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Small Cell Lung Cancer

Clinical Practice Guidelines in Oncology

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Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (~ 15%) are small cell lung cancer (SCLC), which are treated using the NCCN Guidelines for SCLC.[1–3] In 2011, an estimated 33,000 new cases of SCLC will occur in the United States.[4] 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.[2] Other lung neuroendocrine tumors (LNTs) are treated according to the LNT algorithm on page 1098 (see also the discussion section on page 1107).

Although non–small cell lung cancer (NSCLC) is the most common type of lung cancer (see the NCCN Clinical Practice Guidelines in Oncology

NCCN Clinical Practice Guidelines in Oncology for Small Cell Lung Cancer

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, carcinoma, small cell, neuroendocrine tumors, chemotherapy, radiotherapy, surgical resection *(JNCCN* 2011;9:1086–1113)

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Small Cell Lung Cancer

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Small Cell Lung Cancer panel members can be found on page 1113. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit www.NCCN.org.

[NCCN Guidelines] for Non–Small Cell Lung Cancer; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org), 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, whereas only approximately one-third present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die of recurrent disease.[5,6]

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

Smoking cessation should be strongly promoted (national access to state-based quit-line services is available at 1-800-QUIT-NOW or www.smokefree.gov/). Patients who smoke have increased toxicity during treatment and shorter survival.[12] Programs using behavioral counseling combined with FDA-approved medications that promote smoking cessation can be very useful (www.surgeongeneral.gov/tobacco/index.html).

Text continues on p. 1099

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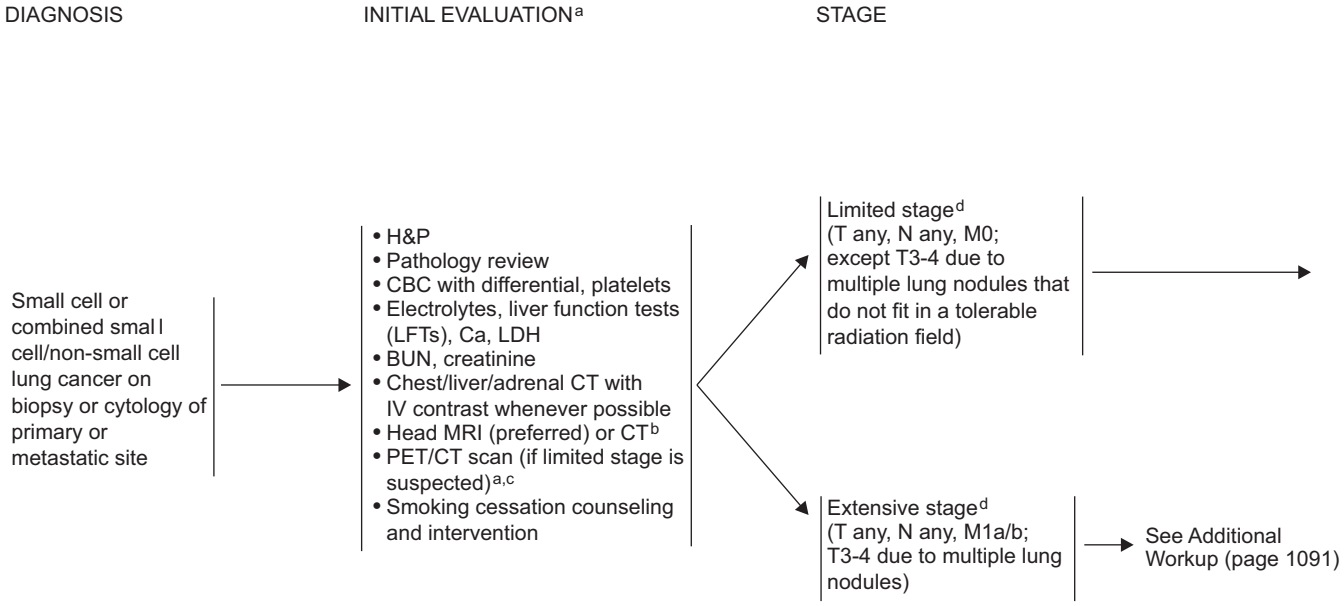

[a] If extensive stage is established, further staging evaluation is optional. However, head MRI (preferred) or CT should be obtained in all patients.
[b] Head MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[c] If PET/CT not available, bone scan may be used to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

