NCCN Guidelines® Insights

Small Cell Lung Cancer, Version 2.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Small Cell Lung Cancer (SCLC) address all aspects of disease management. These NCCN Guidelines Insights focus on recent updates to the NCCN Guidelines for SCLC regarding immunotherapy, systemic therapy, and radiation therapy. For the 2018 update, new sections were added on "Signs and Symptoms of SCLC" and "Principles of Pathologic Review."

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Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes in the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

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Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Small Cell Lung Cancer
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Small Cell Lung Cancer

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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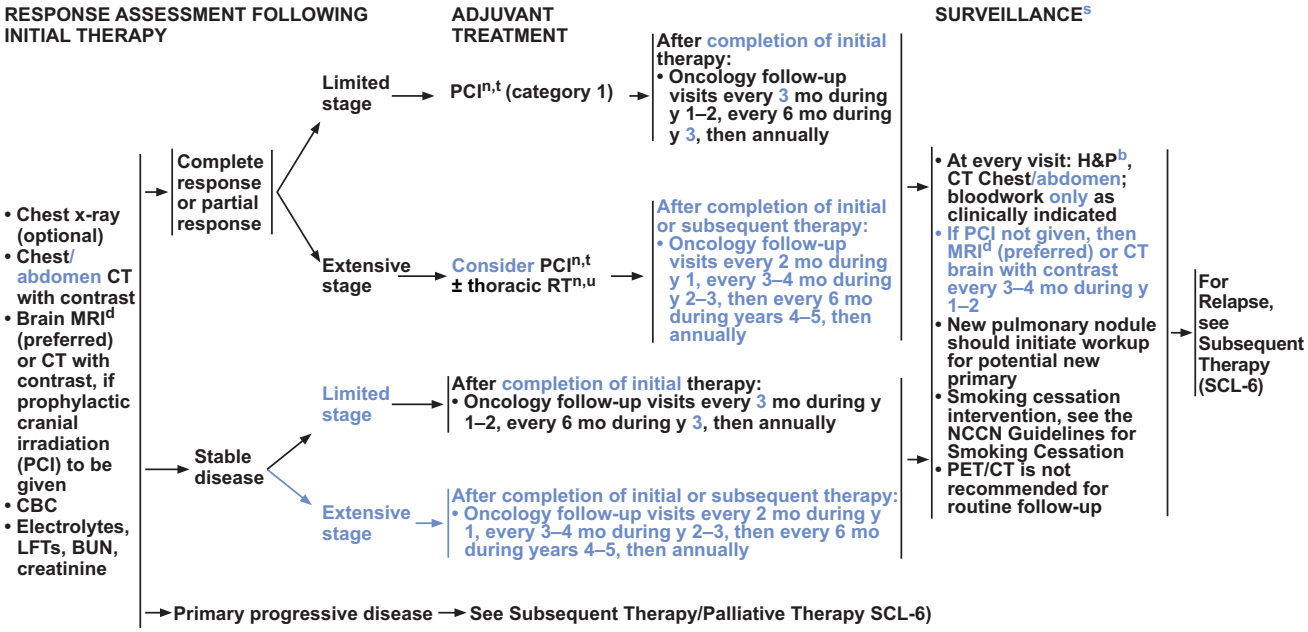

[b]See Signs and Symptoms of Small Cell Lung Cancer (SCL-A).
[d]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[n]See Principles of Radiation Therapy (SCL-F).
[s]See NCCN Guidelines for Survivorship.
[t]Not recommended in patients with poor performance status or impaired neurocognitive function.
[u]Sequential radiotherapy to thorax in selected patients, especially with residual thoracic disease and low-bulk extrathoracic metastatic disease that has responded to systemic therapy.

SCL-5

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 patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (14%) are small cell lung cancer (SCLC).[1,2] In 2018, an estimated 29,501 new cases of SCLC will occur in the United States.[1,3] Nearly all cases of SCLC are attributable to cigarette smoking.[4] Smoking cessation should be strongly promoted in patients with SCLC (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Smoking Cessation, available at NCCN.org).[5] SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. These NCCN Guidelines Insights focus on recent updates in immunotherapy, systemic therapy, and radiation therapy (RT) for patients with SCLC. For a full list of the 2018 updates, see the complete version of the NCCN Guidelines (available at NCCN.org). The NCCN Guidelines for SCLC address all aspects of disease management.

