

**NCCN Clinical Practice Guidelines in Oncology™**

# **Small Cell Lung Cancer**

V.1.2007

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See [NCCN Categories of Consensus](#)

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## Summary of the Guidelines updates

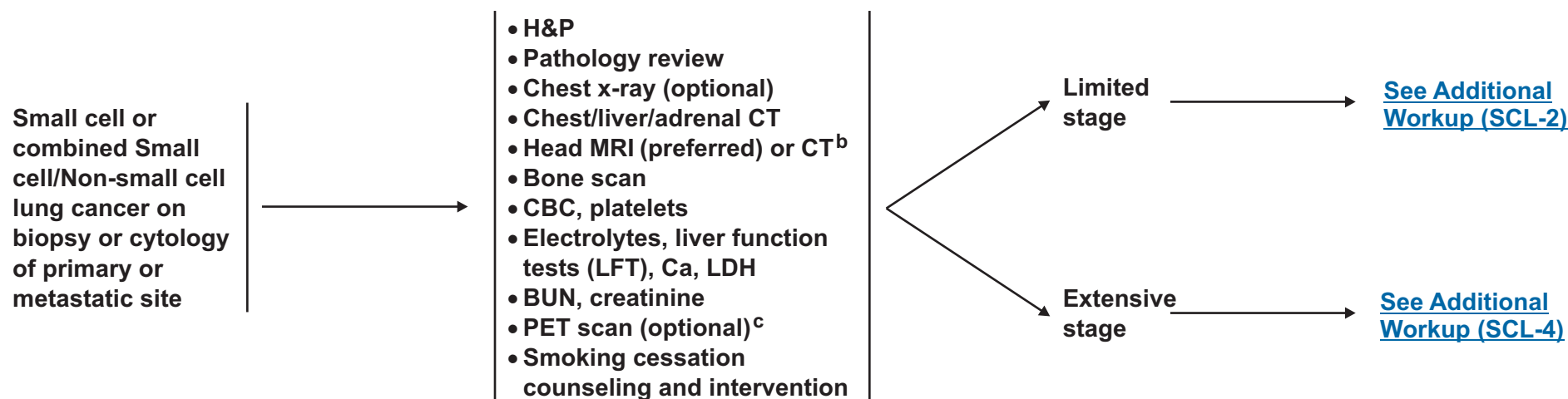
Summary of the changes in the 1.2007 version of the Small Cell Lung Cancer Guidelines from the 1.2006 version include:

- In the Initial Evaluation, "optional" was added to the chest x-ray recommendation ([SCL-1](#)).
- Footnote "f" was clarified that if an effusion is too small to allow image-guided sampling, it should not be considered in staging ([SCL-2](#)).
- Endoscopic staging was added as an option to mediastinal staging with new footnote "i" that if the results are positive, additional mediastinal staging would not be required ([SCL-2](#)).
- A category was added for patients with a Performance Status 3-4 not due to SCLC with the treatment recommendation of "Individualized therapy including supportive care regimens" ([SCL-3](#)).
- Second-line therapy was changed to "Subsequent therapy" ([SCL-6](#)).
- Principles of Surgical Resection - the option for endoscopic staging was added to bullet 4 ([SCL-A](#)).
- Principles of Radiation Therapy - the statement regarding the recommendation for lower fraction regimens was added to the PCI dosing section ([SCL-C](#)).
- Lung Neuroendocrine Tumors - the category designation was changed to 2A for an octreotide scan for atypical carcinoid and carcinoid tumors ([LNT-1](#)).
- The AJCC Staging (6th Edition) was added to the Staging section ([ST-1](#)).

## DIAGNOSIS

## INITIAL EVALUATION<sup>a</sup>

## STAGE<sup>d</sup>



<sup>a</sup>If extensive stage is established, further testing for staging is optional.

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

<sup>c</sup>PET scan can be used as part of the initial evaluation, in addition to the other recommended studies.

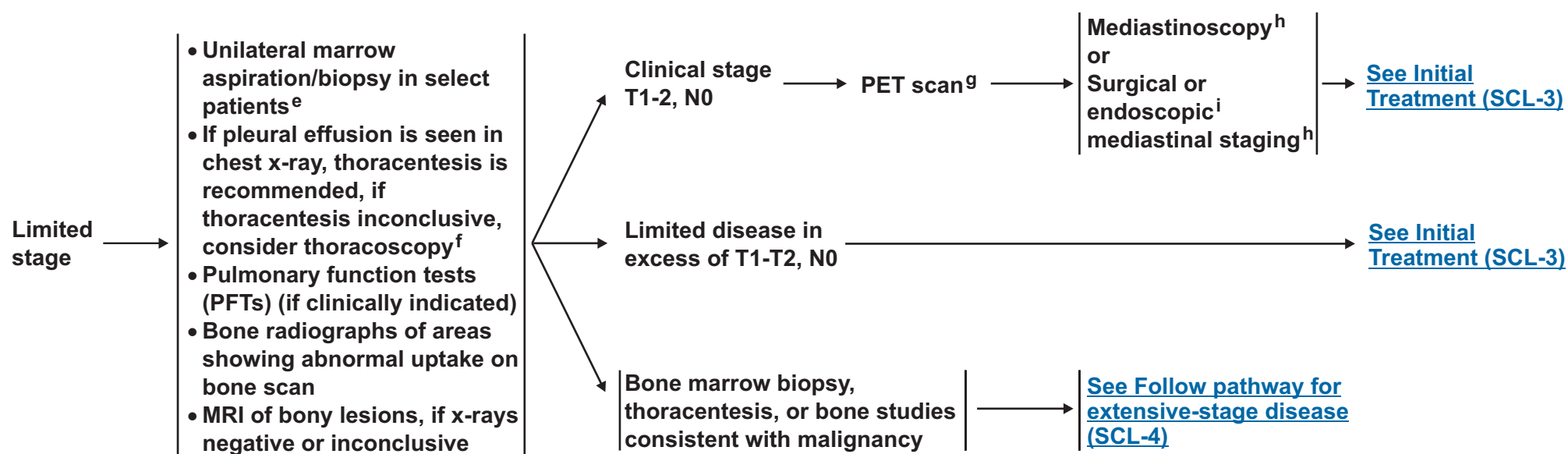
<sup>d</sup>[See Staging on page ST-1.](#)

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## STAGE

## ADDITIONAL WORKUP



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

<sup>f</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 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.

