

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)**

# **Small Cell Lung Cancer**

Version 2.2012

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## Small Cell Lung Cancer

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### [Summary of the Guidelines Updates](#)

#### Small Cell Lung Cancer:

- [Initial Evaluation and Staging \(SCL-1\)](#)
- [Limited Stage, Workup and Treatment \(SCL-2\)](#)
- [Extensive Stage, Workup and Treatment \(SCL-4\)](#)
- [Response Assessment after Initial Therapy \(SCL-5\)](#)
- [Surveillance \(SCL-5\)](#)
- [Subsequent Therapy and Palliative Therapy \(SCL-6\)](#)
- [Principles of Surgical Resection \(SCL-A\)](#)
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#### Lung Neuroendocrine Tumors:

- [Workup and Primary Treatment \(LNT-1\)](#)
  - ▶ [High-grade neuroendocrine carcinoma \(large cell neuroendocarcinoma\)](#)
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  - ▶ [Combined SCLC and NSCLC](#)

### [Staging \(ST-1\)](#)

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

To find clinical trials online at NCCN member institutions, [click here: nccn.org/clinical\\_trials/physician.html](#)

**NCCN Categories of Evidence and Consensus:** All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#)

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# NCCN Guidelines™ Version 2.2012 Updates

## Small Cell Lung Cancer

Summary of changes in the 2.2012 version of the NCCN Small Cell Lung Cancer Guidelines from the 1.2012 version include:

- The discussion section was updated to reflect the changes in the algorithm ([MS-1](#)).

Summary of changes in the 1.2012 version of the NCCN Small Cell Lung Cancer Guidelines from the 2.2011 version include:

General - PET scan was changed to PET/CT scan.

### [SCL-1](#)

Initial Evaluation

- "Differential" was added to CBC.
- Chest x-ray was removed.
- Bone scan was moved from the algorithm and added as footnote "c": "If PET/CT is not available, a bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage."
- PET/CT was clarified by adding "if limited stage is suspected."
- Footnote "a" modified: "...further *staging evaluation is optional*. However, head MRI (preferred) or CT should be obtained in all patients."

Stage

- Limited stage: "that do not fit in a tolerable radiation field" added.

### [SCL-2](#)

Additional Workup

- "If pleural effusion is seen on chest x-ray" changed to "If pleural effusion is present".
- Footnote "e": number associated with cytological examinations removed.
- Combined 3rd and 4th bullets dealing with bone mets: "Bone radiographs of areas showing abnormal uptake on PET/CT or bone scan to evaluate potential metastases; consider MRI of bony lesions if radiographs are equivocal."

### [SCL-4](#)

- Bone radiographs removed as additional workup.

Initial Treatment

- For management of osseous structural impairment: "Consider palliative external-beam RT and orthopedic stabilization if risk of fracture" added.

### [SCL-5](#)

- Changed oncology follow-up visits to the following: 3-4 mo during y 1-2 and every 6 mo during y 3-5.

### [SCL-5](#)

- Added 4th bullet under surveillance "PET/CT is not recommended for routine follow-up."

### [SCL-A](#)

- Last bullet added, "PCI is not recommended in patients with poor performance status or impaired mental functioning."
- References 3 and 4 are new to the page.

### [SCL-B 1 of 2](#)

- Limited stage: "The use of myeloid growth factors is not recommended during concurrent chemotherapy plus radiotherapy" added to chemotherapy + RT.
- References added for subsequent chemotherapy options.

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

- References added for subsequent chemotherapy options.

### [SCL-C 1 of 2](#)

- Limited stage:
  - Bullet 3 modified: Radiation target volumes should be defined based on the *pretreatment PET scan and CT scan* obtained at the time of radiotherapy planning, following ICRU definitions (Reports 50 and 62). Radiation doses should be calculated with inhomogeneity corrections.
  - Bullet 4 modified: Three-dimensional conformal radiation techniques are preferred. *In selected patients, IMRT may be considered ([http://www.icru.org/index.php?option=com\\_content&task=view&id=171](http://www.icru.org/index.php?option=com_content&task=view&id=171)).*<sup>11</sup> Four-dimensional imaging *and/or other available techniques* should also be performed to assess tumor movement *and motion management should be used to achieve movement of less than 1 cm or the PTV margin should be increased appropriately.*
- Prophylactic cranial radiotherapy: "For extensive-stage patients, 20 Gy in 5 fractions may be considered" is new to the page.

### [SCL-C 2 of 2](#)

- References 11, 12 are new to the page.

### [LNT-1](#)

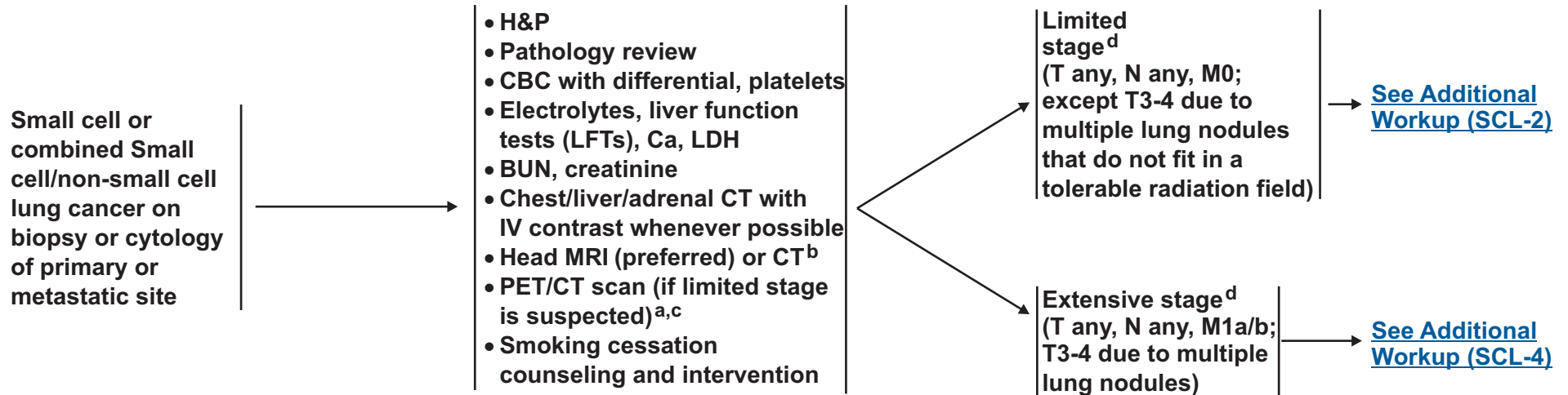
- Footnote "d" modified: *Options include cisplatin/etoposide, temozolomide, sunitinib and everolimus.*
- References added for systemic chemotherapy options.



**DIAGNOSIS**

**INITIAL EVALUATION<sup>a</sup>**

**STAGE**



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

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

<sup>c</sup>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.

<sup>d</sup>[See Staging on page ST-1.](#)

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

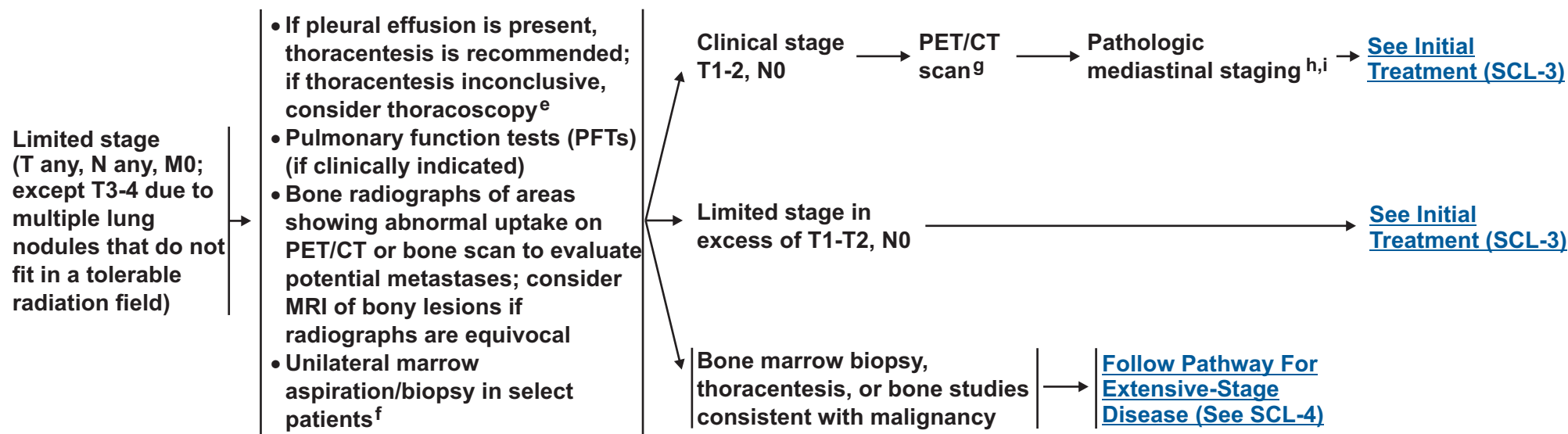
**Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**



# NCCN Guidelines™ Version 2.012

## Small Cell Lung Cancer

**STAGE**                      **ADDITIONAL WORKUP**



<sup>e</sup>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 cytological examination of pleural fluid is 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 evidence of extensive stage disease.

