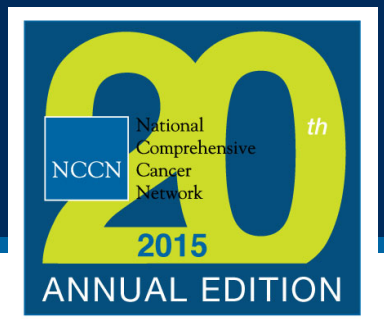

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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Cell Lung Cancer

Version 1.2015

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Discussion

* Gregory P. Kalemkerian, MD/Chair †
University of Michigan
Comprehensive Cancer Center

Billy W. Loo, Jr., MD, PhD/Vice Chair §
Stanford Cancer Institute

Wallace Akerley, MD †
Huntsman Cancer Institute
at the University of Utah

Paul Bogner, MD ≠
Roswell Park Cancer Institute

Laura QM Chow, MD †
Fred Hutchinson Cancer Research
Center/Seattle Cancer Care Alliance

Robert C. Doebele, MD, PhD †
University of Colorado Cancer Center

Robert J. Downey, MD ¶
Memorial Sloan Kettering Cancer Center

Leena Gandhi, MD, PhD † Þ
Dana-Farber/Brigham and Women's
Cancer Center

Apar Kishor P. Ganti, MD †
Fred & Pamela Buffett Cancer Center at
The Nebraska Medical Center

Ramaswamy Govindan, MD †
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

Stefan C. Grant, MD, JD † ‡
University of Alabama at Birmingham
Comprehensive Cancer Center

John C. Grecula, MD §
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Christine L. Hann, MD, PhD
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

James A. Hayman, MD, MBA §
University of Michigan
Comprehensive Cancer Center

Rebecca Suk Heist, MD, MPH †
Massachusetts General Hospital
Cancer Center

Leora Horn, MD, MSc †
Vanderbilt-Ingram Cancer Center

Hatim Husain, MD
UC San Diego Moores Cancer Center

Thierry Jahan, MD † ‡
UCSF Helen Diller Family
Comprehensive Cancer Center

Marianna Koczywas, MD † ‡ Þ
City of Hope Comprehensive Cancer Center

Ranee Mehra, MD †
Fox Chase Cancer Center

Robert E. Merritt, MD ¶
The Ohio State University
Comprehensive Cancer Center
James Cancer Hospital
and Solove Research Institute

Cesar A. Moran, MD ≠
The University of Texas
MD Anderson Cancer Center

Jyoti D. Patel, MD †
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

David C. Portnoy, MD †
The University of Tennessee
Health Science Center

Neal Ready, MD, PhD †
Duke Cancer Institute

Charles C. Williams, Jr., MD †
Moffitt Cancer Center

NCCN
Kristina Gregory, RN, MSN, OCN
Miranda Hughes, PhD

† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
‡ Hematology/Hematology oncology
Þ Internal medicine
≠ Pathology
ф Diagnostic/Interventional radiology
*Writing Committee Member

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NCCN Guidelines Panel Disclosures

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

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

See NCCN Categories of Evidence and Consensus.

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Summary of changes in the 1.2015 version of the NCCN Guidelines for Small Cell Lung Cancer from the 2.2014 version include:

SCL-1

Stage

- **Previous definitions of stage deleted and replaced with a link to ST-1.**

SCL-2

- **Footnote "d" modified: "*While* most pleural effusions in patients with lung cancer are due to *tumor,* ~~cancer; however,~~ *there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. 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. Pericardial effusion is classified using the same criteria."* ~~if the effusion is too small to allow image-guided sampling, then the effusion should not be considered in staging. If cytologic 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.~~**

SCL-3

- **Testing results modified: "Pathologic mediastinal staging positive or medically inoperable *or decision made not to pursue surgical resection."***

SCL-4

- **Initial Treatment, SVC syndrome/Lobar obstruction/Bone metastases: The order of therapy modified to list orthopedic stabilization prior to palliative external-beam RT.**
- **Initial Treatment, Symptomatic extensive stage with brain metastases: "...unless immediate systemic therapy is ~~required~~ *indicated*"**

SCL-6

Subsequent Therapy/Palliative Therapy

- **PS 0-2, after two cycles beyond best response or progression of disease or development of unacceptable toxicity: "Consider subsequent chemotherapy if still PS 0-2" added.**

SCL-B

- **The following reference added to bullet 2: "Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641." (also added to SCL-C 1 of 2).**

SCL-C 1 of 2

- **Chemotherapy as primary or adjuvant therapy, extensive stage, sub-bullet 6: "every 21 days" removed.**
- **Subsequent chemotherapy, relapse <2-3 mo: "PO or IV" added to topotecan.**

SCL-D 1 of 3

- **Limited stage, last bullet, last sentence changed from "A concomitant boost approach of 61.2 Gy in 5 weeks has shown promising local control; this boost approach is currently being compared to 70 Gy in 7 weeks and to the standard arm of 45 Gy (BID) in 3 weeks in the randomized trial CALGB 30610/RTOG 0538" to "The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks; accrual to an experimental concomitant boost arm has closed."**

SCL-D 2 of 3

- **Prophylactic Cranial Irradiation, bullet 2 modified: "Recommended doses for PCI to the whole brain ~~are~~ *include* 25 Gy in 10 daily fractions, 30 Gy in 10 to 15 daily fractions, or 24 Gy in 8 daily fractions. *A shorter course (eg, 20 Gy in 5 fractions) may be appropriate in selected patients with extensive-stage disease.* In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy."**
- **Brain Metastases, bullet 2 modified with the addition of the fractionation schedule of 10 daily fractions.**

SCL-D 3 of 3

- **Reference 18 updated.**

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Summary of changes in the 1.2015 version of the NCCN Guidelines for Small Cell Lung Cancer from the 2.2014 version include:

LNT-1

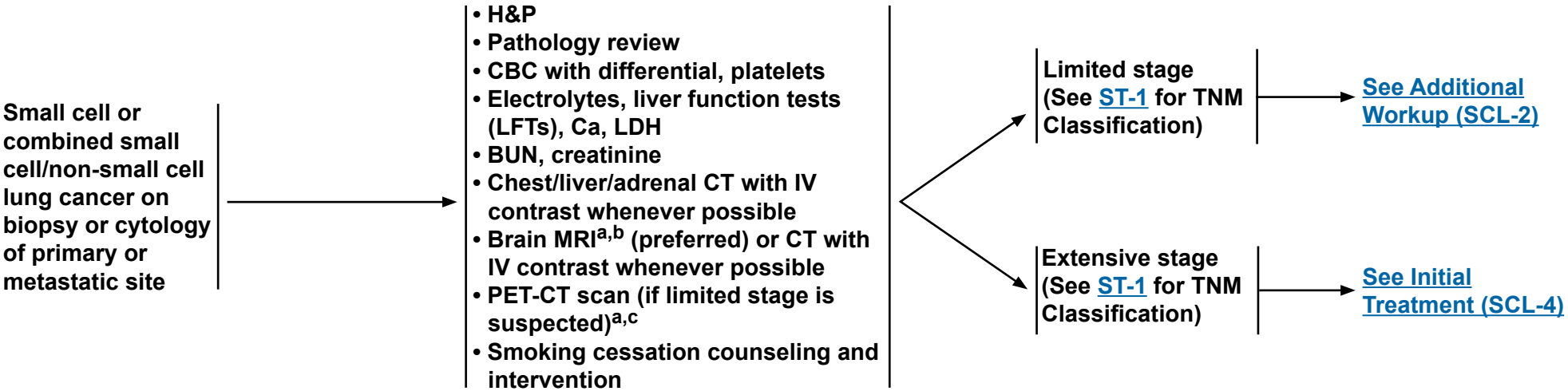
- **Footnote "c" is new to the page: "Stage-specific management of LCNEC follows the NSCLC algorithm. However, available data suggest that chemotherapy regimens commonly used for SCLC (see SCL-C) may represent the most reasonable option when systemic therapy is indicated. Hiho S, Kenmotsu H, Sekine I, et al. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol 2013;8:980-984; Rossi G, Cavazza A, Marchioni A, et al. Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRα, PDGFRβ, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 2005;23:8774-8785."**
- **A new category added for High-grade neuroendocrine carcinoma (small cell carcinoma) with a link to the treatment for the NCCN Guidelines for Small Cell Lung Cancer.**

LNT-2

- **Primary Treatment: Footnote "f" modified: "There is no substantial evidence for a ~~commonly used regimen~~ *preferred regimen."* "± capecitabine" added after temozolomide. Reference added.**
- **New algorithm provided for Stage IIIA.**

ST-1

- **Table 1: The definitions modified as noted below.**
  "(1) Limited-stage: AJCC (7th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules *that are too extensive* or *have* tumor/nodal volume *that is* too large to be encompassed in a tolerable radiation plan.
  (2) Extensive-stage: AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules *that are too extensive* or *have* tumor/nodal volume *that is* too large to be encompassed in a tolerable radiation plan."