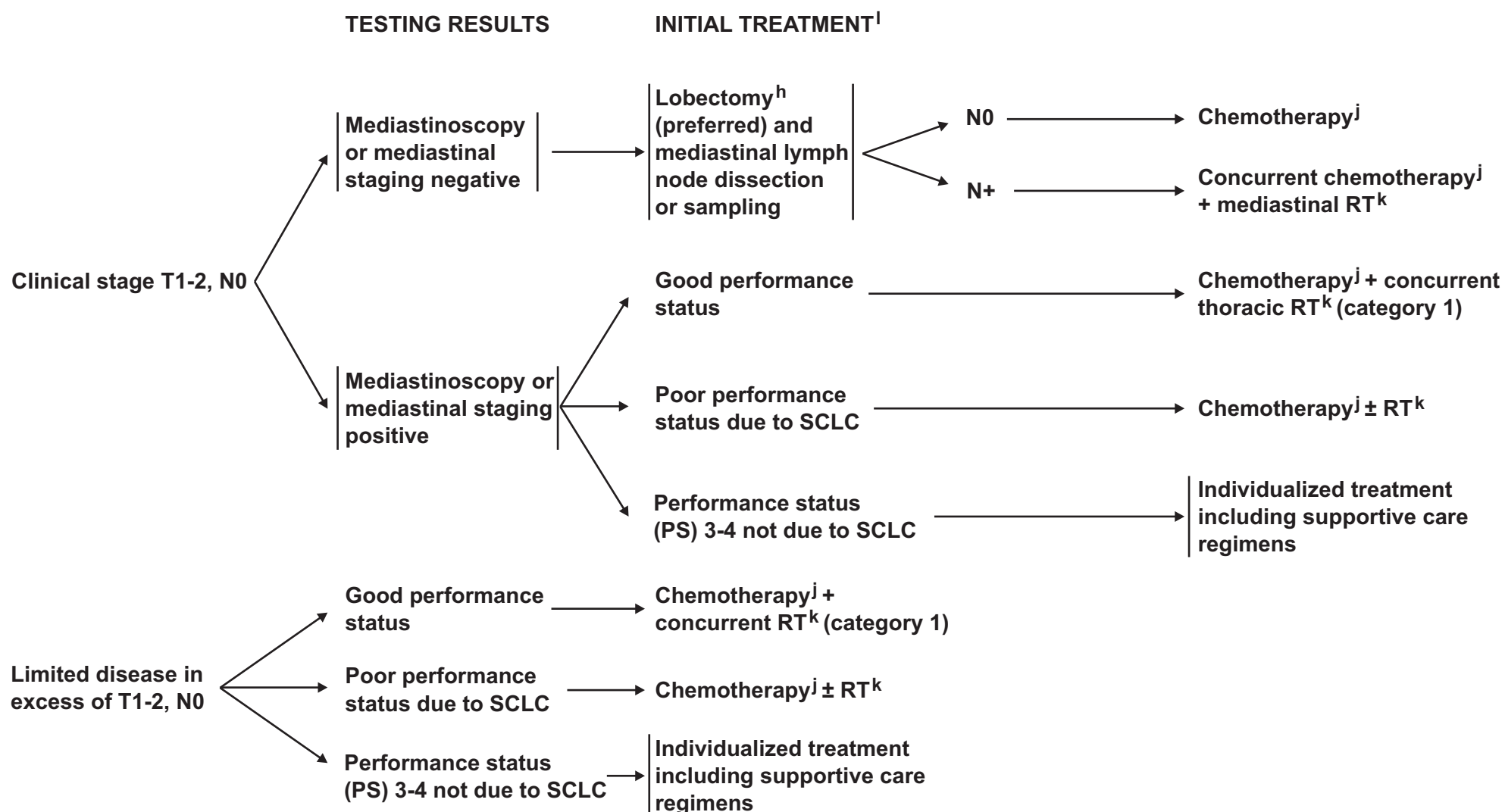
<sup>g</sup>PET scan to identify distant disease and to guide mediastinal evaluation.

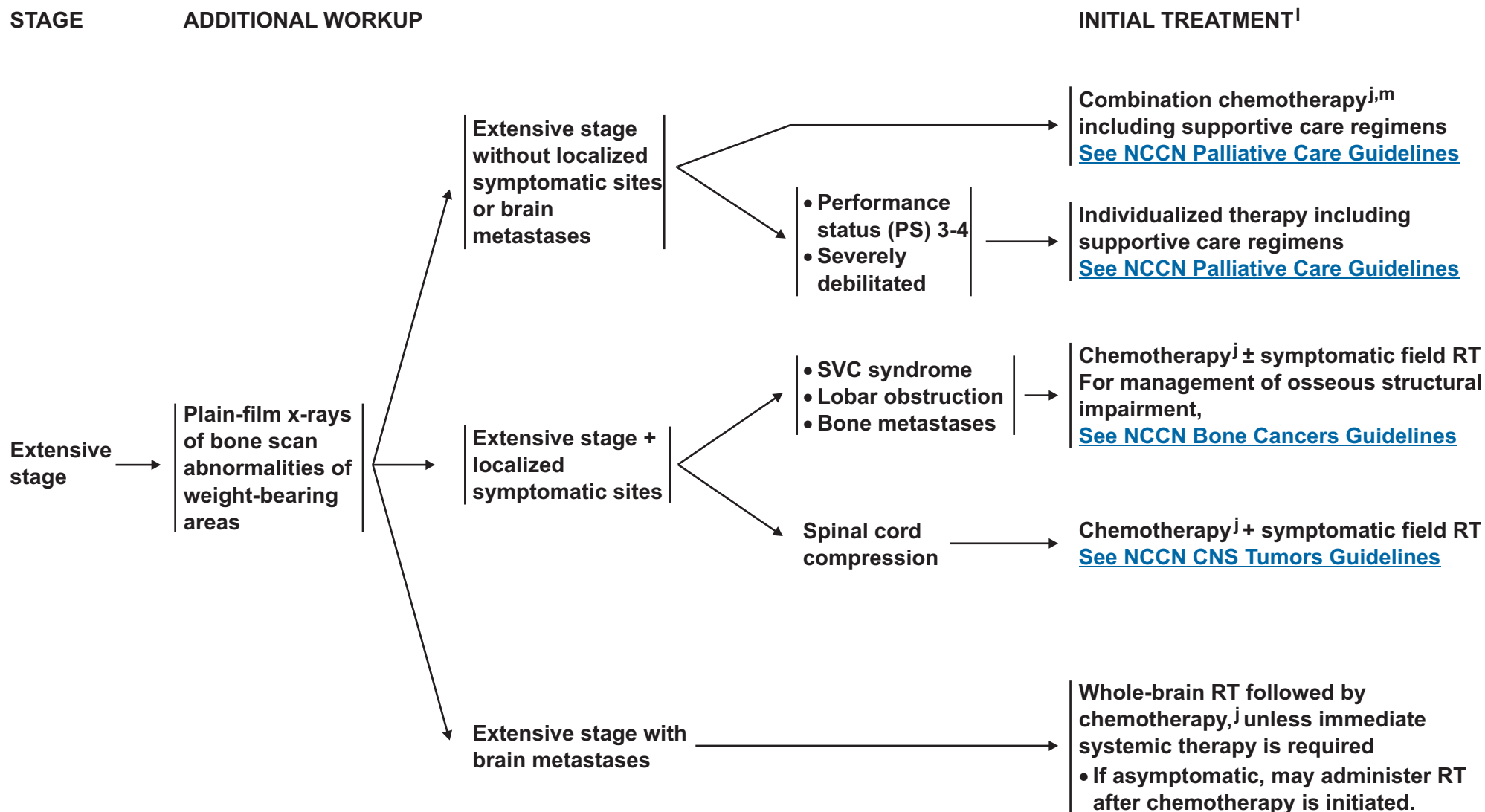
<sup>h</sup>[See Principles of Surgical Resection \(SCL-A\).](#)