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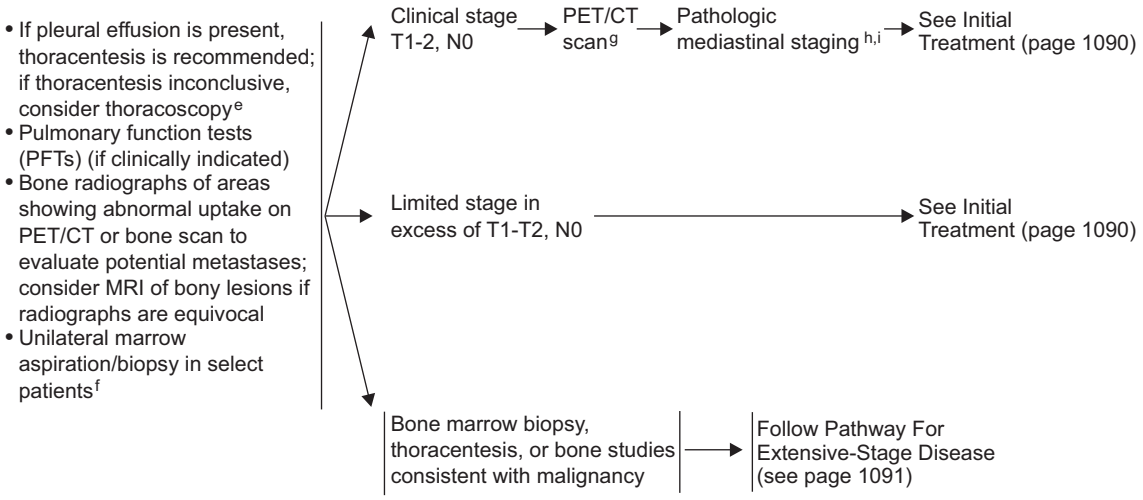
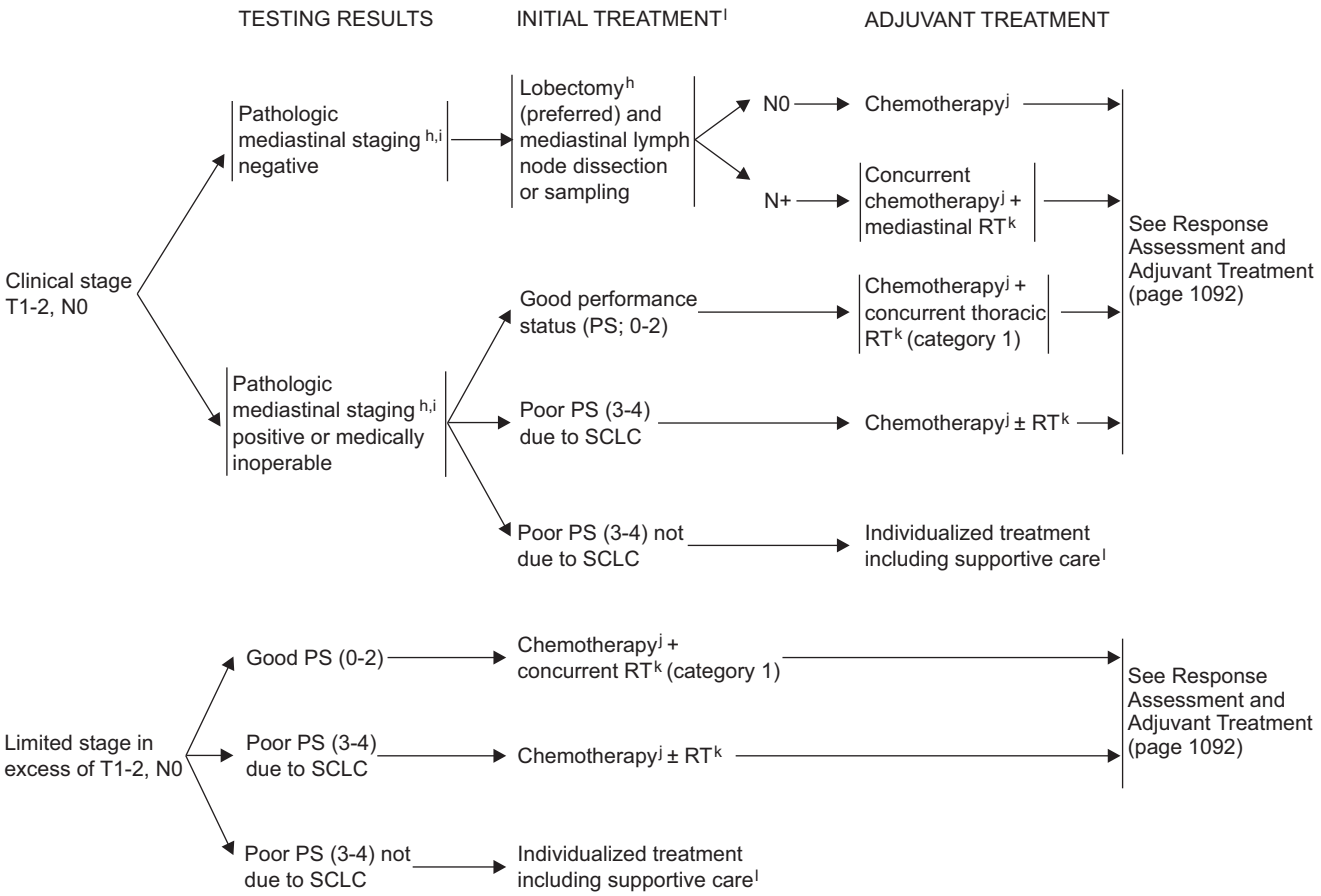
ADDITIONAL WORKUP



[e] Most pleural effusions in patients with lung cancer are from 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.
[f] Selection criteria include: nucleated RBCs on peripheral blood smear, neutropenia, or thrombocytopenia.
[g] PET scan to identify distant disease and to guide mediastinal evaluation, if not previously done.
[h] See Principles of Surgical Resection (page 1094).
[i] 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.



[h] See Principles of Surgical Resection (page 1094).
[i] 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.
[j] See Principles of Chemotherapy (page 1095).
[k] See Principles of Radiation Therapy (page 1096).
[l] See Principles of Supportive Care (page 1097).

