National Comprehensive Cancer Network®

NCCN

Small Cell Lung Cancer

Clinical Practice Guidelines in Oncology

Gregory P. Kalemkerian, MD; Wallace Akerley, MD; Paul Bogner, MD; Hossein Borghaei, DO, MS; Laura QM Chow, MD; Robert J. Downey, MD; Leena Gandhi, MD, PhD; Apar Kishor P. Ganti, MD; Ramaswamy Govindan, MD; John C. Grecula, MD; James Hayman, MD, MBA; Rebecca Suk Heist, MD, MPH; Leora Horn, MD, MSc, FRCPC; Thierry Jahan, MD; Marianna Koczywas, MD; Billy W. Loo Jr, MD, PhD; Robert E. Merritt, MD; Cesar A. Moran, MD; Harvey B. Niell, MD; Janis O'Malley, MD; Jyoti D. Patel, MD; Neal Ready, MD, PhD; Charles M. Rudin, MD, PhD; Charles C. Williams Jr, MD; Kristina Gregory, RN, MSN, OCN; and Miranda Hughes, PhD

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. 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

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. (*JNCCN* 2013;11:78–98)

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.

Please Note

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.

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] Pro-

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NCCN Small Cell Lung Cancer Panel Members

*Gregory P. Kalemkerian, MD/Chair†
University of Michigan Comprehensive Cancer Center
Wallace Akerley, MD†
Huntsman Cancer Institute at the University of Utah
Paul Bogner, MD≠
Roswell Park Cancer Institute
Hossein Borghaei, DO, MS†‡
Fox Chase Cancer Center
Laura QM Chow, MD†
Fred Hutchinson Cancer Research Center/
Seattle Cancer Center Alliance
Robert J. Downey, MD¶
Memorial Sloan-Kettering Cancer Center
Leena Gandhi, MD, PhD†Þ
Dana-Farber/Brigham and Women's Cancer Center
Apar Kishor P. Ganti, MD†
UNMC Eppley Cancer Center at
The Nebraska Medical Center
Ramaswamy Govindan, MD†
Siteman Cancer Center at Barnes-Jewish Hospital and
Washington University School of Medicine
John C. Grecula, MD§
The Ohio State University Comprehensive Cancer Center -
James Cancer Hospital and Solove Research Institute
James Hayman, MD, MBA§
University of Michigan Comprehensive Cancer Center
Rebecca Suk Heist, MD, MPH†
Massachusetts General Hospital Cancer Center
Leora Horn, MD, MSc, FRCPC†
Vanderbilt-Ingram Cancer Center
Thierry Jahan, MD†‡
UCSF Helen Diller Family Comprehensive Cancer Center
Marianna Koczywas, MD†‡Þ
City of Hope Comprehensive Cancer Center
Billy W. Loo Jr, MD, PhD§
Stanford Cancer Institute
Robert E. Merritt, MD¶
Stanford Cancer Institute
Cesar A. Moran, MD≠
The University of Texas MD Anderson Cancer Center
Harvey B. Niell, MD†‡Þ
St. Jude Children's Research Hospital/
University of Tennessee Cancer Institute
Janis O'Malley, MDΦ
University of Alabama at Birmingham
Comprehensive Cancer Center
Jyoti D. Patel, MD†
Robert H. Lurie Comprehensive Cancer Center of
Northwestern University
Neal Ready, MD, PhD†
Duke Cancer Institute
Charles M. Rudin, MD, PhD†Þ
The Sidney Kimmel Comprehensive Cancer Center at
Johns Hopkins
Charles C. Williams Jr, MD†
Moffitt Cancer Center

NCCN Staff: Miranda Hughes, PhD, and Kristina Gregory, RN, MSN, OCN

KEY:
*Writing Committee Member
Specialties: †Medical Oncology; ¶Surgery/Surgical Oncology; §Radiation Oncology/Radiotherapy; ‡Hematology/Hematology Oncology; ÞInternal Medicine; ≠Pathology; ΦDiagnostic/Interventional Radiology