<sup>i</sup>If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

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<sup>h</sup>See Principles of Surgical Resection (SCL-A).<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).[See Response Assessment + Adjuvant Treatment \(SCL-5\)](#)**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>j</sup>See Principles of Chemotherapy (SCL-B).

<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.

[See Response Assessment + Adjuvant Treatment \(SCL-5\)](#)

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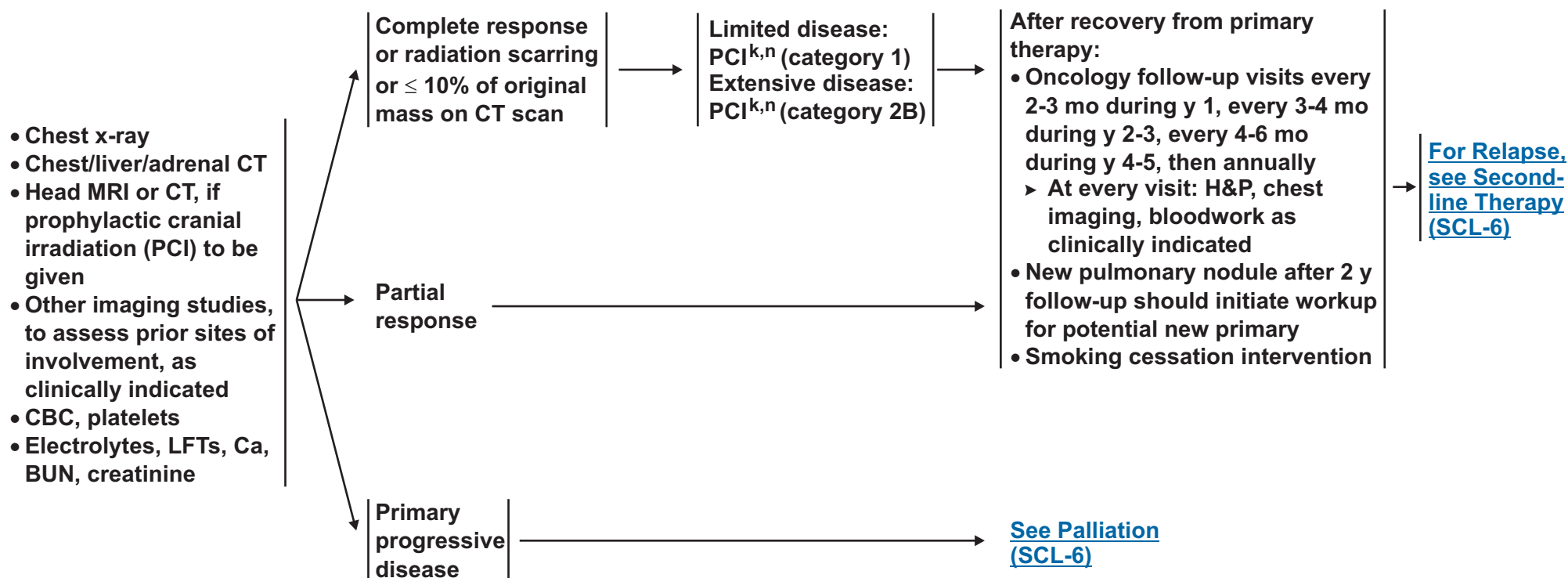
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RESPONSE ASSESSMENT  
FOLLOWING INITIAL THERAPY