[a]If extensive stage is established, further staging evaluation is optional. However, brain imaging, MRI (preferred), or CT with IV contrast should be obtained in all patients.
[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[c]If PET/CT is not available, bone scan may be used to identify metastases. Pathologic confirmation is recommended for lesions detected by PET/CT that alter stage.

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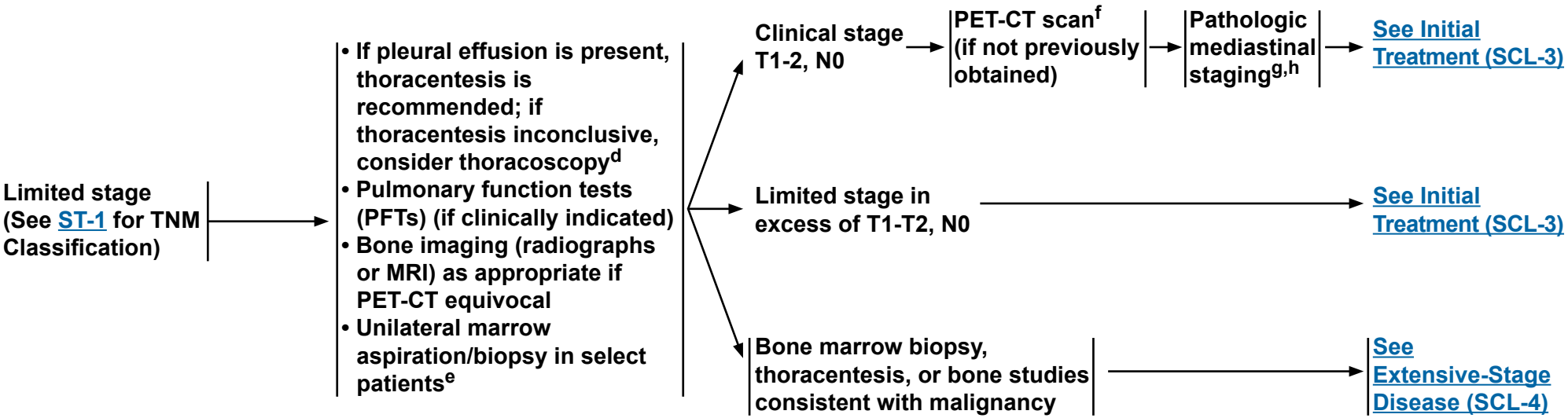
STAGE | **ADDITIONAL WORKUP**



[d]While most pleural effusions in patients with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. 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. Pericardial effusion is classified using the same criteria.
[e]Selection criteria include: nucleated red blood cells (RBCs) on peripheral blood smear, neutropenia, or thrombocytopenia.
[f]PET-CT scan to identify distant disease and to guide mediastinal evaluation, if not previously done.
[g]See Principles of Surgical Resection (SCL-A).
[h]Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.

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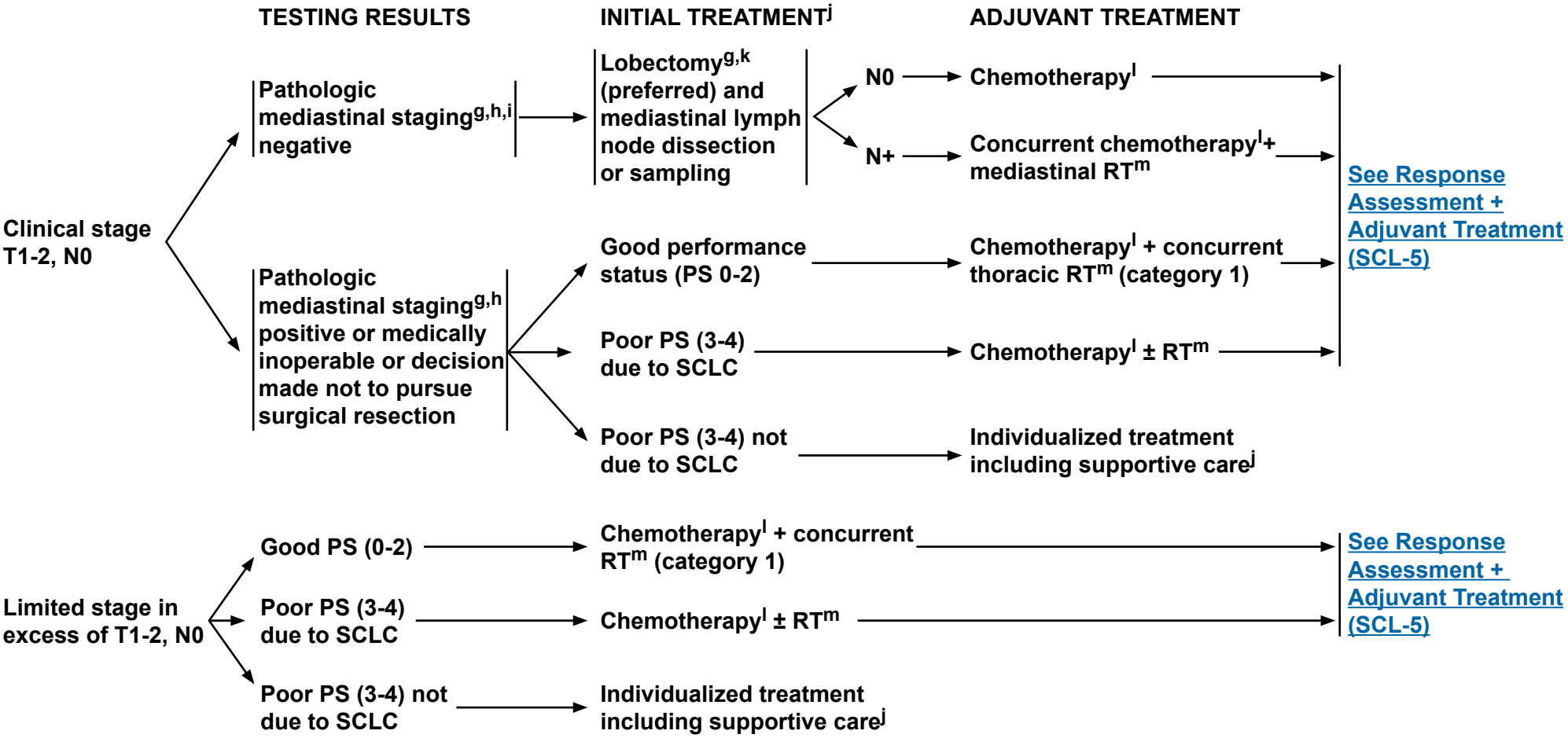

[g] See Principles of Surgical Resection (SCL-A).
[h] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.
[i] Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.
[j] See Principles of Supportive Care (SCL-B).
[k] Select patients may be treated with chemotherapy/RT as an alternative to surgical resection.
[l] See Principles of Chemotherapy (SCL-C).
[m] See Principles of Radiation Therapy (SCL-D).