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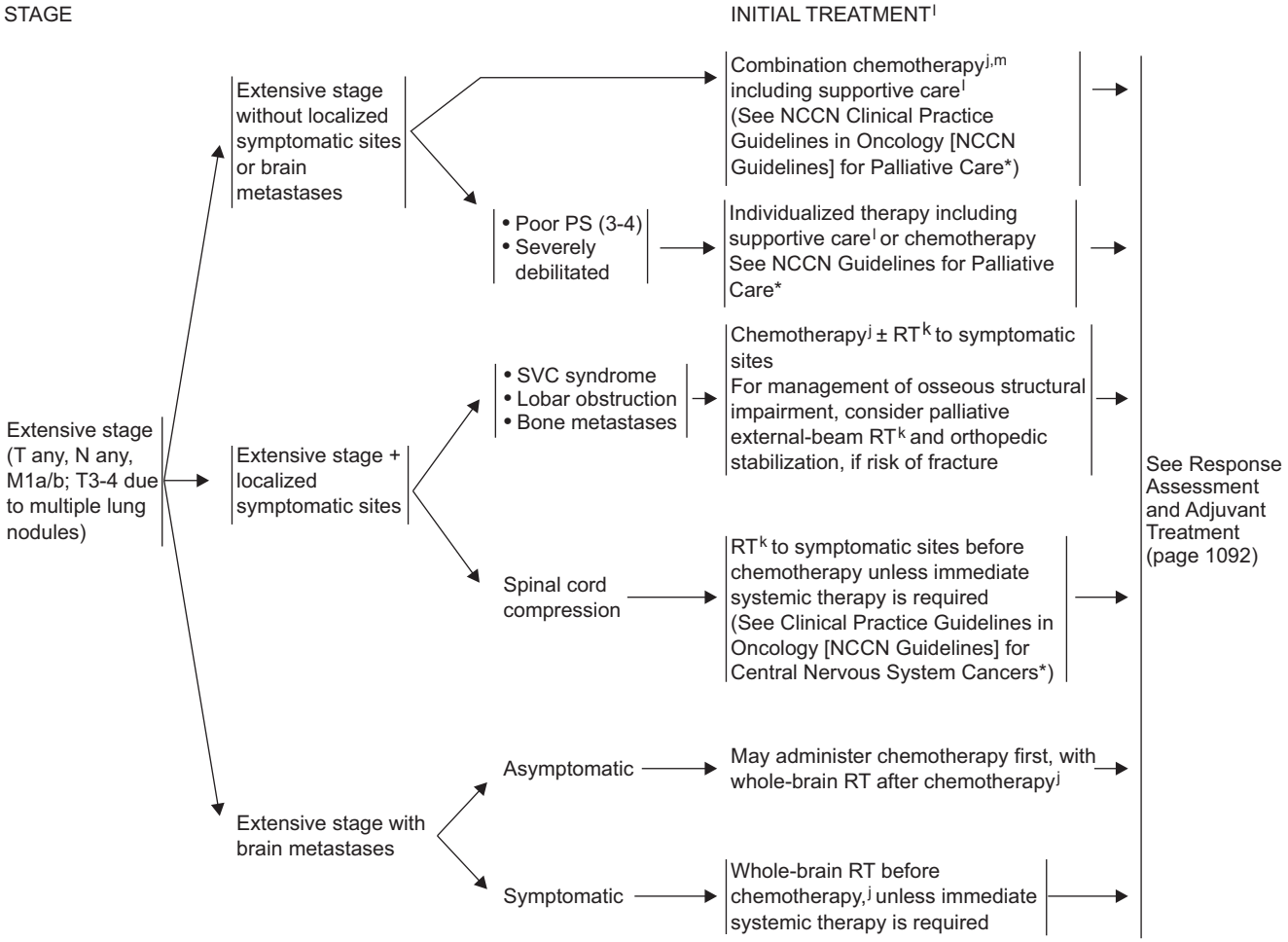
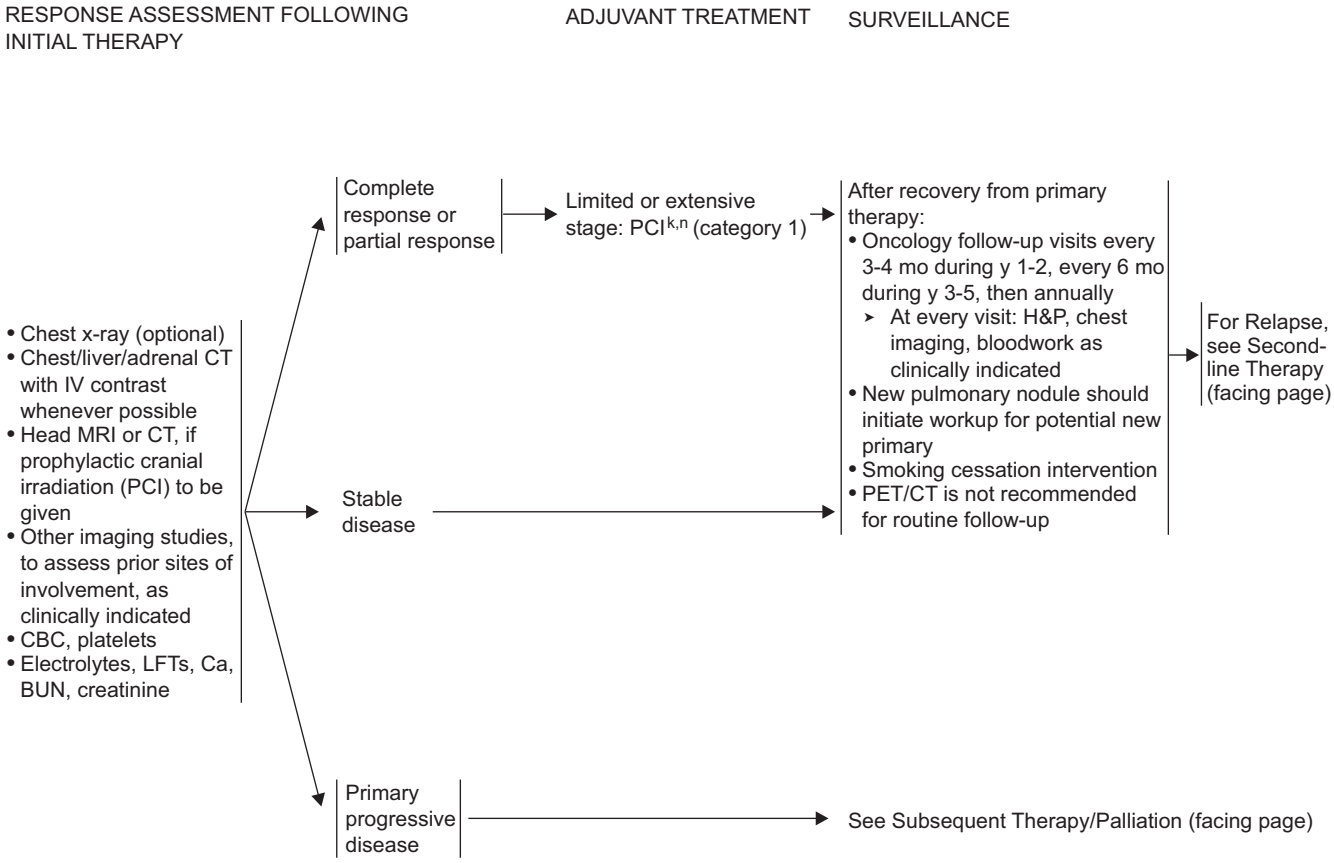


*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[j]See Principles of Chemotherapy (page 1095).
[k]See Principles of Radiation Therapy (page 1096).
[l]See Principles of Supportive Care (page 1097).
[m]Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and CR or near CR after systemic therapy.



[k] See Principles of Radiation Therapy (page 1096).
[n] Not recommended in patients with poor PS or impaired mental function.