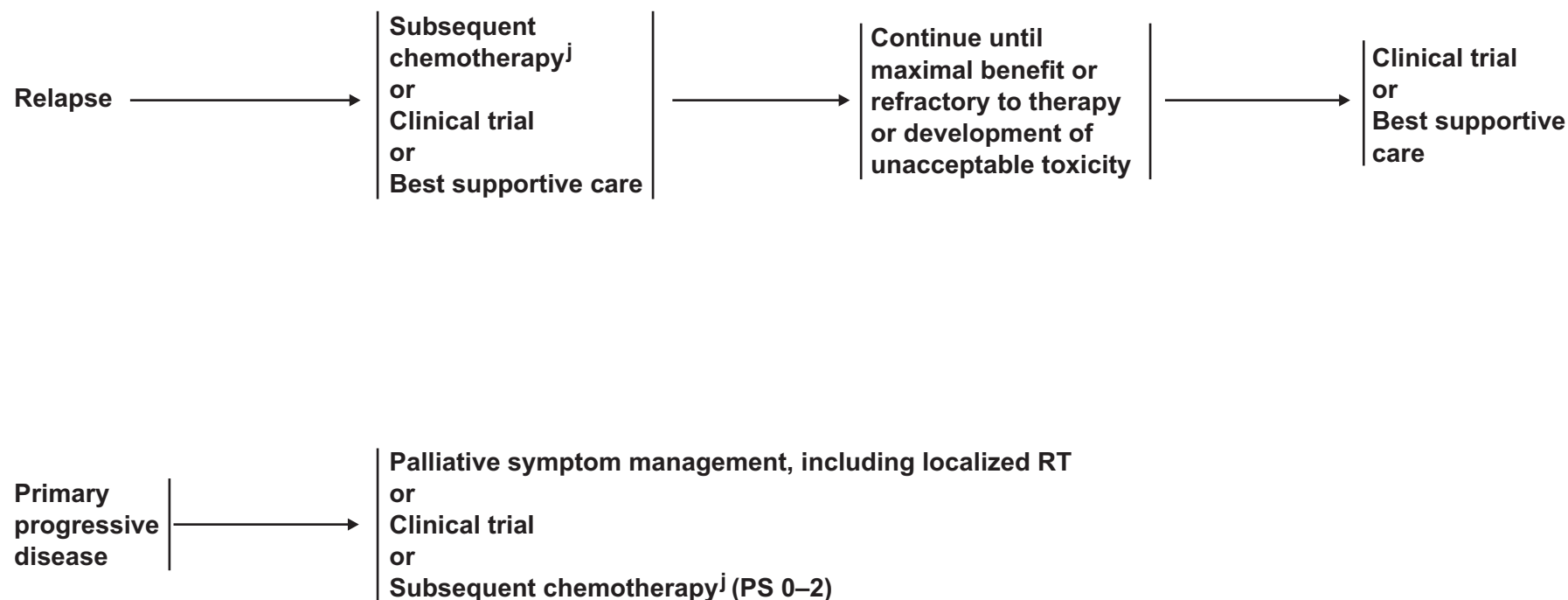
## ADJUVANT TREATMENT

## SURVEILLANCE

<sup>k</sup>See Principles of Radiation Therapy (SCL-C).<sup>n</sup>Not recommended in patients with multiple comorbidities, poor performance status, or impaired mental function.**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.

## PROGRESSIVE DISEASE

## SUBSEQUENT THERAPY/PALLIATION

<sup>j</sup>See [Principles of Chemotherapy \(SCL-B\)](#).**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 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.<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, 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 may be considered for postoperative 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.<sup>2</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;106:320-323S.

<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.

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## PRINCIPLES OF CHEMOTHERAPY\*

## Chemotherapy as primary therapy:

- Limited stage:
  - Cisplatin: 60 mg/m<sup>2</sup> day 1 and Etoposide: 120 mg/m<sup>2</sup> days 1, 2, 3 x 4 cycles<sup>1</sup>
  - Carboplatin: AUC 5-6 day 1 and Etoposide: 100 mg/m<sup>2</sup> days 1, 2, 3 x 4 cycles<sup>2</sup>
- During chemotherapy + RT, cisplatin/etoposide is recommended (category 1)
- Extensive stage:
  - Cisplatin: 75 mg/m<sup>2</sup> day 1 and Etoposide: 100 mg/m<sup>2</sup> days 1, 2, 3 x 4-6 cycles<sup>3</sup>
  - Carboplatin: AUC 5-6 day 1 and Etoposide: 100 mg/m<sup>2</sup> days 1, 2, 3 x 4-6 cycles<sup>2</sup>
  - Irinotecan: 60 mg/m<sup>2</sup> on days 1, 8, 15 and Cisplatin: 60 mg/m<sup>2</sup> on day 1<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>
  - Cyclophosphamide 1000 mg/m<sup>2</sup> day 1 and doxorubicin 45 mg/m<sup>2</sup> day 1 and vincristine 1.4 mg/m<sup>2</sup> day 1<sup>7</sup>
  - Cyclophosphamide 1000 mg/m<sup>2</sup> day 1 and doxorubicin 45 mg/m<sup>2</sup> day 1 and etoposide 100 mg/m<sup>2</sup> days 1, 2, 3<sup>8</sup>

## Subsequent chemotherapy:

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

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.

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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):265-71.
- <sup>2</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):1231-8.
- <sup>3</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>4</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>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):2022-34.
- <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):1471-7.
- <sup>7</sup>Hong WK, Nicaise C, Lawson R, et al. Etoposide combined with cyclophosphamide plus vincristine compared with doxorubicin plus cyclophosphamide plus vincristine and with high-dose cyclophosphamide plus vincristine in the treatment of small-cell carcinoma of the lung: a randomized trial of the Bristol Lung Cancer Study Group. *J Clin Oncol* 1989;7(4):450-6.
- <sup>8</sup>Ardizzoni A, Tjan-Heijnen VC, Postmus PE, et al. Standard versus intensified chemotherapy with granulocyte colony-stimulating factor support in small-cell lung cancer: a prospective European Organization for Research and Treatment of Cancer- Lung Cancer Group Phase III Trial- 08923. *J Clin Oncol* 2002;20(19):3947-55.

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PRINCIPLES OF RADIATION THERAPY<sup>1-5</sup>**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 50-60 Gy.<sup>1,2,3,4</sup>
  - 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.<sup>5,6</sup>
  - Concurrent chemoradiotherapy preferable to sequential therapy in fit patients (category 1)
- PCI dose 25-36 Gy (30 Gy in 15 fractions, 36 Gy in 18 fractions, or 25 Gy in 10 fractions)<sup>7,8</sup> Lower fraction regimens are recommended (1.8-2.0 Gy/fraction).

<sup>1</sup> Turisi 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):265-71.

<sup>2</sup> Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;59(4):943-51.

<sup>3</sup> Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;56(2):355-9.

<sup>4</sup> Roof KS, Fidias P, Lymch TJ, et al. Radiation dose escalation in limited-stage small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2003;57(3):701-8.

<sup>5</sup> Bogart JA, Herndon JE, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. *Int J Radiat Oncol Biol Phys* 2004;59(2):460-8.

<sup>6</sup> Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. *J Clin Oncol* 1994;12(3):496-502.

<sup>7</sup> Arriagada R, Le Chevalier T, Riviere A, et al. Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients. *Ann Oncol* 2002;13(5):748-54.

<sup>8</sup> Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group. *N Engl J Med* 1999;341(7):476-84.