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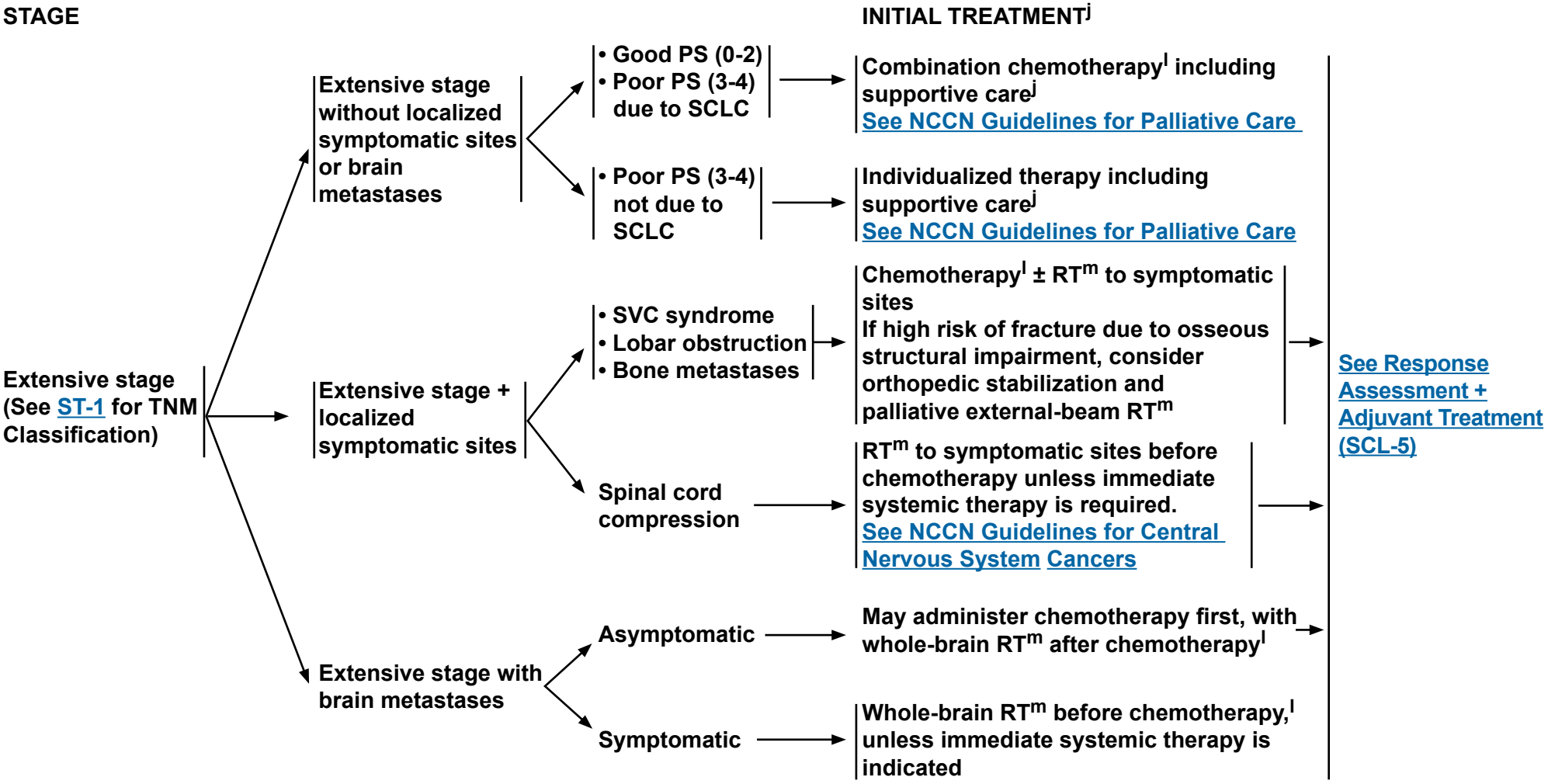

[j] See Principles of Supportive Care (SCL-B).
[l] See Principles of Chemotherapy (SCL-C).
[m] See Principles of Radiation Therapy (SCL-D).

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RESPONSE ASSESSMENT FOLLOWING INITIAL THERAPY

- Chest x-ray (optional)
- Chest/liver/adrenal CT with IV contrast whenever possible
- Brain MRI[b] (preferred) or CT with IV contrast whenever possible, if prophylactic cranial irradiation (PCI) to be given
- Other imaging studies, to assess prior sites of involvement, as clinically indicated
- CBC, platelets
- Electrolytes, LFTs, Ca, BUN, creatinine

Complete response or Partial response → **ADJUVANT TREATMENT:** Limited or extensive stage: PCI[m,n,o] (category 1) → **SURVEILLANCE**

Stable Disease → **SURVEILLANCE**

SURVEILLANCE:
After recovery from primary therapy:
- Oncology follow-up visits every 3-4 mo during y 1-2, every 6 mo during y 3-5, then annually
  - At every visit: H&P, chest imaging, bloodwork as clinically indicated
- New pulmonary nodule should initiate workup for potential new primary
- Smoking cessation intervention
- PET/CT is not recommended for routine follow-up

→ For Relapse, see Subsequent Therapy (SCL-6)

Primary progressive disease → See Subsequent Therapy/ Palliative Therapy (SCL-6)

[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[m]See Principles of Radiation Therapy (SCL-D).
[n]Not recommended in patients with poor performance status or impaired neurocognitive function.
[o]Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and complete response (CR) or near CR after systemic therapy.

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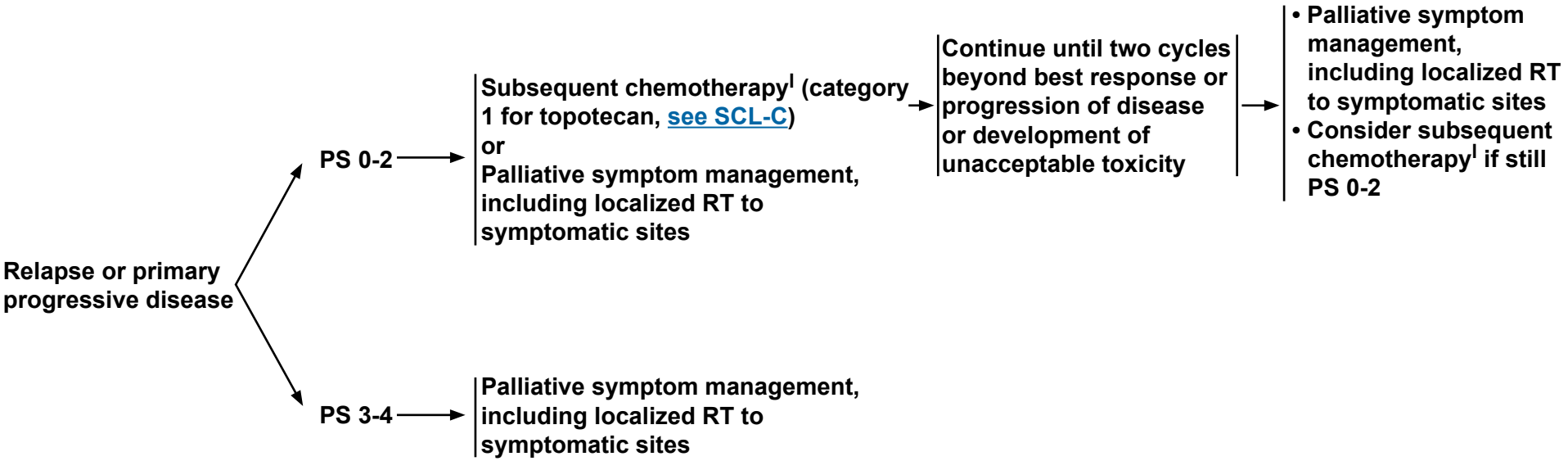
PROGRESSIVE DISEASE **SUBSEQUENT THERAPY/PALLIATIVE THERAPY**



[l] See Principles of Chemotherapy (SCL-C).

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PRINCIPLES OF SURGICAL RESECTION

- **Stage I SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients with disease in excess of T1-2, N0 do not benefit from surgery.[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.**
  - **Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.**
  - **Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy. Patients without nodal metastases should be treated with chemotherapy alone. Patients with nodal metastases should be treated with postoperative concurrent chemotherapy and mediastinal radiation therapy.**
- **Because PCI can improve both disease-free and overall survival in patients with SCLC who have complete or partial response, PCI is recommended after adjuvant chemotherapy in patients who have undergone a complete resection.[2] PCI is not recommended in patients with poor performance status or impaired neurocognitive 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-3S.
[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;341:476-84.
[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(5):467-474.