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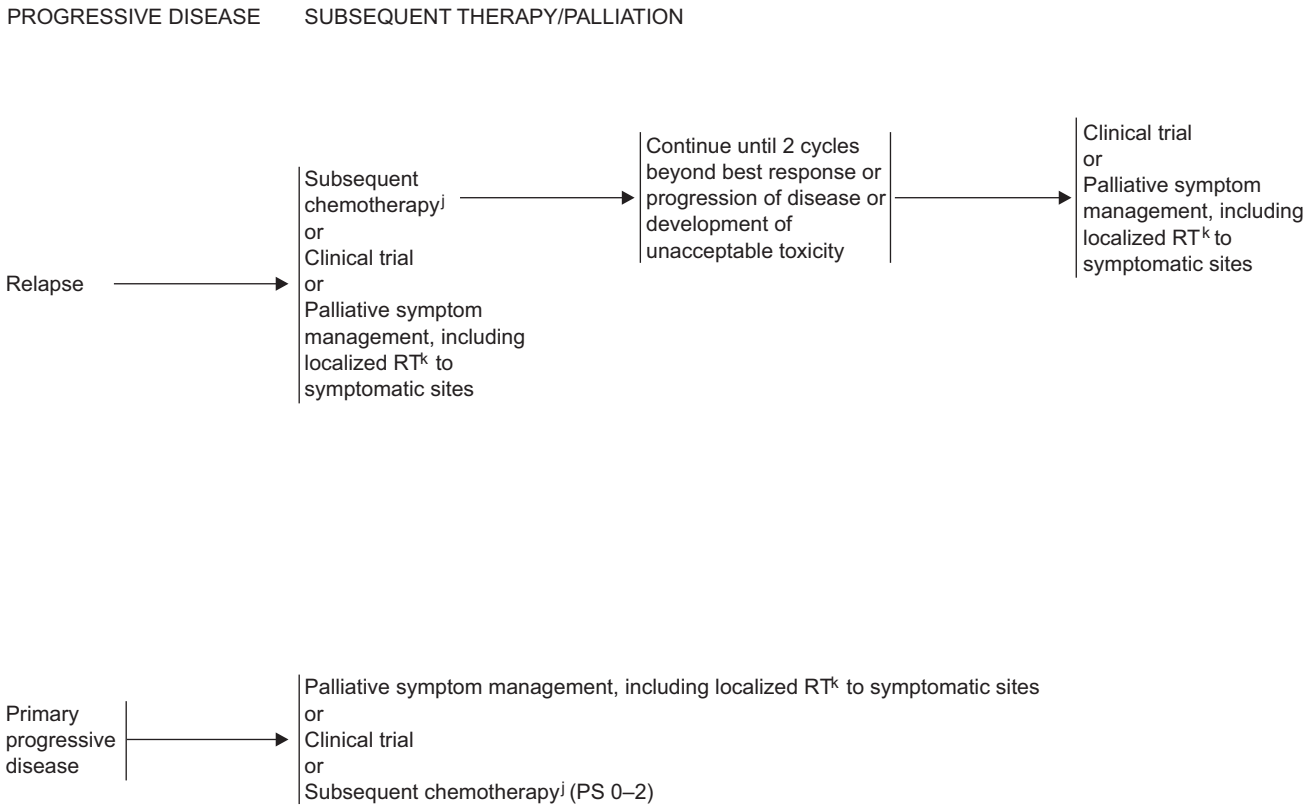

[j] See Principles of Chemotherapy (page 1095).
[k] See Principles of Radiation Therapy (page 1096).

PRINCIPLES OF SURGICAL RESECTION

- Stage I SCLC is diagnosed in fewer than 5% of patients with SCLC.
- Patients with disease in excess of T1-2, N0 do not benefit from surgery.[1]
- Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, brain imaging, and PET/CT imaging) may be considered for surgical resection.
  - Before 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.[2] PCI is not recommended in patients with poor performance status or impaired mental functioning.[3,4]

[1] 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-323S.
[2] 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;341:476-484.
[3] 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.
[4] 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;10:467-474.

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PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary therapy:

- Limited stage (maximum of 4-6 cycles):
  - Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1, 2, 3[1]
  - Cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[2]
  - Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[3]
  - 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^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[4]
  - Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, 3[5]
  - Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3[6]
  - Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[7]
  - Cisplatin 60 mg/m^2 day 1 and irinotecan 60 mg/m^2 days 1, 8, 15[8]
  - Cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 days 1, 8 every 21 days[9]
  - Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, and 15[10]

Subsequent chemotherapy:

- Clinical trial preferred
- Relapse < 2-3 mo, PS 0-2:
  - Paclitaxel[11,12]
  - Docetaxel[13]
  - Topotecan[14,15]
  - Irinotecan[16]
  - Ifosfamide[17]
  - Gemcitabine[18,19]
- Relapse > 2-3 mo up to 6 mo:
  - Topotecan PO or IV (category 1)[14,15,20]
  - Paclitaxel[11,12]
  - Docetaxel[13]
  - Irinotecan[16]
  - Gemcitabine[18,19]
  - Vinorelbine[21,22]
  - Oral etoposide[23,24]
  - Cyclophosphamide/doxorubicin/vincristine (CAV)[14]
- Relapse > 6 mo: original regimen[25,26]

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

*The regimens included are representative of the more commonly used regimens for small cell lung cancer. Other regimens may be acceptable.

[1]Turrisi AT III, 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;340:265-271.
[2]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;24:5247-5252.
[3]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;12:1231-1238.
[4]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.
[5]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.
[6]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.
[7]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.
[8]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.
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[11]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.
[12]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.
[13]Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. Eur J Cancer 1994;30A:1058-1060.
[14]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;17:658-667.
[15]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;24:5441-5447.
[16]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.
[17]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.
[18]Van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. Ann Oncol 2001;12:557-561.
[19]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.
[20]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;25:2086-2092.
[21]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.
[22]Furuse K, Kuboa K, Kawahara M, et al. Phase II study of vinorelbine in heavily previously treated small cell lung cancer. Oncology 1996;53:169-172.
[23]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.
[24]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.
[25]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.
[26]Giaccone G, Ferrati P, Donadio M, et al. Reinduction chemotherapy in small cell lung cancer. Eur J Cancer Clin Oncol 1987;23:1697-1699.

