to chemotherapy but then experience progression after 2 to 3 months. In the algorithm, topotecan is recommended as a subsequent agent for patients with relapsed SCLC (category 1 for relapse >2–3 months up to 6 months; category 2A for relapse <2–3 months).^{105,109,111} Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.^{110,111}

Many practicing oncologists have noted excessive toxicity with the standard regimen of 1.5 mg/m² of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.¹¹² Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC, and this approach remains under investigation.^{113,114}

Recent data from phase II studies suggest that amrubicin, an investigational anthracycline, has promising activity in patients with relapsed or refractory SCLC.^{115–117} However, grade 3/4 toxicity, primarily neutropenia, is common.¹¹⁸ A randomized phase II trial suggests that amrubicin may be more effective than topotecan as second-line therapy in patients with relapsed SCLC, with response rates of 44% and 15%, respectively ($P=.02$).¹¹⁹

The optimal duration of subsequent chemotherapy 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 chemotherapy should be given until 2 cycles beyond best response, progression of disease, or development of unacceptable toxicity.

Radiotherapy

The Principles of Radiation Therapy section in the NCCN SCLC algorithm describes the radiation doses, target volumes, and normal tissue dose volume constraints for SCLC, and

includes references to support the recommendations; PCI and treatment of brain metastases are also discussed. These radiotherapy principles were updated extensively in 2012, especially for PCI (see page 86). The Principles of Radiation Therapy section in the NCCN Guidelines for NSCLC may also be useful (eg, general principles of radiotherapy, palliative radiotherapy; to view the most recent version of these guidelines, visit NCCN.org).

This section describes the studies supporting the NCCN recommendations.

Thoracic Radiotherapy

The minimum standard for thoracic irradiation is CT-planned 3D conformal radiotherapy. More advanced technologies may also be used when needed (eg, 4D CT; see page 86). 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 & Measurement. However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.^{120,121}

The normal tissue constraints used for NSCLC are appropriate when using similar radiotherapy doses (see the NCCN Guidelines for NSCLC, available at NCCN.org). When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALGB 30610/RTOG 0538 protocol can be used as a guide (see page 86).^{122–124} Intensity-modulated radiation therapy may be considered in select patients (see page 86 and the NCCN Guidelines for NSCLC, available at NCCN.org).¹²⁵

Based on the results of a randomized trial by Jeremic et al,¹²⁶ the addition of sequential thoracic radiotherapy may be considered in select patients with low-bulk metastatic 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.¹²⁶ The investigators found that the addition of radiotherapy resulted in improved median overall survival (17 vs. 11 months).

PCI

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.¹²⁷ A meta-analysis of all randomized PCI trials (using individual patient data) 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.¹²⁸ 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.¹²⁸ Although the number of patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in patients with limited- and extensive-stage disease.

A randomized trial from the EORTC 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.¹²⁹ Although late complications may occur with PCI (eg, neurocognitive impairment), this is less of an issue in patients with extensive-stage SCLC because long-term survival is rare.^{130,131}

Before the decision is made to administer PCI, a balanced discussion between the patient and physician is necessary. PCI is recommended (category 1) for patients with extensive-stage disease who attain a complete or partial response.^{129,132} The recommended regimens for PCI include 25 Gy in 10 daily fractions (2.5 Gy/fraction), 30 Gy in 10–15 daily fractions, or 24 Gy in 8 daily fractions (see page 86).^{128,129,132} Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with standard doses (25 Gy).^{132,133} PCI should not be given concurrently with systemic chemotherapy, and high total radiotherapy dose (> 30 Gy) should be avoided because of the increased risk of neurotoxicity. Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.^{132,134}

Palliative Treatment

Radiotherapy can provide excellent palliation for patients with localized symptomatic sites of disease (ie, painful bony lesions, spinal cord compression, obstructive atelectasis) or with brain metastases (see page 81 and the NCCN Guidelines for NSCLC, available at NCCN.org).^{135–137} 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 lifespan, surgery is not usually recommended for spinal cord compression. Whole-brain radiotherapy is recommended for brain metastases in patients with SCLC because of the frequent occurrence of multiple metastases (see page 86 and the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).¹³⁸ Although late complications may occur with whole-brain radiotherapy (eg, neurocognitive impairment), this is less of an issue in patients with brain metastases SCLC because long-term survival is rare.¹³⁰

Surveillance

The schedule for follow-up examinations is shown in the algorithm (see page 82); the frequency of surveillance decreases during subsequent years because of the declining risk of recurrence. PET/CT or brain MRI (or 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.^{139,140} Smoking cessation should be encouraged for all patients with SCLC (www.ahrq.gov/clinic/tobacco/tobaqrg.htm), because second primary tumors occur less commonly in patients who quit smoking.^{141–143} Former smokers should be encouraged to remain abstinent.

