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Summary of the Guidelines updates

The 2.2009 version of the Small Cell Lung Cancer Guidelines represents the addition of the Discussion section correspondent to the changes in the algorithm.

Summary of the changes in the 1.2009 version of the Small Cell Lung Cancer Guidelines from the 1.2008 version include:

**SCL-2**
- PET scan added to “Bone radiographs of areas showing abnormal uptake on bone scan”.

**SCL-4**
- PET scan added to “Bone radiographs of areas showing abnormal uptake on bone scan”.
- Chemotherapy added as a treatment option for patients with extensive stage disease without localized symptomatic sites or brain metastases and poor PS or severely debilitated.

**SCL-6**
- "Best supportive care" was replaced with “Palliative symptom management, including localized RT to symptomatic sites.”

**SCL-A**
- Second bullet below “Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, bone scan, brain imaging and PET imaging) may be considered for surgical resection.”
- “Patients with nodal metastases may be considered for postoperative radiation therapy” was replaced with “should be treated with postoperative concurrent chemotherapy and mediastinal radiation therapy.”

**SCL-B 1 of 2**
- The regimen cyclophosphamide 1000 mg/m² day 1 and doxorubicin 45 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3 (category 2B) was removed as a recommendation for extensive stage.
- The combination regimen of carboplatin plus irinotecan was added as an option for extensive stage.
- Irinotecan was added as an option for “Subsequent chemotherapy with a relapse < 2-3 mo”.

**SCL-C**
- The recommended radiation dose range for 1.8-2.0 Gy was changed from 50-60 Gy to 60-70 Gy.
- The PCI dose of 25-36 Gy (30 Gy in 15 fractions, 36 Gy in 18 fractions) was removed in addition to the accompanying references. The recommended dose is 25 Gy in 10 fractions with the reference of Le Pechoux C, Hatton M, Kobierska A, et al. Randomized trial of standard dose to a higher dose prophylactic cranial irradiation (PCI) in limited-stage small cell cancer (SCLC) complete responders (CR): Primary endpoint analysis (PCI99-01, IFCT 99-01, EORTC 22003-08004, RTOG 0212). J Clin Oncol 26: 2008 (May 20 suppl; abstr LBA7514).
### SMALL CELL LUNG CANCER

#### DIAGNOSIS

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

#### INITIAL EVALUATION\(^a\)

- H&P
- Pathology review
- Chest x-ray (optional)
- Chest/liver/adrenal CT
- Head MRI (preferred) or CT\(^b\)
- Bone scan (optional if PET scan obtained)
- CBC, platelets
- Electrolytes, liver function tests (LFT), Ca, LDH
- BUN, creatinine
- PET scan (optional)\(^c\)
- Smoking cessation counseling and intervention

#### STAGE\(^d\)

- Limited stage
  - See Additional Workup (SCL-2)
- Extensive stage
  - See Additional Workup (SCL-4)

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\(^a\) If extensive stage is established, further testing for staging is optional.

\(^b\) Head MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.

\(^c\) PET scan can be used as part of the initial evaluation, in addition to the other recommended studies.

\(^d\) See Staging on page ST-1.
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

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STAGE  ADDITIONAL WORKUP

Limited stage

- Unilateral marrow aspiration/biopsy in select patients
- If pleural effusion is seen in chest x-ray, thoracentesis is recommended, if thoracentesis inconclusive, consider thoracoscopy
- Pulmonary function tests (PFTs) (if clinically indicated)
- Bone radiographs of areas showing abnormal uptake on bone scan or PET scan
- MRI of bony lesions, if x-rays negative or inconclusive

Clinical stage T1-2, N0

- PET scan

Limited disease in excess of T1-T2, N0

- Bone marrow biopsy, thoracentesis, or bone studies consistent with malignancy

Mediastinoscopy or Surgical or endoscopic mediastinal staging

See Initial Treatment (SCL-3)

Follow Pathway For Extensive-Stage Disease (See SCL-4)

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\[e\] Selection criteria include: nucleated RBCs on peripheral blood smear, neutropenia, or thrombocytopenia.

[1] Most pleural effusions in patients with lung cancer are due to cancer; however, if the effusion is too small to allow image-guided sampling, then the effusion should not be considered in staging. If multiple cytological examinations of pleural fluid are negative for cancer, fluid is not bloody and not an exudate and clinical judgment suggests that the effusion is not directly related to the cancer, then the effusion should not be considered in staging.