PRINCIPLES OF RADIATION THERAPY

Limited Stage:

- Radiotherapy should be delivered as either 1.5 Gy twice daily to a total dose of 45 Gy (category 1), or 2 Gy once daily to 60-70 Gy.[1-6] If bid fractionation is used, there should be at least a 6-hour interfraction interval to allow for repair of normal tissue.
- Radiotherapy should start concurrent with chemotherapy, cycle 1 or 2 (category 1).[7]
- Radiation target volumes should be defined based on the pretreatment PET and CT scans obtained at the time of radiotherapy planning, following ICRU definitions (Reports 50 and 62).[8-10] 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).[11] 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.[12]

Normal Tissue Constraints:[13,14]

- 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 twice-daily accelerated hyperfractionation (i.e., 45 Gy/ 30 twice daily treatments) irradiation schema is used, the maximum spinal cord dose should be limited to ≤ 41 Gy (including scatter irradiation). If once daily dose irradiation is utilized, the maximum spinal cord dose should be limited to ≤ 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 ≤ 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 used 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 patients with extensive-stage disease, 20 Gy in 5 fractions may be considered.[15,16]

[1]Turisi AT III, 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;340:265-271.
[2]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.
[3]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;56:355-359.
[4]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;57:701-708.
[5]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;59:460-468.
[6]Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in Intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer 2000;89:1953-1960.
[7]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.
[8]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;12:496-502.
[9]The International Commission on Radiation Units and Measurement (ICRU) Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy: Library of Congress Cataloging-in-Publication Data; 1993.
[10]The International Commission on Radiation Units and Measurements Prescribing, Recording and Reporting Photon Beam Therapy: Supplement to ICRU Report 50, Library of Congress Cataloging-in-Publication Data; 1999.
[11]International Commission on Radiation Units & Measurements. Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IRT). (ICRU Report 83). Available at: http://www.icru.org/index.php?option=com_content&task=view&id=171. Accessed August 18, 2011.
[12]Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 2006;33:3874-3900.
[13]Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-215.
[14]Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 2009;91:dd282-287.
[15]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;10:467-474.
[16]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.

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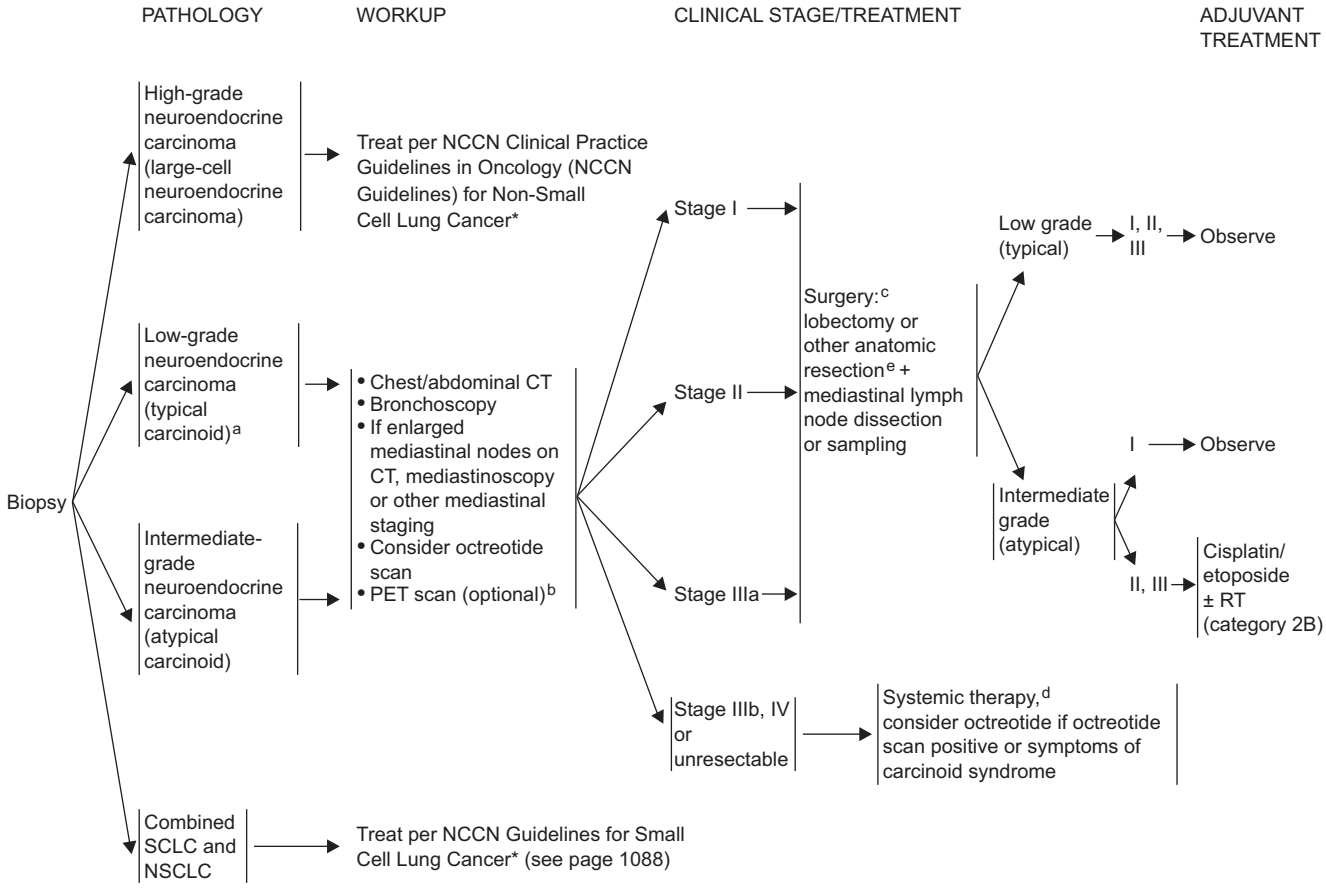
PRINCIPLES OF SUPPORTIVE CARE

- 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 syndrome
  - Consider ketoconazole
  - Try to control before initiation of antineoplastic therapy
- Leptomeningeal disease: See NCCN Guidelines for Central Nervous System Cancers*
- Pain Management: See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Adult Cancer Pain*
- Nausea/Vomiting: See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Antiemesis*
- Psychosocial distress: See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Distress Management*
- See NCCN Guidelines for Palliative Care* as indicated

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.