References

1. Oberg K, Hellman P, Kwekkeboom D, Jelic S. Neuroendocrine bronchial and thymic tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2010; 21(Suppl 5):v220–222. [PubMed: 20555085]
2. 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. [PubMed: 17008692]
3. Navada S, Lai P, Schwartz A, Kalemkerian G. Temporal trends in small cell lung cancer: analysis of the national Surveillance, Epidemiology, and End-Results (SEER) database [abstract]. *J Clin Oncol*. 2006; 24(Suppl 18):Abstract 7082.
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin*. 2012; 62:10–29. [PubMed: 22237781]
5. Murray N, Turrisi AT III. A review of first-line treatment for small-cell lung cancer. *J Thorac Oncol*. 2006; 1:270–278. [PubMed: 17409868]
6. Hann CL, Rudin CM. Management of small-cell lung cancer: incremental changes but hope for the future. *Oncology (Williston Park)*. 2008; 22:1486–1492. [PubMed: 19133604]

7. Johnson BE, Janne PA. Basic treatment considerations using chemotherapy for patients with small cell lung cancer. *Hematol Oncol Clin North Am.* 2004; 18:309–322. [PubMed: 15094173]
8. 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. [PubMed: 20044461]
9. Videtic GM, 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. [PubMed: 12697879]
10. Zakowski MF. Pathology of small cell carcinoma of the lung. *Semin Oncol.* 2003; 30:3–8. [PubMed: 12635085]
11. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. *J Clin Oncol.* 2004; 22:2730–2739. [PubMed: 15226341]
12. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer.* 1997; 79:1729–1736. [PubMed: 9128989]
13. Remick SC, Ruckdeschel JC. Extrapulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. *Med Pediatr Oncol.* 1992; 20:89–99. [PubMed: 1310345]
14. Johnson BE, Whang-Peng J, Naylor SL, et al. Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. *J Natl Cancer Inst.* 1989; 81:1223–1228. [PubMed: 2569043]
15. 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. [PubMed: 7524299]
16. Travis WD. Advances in neuroendocrine lung tumors. *Ann Oncol.* 2010; 21(Suppl 7):vii65–71. [PubMed: 20943645]
17. Gustafsson BI, Kidd M, Chan A, et al. Bronchopulmonary neuroendocrine tumors. *Cancer.* 2008; 113:5–21. [PubMed: 18473355]
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. [PubMed: 15859631]
19. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-mortality with low-dose computed tomographic screening. *N Engl J Med.* 2011; 365:395–409. [PubMed: 21714641]
20. 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. [PubMed: 21623258]
21. Gandhi L, Johnson BE. Paraneoplastic syndromes associated with small cell lung cancer. *J Natl Compr Canc Netw.* 2006; 4:631–638. [PubMed: 16813730]
22. 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. [PubMed: 21450098]
23. Marchioli CC, Graziano SL. Paraneoplastic syndromes associated with small cell lung cancer. *Chest Surg Clin N Am.* 1997; 7:65–80. [PubMed: 9001756]
24. 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. [PubMed: 18779614]
25. 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. [PubMed: 8957015]
26. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain.* 2001; 124:1138–1148. [PubMed: 11353730]
27. Delisle L, Boyer MJ, Warr D, et al. Ectopic corticotropin and small-cell carcinoma of the lung. Clinical features, outcome, and complications. *Arch Intern Med.* 1993; 153:746–752. [PubMed: 8383484]