Patients with SCLC typically present with a large hilar mass and bulky mediastinal lymphade-

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SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and symptoms due to local primary tumor growth
- Cough–endobronchial irritation, bronchial compression
- Hemoptysis–usually central or cavitary lesion
- Wheezing–partially obstructing endobronchial lesion
- Fever–post-obstructive pneumonia
- Dyspnea–bronchial obstruction, pneumonia, pleural effusion

Signs and symptoms due to primary tumor invasion or regional lymphatic metastases
- Hoarseness–left vocal cord paralysis due to tumor invasion or lymphadenopathy in the aorto-pulmonary window
- Hemidiaphragm elevation–due to phrenic nerve compression
- Dysphagia–due to esophageal compression
- Chest pain–involvement of pleura or chest wall, often dull and non-localized
- Superior vena cava syndrome–due to local invasion into mediastinum or lymphadenopathy in right paratracheal region
- Pericardial effusion and tamponade
- Cervical or supraclavicular lymph node enlargement

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

nopathy that cause cough and dyspnea.[6] They also frequently present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. For the 2018 update, the NCCN panel added a new section describing signs and symptoms of SCLC based on the tumor location and type of metastases (see SCL-A, pages 1174 and 1175). Most patients with SCLC present with extensive-stage disease with hematogenous metastases; approximately one-third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and RT; however, most patients eventually die of treatment-resistant recurrent disease.[7] Surgery is only appropriate for the few patients (2%–5%) with surgically resectable stage I SCLC.[8] Adjuvant chemotherapy is recommended for all patients after resection. In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic RT and prophylactic cranial irradiation (PCI), when appropriate.[9,10] In most patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival; however, long-term survival is rare.[11]

For the 2018 update, the NCCN panel added a new section on pathology to the Guidelines (see SCL-B 1 of 2, page 1176). The WHO classification system is currently used to classify lung tumors.[12–14] SCLC is a poorly differentiated tumor that is categorized as a high-grade neuroendocrine carcinoma. 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.[15,16] The cells are round, oval, or spindle-shaped, and nuclear molding is prominent.[17] The classic and distinctive histology on hematoxylin and eosin may be sufficient for identifying SCLC in good-quality histologic samples.[15]

Editor's Note: Additional updates were made to the NCCN Guidelines for SCLC (Version 1.2019) after the final review/approval of these NCCN

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SIGNS AND SYMPTOMS OF SMALL CELL LUNG CANCER

Signs and symptoms of paraneoplastic syndromes:
- Presence does not imply metastases or incurability

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

- Neurologic: All specific syndromes are rare
  - Subacute cerebellar degeneration [anti-Yo antibody]–ataxia, dysarthria
  - Encephalomyelitis [ANNA-1 (anti-Hu) antibody]–confusion, obtundation, dementia
  - Sensory neuropathy [anti-dorsal root ganglion antibody]–pain, sensory loss
  - Eaton-Lambert syndrome [anti-voltage-gated calcium channel antibody]–weakness, autonomic dysfunction
  - Cancer-associated retinopathy [anti-recoverin antibody]–visual loss, photosensitivity

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

SCL-A
2 OF 2

Guidelines Insights; readers should refer to the latest version of the NCCN Guidelines for SCLC for the most current recommendations, including new regimens (available at NCCN.org).

Radiation Therapy

Thoracic RT

The addition of thoracic RT to chemotherapy has improved survival for patients with limited-stage SCLC. A meta-analysis of >2,000 patients (individual data) showed that chemotherapy/RT for limited-stage SCLC yields a 14% reduction in the mortality rate (relative risk of death, 0.86; 95% CI, 0.78–0.94; *P*=.001) and a corresponding absolute difference of 5.4% (±1.4%) in the 3-year survival rate compared with chemotherapy alone.[18] The 3-year survival rates were 14.3% (±1.1%) for chemotherapy/RT versus 8.9% (±0.9%) for chemotherapy alone. Another meta-analysis in >1,900 patients with limited-stage SCLC showed an absolute difference of 5.4% (95% CI, 1.1%–9.7%) in the 2-year survival rate for chemotherapy/RT versus chemotherapy alone.[19] Local control improved by 25.3% (95% CI, 16.5%–34.1%) for chemotherapy/RT versus chemotherapy alone. However, achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge.