*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[a]Management of endocrine symptoms as indicated (see the Carcinoid Tumors section in the NCCN Guidelines for Neuroendocrine Tumors*).
[b]PET scan is undergoing evaluation in clinical trials and should only be considered as a supplement and not a replacement to other studies.
[c]For stage III, typical: RT recommended if surgery is not feasible. For stage III, atypical: chemotherapy/RT is recommended if surgery is not feasible.
[d]There is no substantial evidence for a commonly used regimen. Options include cisplatin/etoposide, temozolomide, sunitinib, or everolimus.
References: Moertel CG, Kvols LK, O'Connell MJ, Rubin J. Treatment of neuroendocrine carcinomas with combined etoposide and cisplatin. Evidence of major therapeutic activity in the anaplastic variants of these neoplasms. Cancer 1991;68:227-232; Ekebald S, Sundin A, Janson ET, et al. Temozolomide as monotherapy is effective in treatment of advanced malignant neuroendocrine tumors. Clin Cancer Res 2007;13:2986-2991; Kulke MH, Lenz HJ, Meropol NJ, et al. Activity of sunitinib in patients with advanced neuroendocrine tumors. J Clin Oncol 2008;26:3403-3410; Yao JC, Phan AT, Chang DZ, et al. Efficacy of RAD001 (everolimus) and octreotide LAR in advanced low-to intermediate-grade neuroendocrine tumors: results of a phase II study. J Clin Oncol 2008;26:4311-4318.
[e]Wedge resection for peripheral low-grade neuroendocrine carcinoma (category 2B).

Text continued from p. 1087

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.[13] 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.[14–16] 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.[17]

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor-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.[18]

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. Uncommonly, patients 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 page 1098 and the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Neuroendocrine Tumors; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).[19,20]

Preliminary reports from the National Lung Screening Trial (NLST) suggest that screening with annual, low-dose, spiral CT scans can improve lung cancer–specific and overall mortality in asymptomatic high-risk individuals.[21] Although CT screening can detect early-stage NSCLC, it does not seem to be useful for detecting SCLC. This is probably because of the aggressiveness of SCLC, which results in the development of symptomatic disease between annual scans, thereby limiting the potential effect on mortality.[22]

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.[23,24] 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.[25,26] 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.[27] SCLC cells also can produce numerous polypeptide hormones, including adrenocorticotropic hormone (ACTH) and vasopressin (ADH), which cause Cushing syndrome and hyponatremia of malignancy, respectively.[28,29]

Staging

The Veteran's Administration Lung Group's 2-stage classification scheme has been routinely used to define the extent of disease in patients with SCLC: 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.[30] Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-

stage disease, whereas the classification of contralateral hilar and supraclavicular lymphadenopathy is more controversial. 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) (see Definitions of TNM and Anatomic Stage/Prognostic Groups, available online, in these guidelines, at www.NCCN.org [ST-1 and ST-2]).[31–35] This new staging system is applicable to both NSCLC and SCLC based on studies by the IASLC that showed the prognostic significance of the various stage designations in both diseases.[31,35] Using the new TNM staging system, limited-stage SCLC is T_{any},N_{any},M0 except T3–4 because of multiple lung nodules that do not fit in a tolerable radiation field. Extensive-stage SCLC is T_{any},N_{any},M1a/b, and T3–4 because of 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 use the TNM system, because it will allow for more precise assessments of prognosis and specific therapy in the future. Therefore, the SCLC algorithm was revised in 2011 to include the TNM staging information.

All patients with SCLC, 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; CT scan (with intravenous contrast) of the chest, liver, and adrenal glands; and an MRI scan (preferred) or a 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 fewer than 5% of patients. If limited-stage disease is suspected, a PET/CT scan can be performed to assess for distant metastases. A bone scan can be performed if PET/CT is not available.

PET scans can increase staging accuracy in patients with SCLC.[36–40] PET/CT is superior to PET alone.[40] Approximately 15% of patients who undergo PET are upstaged from limited- to extensive-stage, whereas 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 detecting brain metastases.[41] Changes in management based on PET staging were reported in 16% to 38% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease.[37,42,43] Although PET/CT seems to improve staging accuracy in SCLC, pathologic confirmation is still required for PET/CT-detected lesions that result in upstaging. Before surgical resection, pathologic mediastinal staging is required to confirm PET/CT scan results in patients who seem to have clinical stage T1–2,N0 disease.

Mediastinal staging can be performed through either conventional mediastinoscopy or minimally invasive techniques such as transesophageal endoscopic ultrasound–guided FNA, endobronchial ultrasound–guided transbronchial needle aspiration, or video-assisted thoracoscopy.[44,45]

Thoracentesis with cytologic 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 those 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 metastases in 10% to 15% of patients at diagnosis, of which approximately 30% are

asymptomatic. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the usefulness of early diagnosis in asymptomatic patients. Because of the aggressive nature of SCLC, staging should not delay the onset of treatment for more than 1 week; otherwise, many patients may become more seriously ill in the interval, with a significant decline in their performance status (PS).

Prognostic Factors

Poor PS (3–4), extensive-stage disease, weight loss, and markers associated with excessive bulk of disease (e.g., 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.[46–48]

Chemotherapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment.[9] 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).[8,49,50] For patients with extensive-stage disease, chemotherapy alone is the recommended treatment (see page 1095 for recommended regimens). In patients with extensive disease and brain metastases, chemotherapy can be given either before or after whole-brain radiotherapy, depending on whether the patient has neurologic symptoms (see page 1091).[10,51]

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.[52–54] Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see page 1095).[9,55,56] This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.[57] EP plus concurrent thoracic radiotherapy is now the recommended therapy for patients with limited-stage disease (category 1).[49,50,58]

In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.[59] The use of myeloid growth factors is not recommended in patients undergoing concurrent chemoradiation.[60] In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin is associated with a greater risk of myelosuppression.[61] The substitution of carboplatin for cisplatin in patients with limited-stage disease has not been adequately evaluated and should only occur when cisplatin is contraindicated or poorly tolerated.[62,63] 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.[64]

Many other combinations have been evaluated in patients with extensive-stage disease, with little consistent evidence of benefit when compared with EP. Recently, the combination of irinotecan and a platinum agent has provided the greatest challenge to EP. Initially, a small phase III trial performed in Japan reported that patients with extensive-stage SCLC who were treated with irinotecan plus cisplatin experienced a median survival of 12.8 months compared with 9.4 months for patients treated with EP (P = .002).[65] In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.[65] However, 2 subsequent large phase III trials performed in the United States comparing irinotecan plus cisplatin with EP failed to show a significant difference in response rate or overall survival between the regimens.[66,67]