<sup>f</sup>Selection criteria include: nucleated RBCs on peripheral blood smear, neutropenia, or thrombocytopenia.

<sup>g</sup>PET scan to identify distant disease and to guide mediastinal evaluation, if not previously done.

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

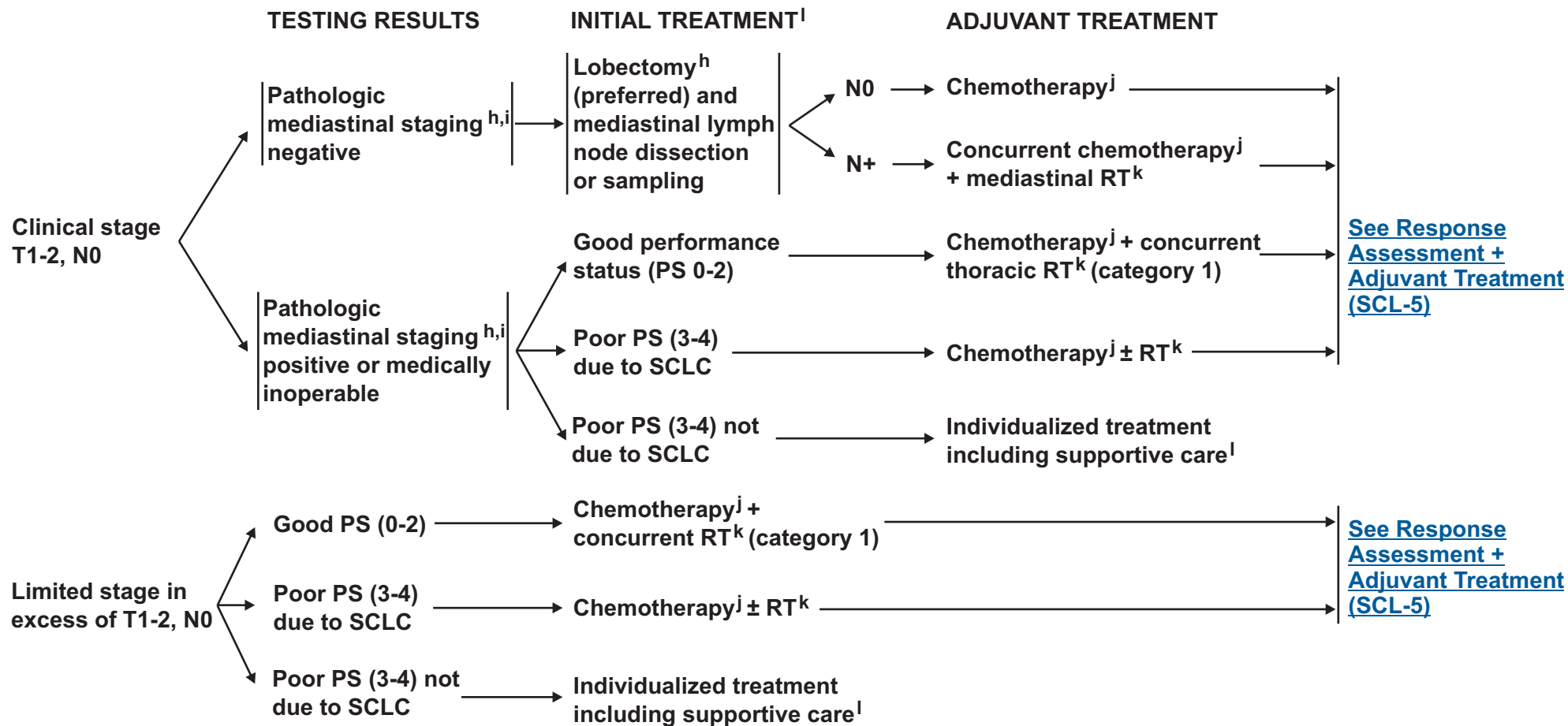
<sup>i</sup>Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

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# NCCN Guidelines™ Version 2.2012

## Small Cell Lung Cancer



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

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

<sup>j</sup>See Principles of Chemotherapy (SCL-B).

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

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

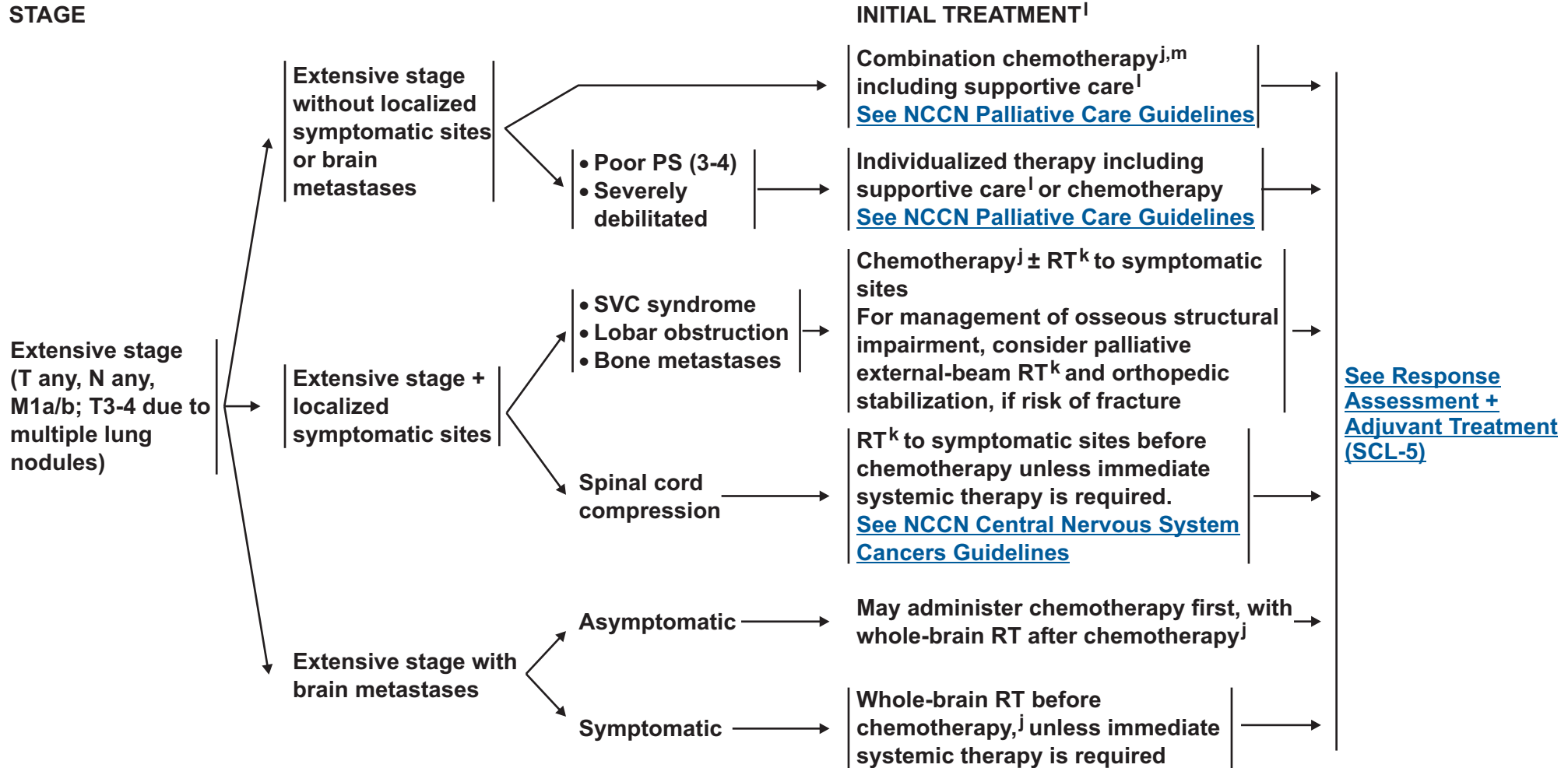
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## Small Cell Lung Cancer



<sup>j</sup>See Principles of Chemotherapy (SCL-B).