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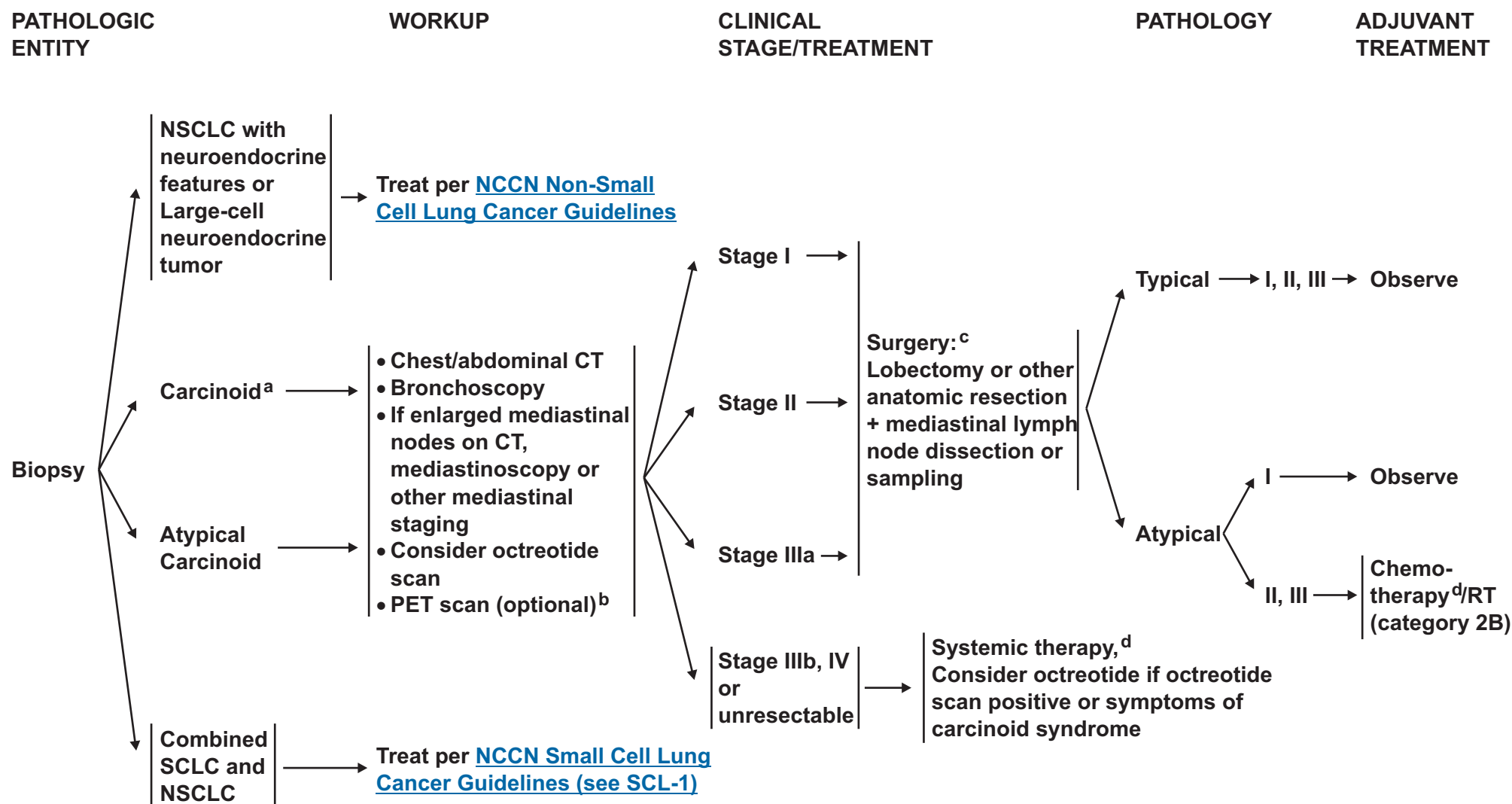
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## PRINCIPLES OF SUPPORTIVE CARE

- 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

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<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: Chemo-therapy/RT is recommended if surgery is not feasible.

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

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## Staging

**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\*****Primary Tumor (T)**

- 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† (ie, not in the main bronchus)
- 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
- 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
- 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‡

**Regional Lymph Nodes (N)**

- 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 of the primary tumor
- N2 Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
- N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

**Distant Metastasis (M)**

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis present§

† 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 nodule(s) in a different lobe (ipsilateral or contralateral).

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**Manuscript** This manuscript is being updated to correspond with the newly updated algorithm.

### NCCN Categories of Consensus

**Category 1:** There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

**Category 2A:** There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 2B:** There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

**Category 3:** There is major NCCN disagreement that the recommendation is appropriate.

**All recommendations are category 2A unless otherwise noted.**

### Overview

Small cell lung cancer (SCLC) accounts for 15% of all lung cancers. In 2005, approximately 26,000 new cases of SCLC will be diagnosed in the United States.<sup>1</sup> Most cases of SCLC are attributable to cigarette smoking, whereas the remaining cases are presumably caused by environmental or genetic factors. 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. Approximately 67% of patients with SCLC present with overt, metastatic disease outside the chest, whereas only 33% of patients present with limited disease confined to the chest within a single radiation port. SCLC is highly sensitive to initial chemotherapy and radiotherapy;<sup>2</sup> however, most

patients eventually die from recurrent disease.<sup>3</sup> Treatment using chemotherapy plus chest radiotherapy can be curative for some patients with limited-stage SCLC, while chemotherapy alone can palliate symptoms and prolong survival in most patients with extensive-stage disease.<sup>4</sup> Surgery is appropriate for the few patients (2%-5%) with surgically resectable SCLC.

### Pathology

SCLC is a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.<sup>5</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 have 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.

The differential diagnosis of small blue tumors includes SCLC, extrapulmonary small cell carcinoma, Merkel cell tumors, carcinoid tumors, atypical carcinoid tumors, large cell neuroendocrine carcinoma, lymphoma, small cell sarcomas, and other neuroendocrine tumors. Small cell carcinomas can also originate in extrapulmonary sites, including the nasopharynx, gastrointestinal tract, and genitourinary tract.<sup>6,7</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, which suggests a different pathogenesis.<sup>8</sup>

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor 1 (TTF1). Many 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.<sup>9</sup>

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC. These 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.<sup>10</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>11,12</sup> SCLC cells also can produce numerous polypeptide hormones, including adrenocorticotrophic hormone (ACTH) and vasopressin (ADH), which cause Cushing's syndrome and hyponatremia of malignancy, respectively.<sup>13,14</sup>

### 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 metastases, 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.

The Veteran's Administration Lung Group two-stage classification scheme is routinely used to define the extent of disease in patients with SCLC: (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. 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.

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 but not typically for those with extensive-stage disease. Full staging includes a chest radiograph; 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. Unilateral or bilateral bone marrow aspirates and biopsies may be indicated in patients with cytopenias 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. A positron emission tomography (PET) scan 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: (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 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 to 2 weeks; otherwise, many patients may become more seriously ill in the interval with a decline in their performance status (PS).

Poor PS, 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, 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.<sup>15,16</sup>

## Chemotherapy

Chemotherapy is an essential component of appropriate treatment for all patients with SCLC.<sup>4</sup> For those who have undergone successful surgical resection, adjuvant chemotherapy is recommended. For most patients with limited-stage SCLC, recommended treatment consists of chemotherapy with thoracic radiotherapy. For most patients with extensive-stage disease, combination chemotherapy is the recommended treatment.