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.[68] A phase III randomized trial (n = 220) found that median overall survival was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 vs 7.1 months; P = .04).[69] Based on these findings, the carboplatin and irinotecan regimen has been added to the NCCN Guidelines 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 with etoposide plus platinum regimens.[70] However, this meta-analysis was not performed using individual patient data. In addition, the relatively small absolute survival benefit

must be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the panel continues to 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, whereas in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.[52] Unfortunately, median survival rates are only 14 to 20 months and 9 to 11 months for patients with limited- and extensive-stage disease, respectively. After appropriate treatment, the 2-year survival rate is approximately 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease.[71] Thoracic radiotherapy improves local control rates by 25% in patients with limited-stage disease and is associated with improved survival.[49,50] 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.[72,73]

Many strategies have been evaluated in an effort to improve on the results that have been achieved with standard treatment for extensive-stage SCLC, including the addition of a third agent to standard 2-drug regimens. In 2 trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP showed a modest survival advantage for patients with extensive disease.[74,75] However, these 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.[76] 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.[77] 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 is associated with a greater risk of cumulative toxicity.[78]

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.[79] However, randomized trials have failed to show improved PFS or overall survival with this approach.[80,81]

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.[82,83] Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.[84–87]

The role of higher-dose therapy for patients with SCLC remains controversial.[88] 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.[89] 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 rates or survival.[90–93] 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.[94]

Currently available cytokines (e.g., granulocyte-macrophage colony-stimulating factor, granulocyte colony-stimulating factor) can ameliorate chemotherapy-induced myelosuppression and reduce the incidence of febrile neutropenia, but cumulative thrombocytopenia remains dose-limiting. Although trials involving patients with SCLC were instrumental in obtaining FDA approval for the clinical use of cytokines,[95] little evidence suggests that maintenance of dose intensity with growth factors prolongs disease-free or overall survival, and the routine use of growth factors at the initiation of chemotherapy is not recommended.

The potential benefits of antiangiogenic therapy have begun to be evaluated in SCLC. In patients with limited-stage SCLC, a phase II study of irinotecan, carboplatin, and bevacizumab with concurrent radiotherapy followed by maintenance bevacizumab (phase II trial) was terminated early because of an unacceptable incidence of tracheoesophageal fistulae.[96] In

extensive-stage SCLC, 2 phase II trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.[97–99] Randomized phase III trials are ongoing to determine if the addition of bevacizumab to chemotherapy improves survival in patients with extensive-stage SCLC. Currently, the panel does not recommend the 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 underrepresented in clinical trials.[100] Although advanced chronologic age adversely affects tolerance to treatment, an individual patient's functional status is much more useful than age in guiding clinical decision-making (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Senior Adult Oncology; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). Older patients who are functional in terms of the ability to perform activities of daily living should be treated with standard combination chemotherapy (and radiotherapy, if indicated). However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in elderly patients; therefore, they must be watched carefully during treatment to avoid excessive risk.

Greater attention to the needs and support systems of elderly patients is recommended to provide optimal care. Overall, elderly patients have a similar prognosis as stage-matched younger patients. Randomized trials have indicated that less-intensive treatment (e.g., single-agent etoposide) is inferior to combination chemotherapy (e.g., platinum plus etoposide) in elderly patients with good PS (0–2).[101,102] Several other strategies have been evaluated in elderly patients with SCLC.[64,103–105] The use of 4 cycles of carboplatin plus etoposide seems to yield favorable results, because the area-under-the-curve (AUC) dosing of carboplatin takes into account the declining renal function of the aging patient.[105] However, targeting carboplatin to an AUC of 5, rather than 6, may be more reasonable in this population.[106] The usefulness of short-course, full-intensity chemotherapy has also been explored in elderly or infirm patients, and the results with only 2 cycles of chemotherapy seem to be acceptable, although this approach has not been directly compared with standard therapy.[107]

Second-Line (Subsequent) Therapy

Although SCLC is very responsive to initial treatment, most patients experience relapse with relatively resistant disease.[108,109] 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%). 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 page 1095).[56,110–113] A randomized phase III trial compared single-agent intravenous topotecan with the combination regimen CAV.[114] Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase III trial, oral topotecan improved overall survival compared with best supportive care (26 vs. 14 weeks).[115] Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who experience initial response to chemotherapy but then experience progression after 2 to 3 months. In the algorithm, topotecan is recommended as a subsequent agent for patients with relapsed SCLC (category 1 for relapse > 2–3 months up to 6 months).[110,114,116] Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.[115,116]

Many practicing oncologists have noted excessive toxicity with the standard regimen of 1.5 mg/m^2 of intravenous topotecan for 5 days, and studies suggest that an attenuated dose may be equally efficacious with lower toxicity.[117] Published studies have yielded conflicting data regarding the usefulness of weekly

topotecan in patients with relapsed SCLC, and this approach remains under investigation.[118,119]

Recent data from phase II studies suggest that amrubicin, an investigational anthracycline, has promising activity in patients with relapsed or refractory SCLC.[120–122] However, grade 3/4 toxicity, primarily neutropenia, is common.[123] 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).[124]

The optimal duration of subsequent chemotherapy has not been fully explored, although its duration is usually short and the cumulative toxicity is frequently limiting even in patients who experience response. For these reasons, subsequent chemotherapy should be given until 2 cycles beyond best response, progression of disease, or development of unacceptable toxicity.

Radiotherapy

The Principles of Radiation Therapy section on page 1096 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 Principles of Radiation Therapy section in the NCCN Guidelines for Non–Small Cell Lung Cancer may also be useful (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org [NSCL-C]).

This 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.[125] 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 compared with chemotherapy alone.[49,50] 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 vs. sequential), timing of radiotherapy (early vs. late), volume of the radiation port (original tumor volume vs. 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.[59] Another randomized phase III trial (by the National Cancer Institute of Canada) comparing radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy showed that early radiotherapy was associated with improved local and systemic control and longer survival.[126] 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 compared with late concurrent or sequential radiotherapy.[127] Another meta-analysis also found that early concurrent thoracic radiation with platinum-based chemotherapy increases 2- and 5-year overall survival.[128]

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.[129] 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 a higher incidence of grade 3/4 esophagitis was seen compared with the once-daily regimen. Median survivals were 23 versus 19 months (P = .04), and 5-year survival rates were 26% versus 16% in the twice-daily and once-daily radiotherapy arms, respectively.[129] A significant criticism of this trial is that the doses of radiation in the 2 arms were not biologically equivalent. In light of this, ongoing trials are evaluating biologically equivalent doses of 45 Gy delivered twice daily versus 60 to 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 showed no survival difference between once-daily thoracic

radiotherapy to 50.4 Gy with concurrent EP and a split-course of twice-daily thoracic radiotherapy to 48 Gy with concurrent EP.[130] 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-daily radiotherapy must have an excellent PS and good baseline pulmonary function.