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

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

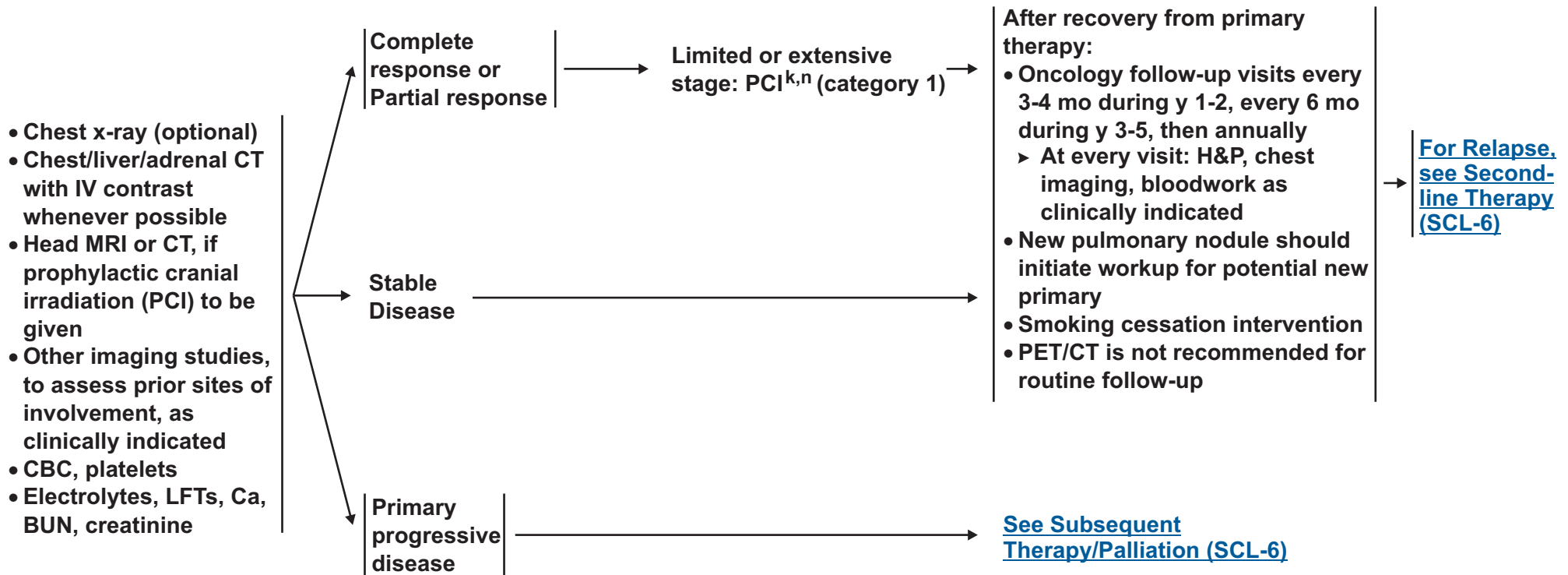
<sup>m</sup>Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and CR or near CR after systemic therapy.

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**RESPONSE ASSESSMENT FOLLOWING INITIAL THERAPY    ADJUVANT TREATMENT    SURVEILLANCE**



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

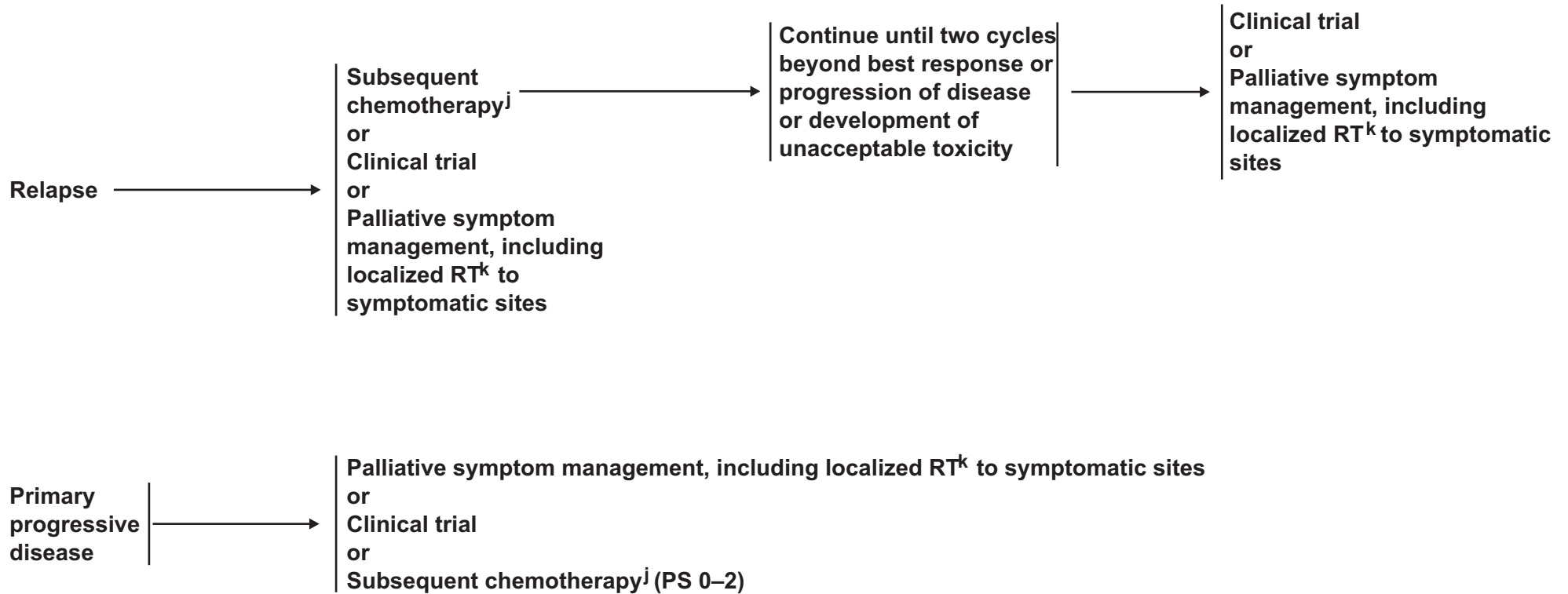
<sup>n</sup>Not recommended in patients with poor performance status or impaired mental function.

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### PROGRESSIVE DISEASE

### SUBSEQUENT THERAPY/PALLIATION



<sup>j</sup>See Principles of Chemotherapy (SCL-B).

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

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## PRINCIPLES OF SURGICAL RESECTION

- **Stage I SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients with disease in excess of T1-2, N0 do not benefit from surgery.<sup>1</sup>**
- **Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging) may be considered for surgical resection.**
  - ▶ **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 who have complete or partial response, PCI is recommended (category 1) after adjuvant chemotherapy in patients who have undergone a complete resection.<sup>2</sup> PCI is not recommended in patients with poor performance status or impaired mental functioning.<sup>3,4</sup>**

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

<sup>2</sup>Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341:476-84.

<sup>3</sup>Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664-672.