DIAGNOSIS | INITIAL EVALUATION[a] | STAGE

DIAGNOSIS

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

INITIAL EVALUATION[a]

- H&P
- Pathology review
- CBC with differential, platelets
- Electrolytes, liver function tests (LFTs), Ca, LDH
- BUN, creatinine
- Chest/liver/adrenal CT with IV contrast whenever possible
- Brain MRI[a,b] (preferred) or CT with IV contrast whenever possible
- PET/CT scan (if limited stage is suspected)[a,c]
- Smoking cessation counseling and intervention

STAGE

Limited stage[d] (T any, N any, M0; except T3-4 due to multiple lung nodules that do not fit in a tolerable radiation field) → See the full version of these guidelines, available at NCCN.org

Extensive stage[d] (T any, N any, M1a/b; T3-4 due to multiple lung nodules) →

[a]If extensive stage is established, further staging evaluation is optional. However, brain imaging with MRI (preferred) or CT with IV contrast should be obtained in all patients.
[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[c]If PET/CT not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage.
[d]See staging table, available online, in these guidelines, at NCCN.org [ST-1].

SCL-1

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STAGE

INITIAL TREATMENT[e]

Extensive stage (T any, N any, M1a/b; T3-4 due to multiple lung nodules)

- Extensive stage without localized symptomatic sites or brain metastases
  - • Good PS (0-2)
    • Poor PS (3-4) due to SCLC
    → Combination chemotherapy[f] including supportive care[e]
    See the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Palliative Care* → See Response Assessment and Adjuvant Treatment (page 82)
  - • Poor PS (3-4) not due to SCLC → Individualized therapy including supportive care[e] or chemotherapy[f]
    See NCCN Guidelines for Palliative Care* → See Response Assessment and Adjuvant Treatment (page 82)
- Extensive stage + localized symptomatic sites
  - • SVC syndrome
    • Lobar obstruction
    • Bone metastases
    → Chemotherapy[f] ± RT[g] to symptomatic sites
    If high risk of fracture due to osseous structural impairment, consider palliative external-beam RT[g] and orthopedic stabilization → See Response Assessment and Adjuvant Treatment (page 82)
  - Spinal cord compression → RT[g] to symptomatic sites before chemotherapy unless immediate systemic therapy is required
    See NCCN Guidelines for Central Nervous System Cancers* → See Response Assessment and Adjuvant Treatment (page 82)
- Extensive stage with brain metastases
  - Asymptomatic → May administer chemotherapy first, with whole-brain RT[g] after chemotherapy[f] → See Response Assessment and Adjuvant Treatment (page 82)
  - Symptomatic → Whole-brain RT[g] before chemotherapy,[f] unless immediate systemic therapy is required → See Response Assessment and Adjuvant Treatment (page 82)

*To view the most recent version of these guidelines, visit NCCN.org.

[e] See Principles of Supportive Care (page 84).
[f] See Principles of Chemotherapy (page 85).
[g] See Principles of Radiation Therapy (page 86).

SCL-4

RESPONSE ASSESSMENT FOLLOWING INITIAL THERAPY		ADJUVANT TREATMENT	SURVEILLANCE	
• Chest x-ray (optional) • Chest/liver/adrenal CT with IV contrast whenever possible • Brain MRI[b] (preferred) or CT with IV contrast whenever possible, if prophylactic cranial irradiation (PCI) to be given • Other imaging studies, to assess prior sites of involvement, as clinically indicated • CBC, platelets • Electrolytes, LFTs, Ca, BUN, creatinine	Complete response or partial response →	Limited or extensive stage: PCI[g,h,i] (category 1) →	After recovery from primary therapy: • Oncology follow-up visits every 3-4 mo during y 1-2, every 6 mo during y 3-5, then annually ➤ At every visit: H&P, chest imaging, bloodwork as clinically indicated • New pulmonary nodule should initiate workup for potential new primary • Smoking cessation intervention • PET/CT is not recommended for routine follow-up	→ For Relapse, see Second-Line Therapy (facing page)
	Stable disease →		(→ Surveillance, above)	
	Primary progressive disease →		See Subsequent Therapy/Palliation (facing page)	

[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[g]See Principles of Radiation Therapy (page 86).
[h]Not recommended in patients with poor PS or impaired mental function.
[i]Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and CR or near-CR after systemic therapy.