ECOG/RTOG compared once-daily versus twice-daily RT with etoposide and cisplatin.[20] In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiotherapy using a total thoracic RT dose of 45 Gy delivered either twice daily for 3 weeks or once daily for 5 weeks. The 3-week regimen produced a survival advantage, but a higher incidence of grade 3 to 4 esophagitis was observed compared with the 5-week regimen. Median overall survival (OS) rates were 23 versus 19 months (*P*=.04), and 5-year OS rates were 26% versus 16% in the 3-week and 5-week RT arms, respectively, thus demonstrating the higher biologi-

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PRINCIPLES OF PATHOLOGIC REVIEW*

Pathologic Evaluation

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

Immunohistochemical Staining

- Immunohistochemistry can be very helpful in diagnosing SCLC in limited samples.[5,7]
  - Nearly all SCLCs are positive for cytokeratin antibody mixtures with broad reactivity, such as AE1/AE3 and CAM5.2.[1,10]
  - The majority of SCLCs are reactive to markers of neuroendocrine differentiation, including CD56/NCAM, synaptophysin, and chromogranin A. Fewer than 10% of SCLCs are negative for all neuroendocrine markers.
  - Thyroid transcription factor-1 (TTF1) is positive in 85% to 90% of SCLCs.[11-14]
- Ki-67 immunostaining can be very helpful in distinguishing SCLC from carcinoid tumors, especially in small biopsy samples with crushed or necrotic tumor cells in which counting mitotic figures is difficult.[4,5]
  - The Ki-67 proliferative index in SCLC is typically 50% to 100%.[1]

*References available in these guidelines at NCCN.org.

cal effectiveness of accelerated RT.[20] However, the radiation doses in the 2 arms were not biologically equivalent. Patients in the 5-week arm received a radiation dose less than the current standard of care, whereas those in the 3-week arm received a biologically higher dose due to the shorter time frame for complete delivery of RT.

A randomized phase III trial (CONVERT) assessed once versus twice daily thoracic RT at doses that were biologically similar, 45 Gy twice daily for 3 weeks versus 66 Gy once daily for 6.5 weeks, in patients with limited-stage SCLC.[21] Median OS was similar between the 2 arms (30 vs 25 months; hazard ratio [HR] for death in the once-daily group, 1.18; 95% CI, 0.95–1.45; *P*=.14). Although toxicity was generally similar between the arms, patients receiving 45 Gy of accelerated RT had more grade 4 neutropenia than those receiving 66 Gy of conventional RT (49% [129/266] vs 38% [101/263]; *P*=.05). Based on data from randomized trials, the optimal dose and fractionation of thoracic RT for SCLC remain unresolved. The NCCN panel recommends 2 options depending on individual patient characteristics: (1) 45 Gy with twice-daily fractionation for 3 weeks, or (2) 60 to 70 Gy with once-daily fractionation for 6 to 7 weeks (see SCL-F 1 of 3, page 1178). Twice-daily thoracic RT is technically challenging for patients with bilateral mediastinal adenopathy and logistically challenging for many patients and RT centers.

Prophylactic Cranial Irradiation

Intracranial metastases occur in >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.[22] A 1999 meta-analysis of 7 randomized PCI trials (using data from individual patients) reported an absolute 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.[23] This

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PRINCIPLES OF SYSTEMIC THERAPY*

Systemic therapy as primary or adjuvant therapy:

- **Limited stage (maximum of 4–6 cycles):**
  - **Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[1]**
  - **Cisplatin 80 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]**
  - **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[3]**
  - **During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).**
  - **The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).[4]**
- **Extensive stage (maximum of 4–6 cycles):†**
  - **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[5]**
  - **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[6]**
  - **Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[7]**
  - **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[8]**
  - **Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[9]**
  - **Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[10]**
  - **Cisplatin 30 mg/m² days 1, 8 and irinotecan 65 mg/m² days 1, 8[11]**

Subsequent systemic therapy:‡

- **Clinical trial preferred.**
- **Relapse ≤6 mo, PS 0-2:**
  - **Topotecan PO or IV[12-14]**
  - **Irinotecan[15]**
  - **Paclitaxel[16,17]**
  - **Docetaxel[18]**
  - **Temozolomide[19,20]**
  - **Nivolumab ± ipilimumab[21,22]**
  - **Vinorelbine[23,24]**
  - **Oral etoposide[25,26]**
  - **Gemcitabine[27,28]**
  - **Cyclophosphamide/doxorubicin/vincristine (CAV)[12]**
  - **Bendamustine (category 2B)[29]**
- **Relapse >6 mo: original regimen[30,31]**

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

Response Assessment SCL-E 2 of 3

References on SCL-E 3 of 3

*The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.
†If not used as original regimen, may be used as therapy for primary progressive disease.
‡Subsequent systemic therapy refers to second-line and beyond therapy.