<sup>4</sup>Le Péchoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy. *Lancet Oncol* 2009;10(5):467-474.

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### PRINCIPLES OF CHEMOTHERAPY\*

#### Chemotherapy as primary therapy:

- **Limited stage (maximum of 4-6 cycles):**
  - ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and etoposide 120 mg/m<sup>2</sup> days 1, 2, 3<sup>1</sup>
  - ▶ Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>2</sup>
  - ▶ Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>3</sup>
  - ▶ During chemotherapy + RT, cisplatin/etoposide is recommended (category 1).
  - ▶ The use of myeloid growth factors is not recommended during concurrent chemotherapy plus radiotherapy.
- **Extensive stage (maximum of 4-6 cycles):**
  - ▶ Cisplatin 75 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>4</sup>
  - ▶ Cisplatin 80 mg/m<sup>2</sup> day 1 and etoposide 80 mg/m<sup>2</sup> days 1, 2, 3<sup>5</sup>
  - ▶ Cisplatin 25 mg/m<sup>2</sup> days 1, 2, 3 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>6</sup>
  - ▶ Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>7</sup>
  - ▶ Cisplatin 60 mg/m<sup>2</sup> day 1 and irinotecan 60 mg/m<sup>2</sup> days 1, 8, 15<sup>8</sup>
  - ▶ Cisplatin 30 mg/m<sup>2</sup> and irinotecan 65 mg/m<sup>2</sup> days 1, 8 every 21 days<sup>9</sup>
  - ▶ Carboplatin AUC 5 day 1 and Irinotecan 50 mg/m<sup>2</sup> days 1, 8, and 15<sup>10</sup>

#### Subsequent chemotherapy:

- **Clinical trial preferred.**
- **Relapse < 2-3 mo, PS 0-2:**
  - ▶ paclitaxel<sup>11,12</sup>
  - ▶ docetaxel<sup>13</sup>
  - ▶ topotecan<sup>14,15</sup>
  - ▶ irinotecan<sup>16</sup>
  - ▶ ifosfamide<sup>17</sup>
  - ▶ gemcitabine<sup>18,19</sup>
- **Relapse > 2-3 mo up to 6 mo:**
  - ▶ topotecan PO or IV (category 1)<sup>14,15, 20</sup>
  - ▶ paclitaxel<sup>11,12</sup>
  - ▶ docetaxel<sup>13</sup>
  - ▶ irinotecan<sup>16</sup>
  - ▶ gemcitabine<sup>18,19</sup>
  - ▶ vinorelbine<sup>21,22</sup>
  - ▶ oral etoposide<sup>23,24</sup>
  - ▶ cyclophosphamide/doxorubicin/vincristine (CAV)<sup>14</sup>
- **Relapse > 6 mo: original regimen<sup>25,26</sup>**

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

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

\*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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**PRINCIPLES OF CHEMOTHERAPY**

**References**

- <sup>1</sup>Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *N Engl J Med* 1999;340(4):265-271.
- <sup>2</sup>Saito H, Takada Y, Ichinose Y, et al. Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. *J Clin Oncol* 2006;24(33): 5247-5252.
- <sup>3</sup>Skarlos DV, Samantas E, Briassoulis E, et al. Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG). *Ann Oncol* 2001;12(9):1231-1238.
- <sup>4</sup>Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years follow-up. *J Clin Oncol* 2002;20(24):4665-4672.
- <sup>5</sup>Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12(10):2022-2034.
- <sup>6</sup>Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985;3(11):1471-1477.
- <sup>7</sup>Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small cell lung cancer. *J Clin Oncol* 1999;17(11):3540-3545.
- <sup>8</sup>Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346(2): 85-91.
- <sup>9</sup>Hanna N, Bunn Jr. PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. *J Clin Oncol* 2006;24(13):2038-2043.
- <sup>10</sup>Schmittel A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. *Ann Oncol* 2006;17:663-667.
- <sup>11</sup>Smit EF, Fokkema E, Biesma B, et al. A phase II study of paclitaxel in heavily pretreated patients with small-cell lung cancer. *Br J Cancer* 1998; 77:347-351.
- <sup>12</sup>Yamamoto N, Tsurutani J, Yoshimura N, et al. Phase II study of weekly paclitaxel for relapsed and refractory small cell lung cancer. *Anticancer Res* 2006; 26:777-781.
- <sup>13</sup>Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. *Eur J Cancer* 1994; 30A:1058-1060.
- <sup>14</sup>von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. *J Clin Oncol* 1999;17(2):658-667.
- <sup>15</sup>O'Brien ME, Ciuleanu TE, Tsekov H, et al. Phase III trial comparing supportive care alone with supportive care with oral topotecan in patients with relapsed small-cell lung cancer. *J Clin Oncol* 2006;24(34):5441-5447.
- <sup>16</sup>Masuda N, Fukuoka M, Kusunoki Y, et al. CPT-11: a new derivative of camptothecin for the treatment of refractory or relapsed small-cell lung cancer. *J Clin Oncol* 1992; 10:1225-1229.
- <sup>17</sup>Cantwell BM, Bozzino JM, Corris P, et al. The multidrug resistant phenotype in clinical practice; evaluation of cross resistance to ifosfamide and mesna after VP16-213, doxorubicin and vincristine (VPAV) for small cell lung cancer. *Eur J Cancer Clin Oncol* 1988; 24:123-129.
- <sup>18</sup>Van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. *An Oncol* 2001; 12:557-561.
- <sup>19</sup>Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer. *J Clin Oncol* 2003; 21:1550-1555.
- <sup>20</sup>Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. *J Clin Oncol* 2007;25(15):2086-2092.
- <sup>21</sup>Jassem J, Karnicka-Mlodkowska H, van Pottelsberghe C, et al. Phase II study of vinorelbine (Navelbine) in previously treated small cell lung cancer patients. *Eur J Cancer* 1993; 29A:1720-1722.
- <sup>22</sup>Furuse K, Kubo K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. *Oncology* 1996; 53:169-172.
- <sup>23</sup>Einhorn LH, Pennington K, McClean J. Phase II trial of daily oral VP-16 in refractory small cell lung cancer. *Semin Oncol* 1990; 17:32-35.
- <sup>24</sup>Johnson DH, Greco FA, Strupp J, et al. Prolonged administration of oral etoposide in patients with relapsed or refractory small-cell lung cancer: a phase II trial. *J Clin Oncol* 1990; 8:1613-1617.
- <sup>25</sup>Postmus PE, Berendsen HH, van Zandwijk N, et al. Retreatment with the induction regimen in small cell lung cancer relapsing after an initial response to short term chemotherapy. *Eur J Cancer Clin Oncol* 1987;23:1409-1411.
- <sup>26</sup>Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. *Eur J Cancer Clin Oncol* 1987;23:1697-1699.

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## PRINCIPLES OF RADIATION THERAPY

### Limited Stage:

- Radiotherapy should be delivered as either 1.5 Gy bid (twice daily) to a total dose of 45 Gy (category 1), or 2 Gy once daily to 60-70 Gy.<sup>1-6</sup> If bid fractionation is utilized, there should be at least a 6 hour inter-fraction interval to allow for repair of normal tissue.
- Radiotherapy should start concurrent with chemotherapy, cycle 1 or 2 (category 1).<sup>7</sup>
- Radiation target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of radiotherapy planning, following ICRU definitions (Reports 50 and 62).<sup>8-10</sup> Radiation doses should be calculated with inhomogeneity corrections.
- Three-dimensional conformal radiation techniques are preferred. In selected patients, IMRT may be considered ([http://www.icru.org/index.php?option=com\\_content&task=view&id=171](http://www.icru.org/index.php?option=com_content&task=view&id=171)).<sup>11</sup> Four-dimensional imaging and/or other available techniques should also be performed to assess tumor movement and motion management should be used to achieve movement of less than 1 cm or the PTV margin should be increased appropriately.<sup>12</sup>

### Normal Tissue Constraints:<sup>13,14</sup>

- Normal tissue doses will be dependent on tumor size and location. The following normal tissue constraints from CALGB 30610/ RTOG 0538 protocol should be used as a guide:
  - ▶ If BID accelerated hyperfractionation (i.e. 45 Gy/ 30 twice daily treatments) irradiation schema is utilized, the maximum spinal cord dose should be limited to  $\leq 41$  Gy (including scatter irradiation). If once daily dose irradiation is utilized, the maximum spinal cord dose should be limited to  $\leq 50$  Gy (including scatter irradiation).
  - ▶ The volume of both lungs (total lungs minus the clinical target volume) that receives  $> 20$  Gy ( $V_{20}$ ) should be  $< 40\%$ . Alternatively the mean dose to the total lung volume should be  $\leq 20$  Gy.
  - ▶ Mean dose to the esophagus should be  $< 34$  Gy.
  - ▶ Heart: 60 Gy to  $< 1/3$ , 45 Gy to  $< 2/3$ , 40 Gy to  $< 100\%$ .