28. Johnson BE, Chute JP, Rushin J, et al. A prospective patients with lung cancer and hyponatremia of malignancy. *Am J Respir Crit Care Med*. 1997; 156:1669–1678. [PubMed: 9372692]
29. Castillo JJ, Vincent M, Justice E. Diagnosis and management of hyponatremia in cancer patients. *Oncologist*. 2012; 17:756–765. [PubMed: 22618570]
30. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. *Mayo Clin Proc*. 2010; 85:838–854. [PubMed: 20810794]
31. Schrier RW, Gross P, Gheorghiade M, et al. Tolvaptan, a oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006; 355:2099–2112. [PubMed: 17105757]
32. Verbalis JG, Zeltser D, Smith N, et al. Assessment of the efficacy and safety of intravenous conivaptan in patients with euvoalaemic hyponatraemia: subgroup analysis of a randomized, controlled study. *Clin Endocrinol (Oxf)*. 2008; 69:159–168. [PubMed: 18034777]
33. Micke P, Faldum A, Metz T, et al. Staging small cell lung Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer—what limits limited disease? *Lung Cancer*. 2002; 37:271–276. [PubMed: 12234695]
34. Kalemkerian GP. Staging and imaging of small cell lung cancer. *Cancer Imaging*. 2011; 11:253–258. [PubMed: 22245990]
35. Shepherd FA, Crowley J, Van Houtte P, et al. The Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. *J Thorac Oncol*. 2007; 2:1067–1077. [PubMed: 18090577]
36. 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. [PubMed: 19156001]
37. Vallieres E, Shepherd FA, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2009; 4:1049–1059. [PubMed: 19652623]
38. Edge, SB.; Byrd, DR.; Compton, CC., et al. *AJCC Cancer Staging Manual*. 7. New York, NY: Springer; 2010.
39. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. *J Thorac Oncol*. 2007; 2:706–714. [PubMed: 17762336]
40. 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. [PubMed: 19555588]
41. 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. [PubMed: 15310768]
42. Kut V, Spies W, Spies S, et al. Staging and monitoring of cell lung cancer using [18F]fluoro-2-deoxy-D-glucose-positron emission tomography (FDG-PET). *Am J Clin Oncol*. 2007; 30:45–50. [PubMed: 17278894]
43. Azad A, Chionh F, Scott AM, et al. High impact of 18F-FDG-PET on management and prognostic stratification of newly diagnosed small cell lung cancer. *Mol Imaging Biol*. 2010; 12:443–451. [PubMed: 19921339]
44. Fischer BM, Mortensen J, Langer SW, et al. A prospective 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. [PubMed: 17060487]
45. Brink I, Schumacher T, Mix M, et al. Impact of [18F]FDG-PET the primary staging of small-cell lung cancer. *Eur J Nucl Med Mol Imaging*. 2004; 31:1614–1620. [PubMed: 15258700]
46. 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. [PubMed: 14660716]
47. Vinjamuri M, Craig M, Campbell-Fontaine A, et al. Can positron emission tomography be used as a staging tool for small-cell lung cancer? *Clin Lung Cancer*. 2008; 9:30–34. [PubMed: 18282355]
48. 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. [PubMed: 19402175]

49. 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. [PubMed: 2167954]
50. Yip D, Harper PG. Predictive and prognostic factors in small cell lung cancer: current status. *Lung Cancer.* 2000; 28:173–185. [PubMed: 10812187]
51. Postmus PE, Haaxma-Reiche H, Gregor A, et al. Brain metastases of small cell lung cancer; efficacy of whole brain radiotherapy. An EORTC phase II study. *Radiother Oncol.* 1998; 46:29–32. [PubMed: 9488124]
52. Simon M, Argiris A, Murren JR. Progress in the therapy of small cell lung cancer. *Crit Rev Oncol Hematol.* 2004; 49:119–133. [PubMed: 15012973]
53. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med.* 2004; 350:379–392. [PubMed: 14736930]
54. Johnson BE. Management of small cell lung cancer. *Clin Chest Med.* 2002; 23:225–239. [PubMed: 11901913]
55. 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. [PubMed: 2997406]
56. Jackman DM, Johnson BE. Small-cell lung cancer. *Lancet.* 2005; 366:1385–1396. [PubMed: 16226617]
57. 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. [PubMed: 12488411]
58. Bishop JF, Raghavan D, Stuart-Harris R, et al. (CBDCA, JM-8) and VP-16-213 in previously untreated patients with small-cell lung cancer. *J Clin Oncol.* 1987; 5:1574–1578. [PubMed: 2821197]
59. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized 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. [PubMed: 7993835]
60. 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. [PubMed: 17579629]
61. 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. [PubMed: 22473169]
62. 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. [PubMed: 11784874]
63. Lara PN Jr, Natale R, Crowley J, et al. Phase III trial of 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. [PubMed: 19349543]
64. 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. [PubMed: 16648503]
65. 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. [PubMed: 16423848]
66. 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. [PubMed: 18779613]
67. Lima JP, dos Santos LV, Sasse EC, et al. Camptothecins 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. [PubMed: 20978445]
68. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol.* 1999; 17:1794–1801. [PubMed: 10561217]