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PRINCIPLES OF SUPPORTIVE CARE

- **Smoking cessation advice, counseling, and pharmacotherapy**
  - **Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange (http://www.ahrq.gov/clinic/tobacco/5steps.htm)**
  - **See NCCN Guidelines for Lung Cancer Screening**

- **Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended during concurrent chemotherapy plus radiotherapy (category 1 for GM-CSF).[1]**

- **Syndrome of inappropriate antidiuretic hormone**
  - **Fluid restriction**
  - **Saline infusion for symptomatic patients**
  - **Antineoplastic therapy**
  - **Demeclocycline**
  - **Vasopressin receptor inhibitors (conivaptan, tolvaptan)**

- **Cushing's syndrome**
  - **Consider ketoconazole. If not effective, consider metyrapone.**
  - **Try to control before initiation of antineoplastic therapy**

- **Leptomeningeal disease: See NCCN Guidelines for Carcinomatous/Lymphomatous Meningitis**

- **Pain Management: See NCCN Guidelines for Adult Cancer Pain**

- **Nausea/Vomiting: See NCCN Guidelines for Antiemesis**

- **Psychosocial distress: See NCCN Guidelines for Distress Management**

- **See NCCN Guidelines for Palliative Care as indicated**

[1]Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641.

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PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary or adjuvant 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 (category 1 for GM-CSF).****
- **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**[9]
  - **Carboplatin AUC 5 day 1 and irinotecan 50 mg/m^2 days 1, 8, 15**[10]

Subsequent chemotherapy:

- **Clinical trial preferred.**
- **Relapse <2-3 mo, PS 0-2:**
  - **paclitaxel**[11,12]
  - **docetaxel**[13]
  - **topotecan PO or IV**[14,15]
  - **irinotecan**[16]
  - **temozolomide 75 mg/m^2/day x 21 days**[17]
  - **gemcitabine**[18,19]
  - **ifosfamide**[20]
- **Relapse >2-3 mo up to 6 mo:**
  - **topotecan PO or IV (category 1)**[14,15, 21]
  - **paclitaxel**[11,12]
  - **docetaxel**[13]
  - **irinotecan**[16]
  - **gemcitabine**[18,19]
  - **vinorelbine**[22,23]
  - **oral etoposide**[24,25]
  - **temozolomide 75 mg/m^2/day x 21 days**[17]
  - **cyclophosphamide/doxorubicin/vincristine (CAV)**[14]
- **Relapse >6 mo: original regimen**[26,27]

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

See References on SCL-C 2 of 2

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

**Bunn PA, Crowley J, Kelly K, et al. Chemoradiotherapy with or without granulocyte-macrophage colony-stimulating factor in the treatment of limited-stage small-cell lung cancer: a prospective phase III randomized study of the Southwest Oncology Group. J Clin Oncol 1995;13:1632-1641.

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PRINCIPLES OF CHEMOTHERAPY
References

[1]Turrisi AT 3rd, Kim K, Blum R, et al. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340(4):265-271.
[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(33): 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(9):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(24):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(10):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(11):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(11):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(2): 85-91.
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[10]Schmittel A, Fischer von Weikersthal L, Sebastian M, et al. A randomized phase II trial of irinotecan plus carboplatin versus etoposide plus carboplatin treatment in patients with extended disease small-cell lung cancer. Ann Oncol 2006;17:663-667.
[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(2):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(34):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]Pietanza MC, Kadota K, Huberman K, et al. Phase II trial of temozolomide with relapsed sensitive or refractory small cell lung cancer, with assessment of methylguanine-DNA methyltransferase as a potential biomarker. Clin Cancer Res 2012;18:1138-1145.
[18]Van der Lee I, Smit EF, van Putten JW, et al. Single-agent gemcitabine in patients with resistant small-cell lung cancer. An Oncol 2001;12:557-561.
[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]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.
[21]Eckardt JR, von Pawel J, Pujol JL, et al. Phase III study of oral compared with intravenous topotecan as second-line therapy in small-cell lung cancer. J Clin Oncol 2007;25(15):2086-2092.
[22]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.
[23]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.
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Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

PRINCIPLES OF RADIATION THERAPY

General Principles:

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

Limited Stage:

- Timing: RT concurrent with chemotherapy is standard and preferred to sequential chemo/RT.[1] RT should start early, with cycle 1 or 2 of chemotherapy (category 1).[2] A shorter time from the start of any therapy to the end of RT (SER) is significantly associated with improved survival.[3]
- Target definition: RT target volumes should be defined based on the pretreatment PET scan and CT scan obtained at the time of radiotherapy planning. PET-CT should be obtained, preferably within 4 weeks and no more than 8 weeks, before treatment. Ideally, PET/CT should be obtained in the treatment position.
- Historically, clinically uninvolved mediastinal nodes have been included in the RT target volume, whereas uninvolved supraclavicular nodes generally have not been included. Consensus on elective nodal irradiation (ENI) is evolving.[4] Several more modern series, both retrospective and prospective, suggest that omission of ENI results in low rates of isolated nodal recurrences (0%-11%, most <5%), particularly when incorporating PET staging/target definition (1.7%-3%).[5-10] ENI has been omitted in current prospective clinical trials (including CALGB 30610/RTOG 0538 and the EORTC 08072 [CONVERT] trial).
- In patients who start chemotherapy before RT, the gross tumor volume (GTV) can be limited to the post-induction chemotherapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-chemotherapy volume) should be covered.[7,11]
- Dose and schedule: For limited-stage SCLC, the optimal dose and schedule of RT have not been established; 45 Gy in 3 weeks (1.5 Gy twice daily [BID]) is superior (category 1) to 45 Gy in 5 weeks (1.8 Gy daily).[12,13] When BID fractionation is used, there should be at least a 6-hour inter-fraction interval to allow for repair of normal tissue. If using once-daily RT, higher doses of 60-70 Gy should be used.[14-17] The current randomized trial CALGB 30610/RTOG 0538 is comparing the standard arm of 45 Gy (BID) in 3 weeks to 70 Gy in 7 weeks; accrual to an experimental concomitant boost arm[18] has closed.

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

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIATION THERAPY

Extensive Stage:

- Consolidative thoracic RT may be beneficial for selected patients with extensive-stage SCLC who respond to chemotherapy. Studies have demonstrated that consolidative thoracic RT is well tolerated, results in fewer symptomatic chest recurrences, and improves long-term survival in some patients.[19,20] This approach is currently being evaluated in prospective clinical trials (RTOG 0937; Dutch CREST trial NTR1527).

Normal Tissue Dose Constraints:

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

Prophylactic Cranial Irradiation (PCI):

- In patients with limited- or extensive-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).[21,22,23]
- Recommended doses for PCI to the whole brain include 25 Gy in 10 daily fractions, 30 Gy in 10 to 15 daily fractions, or 24 Gy in 8 daily fractions. A shorter course (eg, 20 Gy in 5 fractions) may be appropriate in selected patients with extensive-stage disease. In a large randomized trial (PCI 99-01), patients receiving a dose of 36 Gy had higher mortality and higher chronic neurotoxicity compared to patients treated with 25 Gy.[24,25]
- Neurocognitive Function: Increasing age and higher doses are the most predictive factors for development of chronic neurotoxicity. In trial RTOG 0212, 83% of patients older than 60 years of age experienced chronic neurotoxicity 12 months after PCI versus 56% of patients younger than 60 years of age (P = .009).[25] Concurrent chemotherapy and high total RT dose (>30 Gy) should be avoided in patients receiving PCI.
- Administer PCI after resolution of acute toxicities of initial therapy. PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.

Brain Metastases:

- Brain metastases should be treated with whole brain radiation therapy (WBRT) rather than stereotactic radiotherapy/radiosurgery (SRT/SRS) alone, because these patients tend to develop multiple CNS metastases. In patients who develop brain metastases after PCI, repeat WBRT may be considered in carefully selected patients.[26,27] SRS may also be considered, especially if there has been a long-time interval from initial diagnosis to occurrence of brain metastases and there is no extracranial disease.[28,29]
- Recommended dose for WBRT is 30 Gy in 10 daily fractions.