SCL-E 1 OF 3

meta-analysis also reported a 5.4% increase in 3-year OS in patients treated with PCI, from 15.3% in the control group to 20.7% in the PCI group. Although the number of patients with extensive-stage disease was small (14%), the observed benefit was similar in patients with both limited-stage and extensive-stage disease. Because patients with limited-stage disease have potential for cure, PCI remains a recommendation for those without high-risk factors for developing cognitive dysfunction.

In a randomized EORTC trial that assessed PCI versus observation in 286 patients with extensive-stage SCLC whose disease had responded to initial chemotherapy, use of PCI decreased symptomatic brain metastases (14.6% vs 40.4%) and increased the 1-year OS rate (27.1% vs 13.3%) compared with observation.[24] However, the trial did not require brain imaging prior to PCI or at follow-up and allowed several PCI doses and fractionation schemes. The survival advantage of PCI was recently challenged by a randomized phase III Japanese trial of 224 patients with extensive-stage SCLC.[25] Patients were required to have an MRI before PCI to confirm the absence of brain metastases and to undergo surveillance MRI every 3 months during year 1 and every 6 months during year 2 to allow for early treatment of asymptomatic metastases. In addition, this trial used a single PCI regimen of 25 Gy in 10 fractions. Median OS was not improved in patients receiving PCI (11.6 months; 95% CI, 9.5–13.3) versus observation (13.7 months; 95% CI, 10.2–16.4) (HR, 1.27; 95% CI, 0.96–1.68; *P*=.094).[25]

Synthesizing these trial results, for the 2018 update the panel softened the recommendation for PCI in patients with extensive-stage disease to *consider* PCI. The panel also added detailed imaging recommendations for patients who do not undergo PCI (see SCL-5, page 1173). For patients with extensive-stage SCLC and good response to initial chemotherapy, reasonable options (depending on individual patient factors) include either PCI or close surveillance of the brain with MRI (preferred)

PRINCIPLES OF RADIATION THERAPY

General Principles:

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

Limited Stage:

- **Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[2] RT should start early, with cycle 1 or 2 of systemic therapy (category 1).[3] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[4]**
- **Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of radiotherapy planning. PET/CT should be obtained, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, PET/CT should be obtained in the treatment position.**
- **Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Consensus on elective nodal irradiation (ENI) is evolving.[5] Several more modern series, both retrospective and prospective, suggest that omission of ENI results in low rates of isolated nodal recurrences (0%–11%, most <5%), particularly when incorporating PET staging/target definition (1.7%–3%).[6-11] ENI has been omitted in current prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial).**
- **In patients who start systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy volume) should be covered.[8,12]**
- **Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established; 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).[13,14] When BID fractionation is used, there should be at least a 6-hour inter-fraction interval to allow for repair of normal tissue. If using once-daily RT, higher doses of 60–70 Gy should be used.[15-18] The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks; accrual to an experimental concomitant boost arm[19] has closed. The European CONVERT trial demonstrated comparable overall survival and toxicity between 45 Gy (BID) and 66 Gy (daily).[20]**

See Extensive Stage, Normal Tissue Dose Constraints, Prophylactic Cranial Irradiation, Brain Metastases on SCL-F 2 of 3
See references on SCL-F 3 of 3

or CT with contrast (in those unable to undergo MRI).

Second-Line and Beyond (Subsequent) Systemic Therapy

Although SCLC is very responsive to initial treatment, most patients experience relapse with relatively resistant disease.[26–28] Randomized phase III trials have demonstrated the benefit of single-agent topotecan orally or intravenously in patients with recurrent SCLC.[29–31] Based on phase II trials, a number of other agents have been recommended as options for subsequent systemic therapy in patients with relapsed disease, including irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab ± ipilimumab, vinorelbine, oral etoposide, gemcitabine, cyclophosphamide/doxorubicin/vincristine (CAV), and bendamustine (category 2A for all agents except bendamustine, which is category 2B) (see SCL-E 1 of 3, page 1177).[32–41] These agents are listed in order of preference in the NCCN Guidelines. Data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O^6-methylguanine-DNA methyltransferase (MGMT).[42–44] Bendamustine has modest activity based on 2 small phase II trials (response rate of 17% for chemoresistant disease and 33% for chemosensitive disease).[45,46] Therefore, bendamustine has a category 2B recommendation in the NCCN Guidelines. Ifosfamide was recently deleted from the NCCN Guidelines because panel members no longer use this agent. A phase III trial (JCOG0605) in Japanese patients with sensitive relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival (median, 18.2 months; 95% CI, 15.7–20.6) compared with topotecan (12.5 months; 95% CI, 10.8–14.9) (HR, 0.67; 90% CI, 0.51–0.88; P=.0079). However, this combination regimen had significant toxicity, and is not recommended as subsequent therapy in the NCCN Guidelines.[47]