NCCN Guidelines: For limited-stage disease, the NCCN Guidelines recommend that radiotherapy should be used concurrently with chemotherapy and that radiotherapy should start with the first or second cycle (category 1) at a dose of either 1.5 Gy twice daily to a total dose of 45 Gy (category 1), or 2.0 Gy once daily to a total dose of 60 to 70 Gy (see page 1096).[49,127,129–134] Concurrent chemoradiotherapy (category 1) is preferable to sequential therapy in patients with good PS (0–2).[59,135]

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 radiotherapy planning using definitions in reports 50 and 62 from the International Commission on Radiation Units & Measurements. However, the prechemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.[133,136] The CALGB 30610/RTOG 0538 protocol should be used as a guide to determine the normal tissue dose-volume constraints (see page 1096).[137–139] Intensity-modulated RT (IMRT) may be considered in select patients.[140,141]

Based on the results of a randomized trial by Jeremic et al.,[142] the addition of sequential thoracic radiotherapy may be considered in select patients with low-bulk metastatic disease who have a complete or near complete response after initial chemotherapy. The investigators randomized patients experiencing a complete response at distant metastatic sites after 3 cycles of EP to receive either further EP or accelerated hyperfractionated radiotherapy (i.e., 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide,[142] and found that the addition of radiotherapy resulted in improved median overall survival (17 vs. 11 months).

Prophylactic Cranial Irradiation

Intracranial metastases occur in more than 50% of patients with SCLC. Randomized studies have shown that prophylactic cranial irradiation (PCI) is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to demonstrate a meaningful survival advantage.[143] 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 neurologic 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.[144] Thus, PCI seems to prevent and not simply delay the emergence of brain metastases. This meta-analysis also reported a 5.4% increase in 3-year survival in patients treated with PCI, from 15.3% in the control group to 20.7% in the PCI group.[144] Although the number of patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in both limited- 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 compared with those who did not receive PCI.[145]

A randomized trial from the EORTC assessed PCI versus no PCI in 286 patients with extensive-stage SCLC whose disease had responded to initial chemotherapy. PCI decreased symptomatic brain metastases (14.6% vs. 40.4%) and increased the 1-year survival rate (27.1% vs. 13.3%) compared with controls.[146]

Before the decision is made to administer PCI, a balanced discussion between the patient and physician is necessary. PCI is recommended (category 1) for patients with either limited- or extensive-stage disease who attain a complete or partial response.[146,147] 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 page 1096).[146,147] However, a total dose of 20 Gy in 5 fractions may be considered for patients

with extensive-stage SCLC.[146] 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.[147,148]

Palliative Treatment

For patients with localized symptomatic sites of disease (e.g., painful bony lesions, obstructive atelectasis, brain metastases), radiotherapy can provide excellent palliation (see page 1091).[149,150] 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 on page 1094. Studies supporting these recommendations are described in this section. Briefly, the algorithm states that surgery should only be considered for patients with stage I (T1–2,N0) SCLC in whom biopsy has confirmed that mediastinal lymph nodes are not involved.[151] Data show that patients with clinically staged disease in excess of T1–2,N0 do not benefit from surgery.[151] Note that only 5% of patients with SCLC have true stage I SCLC.[32]

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[151] Patients with limited-stage disease, excluding those with solitary peripheral nodules, were treated with 5 cycles of chemotherapy with CAV; those showing 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.

Most data regarding the benefit of surgery are from retrospective reviews.[152–156] These studies report favorable 5-year survival rates of 40% to 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.[11,157] However, these studies are limited by the lack of information on chemotherapy use in the 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 from trials comparing surgery plus adjuvant chemotherapy versus 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 through mediastinal staging before resection.[158] If resection is performed, the panel favors lobectomy and does not believe that segmental or wedge resections are appropriate for patients with SCLC. After complete resection, adjuvant chemotherapy or chemoradiation is recommended.[154,159,160] Adjuvant chemotherapy alone is recommended for patients without nodal metastases, whereas concurrent chemotherapy and postoperative mediastinal radiotherapy are recommended for patients with nodal metastases (see page 1090). PCI should be considered after adjuvant therapy because it can improve survival (see Prophylactic Cranial Irradiation, page 1105).[144]

Surveillance

Follow-up examinations are recommended every 3 to 4 months during years 1 and 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 page 1092). PET/CT or brain MRI (or CT) is not recommended for routine follow-up. If a new pulmonary nodule develops, it should prompt evaluation for a new primary lung cancer, because second primary tumors are a frequent occurrence in patients who are cured of their initial SCLC.[161,162] Smoking cessation should be encouraged for all patients with SCLC (www.ahrq.gov/clinic/tobacco/tobaqrg.htm), because second primary tumors occur less commonly in those who quit smoking.[163–165]

Lung Neuroendocrine Carcinomas

Using the 2004 WHO 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).[166,167]

Most lung neuroendocrine carcinomas are SCLC, which are treated using these guidelines,[1] whereas LCNEC is treated using the NCCN Guidelines for Non–Small Cell Lung Cancer (to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).[168] Low- and intermediate-grade lung neuroendocrine carcinomas account for 1% to 2% of lung cancers and are treated using the LNT guideline. Both histologic and cytologic features can be useful for distinguishing lung neuroendocrine carcinoma from SCLC and LCNEC, although diagnosis can be difficult (see also the NCCN Guidelines for Non–Small Cell Lung Cancer, available at www.NCCN.org).The proliferative marker Ki-67 may also be useful.[19,20]

Lung neuroendocrine carcinomas are staged using the 7th edition of the AJCC staging system for lung tumors (see Definitions of TNM and Anatomic Stage/Prognostic Groups, available online, in these guidelines, at www.NCCN.org [ST-1 and ST-2]).[34,169] 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 with 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 page 1098). 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% to 60% for patients with atypical carcinoid.[170–172] Lymph node involvement decreases long-term survival in both typical and atypical carcinoid.[170–172]

Systemic therapy (e.g., cisplatin/etoposide, temozolomide, sunitinib, or everolimus) is recommended for patients with unresectable or advanced disease, although response rates are modest.[1,173–177] Octreotide may be considered for select patients with positive octreotide scans or symptoms of carcinoid syndrome.

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