[9] PET scan to identify distant disease and to guide mediastinal evaluation.


[4] If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.
**Small Cell Lung Cancer**

**INITIAL TREATMENT**

**TESTING RESULTS**

- **Mediastinoscopy or mediastinal staging negative**
  - Clinical stage T1-2, N0
    - **Lobectomy (preferred) and mediastinal lymph node dissection or sampling**
      - N0 → Chemotherapy
      - N+ → Concurrent chemotherapy + mediastinal RT
  - **Good performance status (PS 0-2)**
    - Chemotherapy + concurrent thoracic RT (category 1)
  - **Poor PS (3-4) due to SCLC**
    - Chemotherapy ± RT
  - **Poor PS (3-4) not due to SCLC**
    - Individualized treatment including supportive care regimens

- **Mediastinoscopy or mediastinal staging positive**
  - Limited disease in excess of T1-2, N0
    - **Good PS (0-2)**
      - Chemotherapy + concurrent RT (category 1)
    - **Poor PS (3-4) due to SCLC**
      - Chemotherapy ± RT
    - **Poor PS (3-4) not due to SCLC**
      - Individualized treatment including supportive care regimens

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

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**References**

- See Principles of Surgical Resection (SCL-A).
- See Principles of Chemotherapy (SCL-B).
- See Principles of Radiation Therapy (SCL-C).
- See Principles of Supportive Care (SCL-D).

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**See Response Assessment + Adjuvant Treatment (SCL-5)**
Small Cell Lung Cancer

STAGE

Extensive stage

ADDITIONAL WORKUP

Bone radiographs of areas showing abnormal uptake on bone scan or PET scan

Extensive stage without localized symptomatic sites or brain metastases

Combination chemotherapy\(^1\) including supportive care regimens

\[\text{See NCCN Palliative Care Guidelines}\]

Extensive stage + localized symptomatic sites

\[\begin{align*}
&\cdot \text{Poor PS (3-4)} \\
&\cdot \text{Severely debilitated}
\end{align*}\]

Individualized therapy including supportive care regimens or chemotherapy

\[\text{See NCCN Palliative Care Guidelines}\]

\[\begin{align*}
&\cdot \text{SVC syndrome} \\
&\cdot \text{Lobar obstruction} \\
&\cdot \text{Bone metastases}
\end{align*}\]

Chemotherapy\(^{\pm}\) RT to symptomatic sites

For management of osseous structural impairment,

\[\text{See NCCN Bone Cancers Guidelines}\]

Spinal cord compression

Chemotherapy\(^{\pm}\) + RT to symptomatic sites

\[\text{See NCCN CNS Tumors Guidelines}\]

Asymptomatic

May administer chemotherapy first, with whole-brain RT after chemotherapy\(^{\pm}\)

Symptomatic

Whole-brain RT before chemotherapy\(^{\pm}\) unless immediate systemic therapy is required

INTIAL TREATMENT\(^1\)

\[\begin{align*}
&\text{Combination chemotherapy}^{\pm}\text{ including supportive care regimens} \\
&\text{See NCCN Palliative Care Guidelines}
\end{align*}\]

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\(^{\text{See Principles of Chemotherapy (SCL-B)}}\)

\(^{\text{See Principles of Supportive Care (SCL-D)}}\)

\(^{\text{m}}\)Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and CR or near CR after systemic therapy.

\(^{\text{See Response Assessment + Adjuvant Treatment (SCL-5)}}\)
**Response Assessment Following Initial Therapy**

- Complete response or radiation scarring or ≤ 10% of original mass on CT scan
- Partial response
- Primary progressive disease

**Adjuvant Treatment**

- Limited or extensive disease: PCI<sup>k,n</sup> (category 1)
- Consider PCI<sup>k,n</sup>

**Surveillance**

- After recovery from primary therapy:
  - Oncology follow-up visits every 2-3 mo during y 1, every 3-4 mo during y 2-3, every 4-6 mo during y 4-5, then annually
  - At every visit: H&amp;P, chest imaging, bloodwork as clinically indicated
  - New pulmonary nodule after 2 y follow-up should initiate workup for potential new primary
  - Smoking cessation intervention

For Relapse, see Second-line Therapy (SCL-6)

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<sup>k</sup>See Principles of Radiation Therapy (SCL-C).

<sup>n</sup>Not recommended in patients with multiple comorbidities, poor performance status, or impaired mental function.