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PRINCIPLES OF RADIATION THERAPY

Extensive Stage:

- Consolidative thoracic RT is beneficial for selected patients with extensive-stage SCLC with CR or good response to systemic therapy. Studies have demonstrated that consolidative thoracic RT up to definitive doses is well tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.[21,22] The Dutch CREST randomized trial of modest-dose thoracic RT (30 Gy in 10 fractions) in patients with extensive stage SCLC that responded to systemic therapy demonstrated significantly improved 2-year overall survival and 6-month PFS, although the protocol-defined primary endpoint of 1-year overall survival was not significantly improved.[23] Subsequent exploratory analysis found the benefit of consolidative thoracic RT is limited to the majority of patients who had residual thoracic disease after systemic therapy.[24]
- Dosing and fractionation of consolidative thoracic RT should be individualized within the range of 30 Gy in 10 daily fractions to 60 Gy in 30 daily fractions, or equivalent regimens in this range.

Normal Tissue Dose Constraints:

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

Prophylactic Cranial Irradiation (PCI):

- In patients with limited-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).[25,26] In patients with extensive-stage SCLC that has responded to systemic therapy, PCI decreases brain metastases. A randomized trial conducted by the EORTC found improved overall survival with PCI. However, a Japanese randomized trial found that in patients who had no brain metastases on baseline MRI, PCI[27] did not improve overall survival compared with routine surveillance MRI and treatment of asymptomatic brain metastases upon detection.[28] In patients not receiving PCI, surveillance for metastases by brain imaging should be performed.
- The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions. A shorter course (eg, 20 Gy in 5 fractions) may be appropriate in selected patients with extensive-stage disease. In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy.[29,30]
- Neurocognitive Function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 56% of patients younger than 60 years of age ($P = .009$).[30] Concurrent systemic therapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.
- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.
- When administering PCI, consider adding memantine during and after RT, which has been shown to decrease neurocognitive impairment following whole brain radiation therapy (WBRT) for brain metastases.[31]

Brain Metastases:

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

See General Principles, Limited Stage (SCL-F 1 of 3)
References on SCL-F 3 of 3

Nivolumab, ipilimumab, and pembrolizumab are immune checkpoint inhibitors that stimulate the immune system and thus have different mechanisms of action than standard cytotoxic chemotherapy.[48] The NCCN panel recently added recommendations for nivolumab and nivolumab + ipilimumab (both are category 2A) as subsequent therapy options for patients who have experienced disease relapse ≤6 months after primary therapy.[49] These recommendations are based on a phase I/II trial of patients who received either nivolumab alone or various doses of nivolumab + ipilimumab for relapsed SCLC.[50] Response rates were 10% (10/98) for nivolumab at 3 mg/kg; 23% (14/61) for nivolumab at 1 mg/kg + ipilimumab at 3 mg/kg; and 19% (10/54) for nivolumab at 3 mg/kg + ipilimumab at 1 mg/kg. Responses did not correlate with PD-L1 expression; SCLC has a lower rate of PD-L1 expression than non–small cell lung cancer.[50] Diarrhea was the most common grade 3 or 4 treatment-related adverse event (AE). Overall frequency of grade 3 or 4 AEs was approximately 20%, and <10% of patients discontinued treatment due to treatment-related AEs. Updated preliminary data from an expansion cohort of this trial reported a 1-year OS rate of 42% in patients receiving nivolumab + ipilimumab and 30% in those receiving nivolumab alone.[51] Preliminary data showed a 2-year survival rate of 26% with nivolumab + ipilimumab and 14% with nivolumab alone.[51,52] Recent data suggest that high tumor mutational burden (TMB) correlates with efficacy of nivolumab ± ipilimumab in SCLC.[52] In patients with high TMB, the 1-year OS rate was 62% for nivolumab + ipilimumab and 35% for nivolumab alone. A phase IB study assessed pembrolizumab in 24 patients with pretreated, PD-L1–expressing (≥1%), extensive-stage SCLC.[53] The overall response rate (ORR) was 33% (95% CI, 16%–55%). A broader phase II study evaluated pembrolizumab in 107 patients with relapsed SCLC regardless of PD-L1 expression and reported an ORR of 18.7% (35.7% in patients with PD-L1–positive tumors and 6% in those with PD-L1–negative

tumors).[54] Note that pembrolizumab was not recommended in the NCCN Guidelines for SCLC, Version 2.2018 (see SCL-E 1 of 3, page 1177).