69. 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. [PubMed: 7595712]
70. 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. [PubMed: 11181777]
71. 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. [PubMed: 1334539]
72. Niell HB, Herndon JE II, Miller AA, et al. Randomized 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. [PubMed: 15923572]
73. 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. [PubMed: 11304763]
74. 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. [PubMed: 526911]
75. 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. [PubMed: 1648142]
76. 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. [PubMed: 1310103]
77. Miles DW, Earl HM, Souhami RL, et al. Intensive chemotherapy for good-prognosis patients with small-cell lung cancer. *J Clin Oncol.* 1991; 9:280–285. [PubMed: 1846406]
78. 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.
79. Sculier JP, Paesmans M, Bureau G, et al. Multiple-drug 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. [PubMed: 8410110]
80. 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. [PubMed: 8083704]
81. 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. [PubMed: 9010043]
82. Murray N, Livingston RB, Shepherd FA, et al. Randomized 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. [PubMed: 10561291]
83. Teicher, BA. Preclinical models for high-dose therapy. In: Armitage, JO.; Antman, KH., editors. *High-Dose Cancer Therapy: for Pharmacology, Hematopoietins, Stem Cells.* 2. Baltimore, MD: Williams and Wilkins; 1995. p. 14-42.
84. Cohen MH, Creaven PJ, Fossieck BE Jr, et al. Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep.* 1977; 61:349–354. [PubMed: 194691]
85. 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. [PubMed: 2824707]

86. 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. [PubMed: 7931470]
87. 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. [PubMed: 8247036]
88. 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. [PubMed: 10637255]
89. 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. [PubMed: 1847968]
90. 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. [PubMed: 1711156]
91. 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. [PubMed: 21502556]
92. 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. [PubMed: 19875975]
93. 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. [PubMed: 19826110]
94. Hurria A, Kris MG. Management of lung cancer in older adults. *CA Cancer J Clin.* 2003; 53:325–341. [PubMed: 15224973]
95. 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. [PubMed: 8774567]
96. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst.* 1997; 89:577–580. [PubMed: 9106647]
97. 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. [PubMed: 15143079]
98. 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. [PubMed: 9586913]
99. 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. [PubMed: 10550152]
100. 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. [PubMed: 11506300]
101. 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. [PubMed: 9779708]
102. 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. [PubMed: 19819917]
103. Schneider BJ. Management of recurrent small cell lung. *Natl Compr Canc Netw.* 2008; 6:323–331.

104. 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. [PubMed: 22228633]
105. 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. [PubMed: 17409809]
106. Ettinger DS. New drugs for chemotherapy-naïve patients with extensive-disease small cell lung cancer. *Semin Oncol.* 2001; 28:27–29. [PubMed: 11479894]
107. Kelly K. New chemotherapy agents for small cell lung cancer. *Chest.* 2000; 117:156S–162S. [PubMed: 10777472]
108. Masters GA, Declerck L, Blanke C, et al. Phase II trial gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group trial 1597. *J Clin Oncol.* 2003; 21:1550–1555. [PubMed: 12697880]
109. 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. [PubMed: 10080612]
110. 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. [PubMed: 17135646]
111. 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. [PubMed: 17513814]
112. 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. [PubMed: 16481389]
113. 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. [PubMed: 17399850]
114. Shipley DL, Hainsworth JD, Spigel DR, et al. Topotecan: 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.
115. 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. [PubMed: 20385980]
116. 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. [PubMed: 18854562]
117. 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. [PubMed: 17135647]
118. 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. [PubMed: 19225927]
119. 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. [PubMed: 21135284]
120. Bogart JA, Herndon JE II, 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. [PubMed: 15145163]
121. 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. [PubMed: 8120547]