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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PROGRESSIVE DISEASE  SUBSEQUENT THERAPY/PALLIATION

Relapse

Subsequent chemotherapy or Clinical trial or Palliative symptom management, including localized RT to symptomatic sites

Continue until maximal benefit or refractory to therapy or development of unacceptable toxicity

Clinical trial or Palliative symptom management, including localized RT to symptomatic sites

Primary progressive disease

Palliative symptom management, including localized RT to symptomatic sites or Clinical trial or Subsequent chemotherapy\(^j\) (PS 0–2)

\(^j\)See Principles of Chemotherapy (SCL-B).

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PRINCIPLES OF SURGICAL RESECTION

- Stage I SCLC is diagnosed in less than 5% of patients with SCLC.
- Patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery.\(^1\)
- Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, bone scan, brain imaging, and PET imaging) may be considered for surgical resection.
  - Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.
  - Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy. Patients without nodal metastases should be treated with chemotherapy alone. Patients with nodal metastases should be treated with postoperative concurrent chemotherapy and mediastinal radiation therapy.
- Because prophylactic cranial irradiation (PCI) can improve both disease-free and overall survival in patients with SCLC in complete remission, PCI should be considered after adjuvant chemotherapy in patients who have undergone a complete resection.\(^2\)

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PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary therapy:
- Limited stage:
  - Cisplatin: 60 mg/m^2 day 1 and Etoposide: 120 mg/m^2 days 1, 2, 3 x 4 cycles
  - Carboplatin: AUC 5-6 day 1 and Etoposide: 100 mg/m^2 days 1, 2, 3 x 4 cycles
- During chemotherapy + RT, cisplatin/etoposide is recommended (category 1)

- Extensive stage:
  - Cisplatin: 75 mg/m^2 day 1 and Etoposide: 100 mg/m^2 days 1, 2, 3 x 4-6 cycles
  - Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, 3
  - Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3
  - Carboplatin: AUC 5-6 day 1 and Etoposide: 100 mg/m^2 days 1, 2, 3 x 4-6 cycles
  - Cisplatin: 60 mg/m^2 on day 14 and irinotecan: 60 mg/m^2 on days 1, 8, 15
  - Carboplatin AUC 5 and irinotecan 50 mg/m^2 on days 1, 8, and 15
  - Cyclophosphamide 1000 mg/m^2 day 1 and doxorubicin 45 mg/m^2 day 1 and vincristine 1.4 mg/m^2 day 1 (category 2B)

Subsequent chemotherapy:
- Clinical trial preferred.
- Relapse < 2-3 mo, PS 0-2: ifosfamide, paclitaxel, docetaxel, gemcitabine, irinotecan, topotecan.
- Relapse > 2-3 mo up to 6 mo: topotecan (category 1), irinotecan, cyclophosphamide/doxorubicin/vincristine (CAV), gemcitabine, paclitaxel, docetaxel, oral etoposide, vinorelbine.
- Relapse > 6 mo: original regimen.

Consider dose reductions versus growth factors in the poor performance status patient

*The regimens included are representative of the more commonly used regimens for Small Cell Lung Cancer.

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

References


### PRINCIPLES OF RADIATION THERAPY

**Radiotherapy for limited disease:**
- Radiotherapy should be delivered as either 1.5 Gy bid to a total dose of 45 Gy, or 1.8-2.0 Gy once daily to 60-70 Gy.\(^1\)\(^-\)\(^4\)
- Start with chemotherapy cycle 1 or 2 (category 1)
- The radiation target volumes should be defined on the CT scan obtained at the time of radiotherapy planning. However, the pre-chemotherapy CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.\(^5\)\(^,\)\(^6\)
- Concurrent chemoradiotherapy preferable to sequential therapy in fit patients (category 1)
- Three-dimensional (3D) conformal radiation techniques are preferred, if available.
- PCI dose 25 Gy in 10 fractions\(^7\)

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PRINCIPLES OF SUPPORTIVE CARE

- Smoking cessation counseling

- Granulocyte colony-stimulating factor (GCSF) or granulocyte-macrophage colony-stimulating factor (GMCSF) during RT is not recommended (category 1 for GMSCF). See the NCCN Myeloid Growth Factor Guidelines

- Syndrome of inappropriate antidiuretic hormone
  - Fluid restriction
  - Saline infusion for symptomatic patients
  - Demeclocycline
  - Antineoplastic therapy