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.<sup>3,17,18</sup> The most commonly used initial combination chemotherapy regimen is etoposide and cisplatin (EP).<sup>4,19</sup> This combination was developed based on the finding of preclinical synergy using cisplatin and etoposide, and it supplanted alkylator/anthracycline-based regimens based on superiority in both efficacy and toxicity in the limited-stage setting.<sup>20</sup> EP 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. 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>21</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>22</sup> The substitution of carboplatin for cisplatin is more acceptable in patients with extensive-stage disease, because chemotherapy is rarely curative in these patients.<sup>22</sup>



Other combinations have been evaluated in patients with extensive-stage disease with little consistent evidence of benefit when compared with EP. A 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>23</sup> In addition, 2-year survival was 19.5% in the irinotecan plus cisplatin group and 5.2% in the EP group.<sup>23</sup> However, a larger trial with a similar design 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>24</sup>

In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with etoposide plus thoracic radiotherapy, while in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.<sup>3</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>25</sup> Thoracic radiotherapy improves the local control rates by 25% in limited-stage disease patients and is associated with improved survival.<sup>26,27</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 two-drug regimens. In two trials, the addition of ifosfamide, or cyclophosphamide plus an anthracycline, to EP demonstrated a modest survival advantage for patients with extensive disease.<sup>28,29</sup> However, such findings have not been uniformly observed, and the

addition of ifosfamide with or without an anthracycline significantly increased hematologic toxicity when compared to EP alone.<sup>30</sup> 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.<sup>31</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>32</sup>

The inability to destroy residual cells despite 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.<sup>33</sup> However, randomized trials have failed to show improved disease-free or overall survival with this approach.<sup>34,35</sup>

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.<sup>36,37</sup> Nevertheless, no survival benefits were documented in randomized trials and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.<sup>38-41</sup>

The role of higher-dose therapy for patients with SCLC remains controversial.<sup>42</sup> A meta-analysis was performed to assess whether the dose-intensity of individual agents or regimens correlated with response or survival in SCLC trials. This study evaluated trials in

which the relative dose-intensities of the CAV, CAE, and EP regimens were analyzed over relatively narrow ranges. It found only a small, clinically insignificant enhancement of median survival in patients with extensive-stage disease when using increased relative dose-intensity.<sup>43</sup>

Higher complete and partial response rates, as well as 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>44</sup> In general, however, randomized trials comparing an incremental dose-intensity between one and two times the full conventional dose have not consistently shown an increased response rate or survival advantage.<sup>45-48</sup>

Currently available cytokines (eg, 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,<sup>49</sup> there is little evidence to suggest that maintenance of dose intensity prolongs disease-free or overall survival.

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.<sup>50</sup> Although advanced chronological

age adversely affects tolerance to treatment, an individual patient's functional status is much more helpful in guiding clinical decision making. If an older person is functional in terms of the ability to perform activities of daily living, then the clear recommendation would be to treat this patient with the recommended combination chemotherapy (and radiotherapy, if indicated). Myelosuppression and fatigue as well as lower organ reserves may be encountered more frequently in elderly patients, particularly during the first cycle, because the toxicities of chemotherapy overlap with the adverse effects of the cancer.

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 (eg, single-agent etoposide) is inferior to combination chemotherapy (such as platinum plus etoposide regimens) in elderly patients with good PS.<sup>51,52</sup> Several other strategies have been evaluated in elderly patients with SCLC.<sup>53-55</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. However, some patients may not tolerate a dose of carboplatin with an AUC as high as 6.<sup>56</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.<sup>57</sup> 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

chemotherapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from last 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 second-line agents include topotecan (category 1), irinotecan, paclitaxel, docetaxel, ifosfamide, oral etoposide, gemcitabine, and vinorelbine.<sup>58-60</sup> In a randomized phase III trial, single-agent topotecan was compared to the combination regimen CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine). Both arms had similar response rates and survival, but topotecan caused less toxicity and is now recommended as the second-line agent for patients with relapsed SCLC (category 1).<sup>60</sup> Second-line 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.<sup>2</sup> 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.<sup>26,27</sup>

However, achieving 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, and reported that patients treated with concurrent radiotherapy lived longer than those treated with sequential radiotherapy.<sup>61</sup> Another randomized phase III trial by the National Cancer Institute of Canada compared radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy, and demonstrated that early radiotherapy was associated with improved local and systemic control and longer survival.<sup>62</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>63</sup>

Based on a phase II study by Turrisi et al,<sup>64</sup> 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 along with a higher incidence of grade 3-4 esophagitis. 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>65</sup>

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.<sup>66</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.

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 at a dose of either 1.5 Gy twice daily to a total dose of 45 Gy, or 1.8 Gy/day to at least 50 Gy. 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.

### Prophylactic Cranial Radiotherapy

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 the individual studies did not have sufficient power to demonstrate a meaningful survival advantage.<sup>67</sup> 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.<sup>68</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>68</sup> 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 balanced discussion between the patient and physician is necessary before making a decision to administer PCI. On the basis of the meta-analysis, PCI is recommended for patients with limited-stage disease (category 1) who attain a complete response after initial chemoradiotherapy and can be used for patients with extensive-stage disease (category 2B) who achieve a complete response.<sup>68</sup> PCI is not recommended for patients with multiple comorbidities, poor PS, or impaired mental function. Doses ranging from 25 Gy in 10 fractions to 36 Gy in 18 fractions are recommended. 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.<sup>69</sup> 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.<sup>70</sup> 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 two 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.<sup>71</sup> Before resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease.<sup>72</sup> Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy.<sup>73,74</sup> Patients without nodal metastases can be treated with chemotherapy alone, but concurrent chemotherapy and postoperative RT are recommended for patients with nodal metastases. 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.<sup>68</sup>

SCLC can rarely be diagnosed during a thoracotomy performed for a pulmonary nodule that does not have a definitive diagnosis.<sup>73</sup> In this situation, if intraoperative frozen section analysis suggests that all disease can be resected by a lobectomy with a nodal dissection even if nodal involvement is found, the recommendation (category 2B) is to complete the resection if the patient can tolerate the

procedure. If the disease can only be resected by a pneumonectomy, then resection is rarely appropriate because of the greater operative mortality than with a lobectomy, the reduced tolerance for postoperative treatments, and the loss of pulmonary function, as well as the patient's overall medical condition. Postoperative therapy should then proceed as described earlier.