122. 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. [PubMed: 15703313]
123. Rose J, Rodrigues G, Yaremko B, et al. Systematic review of volume parameters in the prediction of esophagitis in thoracic radiotherapy. *Radiother Oncol*. 2009; 91:282–287. [PubMed: 18950881]
124. 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. [PubMed: 20934273]
125. 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. [PubMed: 21489716]
126. 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. [PubMed: 10561263]
127. 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. [PubMed: 7707405]
128. 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. [PubMed: 10441603]
129. 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. [PubMed: 17699816]
130. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive sparing during the administration of whole brain radiotherapy and prophylactic cranial irradiation: current concepts and approaches. *J Oncol*. 2010; 2010:198–208.
131. 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. [PubMed: 21353159]
132. 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. [PubMed: 19386548]
133. 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. [PubMed: 20800380]
134. 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. [PubMed: 19047288]
135. 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. [PubMed: 19520448]
136. 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. [PubMed: 21277118]
137. Ferrell B, Koczywas M, Grannis F, Harrington A. Palliative care in lung cancer. *Surg Clin North Am*. 2011; 91:403–417. [PubMed: 21419260]
138. 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. [PubMed: 22513917]
139. Johnson BE, Linnoila RI, Williams JP, et al. Risk of 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. [PubMed: 7799009]

140. Johnson BE. Second lung cancers in patients after treatment for an initial lung cancer. *J Natl Cancer Inst.* 1998; 90:1335–1345. [PubMed: 9747865]
141. 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. [PubMed: 8393311]
142. 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. [PubMed: 9703291]
143. 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.* 2010; 340:b5569. [PubMed: 20093278]

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φDiagnostic/Interventional Radiology

Table 1

Individual Disclosures for the NCCN Small Cell Lung Cancer Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Wallace Akerley, MD	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	Genentech, Inc.	None	None	11/8/11
Paul Bogner, MD	None	None	None	None	1/31/12
Hossein Borghaei, DO, MS	Genentech, Inc.; and Millennium Pharmaceuticals, Inc.	Amgen Inc.; and Genentech, Inc.	None	None	7/2/12
Laura QM Chow, MD	None	None	None	None	3/26/12
Robert J. Downey, MD	None	None	None	None	3/22/12
Leena Gandhi, MD, PhD	None	None	None	None	12/17/11
Apar Kishor P. Ganti, MD	Pfizer Inc.	None	None	None	3/27/12
Ramaswamy Govindan, MD	None	AstraZeneca Pharmaceuticals LP; Boehringer Ingelheim GmbH; Bristol-Myers Squibb Company; Covidien AG; Genentech, Inc.; GlaxoSmithKline; and Pfizer Inc.	None	None	3/28/12
John C. Greco, MD	Sci-Clone; and Teva/Cephalon	None	None	None	4/18/2012
James A. Hayman, MD, MBA	None	None	None	None	2/16/12
Rebecca Suk Heist, MD, MPH	None	None	None	None	11/18/12
Leora Horn, MD, MSc, FRCPC	Boehringer Ingelheim GmbH	Genentech, Inc.; and OSI Pharmaceuticals, Inc.	None	None	8/16/12
Thierry M. Jahan, MD	Eli Lilly and Company; Genentech, Inc.; ImClone Systems Incorporated; Morphotek Inc.; Novartis Pharmaceuticals Corporation; and Merrimack pharmaceuticals	None	None	None	3/27/12
Gregory P. Kalemkerian, MD	Eli Lilly and Company	None	None	None	10/10/12
Marianna Koczywas, MD	None	None	None	None	3/28/12
Billy W. Loo Jr, MD, PhD	None	None	None	Siemens Medical Solutions Diagnostics; and Varian Medical Systems, Inc.	1/31/12
Robert E. Merritt, MD	None	None	None	None	10/11/12
Cesar A. Moran, MD	None	None	None	None	3/27/12
Harvey B. Niell, MD	None	None	None	None	4/7/12
Jamis O'Malley, MD	None	None	None	None	4/13/11

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Jyoti D. Patel, MD	Eli Lilly and Company	Genentech, Inc.	None	None	3/26/12
Neal Ready, MD, PhD	Pfizer Inc.	None	None	None	3/27/12
Charles M. Rudin, MD, PhD	None	Aveo Pharmaceuticals; and Oncothyreon	None	None	12/7/11
Charles C. Williams Jr, MD	None	None	None	None	2/24/12

The NCCN guidelines staff have no conflicts to disclose.