- Cushing’s syndrome
  - Consider ketoconazole
  - Try to control before initiation of antineoplastic therapy

- Leptomeningeal disease
  See NCCN Carcinomatous/Lymphomatous Meningitis Guidelines

- Pain Management: See NCCN Adult Cancer Pain Guidelines

- Nausea/Vomiting: See NCCN Antiemesis Guidelines

- Psychosocial distress: See NCCN Distress Management Guidelines

- See NCCN Palliative Care Guidelines as indicated

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Management of endocrine symptoms as indicated (See the Carcinoid Tumors section in the NCCN Neuroendocrine Tumors Guidelines)

PET scan is undergoing evaluation in clinical trials and should only be considered as a supplement and not a replacement to other studies.

For Stage III, typical: RT recommended if surgery is not feasible.

For Stage III, atypical: Chemotherapy/RT is recommended if surgery is not feasible.

There is no substantial evidence for a commonly used regimen. Cisplatin/etoposide is a regimen commonly used at NCCN institutions.

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Table 1 - Definition of Small cell lung cancer consists of two stages:
(1) Limited-stage disease: disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field.
(2) Extensive-stage disease: disease beyond ipsilateral hemithorax which may include malignant pleural or pericardial effusion or hematogenous metastases.

Table 2 - Revised Definition of TNM*

<table>
<thead>
<tr>
<th>Primary Tumor (T)</th>
<th>Regional Lymph Nodes (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy</td>
<td>NX Regional lymph nodes cannot be assessed</td>
</tr>
<tr>
<td>T0 No evidence of primary tumor</td>
<td>N0 No regional lymph node metastasis</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension of the primary tumor</td>
</tr>
<tr>
<td>T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus† (ie, not in the main bronchus)</td>
<td>N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)</td>
</tr>
<tr>
<td>T2 Tumor with any of the following features of size or extent: More than 3 cm in greatest dimension; Involves main bronchus, 2 cm or more distal to the carina; Invades the visceral pleura; Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
<td>N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)</td>
</tr>
<tr>
<td>T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung</td>
<td>MX Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion‡</td>
<td>M0 No distant metastasis</td>
</tr>
<tr>
<td></td>
<td>M1 Distant metastasis present§</td>
</tr>
</tbody>
</table>

§ Most pleural effusions associated with lung cancer are due to tumor. However, in a few patients, multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is not bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be staged T1, T2, or T3.

§ M1 includes separate tumor node(s) in a different lobe (ipsilateral or contralateral).

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.
Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Small cell lung cancer (SCLC) accounts for 15% of all lung cancers. In 2008, approximately 32,000 new cases of SCLC will be diagnosed in the United States. Nearly all cases of SCLC are attributable to cigarette smoking. When compared with non-small cell lung cancer, 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, while only about one third of patients present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die from recurrent disease. In patients with limited-stage SCLC, the goal of treatment with chemotherapy plus thoracic radiotherapy is to achieve a cure. In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients, but long-term survival is rare. Surgery is appropriate for the few patients (2%-5%) with surgically resectable stage I SCLC.

Smoking cessation should be strongly encouraged (http://www.smokefree.gov/hp.html). Patients who smoke have increased toxicity during treatment and shorter survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA [Food and Drug Administration]) can be very useful (http://www.ahrq.gov/path/tobacco.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. The cells are round, oval, or spindle shaped, and 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, which are less commonly detected in specimens from previously untreated patients. This finding has led to the proposal that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along several 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. Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases. However, unlike SCLC, malignant cells from patients with extrapulmonary small cell carcinoma do not exhibit macromolecular 3p deletions, which suggests a different pathogenesis.

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor 1 (TTF1). Most SCLCs also stain positively for markers of neuroendocrine differentiation, including...
chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from non-small cell lung cancer, because approximately 10% of non-small cell lung cancers will be immunoreactive for at least one of these neuroendocrine markers.10

Clinical Manifestations, Staging, and Prognostic Factors

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. Presentation as a solitary peripheral nodule without central adenopathy is uncommon, and, in this situation, fine-needle aspiration may not adequately differentiate small cell carcinoma from typical or atypical carcinoid tumor or from large cell neuroendocrine carcinoma (see LNT-1 and the NCCN Neuroendocrine Tumors Guidelines).