SCL-5

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

PROGRESSIVE DISEASE

SUBSEQUENT THERAPY/PALLIATION

Relapse or primary progressive disease

- PS 0-2 → Subsequent chemotherapy[f] (category 1 for topotecan, see page 85) or Clinical trial or Palliative symptom management, including localized RT to symptomatic sites
  - → Continue until two cycles beyond best response or progression of disease or development of unacceptable toxicity → Clinical trial or Palliative symptom management, including localized RT to symptomatic sites
- PS 3-4 → Palliative symptom management, including localized RT to symptomatic sites

[f]See Principles of Chemotherapy (page 85).

SCL-6

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 ketoconazole. 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

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

PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary therapy:
- Extensive stage (maximum of 4-6 cycles):
  - Cisplatin, 75 mg/m^2 day 1 and etoposide, 100 mg/m^2 days 1, 2, 3[1]
  - Cisplatin, 80 mg/m^2 day 1 and etoposide, 80 mg/m^2 days 1, 2, 3[2]
  - Cisplatin, 25 mg/m^2 days 1, 2, 3 and etoposide, 100 mg/m^2 days 1, 2, 3[3]
  - Carboplatin, AUC 5-6 day 1 and etoposide, 100 mg/m^2 days 1, 2, 3[4]
  - Cisplatin, 60 mg/m^2 day 1 and irinotecan, 60 mg/m^2 days 1, 8, 15[5]
  - Cisplatin, 30 mg/m^2 and irinotecan, 65 mg/m^2 days 1, 8 every 21 days[6]
  - Carboplatin, AUC 5 day 1 and irinotecan, 50 mg/m^2 days 1, 8, and 15[7]

Subsequent chemotherapy:
- Clinical trial preferred.
- Relapse < 2-3 mo, PS 0-2:
  - Paclitaxel[8,9]
  - Docetaxel[10]
  - Topotecan[11,12]
  - Irinotecan[13]
  - Temozolomide, 75 mg/m^2/d x 21 days[14]
  - Gemcitabine[15,16]
  - Ifosfamide[17]
- Relapse > 2-3 mo up to 6 mo:
  - Topotecan PO or IV (category 1)[11,12,18]
  - Paclitaxel[8,9]
  - Docetaxel[10]
  - Irinotecan[13]
  - Gemcitabine[15,16]
  - Vinorelbine[19,20]
  - Oral etoposide[21,22]
  - Temozolomide, 75 mg/m^2/d x 21 days[14]
  - Cyclophosphamide/doxorubicin/vincristine (CAV)[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.

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SCL-C

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 [NSCL-B]) 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, 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/VMAT, IGRT, and motion management strategies. Quality assurance measures are essential and are covered in the NCCN Guidelines for NSCLC (available online at NCCN.org [NSCL-B]).

Extensive Stage:

- Consolidative thoracic RT may be beneficial for selected patients with extensive-stage SCLC who respond to chemotherapy. Studies have demonstrated that consolidative 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 [NSCL-B]).
- 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: the maximum spinal cord dose should be limited to ≤41 Gy (including scatter irradiation) for a prescription of 45 Gy BID in 3 weeks and limited to ≤50 Gy for more protracted schedules.

Prophylactic Cranial Irradiation (PCI):

- In patients with limited- or extensive-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).[3,4]
- Recommended doses for PCI to 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.[5,6]
- 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).[7] 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/radiosurgery (SRS) alone, because these patients tend to develop multiple CNS metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[8,9] 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.[10,11]

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SCL-D

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grams using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful (www.ahrq.gov/clinic/tobacco/tobaqrg.htm).

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 nonsurgical 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/m^2 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 prechemotherapy 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.

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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. Grecula, 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
Janis O'Malley, MD	None	None	None	None	4/13/11
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

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