See General Principles, Limited Stage on SCL-D 1 of 3

See References on SCL-D 3 of 3

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PRINCIPLES OF RADIATION THERAPY
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NCCN Guidelines Version 1.2015
Lung Neuroendocrine Tumors

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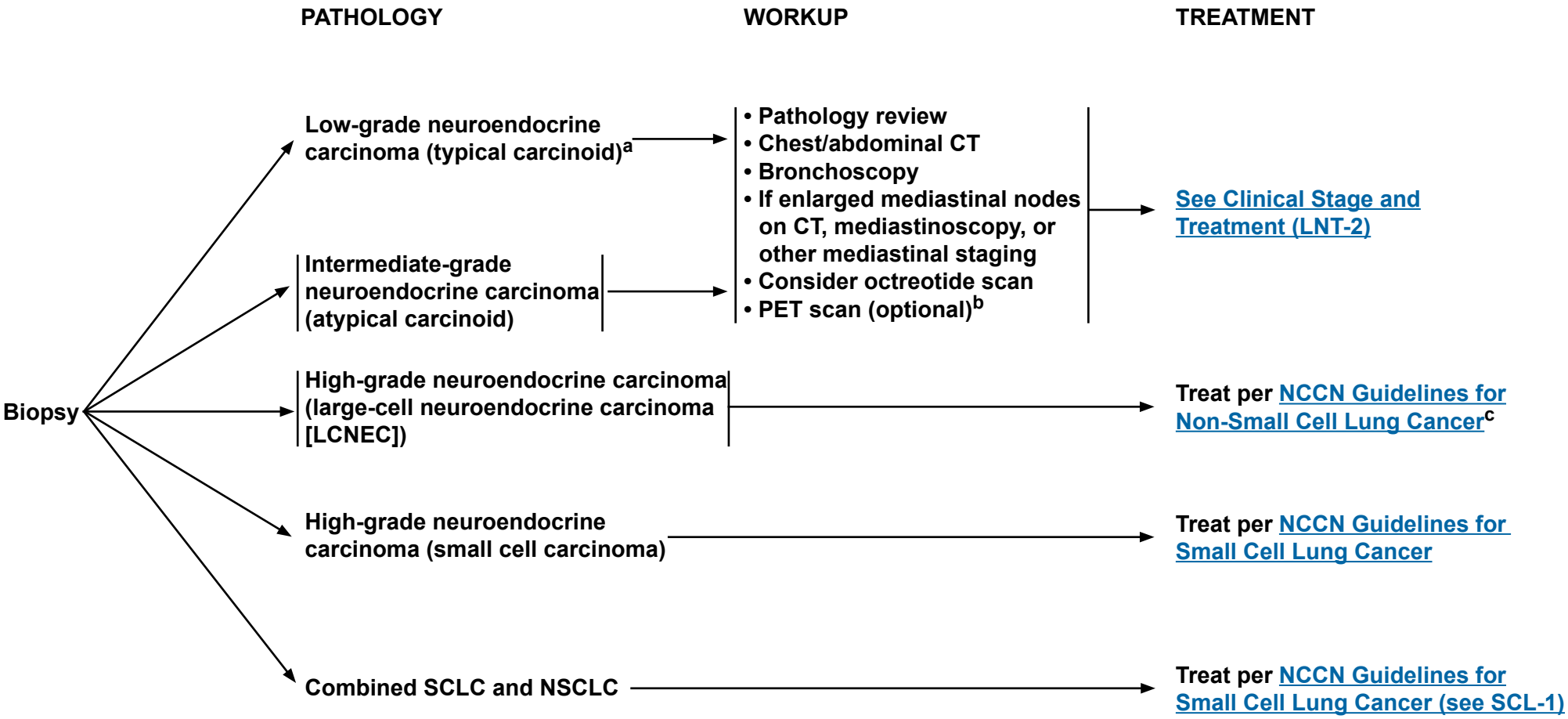

[a]Management of endocrine symptoms as indicated (See the Carcinoid Tumors section in the NCCN Guidelines for Neuroendocrine Tumors).
[b]PET scan is undergoing evaluation in clinical trials and should only be considered as a supplement and not a replacement to other studies.
[c]Stage-specific management of LCNEC follows the NSCLC algorithm. However, available data suggest that chemotherapy regimens commonly used for SCLC (see SCL-C) may represent the most reasonable option when systemic therapy is indicated. Niho S, Kenmotsu H, Sekine I, et al. Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. J Thorac Oncol 2013;8:980-984; Rossi G, Cavazza A, Marchioni A, et al. Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRα, PDGFRβ, and Met in large-cell neuroendocrine carcinoma of the lung. J Clin Oncol 2005;23:8774-8785.

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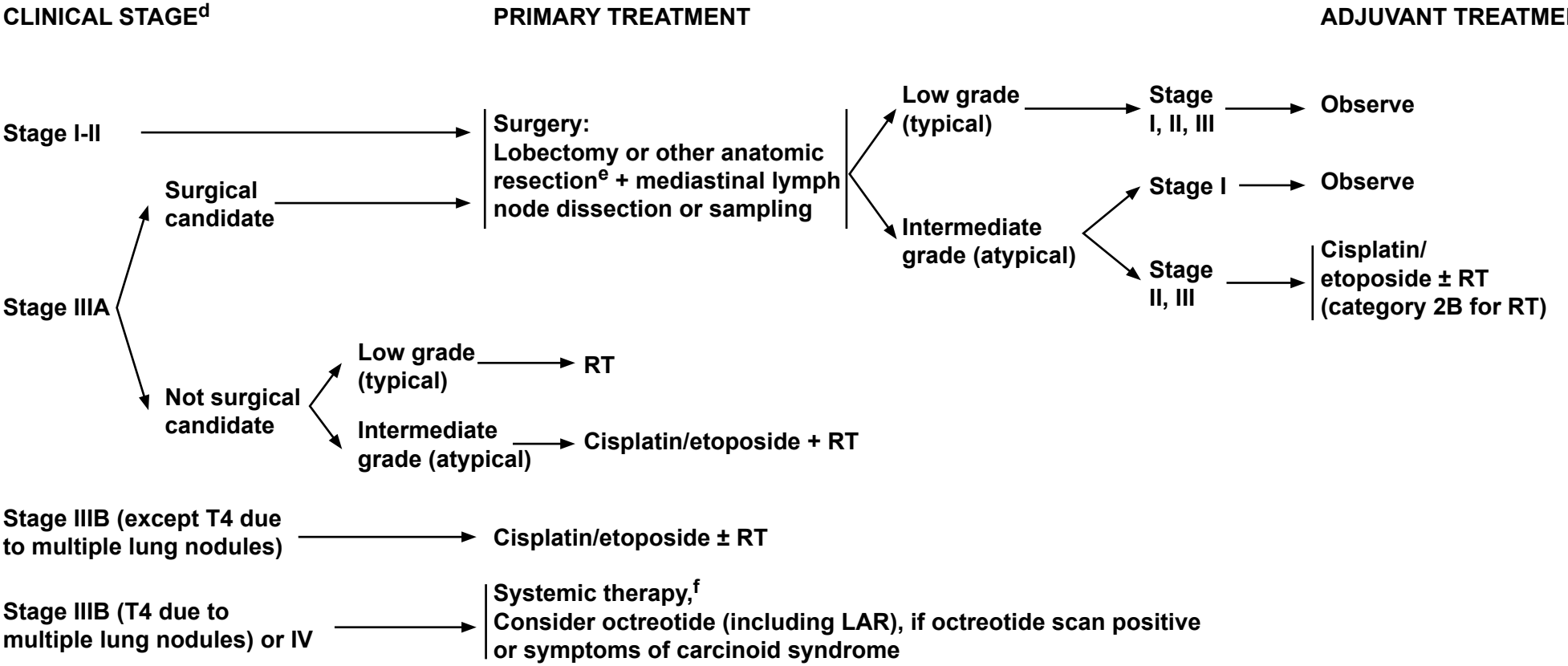

[d] See Staging on page ST-1.

[e] Wedge resection for peripheral low-grade neuroendocrine carcinoma (category 2B).