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC. Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. The Lambert-Eaton syndrome presents with proximal leg weakness and is caused by antibodies directed against the voltage-gated calcium channels.11 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.12,13 SCLC cells also can produce numerous polypeptide hormones, including adrenocorticotropic hormone (ACTH) and vasopressin (ADH), which cause Cushing’s syndrome and hyponatremia of malignancy, respectively.14,15

The Veteran’s Administration Lung Group 2-stage classification scheme is routinely used to define the extent of disease in patients with SCLC as shown in Table 1 (see ST-1): (1) limited-stage disease is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field; and (2) extensive-stage disease is defined as disease beyond the ipsilateral hemithorax and may include malignant pleural or pericardial effusion or hematogenous metastases.16 Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, while contralateral hilar and supraclavicular lymphadenopathy usually are classified as extensive-stage disease. 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. Table 2 provides the definitions for TNM that are used for SCLC (see ST-1).

All SCLC patients, even those with radiographically limited-stage disease, require systemic chemotherapy. Therefore, staging provides a therapeutic guideline for chest radiotherapy, which is indicated for patients with limited-stage disease. Full staging includes a history and physical examination; computed tomography (CT) scan including the chest, liver, and adrenal glands; a magnetic resonance imaging (MRI) scan (preferred) or CT scan of the head; and a bone scan (optional if PET scan is obtained); a chest radiograph is optional. Unilateral or bilateral bone marrow aspirates and biopsies may be indicated in patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia and with no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in less than 5% of patients. A positron emission tomography (PET) scan is optional but can be used as part of the initial evaluation in addition to the other recommended studies.

If a pleural effusion is large enough to be seen by a chest radiograph, then thoracentesis is recommended. If thoracentesis does not show malignant cells, then thoracoscopy can be considered to document...
pleural involvement and thus extensive-stage disease. A patient should be considered to have limited-stage disease if the effusion is too small to allow image-guided sampling or if: (1) multiple cytopathologic examinations of pleural fluid are negative for cancer; (2) the fluid is not bloody and not an exudate; and (3) clinical judgment suggests that the effusion is not directly related to the cancer.

Staging should not be directed only to sites of symptomatic disease or sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or an abnormal alkaline phosphatase level. A head MRI or CT scan can identify central nervous system (CNS) metastases in 10% to 15% of patients at diagnosis, of which about 30% are asymptomatic. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the utility of early diagnosis in asymptomatic patients. Due to the aggressive nature of SCLC, staging should not delay the onset of treatment more than 1 week; otherwise, many patients may become more seriously ill in the interval with a decline in their performance status (PS).

Poor PS (3-4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease are the most important adverse prognostic factors. In patients with limited-stage disease, good PS (0-2), female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis. In patients with extensive-stage disease, normal LDH and a single metastatic site are favorable prognostic factors.

Chemotherapy
Chemotherapy is an essential component of appropriate treatment for all patients with SCLC. For those who have undergone successful surgical resection, adjuvant chemotherapy is recommended. For most patients with limited-stage SCLC and good PS (0-2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1). For patients with extensive-stage disease, chemotherapy alone is the recommended treatment. In patients with extensive disease and brain metastases, chemotherapy can be given either before or after whole-brain RT depending on whether or not the patient has neurologic symptoms (see SCL-4).

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC. The most commonly used initial combination chemotherapy regimen is etoposide and cisplatin (EP) (see SCL-B). This combination supplants alkylator/anthracycline-based regimens based on superiority in both efficacy and toxicity in the limited-stage setting. Etoposide and cisplatin plus concurrent thoracic radiotherapy is now the recommended therapy for patients with limited-stage disease (category 1). In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis and pulmonary toxicity. The hematologic toxicity is manageable with dose reductions or growth factor support (see the NCCN Myeloid Growth Factors in Cancer Treatment Guidelines). In clinical practice, carboplatin is frequently substituted for cisplatin in order to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin carries a greater risk of myelosuppression. The substitution of carboplatin for cisplatin in patients with limited-stage disease has not been adequately evaluated and should only be done when cisplatin is contraindicated or poorly tolerated. The substitution of carboplatin for cisplatin is more acceptable in patients with extensive-stage disease, because there is ample data regarding the therapeutic equivalence of the drugs in this setting.