### Prophylactic Cranial Radiotherapy:

- Parallel opposed fields should be utilized to encompass the whole brain. The field edges should be at least 1 cm from the outer skull margin. The recommended dose is 25 Gy in 10 fractions or 30 Gy in 15 fractions. For extensive-stage patients, 20 Gy in 5 fractions may be considered.<sup>15,16</sup>

**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.



## PRINCIPLES OF RADIATION THERAPY

### References

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- <sup>16</sup>Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664-672.

**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.

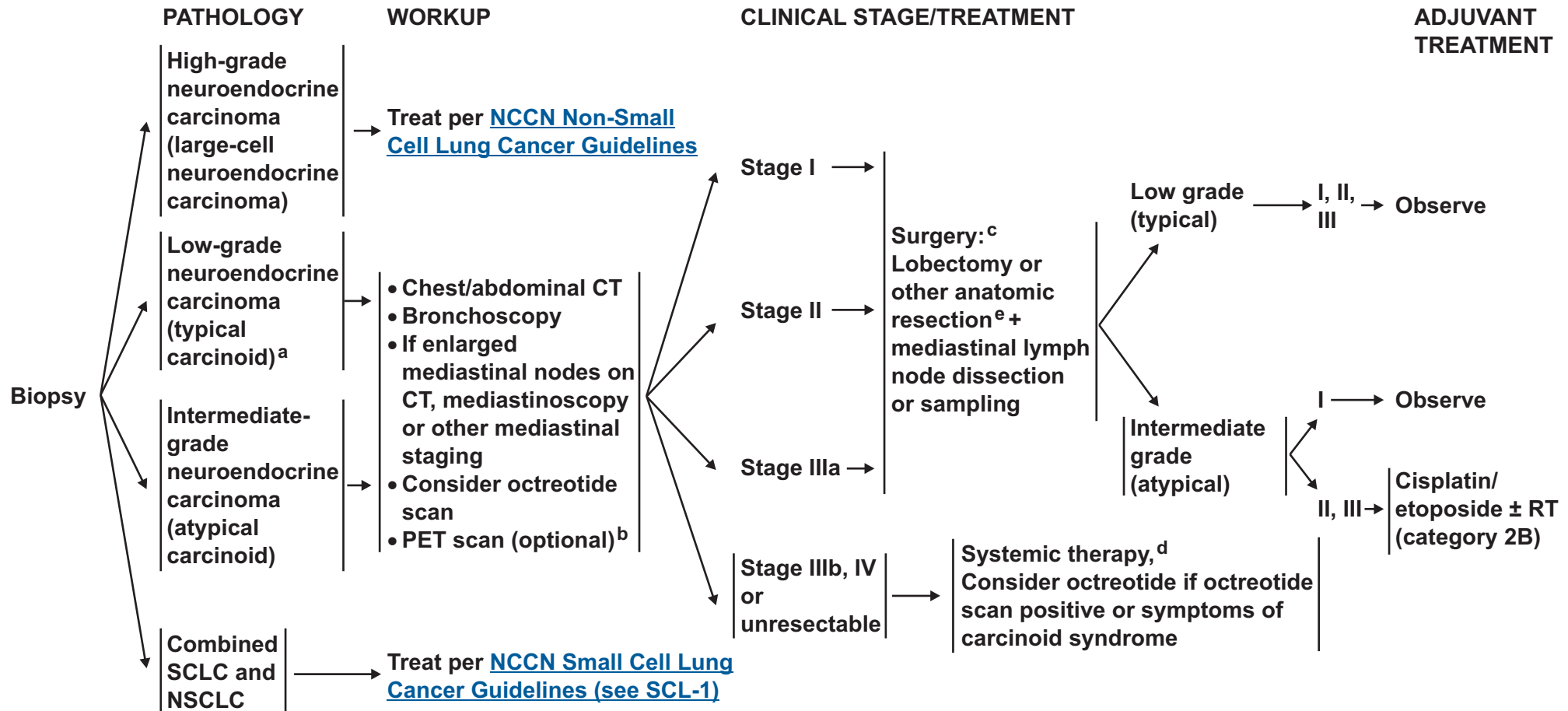


## PRINCIPLES OF SUPPORTIVE CARE

- **Smoking cessation counseling**
- **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**
  - ▶ **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.**



<sup>a</sup>Management of endocrine symptoms as indicated (See the Carcinoid Tumors section in the [NCCN Neuroendocrine Tumors Guidelines](#)).  
<sup>b</sup>PET scan is undergoing evaluation in clinical trials and should only be considered as a supplement and not a replacement to other studies.  
<sup>c</sup>For Stage III, typical: RT recommended if surgery is not feasible.  
 For Stage III, atypical: Chemotherapy/RT is recommended if surgery is not feasible.

<sup>d</sup>There is no substantial evidence for a commonly used regimen. Options include cisplatin/etoposide, temozolomide, sunitinib, or everolimus.  
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<sup>e</sup>Wedge resection for peripheral low-grade neuroendocrine carcinoma (category 2B).

**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 - Definitions of TNM****T Primary Tumor**

- 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
- T0 No evidence of primary tumor
- Tis Carcinoma in situ
- 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 (i.e., not in the main bronchus)\*  
 T1a Tumor 2 cm or less in greatest dimension  
 T1b Tumor more than 2 cm but 3 cm or less in greatest dimension
- T2 Tumor with any of the following features of size or extent:
  - More than 3 cm but 7 cm or less
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura (PL1 or PL2)
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
 T2a Tumor more than 3 cm but 5 cm or less in greatest dimension  
 T2b Tumor more than 5 cm but 7 cm or less in greatest dimension
- T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, 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 or separate tumor nodule(s) in the same lobe
- T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

**N Regional Lymph Nodes**

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension
- N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

**M Distant Metastasis**

- M0 No distant metastasis
- M1 Distant metastasis  
 M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion\*\*  
 M1b Distant metastasis

\*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

\*\*Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleura (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where 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 classified as M0.

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**Table 3 - Anatomic Stage/Prognostic Groups**

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b T1 T2a	N0 N1 N1	M0 M0 M0
Stage IIB	T2b T3	N1 N0	M0 M0
Stage IIIA	T1-2 T3 T4	N2 N1-2 N0-1	M0 M0 M0
Stage IIIB	T1-2 T3 T4	N3 N3 N2-3	M0 M0 M0
Stage IV	Any T Any T	Any N Any N	M1a M1b

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## Discussion

### 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.**

### Overview

Neuroendocrine tumors account for about 20% of lung cancers; most (approximately 15%) are small cell lung cancer (SCLC), which are treated using the NCCN SCLC guideline.<sup>1-3</sup> In 2011, it is estimated that 33,000 new cases of SCLC will occur in the United States.<sup>4</sup> Nearly all cases of SCLC are attributable to cigarette smoking. Although the incidence of SCLC has been decreasing, the incidence in women is increasing and the male-to-female incidence ratio is now 1:1.<sup>2</sup> Other lung neuroendocrine tumors (LNTs) are treated using the NCCN LNTs guideline (see also the section on LNTs at the end of this manuscript).

Non-small cell lung cancer (NSCLC) is the most common type of lung cancer (see the NCCN NSCLC guideline). 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, 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.<sup>5,6</sup>

In patients with limited-stage SCLC, the goal of treatment is to achieve a cure using chemotherapy plus thoracic radiotherapy.<sup>7,8</sup> In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare.<sup>9,10</sup> Surgery is only appropriate for the few patients (2%-5%) with surgically resectable stage I SCLC.<sup>11</sup> Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the standard therapy for SCLC as outlined by the NCCN guideline still needs to be improved. Thus, participation in clinical trials should be strongly encouraged.