[f] There is no substantial evidence for a preferred regimen. Options include cisplatin/etoposide, temozolomide ± capecitabine, 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; Fine RL, Gulati AP, Krantz BA, et al. Capecitabine and temozolomide (CAPTEM) for metastatic well differentiated neuroendocrine cancers: The Pancreas Center at Columbia University experience. Cancer Chemother Pharmacol 2013;71:663-670.

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NCCN Guidelines Version 1.2015 Staging
Small Cell Lung Cancer

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Table 1 **- Definition of small cell lung cancer consists of two stages:**
(1) Limited-stage: AJCC (7th edition) Stage I-III (T any, N any, M0) that can be safely treated with definitive radiation doses. Excludes T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.
(2) Extensive-stage: AJCC (7th edition) Stage IV (T any, N any, M 1a/b), or T3-4 due to multiple lung nodules that are too extensive or have tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

Table 2 **- Definitions of TNM[1]**

T Primary Tumor

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
- T1a Tumor 2 cm or less in greatest dimension
- T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor with any of the following features of size or extent:
- More than 3 cm but 7 cm or less
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura (PL1 or PL2)
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

- T2a Tumor more than 3 cm but 5 cm or less in greatest dimension
- T2b Tumor more than 5 cm but 7 cm or less in greatest dimension

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina); or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

N Regional Lymph Nodes

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

M Distant Metastasis

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

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

**Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleura (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

[1]Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

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

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

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/18/13

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.

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Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).[1-4] In 2013, an estimated 31,000 new cases of SCLC will occur in the United States.[5] 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.[3] Management of SCLC and other lung neuroendocrine tumors (LNTs) is described in the NCCN Guidelines for Small Cell Lung Cancer and for LNTs, which include the algorithms and this supporting manuscript (ie, Discussion) (see also *Lung Neuroendocrine Tumors* in this Discussion). The *Updates* describe the most recent revisions in the algorithms, which have been incorporated into this revised Discussion (see the NCCN Guidelines for Small Cell Lung Cancer).

SCLC is characterized by a rapid doubling time, high growth fraction, and early development of widespread metastases. Most patients with SCLC present with hematogenous metastases; 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.[6,7] In patients with limited-stage SCLC, the goal of treatment is cure using chemotherapy plus thoracic radiotherapy.[8,9] In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients; however, long-term survival is rare.[10,11] Note that the definitions for limited-stage and extensive-stage SCLC have recently been revised to incorporate TNM staging (see *Updates* in the NCCN Guidelines for Small Cell Lung Cancer and see *Staging* in this Discussion). Surgery is only appropriate for the few patients (2%–5%) with surgically resectable stage I SCLC.[12] 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 in patients with SCLC and other high-grade neuroendocrine carcinomas (1-800-QUIT-NOW—the national access number to state-based quitline services) (www.smokefree.gov/); the 5 A's framework is recommended (Ask, Advise, Assess, Assist, Arrange) (http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html). Former smokers should be strongly encouraged to remain abstinent. Patients with SCLC who continue to smoke have increased toxicity during treatment and shorter survival.[13] Programs using behavioral counseling combined with FDA–approved medications that promote smoking cessation can be very useful (http://innovations.ahrq.gov/issue.aspx?id=113).

Small Cell Lung Cancer

Diagnosis

Screening

Ideally, a screening test should detect disease at an early stage when it is still curable. Currently, no effective screening test is available to detect early-stage SCLC; the disease is typically diagnosed when patients present with symptoms indicative of advanced-stage disease.[14] The National Lung Screening Trial (NLST) reported that screening with annual, low-dose, spiral CT scans decreased lung cancer–specific mortality in asymptomatic high-risk individuals (http://www.cancer.gov/newscenter/qa/2002/nlstqaQA) (see the NCCN Guidelines for Lung Cancer Screening).[15] Although CT screening can detect early-stage non-small cell lung cancer (NSCLC), it does not seem to be useful for detecting early-stage SCLC.[15] 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.[14]

Manifestations

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea. Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. It is uncommon for patients to present with a solitary peripheral nodule without central adenopathy. In this situation, fine-needle aspiration (FNA) may not adequately differentiate small cell carcinoma (which is a high-grade neuroendocrine carcinoma) from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or large-cell neuroendocrine (LCNEC) carcinoma (which is also a high-grade neuroendocrine carcinoma) (see the NCCN Guidelines for Lung Neuroendocrine Tumors and *Lung Neuroendocrine Tumors* in this Discussion).[16-18]

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.[19-21] 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.[22,23] 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.[24]

SCLC cells sometimes produce polypeptide hormones, including vasopressin (antidiuretic hormone [ADH]) and adrenocorticotropic hormone (ACTH), which cause hyponatremia of malignancy (ie, syndrome of inappropriate ADH secretion [SIADH]) and Cushing syndrome, respectively.[25,26] In patients with SCLC, SIADH occurs more frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates).[27,28] Treatment for SIADH includes fluid restriction (which is difficult for patients because of increased thirst), demeclocycline, or vasopressin receptor inhibitors (ie, conivaptan, tolvaptan) (see *Principles of Supportive Care* in the NCCN Guidelines for Small Cell Lung Cancer).[27,29,30] ADH levels and hyponatremia usually improve after successful treatment for SCLC.[28]

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.[16,31] The cells are round, oval, or spindle-shaped; nuclear molding is prominent. The mitotic count is high. The classic and distinctive histology on hematoxylin and eosin (H&E) may be sufficient for identifying SCLC; it is a poorly differentiated tumor that is categorized as a high-grade neuroendocrine carcinoma.[16] Up to 30% of autopsies in patients with SCLC reveal areas of NSCLC 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.[32-34] 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.[35]

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor–1 (TTF-1).[16] Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin.[16] However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs will be immunoreactive for at least one of these neuroendocrine markers.[36]

Staging

For the 2014 update, the NCCN Panel adopted a combined approach for staging SCLC using both the AJCC TNM staging system and the older Veterans Administration (VA) scheme for SCLC (see the following 2 paragraphs).[37,38] Historically, 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 and treatment is individualized for the patients.[37-39] 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.

In 2010, the lung cancer TNM staging system was revised by the International Association for the Study of Lung Cancer (IASLC) and adopted by the AJCC (7th edition, 2010) (see Tables 2 and 3).[40-44] This TNM 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.[40,44] In the combined approach for staging SCLC, *limited-stage* SCLC is now defined as stage I to III (T any, N any, M0) that can be safely treated with definitive radiation therapy; however, limited-stage SCLC excludes T3–4 due to multiple lung nodules or a tumor/nodal volume that does not fit in a tolerable radiation plan (see Table 1). *Extensive-stage* SCLC is now defined as stage IV (T any, N any, M1a/b) or T3–4 due to multiple lung nodules or tumor/nodal volume that is too large to be encompassed in a tolerable radiation plan.

The VA Lung Study Group's 2-stage classification scheme was previously used to define the extent of disease in patients with SCLC: 1) limited-stage disease was disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage disease was disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.[45] Because most of the literature on SCLC classifies patients based on the VA's definitions of limited-stage or extensive-stage disease, these definitions are often used for clinical decision making. However, the TNM system is useful for selecting patients with T1-2, N0 disease who are eligible for surgery and for radiation treatment planning.[38] 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.