Many other combinations have been evaluated in patients with extensive-stage disease with little consistent evidence of benefit when compared with EP. Most recently, combinations of a platinum with irinotecan have raised significant interest. Initially, a small phase III trial performed in Japan reported that patients with extensive-stage SCLC
who were treated with irinotecan plus carboplatin achieved a median survival of 12.8 months compared to 9.4 months for patients treated with EP ($P = .002$). In addition, 2-year survival was 19.5% in the irinotecan plus cisplatin group and 5.2% in the EP group. However, a subsequent phase III trial performed in the United States comparing irinotecan plus cisplatin to EP failed to demonstrate a significant difference in response rate or overall survival between the regimens.

Another recent large phase III trial in the United States ($n = 645$) also failed to show a significant difference in survival between cisplatin plus irinotecan and EP. 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. A recent 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 versus 7.1 months, $P = .04$). Therefore, the carboplatin and irinotecan regimen has been added to the guidelines as an option for patients with extensive-stage disease.

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

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 demonstrated a modest survival advantage for patients with extensive disease. However, such findings have not been uniformly observed, and the addition of an alkylating agent with or without an anthracycline significantly increased hematologic toxicity when compared to EP alone. Similarly, the addition of paclitaxel to 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. 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.

The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of tumor 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. However, randomized trials have failed to show improved disease-free or overall survival with this approach. Multidrug cyclic weekly therapy was designed to increase the dose-intensity of treatment by taking advantage of the differing toxicities of the weekly agents. Although patient selection effects were of some concern, early phase II results were promising. Nevertheless, no survival benefits were documented in randomized trials and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.
The role of higher-dose therapy for patients with SCLC remains controversial. Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high doses when compared with those given conventional doses of the same agents. In general, however, randomized trials comparing conventional doses to an incrementally increased dose-intensity up to 2 times the full conventional dose have not consistently shown an increased response rate or survival. In addition, a meta-analysis of trials—that compared standard versus dose-intense variations of the CAV and EP regimens—found only a small, clinically insignificant enhancement of median survival in patients with extensive-stage disease when using increased relative dose-intensity. 

Currently available cytokines (for example, GM-CSF and G-CSF) can ameliorate chemotherapy-induced myelosuppression and reduce the incidence of febrile neutropenia, but cumulative thrombocytopenia remains dose-limiting. Although trials involving SCLC patients were instrumental in obtaining Food and Drug Administration (FDA) approval for the clinical use of cytokines, there is little evidence to suggest that maintenance of dose intensity prolongs disease-free or overall survival.

Maintenance therapy with bevacizumab was associated with tracheoesophageal fistulae in patients with limited stage SCLC who had received bevacizumab, irinotecan, carboplatin, and concurrent RT in a phase 2 trial. Note that the NCCN 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 generally failed to yield significant advantages when compared to standard approaches.

**Elderly Patients**

The incidence of lung cancer increases with age; 66% of patients with lung cancer are 65 years or older. However, elderly patients are under-represented in clinical trials. Although advanced chronological age does adversely affect tolerance to treatment, an individual patient’s functional status is much more useful than age in guiding clinical decision making (see the NCCN Senior Adult Oncology Guidelines). If an older person is functional in terms of the ability to perform activities of daily living, he/she 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.

Greater anticipation of the needs and support systems of elderly patients is recommended. However, elderly patients have similar prognoses when compared with younger patients. Randomized trials have indicated that less intensive treatment (for example, single-agent etoposide) is inferior to combination chemotherapy (for example, platinum plus etoposide) in elderly patients with good PS (0-2). Several other strategies have been evaluated in elderly patients with SCLC. The use of 4 cycles of carboplatin plus etoposide appears to yield favorable results, because the AUC (area-under-the-curve) dosing of carboplatin takes into account the declining renal function of the aging patient. However, some patients may not tolerate a dose of carboplatin with an AUC as high as 6. The utility of short-course, full-intensity chemotherapy has also been explored in elderly or infirm patients, and the results with only 2 cycles of chemotherapy appear to be quite acceptable. However, none of these newer approaches have been directly compared with standard therapy.

**Salvage Therapy**

Most patients with SCLC will relapse or progress after initial treatment; these patients have a median survival of only 4 to 5 months when
treated with further chemotherapy. Second-line (that is, 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, response to most agents or regimens is poor (10% or less), indicating refractory SCLC. If greater than 3 months has elapsed, expected response rates are approximately 25%. In phase II trials, active subsequent agents include topotecan, irinotecan, paclitaxel, docetaxel, ifosfamide, oral etoposide, gemcitabine, and vinorelbine (see SCL-B 1 of 2). 24,64-66 In a randomized phase III trial, single-agent topotecan was compared to the combination regimen CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine). 67 Both arms had similar response rates and survival, but topotecan caused less toxicity and is now recommended as the subsequent agent for patients with relapsed SCLC (category 1 for relapse > 2-3 months up to 6 months). 68 Single-agent topotecan is approved by the U.S. Food and Drug Administration as subsequent therapy for patients with SCLC who initially respond to chemotherapy but then progress after 2-3 months.