Smoking cessation should be strongly promoted (1-800-QUIT-NOW—the national access number to State-based quitline services) (<http://www.smokefree.gov/>). Patients who smoke have increased toxicity during treatment and shorter survival.<sup>12</sup> Programs using behavioral counseling combined with Food and Drug Administration (FDA)–approved medications that promote smoking cessation can be very useful (<http://www.surgeongeneral.gov/tobacco/index.html>).

### 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.<sup>13</sup> 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; this finding is more commonly

detected in specimens from previously treated patients and suggests that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along divergent pathways.

Although 95% of small cell carcinomas originate in the lung, they can also arise from extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract.<sup>14-16</sup> 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, a finding that suggests a different pathogenesis.<sup>17</sup>

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 one of these neuroendocrine markers.<sup>18</sup>

### 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 (FNA) 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 LNT algorithm in the 2012 NCCN SCLC guideline and the NCCN Neuroendocrine Tumors guideline).<sup>19, 20</sup>

Preliminary reports from the National Lung Screening Trial (NLST) suggest that screening with annual low-dose, spiral CT scans can improve lung cancer specific mortality and overall mortality in asymptomatic high-risk individuals (<http://www.cancer.gov/newscenter/pressreleases/2010/NLSTresultsRelease>). While CT screening can detect early-stage NSCLC, it does not appear to be useful for detecting SCLC. This is likely due to the aggressiveness of SCLC, which results in the development of symptomatic disease between annual scans, thereby limiting the potential effect on mortality.<sup>21</sup>

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.<sup>22, 23</sup> Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. Patients with the Lambert-Eaton syndrome present with proximal leg weakness that is caused by antibodies directed against the voltage-gated calcium channels.<sup>24, 25</sup> Paraneoplastic encephalomyelitis and sensory neuropathy are caused by the production of an antibody (anti-Hu) that cross reacts with both small cell carcinoma antigens and human neuronal RNA-binding proteins resulting in multiple neurologic deficits.<sup>26</sup> 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.<sup>27, 28</sup>

### Staging

The Veteran's Administration Lung Group 2-stage classification scheme has been routinely used to define the extent of disease in patients with SCLC as shown in Table 1: (1) *limited-stage disease* is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and (2) *extensive-stage disease* is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.<sup>29</sup> Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, while the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial. 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 new lung cancer TNM staging system was developed by the International Association of the Study of Lung Cancer (IASLC) and adopted by the American Joint Commission for Cancer (AJCC) (7<sup>th</sup> edition, 2010) (see Tables 2 and 3).<sup>30-34</sup> This new staging system is applicable to both NSCLC and SCLC based on studies by the IASLC which demonstrated the prognostic significance of the various stage designations in both diseases.<sup>30, 34</sup> Using the new TNM staging system, limited-stage SCLC is T any, N any, M0 except T3-4 due to multiple lung nodules that do not fit in a tolerable radiation field (see "Stage" in the NCCN 2012 SCLC algorithm). Extensive-stage SCLC is T any, N any, M1a/b, and T3-4 due to multiple lung nodules.

Because most of the literature on SCLC classifies patients based on limited-stage 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 utilize 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 in 2011 to include the TNM staging information (see Table 2).

All SCLC patients, even those with radiographically limited-stage disease, require systemic chemotherapy. Therefore, staging provides a therapeutic guideline for thoracic radiotherapy, which is indicated primarily for patients with limited-stage disease. Full staging includes a history and physical examination; computed tomography (CT) scan (with IV contrast) including the chest, liver, and adrenal glands; and a magnetic resonance imaging (MRI) scan (preferred) or CT scan of the brain. However, once a patient has been found to have extensive-stage disease, further staging is optional, except for brain imaging. 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 less than 5% of patients. If limited-stage disease is suspected, a positron emission tomography (PET)–CT scan can be done to assess for distant metastases. A bone scan can be done if PET/CT is not available.

PET scans can increase staging accuracy in patients with SCLC.<sup>35-39</sup> PET/CT is superior to PET alone.<sup>39</sup> By PET, about 15% of patients are up-staged from limited to extensive stage while only 5% are downstaged from extensive to limited stage. 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.<sup>40</sup> Changes in management based on PET staging were reported in 16%-38% of patients, mainly due to alterations in the planned radiation field due to



improved detection of intrathoracic sites of disease.<sup>36, 41, 42</sup> While PET/CT appears to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT–detected lesions that result in up-staging. Prior to surgical resection, pathologic mediastinal staging is required to confirm PET/CT scan results in patients who appear to have clinical stage T1-2, N0 disease.

Mediastinal staging can be done by either conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound–guided FNA (EUS-FNA), endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA), or video-assisted thoracoscopy (VATS).<sup>43, 44</sup>

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. A patient should be considered to have limited-stage disease if the effusion is too small to allow image-guided sampling or if: (1) cytopathologic examination of pleural fluid is 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 focused 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 brain 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 significant decline in their performance status (PS).

### Prognostic Factors

Poor PS (3-4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease (such as lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis in patients with limited-stage disease. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease.<sup>45-47</sup>

### Chemotherapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment.<sup>9</sup> Adjuvant chemotherapy is recommended for those who have undergone surgical resection. For patients with limited-stage SCLC and good PS (0-2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1).<sup>8, 48, 49</sup> For patients with extensive-stage disease, chemotherapy alone is the recommended treatment (see the 2012 SCLC algorithm for recommended regimens). 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 “Initial Treatment for Extensive Stage” in the 2012 SCLC algorithm).<sup>10, 50</sup>

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.<sup>51-53</sup> Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see “Principles of Chemotherapy” in the 2012 SCLC algorithm).<sup>9, 54, 55</sup> This

combination replaced alkylator/anthracycline-based regimens based on superiority in both efficacy and toxicity in the limited-stage setting.<sup>56</sup> EP plus concurrent thoracic radiotherapy is now the recommended therapy for patients with limited-stage disease (category 1).<sup>48, 49, 57</sup>

In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.<sup>58</sup> The use of myeloid growth factors is not recommended in patients receiving concurrent chemoradiation.<sup>59</sup> 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.<sup>60</sup> 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.<sup>61, 62</sup> The substitution of carboplatin for cisplatin is more acceptable in patients with extensive-stage disease, because data show these drugs are equivalent in this setting.<sup>63</sup>

Many other combinations have been evaluated in patients with extensive-stage disease with little consistent evidence of benefit when compared with EP. In recent years, 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 achieved a median survival of 12.8 months compared to 9.4 months for patients treated with EP ( $P=.002$ ).<sup>64</sup> In addition, 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.<sup>64</sup> However, 2 subsequent large phase III trials 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.<sup>65, 66</sup>

A randomized phase II trial ( $n = 70$ ) comparing carboplatin and irinotecan versus carboplatin and etoposide showed a modest improvement in progression-free survival (PFS) with the irinotecan combination.<sup>67</sup> 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 versus 7.1 months,  $P=.04$ ).<sup>68</sup> Based on these findings, the carboplatin and irinotecan regimen has been added to the guideline as an option for patients with extensive-stage disease. A recent meta-analysis suggests an improvement in PFS and overall survival with irinotecan plus platinum regimens compared to etoposide plus platinum regimens.<sup>69</sup> However, this meta-analysis was not done using individual patient data. In addition, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN panel continues to consider etoposide plus platinum as the standard regimen for patients with SCLC.