All patients with SCLC, even those with radiographically limited-stage disease (per the VA's definition), require systemic chemotherapy either as primary or adjuvant therapy. 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 brain imaging using MRI (preferred) or CT scan (with intravenous contrast).[39] However, once a patient has been found to have extensive-stage disease, further staging

is optional, except for brain imaging.[37] 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.[37,38] A bone scan can be performed if PET-CT is not available.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.[46-50] PET-CT is superior to PET alone.[50] Approximately 19% of patients who undergo PET are upstaged from limited- to extensive-stage disease, whereas only 8% are downstaged from extensive- to limited-stage disease.[39] For most metastatic sites, PET-CT is superior to standard imaging; however, PET-CT is inferior to MRI or CT for the detection of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers).[51] Changes in management based on PET staging were reported in approximately 27% of patients, mainly because of alterations in the planned radiation field as a result of improved detection of intrathoracic sites of disease.[39,47,52,53] 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.[37] However, mediastinal staging is not required if the patient is not a candidate for surgical resection and/or if non-surgical treatment is planned. Invasive mediastinal staging can be performed either by conventional mediastinoscopy or by minimally invasive techniques such as transesophageal endoscopic ultrasound–guided FNA (EUS-FNA), endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA), or video-assisted thoracoscopy (VATS).[54,55]

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 focus only on sites of symptomatic disease or on sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or an abnormal alkaline phosphatase level. Bone imaging with radiographs or MRI may be appropriate if PET-CT is equivocal. Brain imaging (MRI preferred or CT scan) can identify central nervous system (CNS) 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 (such as lactate dehydrogenase [LDH]) are the most important adverse prognostic factors. Female gender, age younger than 70 years, normal LDH, and

stage I disease are associated with a more favorable prognosis in patients with limited-stage disease. Younger age, good PS, normal creatinine level, normal LDH, and a single metastatic site are favorable prognostic factors in patients with extensive-stage disease.[56-58]

Treatment

Chemotherapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment.[10] 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). [9,59,60] For patients with extensive-stage disease, chemotherapy alone is the recommended treatment, although radiotherapy may be used in select patients for palliation of symptoms (see *Initial Treatment* and *Principles of Chemotherapy* in the NCCN Guidelines for Small Cell Lung Cancer). 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 *Initial Treatment* in the NCCN Guidelines for Small Cell Lung Cancer).[11,61]

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.[62-64] Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see *Principles of Chemotherapy* in the NCCN Guidelines for Small Cell Lung Cancer).[10,65,66] This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.[67] EP plus concurrent thoracic radiotherapy is now the recommended therapy for patients with limited-stage disease (category 1).[59,60,68]

In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis, pulmonary toxicity, and hematologic toxicity.[69] The use of myeloid growth factors is not recommended in patients undergoing concurrent chemoradiation.[70] In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin carries a greater risk of myelosuppression.[71] Small randomized trials have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC.[72,73] A meta-analysis of 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.[74] Of 663 patients included in this meta-analysis, 32% had limited-stage disease and 68% had extensive-stage disease. No significant difference was observed in response rate (67% vs. 66%), progression-free survival (5.5 vs. 5.3 months), or overall survival (9.6 vs. 9.4 months) in patients receiving cisplatin- versus carboplatin-containing regimens, suggesting equivalent efficacy in patients with SCLC.

Many other combinations have been evaluated in patients with extensive-stage disease, with little consistent evidence of benefit when compared with EP. 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).[75] In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.[75] 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.[76,77]

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).[78] 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.[79] However, this meta-analysis was not performed using individual patient data. In addition, the relatively small absolute survival benefit needs to be balanced against the toxicity profile of irinotecan-based regimens. Therefore, the NCCN Panel continues to consider etoposide plus platinum as the standard regimen for patients with SCLC.

In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with EP plus thoracic radiotherapy, whereas in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.[62] 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.[80] Thoracic radiotherapy improves local control rates by 25% in limited-stage disease patients and is associated with improved survival.[59,60] 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.[81,82]

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.[83,84] 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.[85] 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.[86] 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.[87]

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.[88] However, randomized trials have failed to show improved PFS or overall survival with this approach.[89,90]

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.[91,92] Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.[93-96] The role of higher-dose therapy for patients with SCLC remains controversial.[97] 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.[98] In general,

however, randomized trials comparing conventional doses to an incrementally increased dose intensity up to 2 times the conventional dose have not consistently shown an increase in response rate or survival.[99-102] 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.[103]

Currently available cytokines (eg, 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,[104] little evidence suggests that maintenance of dose intensity with growth factors prolongs disease-free or overall survival. Thus, the routine use of growth factors at the initiation of chemotherapy is not recommended.

The 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 was terminated early because of an unacceptable incidence of tracheoesophageal fistulae (http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153953.pdf). In extensive-stage SCLC, 2 phase II trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.[105-107] 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 NCCN Panel does not recommend use of bevacizumab in patients with SCLC.

Overall, attempts to improve long-term survival rates in patients with SCLC through the addition of more agents or the use of dose-intense chemotherapy regimens, maintenance therapy, or alternating non–cross-resistant chemotherapy regimens have failed to yield significant advantages when compared to standard approaches.

Elderly Patients

The incidence of lung cancer increases with age. Although the median age at diagnosis is 70 years, elderly patients are under-represented in clinical trials.[108] 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 the NCCN Guidelines for Senior Adult Oncology). 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 (eg, single-agent etoposide) is inferior to combination chemotherapy (eg, platinum plus etoposide) in elderly patients with good PS (0–2).[109,110] Several other strategies have been evaluated in elderly patients with SCLC.[73,111-113] 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.[113] However, targeting carboplatin to an AUC of 5, rather than 6, may be more reasonable in this population.[114] 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.[115]

Second-Line (Subsequent) Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.[116,117] These patients have a median survival of only 4 to 5 months when treated with further chemotherapy. Second-line (ie, 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. Based on phase II trials, active subsequent agents include paclitaxel, docetaxel, topotecan, irinotecan, vinorelbine, gemcitabine, ifosfamide, temozolomide, and oral etoposide (see *Principles of Chemotherapy* in the NCCN Guidelines for Small Cell Lung Cancer).[66,118-122] Preliminary data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated methylguanine-DNA methyltransferase (MGMT).[118]

A randomized phase III trial compared single-agent intravenous topotecan with the combination regimen CAV.[123] Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase III trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).[124] 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 for up to 6 months; category 2A for relapse <2–3 months).[119,123,125] Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.[124,125]

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.[126] Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC, and this approach remains under investigation.[127,128] Amrubicin is an active drug in patients with relapsed or refractory SCLC.[129-132] However, grade 3–4 toxicity, primarily neutropenia, is common,[133,134] and a phase III trial reported that overall survival was not improved with amrubicin as second-line treatment when compared with topotecan.[135]

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* in the algorithm describe the radiation doses, target volumes, and normal tissue dose volume constraints for mainly limited-stage SCLC, and include references to

support the recommendations; prophylactic cranial irradiation (PCI) and treatment of brain metastases are also discussed (see the NCCN Guidelines for Small Cell Lung Cancer). The American College of Radiology (ACR) Appropriateness Criteria® are a useful resource.[136] The *Principles of Radiation Therapy* for NSCLC in the algorithm may also be useful (eg, general principles of radiotherapy, palliative radiotherapy) (see the NCCN Guidelines for Non-Small Cell Lung Cancer). 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.[137] Meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease yields a 25% to 30% reduction in local failure, and a corresponding 5% to 7% improvement in 2-year survival when compared with chemotherapy alone.[59,60] 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 phase III 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.[69] 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 with longer survival.[138] 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 with late concurrent or sequential radiotherapy.[139] Another meta-analysis also found that early concurrent thoracic radiation with platinum-based chemotherapy increases 2- and 5-year overall survival.[140]

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.[141] 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 when 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.[141] A significant criticism of this trial is that the doses of radiation in the 2 arms were not biologically equivalent. In light of this, on-going trials are evaluating biologically equivalent doses of 45 Gy delivered twice daily versus 60 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.[142] 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). The optimal dose and schedule of radiotherapy have not been established. However, 45 Gy in 3 weeks (twice-daily regimen) is superior to 45 Gy once daily in 5 weeks.[141] For twice-daily radiotherapy, the recommended schedule is 1.5 Gy twice daily to a total dose of 45 Gy in 3 weeks (category 1). For once-daily radiotherapy, the recommended schedule is 2.0 Gy once daily to a total dose of 60 to 70 Gy (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer).[143-145] Concurrent chemoradiotherapy (category 1) is preferable to sequential therapy in patients with good PS (0–2).[69,146]

The minimum standard for thoracic irradiation is CT-planned 3-D conformal radiotherapy. More advanced technologies may also be used when needed (eg, 4DCT) (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer). The radiation target volumes can be defined on the PET-CT scan obtained at the time of radiotherapy planning using definitions in reports 50 and 62 from the International Commission on Radiation Units & Measurement (ICRU).[147,148] However, the prechemotherapy PET-CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.[145,149]

The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar radiotherapy doses (see the NCCN Guidelines for Non-Small Cell Lung Cancer). When using accelerated schedules (eg, 3–5 weeks), the spinal cord constraints from the CALCB 30610/RTOG 0538 protocol can be used as a guide (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer).[150-152] Intensity-modulated radiation therapy (IMRT) may be considered in select patients (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Non-Small Cell Lung Cancer) (http://www.acr.org/~/media/ACR/Documents/PGTS/guidelines/IMRT.pdf).[153-156]

Based on the results of a randomized trial by Jeremic et al,[157] 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. In this trial, patients experiencing a complete response at distant metastatic sites after 3 cycles of EP were randomized to receive either 1) further EP; or 2) accelerated hyperfractionated radiotherapy (ie, 54 Gy in 36 fractions over 18 treatment days) in combination with carboplatin plus etoposide.[157] The investigators 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 PCI is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to show a meaningful survival advantage.[158] 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.[159]

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.[159] 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 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.[160] 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.[161]

Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrent with chemotherapy.[162,163] Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.[164] Older age (>60 years) has also been associated with chronic neurotoxicity.[165] 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.