Recent data from phase II studies suggest that amrubicin, an investigational anthracycline, has promising activity in patients with extensive-stage SCLC that is refractory to or progressing after first-line platinum-based chemotherapy. 69

Subsequent chemotherapy should be given until patients achieve maximal benefit, become refractory to therapy, or develop unacceptable toxicity. For patients with localized symptomatic sites of disease (such as painful bony lesions, obstructive atelectasis, or brain metastases), radiotherapy can provide excellent palliation.

Radiotherapy

Thoracic Radiotherapy

The addition of thoracic radiotherapy has improved survival for patients with limited-stage disease. 2 Meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease causes a 25% to 30% reduction in local failure and a corresponding 5% to 7% improvement in 2-year survival. 19,20 However, achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge.

The administration of thoracic radiotherapy requires the assessment of several factors, including the timing of chemotherapy and radiotherapy (concurrent versus sequential versus alternating therapy), timing of radiotherapy (early versus late), volume of the radiation port (original tumor volume versus shrinking field as the tumor responds), dose of radiation, and fractionation of radiotherapy. A randomized trial by the Japanese Cooperative Oncology Group assessed sequential versus concurrent thoracic radiotherapy combined with EP for patients with limited-stage disease; they reported that patients treated with concurrent radiotherapy lived longer than those treated with sequential radiotherapy. 70 Another randomized phase III trial by the National Cancer Institute of Canada compared radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy; they demonstrated that early radiotherapy was associated with improved local and systemic control and with longer survival. 71 A systematic review on the timing of thoracic radiotherapy in limited-stage SCLC determined that early concurrent radiotherapy results in a small, but significant, improvement in overall survival when compared to late concurrent or sequential radiotherapy. 72

Based on a phase II study by Turrisi et al, 73 the Eastern Cooperative Oncology Group/Radiation Therapy Oncology Group (ECOG/RTOG) compared once a day to twice a day radiotherapy with EP. In this trial, 412 patients with limited-stage SCLC were treated with concurrent
chemoradiotherapy using a total dose of 45 Gy delivered either twice a day over 3 weeks or once a day over 5 weeks. The twice-daily schedule produced a survival advantage and a higher incidence of grade 3-4 esophagitis. Median survival was 23 versus 19 months ($P=0.04$), and 5-year survival was 26% versus 16% in the twice-daily and once-daily radiotherapy arms, respectively.\textsuperscript{74}

A caveat to these encouraging long-term survival results is that twice-daily fractionation is technically challenging for patients with bilateral mediastinal adenopathy. In addition, the once-a-day therapy was not delivered at its maximum tolerated dose, so it remains unclear if hyperfractionation is superior to once daily chest radiotherapy given to a biologically equivalent dose. Another randomized phase III trial demonstrated no survival difference between once-a-day thoracic radiotherapy to 50.4 Gy with concurrent EP and a split-course of twice-a-day thoracic radiotherapy to 48 Gy with concurrent EP.\textsuperscript{75}

However, split-course radiotherapy may be less efficacious because of interval tumor regrowth between courses. Overall, patients selected for combined modality treatment that incorporates twice-a-day radiotherapy must have an excellent PS and good baseline pulmonary function.

For limited-stage disease, the NCCN guidelines recommend that radiation should be delivered concurrently with chemotherapy and should start with the first or second cycle (category 1) at a dose of either 1.5 Gy twice daily to a total dose of 45 Gy, or 1.8 to 2.0 Gy/day to 60 to 70 Gy (see SCLC-C).\textsuperscript{19,72,75-77} Concurrent chemoradiotherapy (category 1) is preferable to sequential therapy in patients with good PS (0-2); 3-dimensional (3D) conformal radiation techniques are preferred, if available. The radiation target volumes should be defined on the CT scan obtained at the time of radiotherapy planning. However, the pre-chemotherapy CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.\textsuperscript{78,79}