In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with EP plus thoracic radiotherapy, while in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.<sup>51</sup> 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.<sup>70</sup> Thoracic radiotherapy improves local control rates by 25% in limited-stage disease patients and is associated with improved survival.<sup>48, 49</sup> Recent data suggest that chemoradiotherapy may be indicated for patients with limited-stage disease who have cytologically negative or indeterminate pleural effusions, but not for those with pericardial effusions.<sup>71, 72</sup>

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.<sup>73, 74</sup> However, such findings have not been uniformly observed, and the addition of an alkylating agent with or without an anthracycline significantly increases hematologic toxicity when compared to EP alone.<sup>75</sup> 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.<sup>76</sup> 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.<sup>77</sup>

The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of cancer stem cells that are relatively resistant to cytotoxic therapy. To overcome drug resistance, alternating or sequential combination therapies have been designed to expose the tumor to as many active cytotoxic agents as possible during initial treatment.<sup>78</sup> However, randomized trials have failed to show improved PFS or overall survival with this approach.<sup>79, 80</sup>

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.<sup>81, 82</sup> Nevertheless, no survival benefits were documented in randomized trials and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.<sup>83-86</sup>

The role of higher-dose therapy for patients with SCLC remains controversial.<sup>87</sup> Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high doses when compared with those given conventional doses of the same agents.<sup>88</sup> In general, however, randomized trials comparing conventional doses to an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival.<sup>89-92</sup> 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.<sup>93</sup>

Currently available cytokines (e.g., 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 FDA approval for the clinical use of cytokines,<sup>94</sup> there is little evidence to suggest 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 anti-angiogenic therapy have begun to be evaluated in SCLC. In patients with limited-stage SCLC, a phase II study of irinotecan, carboplatin, and bevacizumab with concurrent RT followed by maintenance bevacizumab (phase II trial) was terminated early due to an unacceptable incidence of tracheoesophageal fistulae (<http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153953.pdf>). In extensive-stage SCLC, two phase II trials of platinum-based

chemotherapy plus bevacizumab have yielded promising response and survival data.<sup>95-97</sup> Randomized phase III trials are ongoing to determine if the addition of bevacizumab to chemotherapy improves survival in patients with extensive-stage SCLC. At present, 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 failed to yield significant advantages when compared to standard approaches.

### Elderly Patients

The incidence of lung cancer increases with age. Although the median age at diagnosis is 70 years, elderly patients are under-represented in clinical trials.<sup>98</sup> While 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 guideline"). 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; therefore, they need to be watched carefully during treatment in order to avoid excessive risk.

Greater attention to the needs and support systems of elderly patients is recommended in order to provide optimal care. Overall, elderly patients have a similar prognosis when compared to stage-matched younger patients. Randomized trials have indicated that less intensive treatment (e.g., single-agent etoposide) is inferior to combination chemotherapy (e.g., platinum plus etoposide) in elderly patients with

good PS (0-2).<sup>99, 100</sup> Several other strategies have been evaluated in elderly patients with SCLC.<sup>63, 101-103</sup> 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.<sup>103</sup> However, targeting carboplatin to an AUC of 5, rather than 6, may be more reasonable in this population.<sup>104</sup> 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, though this approach has not been directly compared to standard therapy.<sup>105</sup>

### Second-Line (Subsequent) Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.<sup>106, 107</sup> These patients have a median survival of only 4 to 5 months when treated with further chemotherapy. Second-line (i.e., 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% or less). If more than 3 months have elapsed (sensitive disease), expected response rates are approximately 25%.

Subsequent chemotherapy generally involves single-agent therapy. In phase II trials, active subsequent agents include paclitaxel, docetaxel, topotecan, irinotecan, vinorelbine, gemcitabine, ifosfamide, and oral etoposide, (see "Principles of Chemotherapy" in the 2012 SCLC algorithm).<sup>55, 108-111</sup> In a randomized phase III trial, single-agent IV topotecan was compared to the combination regimen CAV.<sup>112</sup> Both arms had similar response rates and survival, but IV topotecan caused less toxicity. In another phase III trial, oral topotecan improved overall

survival when compared with best supportive care (26 versus 14 weeks).<sup>113</sup> Single-agent topotecan is approved by the U.S. FDA as subsequent therapy for patients with SCLC who initially respond to chemotherapy but then progress after 2-3 months. In the NCCN algorithm, topotecan is recommended as a subsequent agent for patients with relapsed SCLC (category 1 for relapse > 2-3 months up to 6 months).<sup>108, 112, 114</sup> Either oral or IV topotecan may be used since efficacy and toxicity appear to be similar with either route.<sup>113, 114</sup>

Many practicing oncologists have noted excessive toxicity with the standard regimen of topotecan IV 1.5 mg/m<sup>2</sup> × 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.<sup>115</sup> Published studies have yielded conflicting data regarding the utility of weekly topotecan in patients with relapsed SCLC and this approach remains under investigation.<sup>116, 117</sup>

Recent data from phase II studies suggest that amrubicin, an investigational anthracycline, has promising activity in patients with relapsed or refractory SCLC.<sup>118-120</sup> However, grade 3-4 toxicity, primarily neutropenia, is common.<sup>121</sup> 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 ( $P=.02$ ).<sup>122</sup>

The optimal duration of subsequent chemotherapy has not been fully explored; although even in patients who respond, the duration of response is usually short and cumulative toxicity is frequently limiting. 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 2012 SCLC algorithm describes the radiation doses, target volumes, and normal tissue dose volume constraints for limited-stage SCLC and includes references to support the recommendations; these principles were updated extensively in 2011. The NCCN NSCLC RT guideline may also be useful. This Discussion section describes the studies supporting the NCCN recommendations.

## Thoracic Radiotherapy

### *Trial Data*

The addition of thoracic radiotherapy has improved survival for patients with limited-stage disease.<sup>123</sup> Meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease yields a 25% to 30% reduction in local failure and a corresponding 5% to 7% improvement in 2-year survival when compared with chemotherapy alone.<sup>48, 49</sup> 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), 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. Early concurrent chemoradiotherapy is recommended for patients with limited-stage SCLC based on randomized trials.

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.<sup>58</sup> Another randomized phase III trial (by the National Cancer Institute of Canada)—comparing radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy—demonstrated that early radiotherapy was associated with improved local and systemic control and with longer survival.<sup>124</sup> 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.<sup>125</sup> Another meta-analysis also found that early concurrent thoracic radiation with platinum-based chemotherapy increases 2- and 5-year overall survival.<sup>126</sup>

The Eastern Cooperative Oncology Group/Radiation Therapy Oncology Group (ECOG/RTOG) compared once a day to twice a day radiotherapy with EP.<sup>127</sup> In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiotherapy using a total dose of 45 Gy delivered either twice a day over 3 weeks or once a day over 5 weeks. The twice-daily schedule produced a survival advantage, but there was a higher incidence of grade 3-4 esophagitis when compared with the once daily regimen. Median survival was 23 versus 19 months ( $P=.04$ ), and 5-year survival was 26% versus 16% in the twice-daily and once-daily radiotherapy arms, respectively.<sup>127</sup> A significant criticism of this trial is that the doses of radiation on the two arms were not biologically equivalent. In light of this, on-going trials are evaluating biologically equivalent doses of 45 Gy delivered twice daily versus 60-70 Gy delivered once daily. Another concern regarding hyperfractionation is that twice-daily thoracic radiation is technically challenging for patients with bilateral mediastinal adenopathy.

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-daily thoracic radiotherapy to 48 Gy with concurrent EP.<sup>128</sup> However, split-course radiotherapy may be less efficacious because of interval tumor regrowth between courses. Overall, patients selected for combined modality treatment that incorporates twice-a-day radiotherapy must have an excellent PS and good baseline pulmonary function.

### **NCCN Guideline**

For limited-stage disease, the NCCN guideline recommends that RT should be used concurrently with chemotherapy and that RT should start with the first or second cycle (category 1) at a dose of either 1) 1.5 Gy twice daily to a total dose of 45 Gy (category 1), or 2) 2.0 Gy once daily to a total dose of 60 to 70 Gy (see “Principles of Radiation Therapy” in the 2012 SCLC algorithm).<sup>48, 125, 127-132</sup> Concurrent chemoradiotherapy (category 1) is preferable to sequential therapy in patients with good PS (0-2).<sup>58, 133</sup>

Three-dimensional (3-D) conformal radiation techniques are preferred, if available. The radiation target volumes should 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 and Measurement (ICRU). However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.<sup>131, 134</sup> The CALCB 30610/RTOG 0538 protocol should be used as a guide to determine the normal tissue dose volume constraints (see the NCCN 2012 SCLC algorithm).<sup>135-137</sup> Intensity-modulated RT (IMRT) may be considered in select patients (see “Principles of Radiation Therapy” in the 2012 SCLC algorithm)<sup>138</sup>

[http://www.icru.org/index.php?option=com\\_content&task=view&id=171](http://www.icru.org/index.php?option=com_content&task=view&id=171).