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.[161,166] PCI is also recommended for all patients who have had a complete resection (see *Principles of Surgical Resection* in the NCCN Guidelines for Small Cell Lung Cancer). The recommended regimens for PCI include: 25 Gy in 10 daily fractions (2.5 Gy/fraction), 30 Gy in 10 to 15 daily fractions, or 24 Gy in 8 daily fractions (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer).[159,161,166] Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with standard doses (25 Gy).[165,166] PCI should not be given concurrently with systemic chemotherapy, and high total radiotherapy dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity. Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.[164,166] PCI can be administered after the acute toxicities of initial therapy have resolved.

Palliative Radiotherapy

For patients with localized symptomatic sites of disease (ie, painful bony lesions, spinal cord compression, obstructive atelectasis) or with brain metastases, radiotherapy can provide excellent palliation (see *Initial Treatment* in the NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Non-Small Cell Lung Cancer)[167-169] (http://www.practicalradonc.org/article/S1879-8500(11)00091-9/abstract). Orthopedic stabilization may be useful in patients at high risk for fracture because of osseous structural impairment. Because patients with SCLC often have a short life span, surgery is not usually recommended for spinal cord compression. Whole-brain radiotherapy is recommended for brain metastases in patients with SCLC due to the frequent occurrence of multiple metastases (see *Principles of Radiation Therapy* in the NCCN Guidelines for Small Cell Lung Cancer and the NCCN Guidelines for Central Nervous System Cancers).[170] Although late complications may occur with whole-brain radiotherapy (eg, neurocognitive impairment), this is less of an issue in patients with SCLC as long-term survival is rare.[162] The recommended dose for whole-brain radiotherapy is 30 Gy.

Surgical Resection of Stage I SCLC

The *Principles of Surgical Resection* for SCLC are described in the NCCN algorithm; studies supporting these recommendations are described in this section. Briefly, the NCCN Guidelines state 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.[171,172] Data show that patients with clinically staged disease in excess of T1–2,N0 do not benefit from surgery.[172] Note that only 5% of patients with SCLC have true stage I SCLC.[41]

Trial Data

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[172] Patients with limited-stage disease, excluding those with solitary peripheral nodules, received 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 rates of patients on the 2 arms were equivalent, suggesting no benefit to surgery in this setting. However, only 19% of enrolled patients had clinical stage I (T1–2, N0, M0) disease.

Most data regarding the benefit of surgery are from retrospective reviews.[171,173-177] 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.[12,178] 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 of trials comparing surgery plus adjuvant chemotherapy to concurrent chemoradiotherapy in rigorously staged patients.

NCCN Guidelines

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.[179] If resection is performed, the NCCN Panel favors lobectomy and does not feel that segmental or wedge resections are appropriate for patients with SCLC. After complete resection, adjuvant chemotherapy or chemoradiation is recommended.[175,180,181] 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 *Adjuvant Treatment* in the NCCN Guidelines for Small Cell Lung Cancer). Although panel members agree that postoperative mediastinal radiotherapy is recommended in this setting, it should be based on the extent of nodal sampling/dissection and extent of nodal positivity; however, there are no data to support this recommendation. PCI should be considered after adjuvant therapy in select patients, because it can improve survival (see *Prophylactic Cranial Irradiation* in this Discussion and *Adjuvant Treatment* in the NCCN Guidelines for Small Cell Lung Cancer).[159]

Surveillance

The schedule for follow-up examinations is shown in the algorithm (see *Surveillance* in the NCCN Guidelines for Small Cell Lung Cancer); the frequency of surveillance decreases during subsequent years because of the declining risk of recurrence. 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 SCLC.[182,183] Smoking cessation should be encouraged for all patients with SCLC (http://innovations.ahrq.gov/issue.aspx?id=113), because second primary tumors occur less commonly in patients who quit smoking.[184-186] Former smokers should be encouraged to remain abstinent.

Lung Neuroendocrine Tumors

LNTs encompass a wide spectrum of disease. Using the 2004 WHO criteria, LNTs are characterized as: 1) high-grade neuroendocrine carcinomas (SCLC and LCNEC); 2) intermediate-grade neuroendocrine carcinomas (atypical carcinoids); or 3) low-grade neuroendocrine carcinomas (typical carcinoids)[187,188] (http://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb10/index.php). SCLC and LCNEC are poorly differentiated tumors that often have a poor prognosis, whereas typical carcinoid is a well-differentiated neuroendocrine tumor that usually has a good prognosis. Atypical carcinoid is a moderately differentiated neuroendocrine cancer and, as such, carries an intermediate prognosis. Although many carcinoids occur in the GI tract (68%), they also occur in the bronchopulmonary system (25%). Carcinoids are rare tumors, but a SEER analysis suggests that their incidence is increasing.[189,190]

Diagnosis and Staging

Most LNTs are SCLCs, which are managed using the NCCN Guidelines for Small Cell Lung Cancer.[2] LCNEC is associated with smoking and is managed using the NCCN Guidelines for Non-Small Cell Lung Cancer.[191-193] Low-grade and intermediate-grade lung neuroendocrine carcinomas (typical and atypical carcinoids) account for 1% to 2% of lung cancers and are managed using the NCCN Guidelines for Lung Neuroendocrine Tumors. Both histologic and cytologic features can be useful for distinguishing LNTs from SCLC and LCNEC, although diagnosis can be difficult (see the NCCN Guidelines for Neuroendocrine Tumors and for Non-Small Cell Lung Cancer).[16,194] CD56, chromogranin, and synaptophysin are useful immunohistochemical markers for identifying neuroendocrine tumors.[16] The proliferative marker Ki-67 may also be useful.[17,18] Larger surgical specimens are often needed to diagnose atypical carcinoids or LCNEC, which may be difficult to diagnose using small biopsies or cytology.[16]

LNTs are staged using the 7th edition of the AJCC staging system for lung tumors (see Tables 2 and 3).[43,195] Both low-grade 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-grade and intermediate-grade LNTs.[16,196]

Treatment

Surgery is recommended for patients with stage I, II, or IIIA low-grade or intermediate-grade LNTs (ie, typical or atypical carcinoids) (see *Primary Treatment* in the NCCN Guidelines for Small Cell Lung Cancer).[17,197,198] After surgical resection, 5- and 10-year survival rates are more than 90% for patients with typical carcinoid, whereas 5- and 10-year survival

rates are 70% and 50% to 60% for patients with atypical carcinoid.[198-200] Lymph node involvement decreases long-term survival in both typical and atypical carcinoid.[198-200] If surgery is not feasible, external-beam radiotherapy is recommended for stage III typical carcinoids, and chemotherapy/radiotherapy is recommended for stage III atypical carcinoids.[201] Systemic therapy (eg, cisplatin/etoposide, temozolomide, sunitinib, everolimus) is recommended for patients with unresectable or advanced disease, although response rates are modest and there is no established standard systemic therapy.[2,17,196,202-208] Octreotide (including long-acting release [LAR]) may be considered for select patients with positive octreotide scans or symptoms of carcinoid syndrome.[209]

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