Selected patients with low-bulk metastatic disease who have a complete or near complete response after systemic therapy may be considered for sequential thoracic radiotherapy based on a randomized trial that noted improved survival with this approach.\textsuperscript{80}

**Prophylactic Cranial Irradiation**

Intracranial metastases occur in more than 50% of patients with SCLC. Randomized studies have shown that prophylactic cranial irradiation (PCI) is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to demonstrate a meaningful survival advantage.\textsuperscript{81} Moreover, late neurologic sequelae have been attributed to radiotherapy, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrent with chemotherapy. When given after the completion of chemotherapy and at low doses per fractions, PCI may cause less neurological toxicity. Symptomatic brain relapses result in major morbidity, which frequently does not completely resolve with therapeutic cranial irradiation. A meta-analysis of all randomized PCI trials 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.\textsuperscript{82} Thus, it appears that PCI prevents and does 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.\textsuperscript{82} Although the number of patients in this meta-analysis with extensive-stage disease was small, the observed benefit was similar in both limited- and extensive-stage patients. A recent randomized trial assessed PCI versus no PCI in 286 patients with extensive-stage SCLC who had responded to initial chemotherapy. PCI decreased symptomatic brain metastases (14.6% versus 40.4%) and increased the 1-year survival rate (27.1% versus 13.3%) when compared with controls.\textsuperscript{83}
A balanced discussion between the patient and physician is necessary before making a decision to administer PCI. PCI is recommended (category 1) for patients with limited-stage disease and extensive-stage disease who attain a complete or near complete response PCI can also be considered for patients who have a partial response to initial therapy. However, PCI is not recommended for patients with multiple comorbidities, poor PS (3-4), or impaired mental function. The recommended dose for PCI is 25 Gy in 10 fractions (see SCL-C). PCI should not be given concurrently with systemic chemotherapy because of the increased risk of neurotoxicity.

**Surgical Resection of Early-Stage SCLC**

Early-stage SCLC is diagnosed in less than 5% of patients with SCLC. Patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery. The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC. Patients with limited-stage disease, excluding those with stage I disease, received 5 cycles of chemotherapy with CAV. Patients demonstrating a response to chemotherapy were randomly assigned either to resection plus thoracic radiotherapy or to thoracic radiotherapy alone. The survival of patients on the 2 arms was equivalent, suggesting no benefit to surgery in this setting.

Patients with SCLC that has been determined to be clinical stage I (T1-2, N0) after a standard staging evaluation (including CT of the chest and upper abdomen, bone scan, brain imaging, and probably PET imaging) may undergo surgical resection. Before resection, all patients should undergo mediastinoscopy or other surgical or endoscopic mediastinal staging to rule out occult nodal disease. If an endoscopic lymph node biopsy is positive, additional mediastinal staging is not required. Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy.

Patients without nodal metastases can be treated with chemotherapy alone, but concurrent chemotherapy and postoperative mediastinal RT are recommended for patients with nodal metastases (see SCL-3). Because PCI can improve both disease-free and overall survival in patients with SCLC in complete remission, it is reasonable to administer PCI after adjuvant chemotherapy in patients who have undergone a complete resection.

**Management of Patients Not Participating in Clinical Trials**

Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the standard therapy for SCLC based on prior clinical trials and outlined by the practice guidelines does not yet result in very good outcomes. Thus, participation in clinical trials should be strongly encouraged.

Patients with limited-stage disease who are not enrolled in a clinical trial should be treated with concurrent chemotherapy (cisplatin plus etoposide for 4 cycles) plus early thoracic radiotherapy (category 1). Chest radiotherapy should begin during cycle 1 or 2 and should consist of either 45 Gy as 1.5 Gy twice daily or 1.8 to 2.0 Gy once daily to 60 to 70 Gy (category 1). PCI is recommended for patients who achieve a complete response. Follow-up examinations are recommended every 2 to 3 months during the first year with concomitant chest imaging (see SCL-5). If a new pulmonary nodule appears after 2 years, it should be evaluated as a new primary tumor, because second primary tumors are a frequent occurrence in patients who are cured of SCLC.

For patients with extensive-stage disease, standard combination platinum-based chemotherapy is recommended, with consideration for subsequent PCI in responding patients. It is recognized that more effective approaches are desperately needed.
References


73. Turrisi AT, Glover DJ, Mason BA. A preliminary report: Concurrent twice-daily radiotherapy plus platinum-etoposide chemotherapy for...