Immune checkpoint inhibitors (ie, nivolumab, ipilimumab, and pembrolizumab) are associated with unique immune-mediated AEs not seen with traditional cytotoxic chemotherapy; therefore, healthcare providers need to be aware of the spectrum of potential immune-mediated AEs, know how to manage them, and educate their patients about possible AEs (see the NCCN Guidelines for Management of Immunotherapy-Related Toxicities, available at NCCN.org).[55,56] For patients with immune-mediated AEs, high-dose corticosteroids are generally recommended based on the severity of the reaction. Nivolumab, ipilimumab, and pembrolizumab should be withheld or discontinued for severe or life-threatening immune-mediated AEs when indicated (see prescribing information).

Rovalpituzumab tesirine is a novel antibody-drug conjugate that targets delta-like protein 3 (DLL3) tumor expression, expressed in >80% of SCLCs. A phase I study of rovalpituzumab tesirine (74 patients with recurrent SCLC) showed an objective response rate of 18%.[57] Recent data are available from a phase II study (TRINITY) of rovalpituzumab tesirine as third-line or higher treatment in patients with DLL3-expressing recurrent SCLC (N=177). The objective response rate was 18% and median OS was 6.7 months.[58] Phase III trials are ongoing for treatment with rovalpituzumab tesirine in the first- and second-line setting. Note that rovalpituzumab tesirine is not currently available outside of a clinical trial and is not recommended in the NCCN Guidelines (see SCL-E 1 of 3, page 1177).

Summary

These NCCN Guidelines Insights focus on recent updates to immunotherapy, systemic therapy, and RT in the 2018 NCCN Guidelines for SCLC; major revisions are shown in the algorithm (see blue font). For patients with limited-stage SCLC, the optimal RT dose and schedule have not been established. However, a recent trial (CONVERT) reported that OS and toxicity are comparable when using either 45 Gy twice daily or 66 Gy once daily.[21] Based on results of a recent Japanese trial, NCCN panel softened the recommendation for adjuvant PCI in patients with extensive-stage disease to *consider* PCI.[25] For patients with extensive-stage disease who have not undergone adjuvant PCI, the NCCN panel added detailed brain imaging recommendations for surveillance based on this trial.

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Posttest Questions

1. Which of the following is/are TRUE about immunotherapy for select patients with SCLC?
   a. Nivolumab alone or in combination with ipilimumab is recommended as first-line therapy
   b. Nivolumab plus ipilimumab has a response rate of approximately 20% as subsequent therapy
   c. Of patients treated with nivolumab alone, 50% will discontinue treatment due to toxicity
   d. High TMB correlates with the efficacy of nivolumab alone or in combination with ipilimumab
   e. b and d
   f. a, c, and d

2. A 62-year-old woman with limited-stage SCLC undergoes treatment with 4 cycles of cisplatin plus etoposide and concurrent thoracic RT. At her clinic visit 4 weeks after her last dose of chemotherapy, she is doing well with an ECOG performance status of 1. Repeat CT scans of the chest and abdomen reveal mild left hilar soft-tissue thickening with no residual mass, no enlarged thoracic lymph nodes, and no evidence of systemic metastases. MRI scan of the brain is normal.

   Which of the following is the most appropriate next step in the management of this woman?
   a. Clinical and radiographic surveillance without further therapy
   b. Topotecan × 4 cycles
   c. Maintenance bevacizumab until disease progression
   d. Prophylactic cranial irradiation
   e. Left upper lobectomy with mediastinal lymph node dissection

3. Which of the following statements regarding SCLC is true?
   a. Most patients are lifelong nonsmokers
   b. Two-thirds of patients present with extensive-stage disease
   c. Neurologic paraneoplastic syndromes occur in most patients
   d. Treatment for limited-stage SCLC is given with palliative intent
   e. SCLC is a well-differentiated neuroendocrine tumor with indolent growth