In select patients with low-bulk metastatic disease who have a complete or near complete response after initial chemotherapy, the addition of sequential thoracic radiotherapy may be considered based on the following randomized trial. Patients with a complete response at distant metastatic sites after 3 cycles of EP were randomized to receive further EP or accelerated hyperfractionated RT (i.e., 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide.<sup>139</sup> In this trial, the addition of RT resulted in improved median overall survival (17 versus 11 months).

### Prophylactic Cranial Irradiation (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 demonstrate a meaningful survival advantage.<sup>140</sup> Moreover, late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrent with chemotherapy. Thus, PCI is not recommended for patients with poor PS (3-4) or impaired mental function.

When given after the completion of chemotherapy and at a low dose per fraction, PCI may cause less neurological toxicity. Symptomatic brain metastases result in major morbidity, which frequently does not completely resolve with therapeutic cranial irradiation.

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.<sup>141</sup> 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.<sup>141</sup> Although the number of patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in both limited-stage and extensive-stage patients. A recent retrospective study of patients with limited-stage disease also found that PCI increased survival at 2, 5, and 10 years when compared to those who did not receive PCI.<sup>142</sup>

A randomized trial from the EORTC 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 to controls.<sup>143</sup>

Before making a decision to administer PCI, a balanced discussion between the patient and physician is necessary. PCI is recommended (category 1) for patients with either limited-stage or extensive-stage disease who attain a complete or partial response.<sup>143, 144</sup> The recommended dose for PCI is a total dose of 25 Gy in 10 fractions (using 2.5 Gy/fraction) or a total dose of 30 Gy in 15 fractions (see “Principles of Radiation Therapy” in the 2012 SCLC algorithm).<sup>143, 144</sup> However, a total dose of 20 Gy in 5 fractions may be considered for patients with extensive-stage SCLC.<sup>143</sup> PCI should not be given concurrently with systemic chemotherapy because of the increased risk of neurotoxicity. Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.<sup>144, 145</sup>

### Palliative Treatment

For patients with localized symptomatic sites of disease (i.e., painful bony lesions, obstructive atelectasis, or brain metastases), radiotherapy can provide excellent palliation (see “Initial Treatment for Extensive Stage” in the 2012 SCLC algorithm).<sup>146</sup>

[http://www.practicalradonc.org/article/S1879-8500\(11\)00091-9/abstract](http://www.practicalradonc.org/article/S1879-8500(11)00091-9/abstract).

Orthopedic stabilization may be useful in patients at high risk for fracture.

### Surgical Resection of Stage I SCLC

The “Principles of Surgical Resection” for SCLC are described in the NCCN 2012 SCLC algorithm; studies supporting these NCCN recommendations are described in this section. Briefly, the 2012 SCLC algorithm states that surgery should only be considered for patients with stage I (T1-2 N0) SCLC in whom it has been proven by biopsy that mediastinal lymph nodes are not involved.<sup>147</sup> Data show that patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery.<sup>147</sup> Note that only 5% of patients with SCLC have true stage I SCLC.<sup>31</sup>

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.<sup>147</sup> Patients with limited-stage disease, excluding those with solitary peripheral nodules, received 5 cycles of chemotherapy with CAV; those demonstrating a response to chemotherapy were randomly assigned to undergo resection plus thoracic radiotherapy or thoracic radiotherapy alone. The overall survival of patients on the 2 arms was equivalent, suggesting no benefit to surgery in this setting. However, only 19% of patients enrolled had clinical stage I (T1-2, N0, M0) disease.

Regarding the utility of surgery in SCLC, most of the data are from retrospective reviews.<sup>148-152</sup> These studies report favorable 5-year survival rates of 40%-60% in patients with stage I disease. In most series, survival rates decline significantly in patients with more advanced disease, leading to the general recommendation that surgery should only be considered in those with stage I disease. Interpretation of these results is limited by the selection bias inherent in retrospective

reviews and by the variable use of chemotherapy and radiotherapy in these studies.

Recent analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.<sup>11, 153</sup> However, these studies are limited by the lack of information on chemotherapy use in the SEER database. In addition, comparison of the survival of surgical patients to all those who did not undergo surgery is inherently flawed by selection bias. Ultimately, the role of surgery in SCLC will not be fully defined until results are available of trials comparing surgery plus adjuvant chemotherapy to concurrent chemoradiotherapy in rigorously staged patients.

In all patients with clinical stage I (T1-2, N0) SCLC who are being considered for surgical resection, occult nodal disease should be ruled out by mediastinal staging before resection.<sup>154</sup> If resection is performed, the NCCN panel favors lobectomy and does not feel that segmental or wedge resections are appropriate for patients with SCLC. After complete resection, adjuvant chemotherapy or chemoradiation is recommended.<sup>150, 155, 156</sup> Adjuvant chemotherapy alone is recommended for patients without nodal metastases, while concurrent chemotherapy and postoperative mediastinal RT are recommended for patients with nodal metastases (see “Adjuvant Treatment for Clinical Stage T1-2, N0” in the 2012 SCLC algorithm). PCI should be considered after adjuvant therapy, because PCI can improve survival (see previous section on “Prophylactic Cranial Irradiation” in this Discussion).<sup>141</sup>

### Surveillance

Follow-up examinations are recommended every 3 to 4 months during year 1-2 with concomitant chest imaging (with CT but not PET/CT); the frequency of surveillance decreases during subsequent years in light of the declining risk of recurrence (see “Surveillance” in the 2012 SCLC

algorithm). 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 since second primary tumors are a frequent occurrence in patients who are cured of SCLC.<sup>157, 158</sup>

Smoking cessation should be encouraged for all patients with SCLC (<http://www.ahrq.gov/clinic/tobacco/tobaqrq.htm>), because second primary tumors occur less commonly in patients who quit smoking.<sup>159-161</sup>

### Lung Neuroendocrine Tumors

Using the 2004 World Health Organization criteria, lung neuroendocrine carcinomas are characterized as: 1) high-grade neuroendocrine carcinomas (SCLC and large-cell neuroendocrine carcinoma [LCNEC]); 2) intermediate-grade neuroendocrine carcinomas (atypical carcinoids); or 3) low-grade neuroendocrine carcinomas (typical carcinoids).<sup>162</sup>

<http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb10/index.php>

Most lung neuroendocrine carcinomas are SCLC, which are treated using the NCCN SCLC guideline.<sup>1</sup> LCNEC is treated using the NCCN NSCLC guideline.<sup>163</sup> Low- and intermediate-grade lung neuroendocrine carcinomas account for 1%-2% of lung cancers and are treated using the NCCN LNTs guideline. Both histologic and cytologic features can be useful for distinguishing LNTs from SCLC and LCNEC, although diagnosis can be difficult (see also the NCCN NSCLC algorithm). The proliferative marker Ki-67 may also be useful.<sup>19,20</sup>

Staging of lung neuroendocrine carcinomas is done using the 7<sup>th</sup> edition of the AJCC staging system for lung tumors (see Tables 2 and 3).<sup>33, 164</sup> Both low- and intermediate grade LNTs are usually stage I at diagnosis, although lymph node metastases (stages II-III) are more commonly seen in intermediate-grade tumors. Compared to other lung carcinomas, the prognosis is excellent for many patients with low- and intermediate-grade LNTs.

Surgery is recommended for patients with stage I, II, or IIIA low- or intermediate-grade LNTs (see the NCCN LNT guideline). After surgical resection, 5- and 10-year survival rates are more than 90% for patients with typical carcinoid, whereas survival rates are 70% and 50%-60% for patients with atypical carcinoid.<sup>165-167</sup> Lymph node involvement decreases long-term survival in both typical and atypical carcinoid.<sup>165-167</sup>

Systemic therapy is recommended for patients with unresectable or advanced disease, although response rates are modest (e.g., cisplatin/etoposide, temozolomide, sunitinib, or everolimus).<sup>1, 168-172</sup> Octreotide may be considered for select patients with positive octreotide scans or symptoms of carcinoid syndrome.

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