### 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).<sup>61</sup> Chest radiotherapy should begin during cycle 1 or 2 and should provide at least a biologically equivalent dose of 45 Gy in daily fractions of 1.8 Gy or greater (category 1).<sup>61,62</sup> PCI is recommended for patients who achieve a complete response. Follow-up examinations are recommended every 2 to 3 months over the first several years with concomitant chest radiographs. Smoking cessation should be encouraged, because patients who smoke have increased toxicity during treatment and shorter survival.<sup>75</sup> 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.<sup>76</sup>

For patients with extensive-stage disease, standard combination

platinum-based chemotherapy is recommended, recognizing that new approaches are desperately needed.

### Disclosures for the NCCN Small Cell Lung Cancer Guidelines Panel

At the beginning of each panel meeting to develop NCCN guidelines, panel members disclosed the names of companies, foundations, and/or funding agencies from which they received research support; for which they participate in speakers' bureau, advisory boards; and/or in which they have equity interest or patents. Members of the panel indicated that they have received support from the following: Allos Therapeutics, Inc; Amgen; AstraZeneca; Bristol-Myers Squibb; Eli Lilly; Genentech Inc; GlaxoSmithKline; ImClone Systems Inc; Novartis Pharmaceuticals; Pfizer Inc; Pharmacyclics Inc; and Sanofi-Aventis. Some panel members do not accept any support from industry. The panel did not regard any potential conflicts of interest as sufficient reason to disallow participation in panel deliberations by any member.

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## References

1. Jemal A, Murray T, Ward E, et al. Cancer statistics, 2005. *CA Cancer J Clin* 2005;55:10-30.
2. Simon G, Ginsberg RJ, Ruckdeschel JC. Small-cell lung cancer. *Chest Surg Clin N Am* 2001;11:165-188, ix.
3. Simon M, Argiris A, Murren JR. Progress in the therapy of small cell lung cancer. *Crit Rev Oncol Hematol* 2004;49:119-133.
4. Johnson BE, Jänne PA. Basic treatment considerations using chemotherapy for patients with small cell lung cancer. *Hematol Oncol Clin North Am* 2004;18(2):309-322.
5. Travis WD, Colby TV, Corrin B, et al. Histological Typing of Lung and Pleural Tumours. World Health Organization International Histological Classification of Tumours. Berlin: Springer-Verlag, 1999.
6. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. *Cancer* 1997;79:1729-1736.
7. Remick SC, Ruckdeschel JC. Extrapulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. *Med Pediatr Oncol* 1992;20:89-99.
8. Johnson B, Whang-Peng J, Naylor S, et al. Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. *J Natl Cancer Inst* 1989;81:1223-1228.
9. Guinee DG Jr, Fishback NF, Koss MN, et al. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. *Am J Clin Pathol* 1994;102:406-414..
10. Meriney SD, Hulsizer SC, Lennon VA, et al. Lambert-Eaton myasthenic syndrome immunoglobulins react with multiple types of calcium channels in small-cell lung carcinoma. *Ann Neurol* 1996;40:739-749.
11. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. *Brain* 2001;124:1138-1148.
12. Manley GT, Smitt PS, Dalmau J, et al. Hu antigens: reactivity with Hu antibodies, tumor expression, and major immunogenic sites. *Ann Neurol* 1995;38:102-110.
13. Delisle L, Boyer MJ, Warr D, et al. Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. *Arch Intern Med* 1993;153:746-52.
14. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. *Am J Respir Crit Care Med* 1997;156:1669-1678.
15. Albain KS, Crowley JJ, LeBlanc M, et al. Determinants of improved outcome in small cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. *J Clin Oncol* 1990;8:1563-1574.
16. Yip D, Harper DG. Predictive and prognostic factors in small cell lung cancer: current status. *Lung Cancer* 2000;28:173-185.
17. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. *N Engl J Med* 2004;350:379-392.
18. Johnson BE. Management of small cell lung cancer. *Clin Chest Med*

Med 2002;23(1):225-239.

19. Evans WK, Shepherd FA, Feld R, et al. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985;3:1471-1477.

20. Sundstrom S, Bremnes RM, Kaasa S, et al. Cisplatin and etoposide regimen is superior to cyclophosphamide, epirubicin, and vincristine regimen in small-cell lung cancer: results from a randomized phase III trial with 5 years' follow-up. *J Clin Oncol* 2002;20:4665-4672.

21. Bishop JF, Raghavan D, Stuart-Harris R, et al. Carboplatin (CBDCA, JM-8) and VP-16-213 in previously untreated patients with small cell lung cancer. *J Clin Oncol* 1987;5:1574-1578.

22. Sklaros DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small cell lung cancer: a Hellenic Cooperative Oncology Group study. *Ann Oncol* 1994;5:601-607.

23. Noda K, Nishiwaki Y, Kawahara M, et al. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85-91.

24. Hanna NH, Einhorn L, Sandler A, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage small cell lung cancer. *J Clin Oncol* 2005;23(16S-Part II):1094s.

25. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: Perceptible progress. *J Clin Oncol* 1999;17:1794-1801.

26. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of

thoracic radiotherapy for small-cell lung cancer. *N Engl J Med* 1992;327:1618-1624.

27. Warde P, Payne D. Does thoracic irradiation improve survival and local control in limited-stage small-cell carcinoma of the lung? A meta-analysis. *J Clin Oncol* 1992;10:890-895.

28. Loehrer PJ, Ansari R, Gonin R, et al. Cisplatin plus etoposide with and without ifosfamide in extensive small-cell lung cancer: A Hoosier Oncology Group study. *J Clin Oncol* 1995;13:2594-2599.

29. Pujol JL, Daures JP, Riviere A, et al. Etoposide plus cisplatin with or without the combination of 4'-epidoxorubicin plus cyclophosphamide in treatment of extensive small-cell lung cancer: a French Federation of Cancer Institutes multicenter phase III randomized study. *J Natl Cancer Inst* 2001;93:300-308.

30. Miyamoto H, Nakabayashi T, Isobe H, et al. A phase III comparison of etoposide/cisplatin with or without added ifosfamide in small-cell lung cancer. *Oncology* 1992;49:431-435.

31. Niell HB, Herndon JE, Miller AA, et al. Randomized phase III Intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte colony-stimulating factor in patients with extensive-stage small cell lung cancer: CALGB trial 9732. *J Clin Oncol* 2005;23:3752-3759.

32. Schiller JH, Adak S, Cella D, et al. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593: A phase III trial of the Eastern Cooperative Oncology Group. *J Clin Oncol* 2001;19:2114-2122.

33. Goldie JH, Coldman AJ. A mathematical model for relating the drug sensitivity of tumors to their spontaneous mutation rate. *Cancer Treat Rep* 1979;63:1727-1733.

34. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small cell lung cancer. *J Natl Cancer Inst* 1991;83:855-861.
35. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: A phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992;10:282-291.
36. Miles DW, Earl HM, Souhami RL, et al. Intensive weekly chemotherapy for good-prognosis patients with small-cell lung cancer. *J Clin Oncol* 1991;9:280-285.
37. Murray N, Gelmon K, Shah A, et al. Potential for long-term survival in extensive stage small-cell lung cancer (ESCLC) with CODE chemotherapy and radiotherapy [abstract]. *Lung Cancer* 1994;11(suppl 1):99.
38. Sculier JP, Paesmans M, Bureau G, et al. Multiple drug weekly chemotherapy versus standard combination regimen in small cell lung cancer: A phase III randomized study conducted by the European Lung Cancer Working Party. *J Clin Oncol* 1993;11:1858-1865.
39. Souhami RL, Rudd R, Ruiz de Elvira MC, et al. Randomized trial comparing weekly versus 3-week chemotherapy in small cell lung cancer: A Cancer Research Campaign trial. *J Clin Oncol* 1994;12:1806-1813.
40. Fukuoka M, Masuda N, Negoro S, et al. CODE chemotherapy with or without granulocyte colony stimulating factor in small cell lung cancer. *Br J Cancer* 1997;75:306-309.
41. Murray N, Livingston RB, Shepherd FA, et al. Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an Intergroup Study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. *J Clin Oncol* 1999;17:2300-2308.
42. Teicher BA. Preclinical models for high-dose therapy. In: Armitage JO, Antman KH, eds. *High-Dose Cancer Therapy: Pharmacology, Hematopoietins, Stem Cells*, 2nd edition. Baltimore: Williams and Wilkins, 1995:14-42.
43. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. *J Clin Oncol* 1991;9:499-508.
44. Cohen MH, Creaven PJ, Fossieck BE, et al. Intensive chemotherapy of small cell bronchogenic carcinoma. *Cancer Treat Rep* 1977;61:349-354.
45. Johnson DH, Einhorn LH, Birch R, et al. A randomized comparison of high dose versus conventional dose cyclophosphamide, doxorubicin, and vincristine for extensive stage small cell lung cancer: A phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1987;5:1731-1738.
46. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. *J Clin Oncol* 1994;12:2022-2034.
47. Arriagada R, Le Chevalier T, Pignon J-P, et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. *N Engl J Med* 1993;329:1848-1852.



48. Thatcher N, Girling DJ, Hopwood P, et al. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: Results of a British Medical Research Council multicentre randomized trial. *J Clin Oncol* 2000;18:395-404.
49. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991;325:164-170.
50. Hurria A, Kris MG. Management of lung cancer in older adults. *CA Cancer J Clin* 2003;53:325-341.
51. Medical Research Council Lung Cancer Working Party. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: A stopped multicentre randomised trial. *Lancet* 1996;348:563-566.
52. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: Randomized comparison with intravenous chemotherapy. *J Natl Cancer Inst* 1997;89:577-580.
53. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with Eastern Cooperative Oncology Group performance status of 2, or age 70 years or more. *J Clin Oncol* 2004;22:1872-1877.
54. Weestee V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: A phase II study of the PAVE regimen. *J Clin Oncol* 1998;16:1940-1947.
55. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. *J Clin Oncol* 1999;17:3540-3545.
56. Matsui K, Masuda N, Yana T, et al. Carboplatin calculated with Chatelut's formula plus etoposide for elderly patients with small-cell lung cancer. *Intern Med* 2001;40:603-606.
57. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or non-compliant patients with limited-stage small-cell lung cancer. *J Clin Oncol* 1998;16:3323-3328.
58. Ettinger DS. New drugs for chemotherapy-naïve patients with extensive-disease small cell lung cancer. *Semin Oncol* 2001;28:27-29.
59. Kelly K. New chemotherapy agents for small cell lung cancer. *Chest* 2000;117:156S-162S.
60. von Pawel J, Gatzemeier U, Pujol JL, et al. Phase II comparator study of oral versus intravenous topotecan in patients with chemosensitive small-cell lung cancer. *J Clin Oncol* 2001;19:1743-1749.
61. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20:3054-3060.
62. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited

stage small cell lung cancer. J Clin Oncol 1993;11:336-344.

63. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small cell lung cancer. J Clin Oncol 2004;22:4785-4793.

64. Turrisi AT, Glover DJ, Mason BA. A preliminary report: Concurrent twice-daily radiotherapy plus platinum-etoposide chemotherapy for limited small cell lung cancer. Int J Radiat Oncol Biol Phys 1988;15:183-187.

65. 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 [see comments]. N Engl J Med 1999;340:265-271.

66. Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;59:943-951.

67. Arriagada R, Le Chevalier T, Borie F, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. J Natl Cancer Inst 1995;87:183-190.

68. Auperin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Radiation Overview Collaborative Group. N Engl J Med 1999;341:476-484.

69. Rostad H, Naalsund A, Jacobsen R, et al. Small cell lung cancer in Norway. Should more patients have been offered surgical therapy? Eur J Cardiothorac Surg 2004;26:782-786.

70. 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;106:320-323S.

71. Inoue M, Miyoshi S, Yasumitsu T, et al. Surgical results for small cell lung cancer based on the new TNM staging system. Thoracic Surgery Study Group of Osaka University, Osaka, Japan. Ann Thorac Surg 2000;70:1615-1619.

72. Inoue M, Nakagawa K, Fujiwara K, et al. Results of preoperative mediastinoscopy for small cell lung cancer. Ann Thorac Surg 2000;70:1620-1623.

73. Tsuchiya R, Suzuki K, Ichinose Y, et al. Phase II trial of postoperative adjuvant cisplatin and etoposide in patients with completely resected stage I-IIIa small cell lung cancer: The Japan Clinical Oncology Lung Cancer Study Group Trial (JCOG9101). J Thorac Cardiovasc Surg 2005;129:977-983.

74. Brock MV, Hooker CM, Syphard JE, et al. Surgical resection of limited disease small cell lung cancer in the new era of platinum chemotherapy: Its time has come. J Thorac Cardiovasc Surg 2005;129:64-72.

75. Videtic GMM, Stitt LW, Dar AR, et al. Continued cigarette smoking by patients receiving concurrent chemoradiotherapy for limited-stage small-cell lung cancer is associated with decreased survival. J Clin Oncol 2003;21:1544-1549.

76. Johnson BE, Linnoila RI, Williams JP, et al. Risk of second aerodigestive cancers increases in patients who survive free of small cell lung cancer for more than 2 years. J Clin Oncol 1995;13:101-111.