National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Small Cell Lung Cancer

Version 3.2017 — February 23, 2017

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NCCN Guidelines Version 3.2017 Panel Members
Small Cell Lung Cancer

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NCCN Guidelines Panel Disclosures

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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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Updates in Version 3.2017 of the NCCN Guidelines for Small Cell Lung Cancer from Version 2.2017 include:

General

The algorithm for Lung Neuroendocrine Tumors has been moved to the NCCN Guidelines for Neuroendocrine Tumors.

Updates in Version 2.2017 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2017 include:

MS-1

The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 1.2017 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2016 include:

SCL-1

- **Initial evaluation**
  - **Bullet 3 modified: "CBC ~~with differential, platelets~~"**
  - **Bullet 6 modified: "Chest/liver/adrenal CT with contrast ~~whenever possible~~"**
  - **Bullet 7 modified: "Brain MRI (preferred) or CT with contrast ~~whenever possible~~" (Also for SCL-5)**

SCL-2

- **Clinical stage T1-2, N0**
  - **Pathway statement removed: PET-CT scan "(if not previously obtained)"**
  - **Footnote removed: "PET-CT scan to identify distant disease and to guide mediastinal evaluation, if not previously done."**

SCL-3

- **Initial Treatment**
  - **Clinical stage T1-2, N0; Pathologic mediastinal staging positive or medically inoperable or decision made not to pursue surgical resection: Recommendations combined with Limited stage in excess of T1-2, N0.**
  - **Limited stage in excess of T1-2, N0, initial treatment option modified: "Systemic therapy ± RT *(concurrent or sequential)"***
  - **Footnote "m" added: "For patients receiving adjuvant therapy, response assessment should occur only after completion of initial therapy (SCL-5); do not repeat scans to assess response during adjuvant treatment."**
  - **Footnote "n" added: "For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy (SCL-5); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by CT chest/liver/adrenal with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy (SCL-5)."**

SCL-4

- **Footnote "o" added: "For patients with asymptomatic brain metastases receiving systemic therapy before whole-brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy (SCL-5)."**
- **Footnote "p" added: "During systemic therapy, response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-5)."**

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Updates in Version 1.2017 of the NCCN Guidelines for Small Cell Lung Cancer from Version 1.2016 include:

SCL-5

- **Response Assessment Following Initial Therapy**
  - **Bullet 2 modified: "Chest/liver/adrenal CT with contrast ~~whenever possible~~"**
  - **Bullet 3 modified: "Brain MRI (preferred) or CT with contrast ~~whenever possible~~, if prophylactic cranial irradiation (PCI) to be given"**
  - **Bullet removed: "Other imaging studies, to assess prior sites of involvement, as clinically indicated"**
  - **Bullet 5 modified: "CBC, ~~platelets~~"**
- **Adjuvant Treatment; Extensive disease: "PCI + thoracic RT" changed to "PCI ± thoracic RT."**
- **Surveillance; Bullet 1, sub-bullet 1 modified: "At every visit: H&P, *CT* chest ~~imaging~~*/liver/adrenal*, bloodwork as clinically indicated"**

SCL-6

- **Footnote "s" added: "A response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy."**

SCL-A

- **Reference "5" added: "Yang CE, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-1064."**

SCL-C 1 OF 3

- **Title modified: "Principles of ~~Chemotherapy~~ *Systemic Therapy*" (also applies to SCL-C 2 of 3 and SCL-C 3 of 3)**
- **Systemic therapy as primary therapy or adjuvant therapy; Extensive stage: Carboplatin and etoposide regimen moved from bullet 4 to bullet 1.**
- **Subsequent systemic therapy**
  - **The decision point of "relapse <2–3 mo, PS 0-2" versus "relapse >2–3 mo up to 6 mo" removed.**
  - **Category 1 removed from topotecan.**
  - **Ifosfamide removed as an option.**
  - **Nivolumab ± ipilimumab added as a treatment option as a category 2A.**
  - **Statement modified: "Consider dose reduction ~~versus growth factors in the poor performance status patient~~ *or growth factor support for patients with PS 2*"**

SCL-C 2 OF 3

- **Response Assessment section is new to the guideline (SCL-C 2 of 3).**

SCL-D 2 of 3

- **Brain Metastases**
  - **Bullet 1 modified: "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. 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 *uncontrolled* extracranial disease."**

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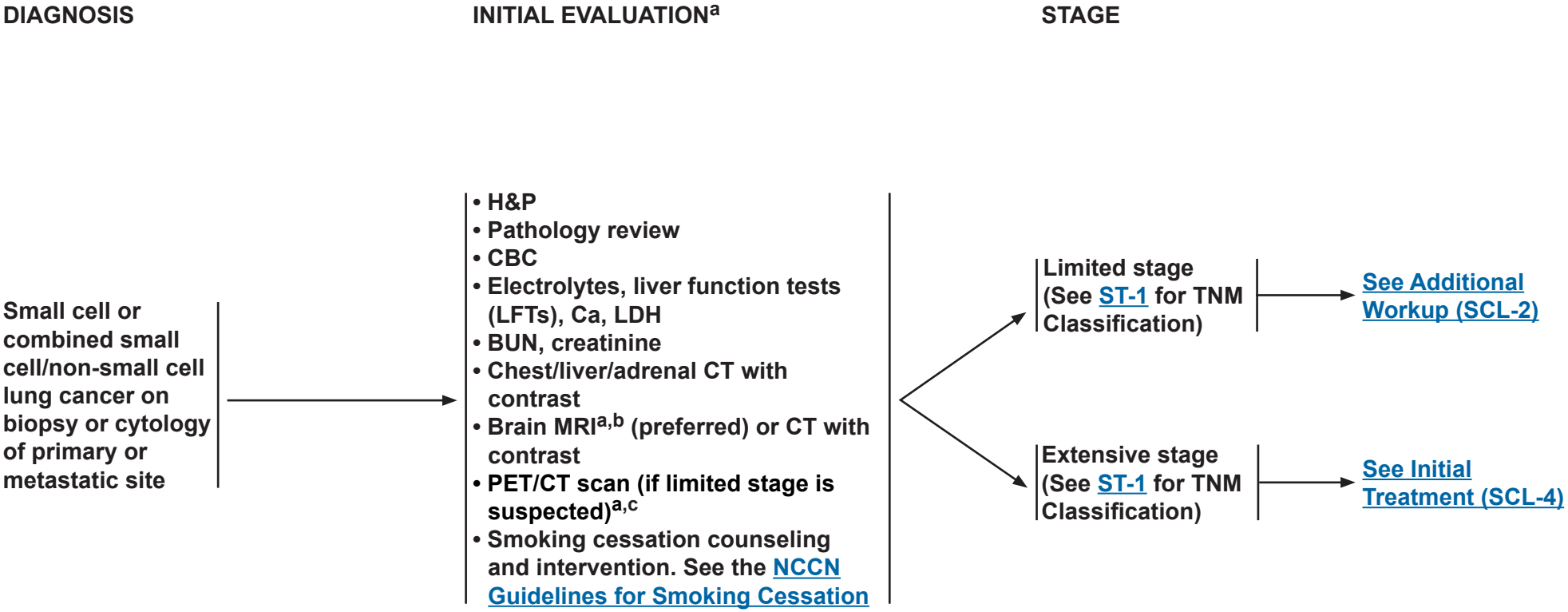
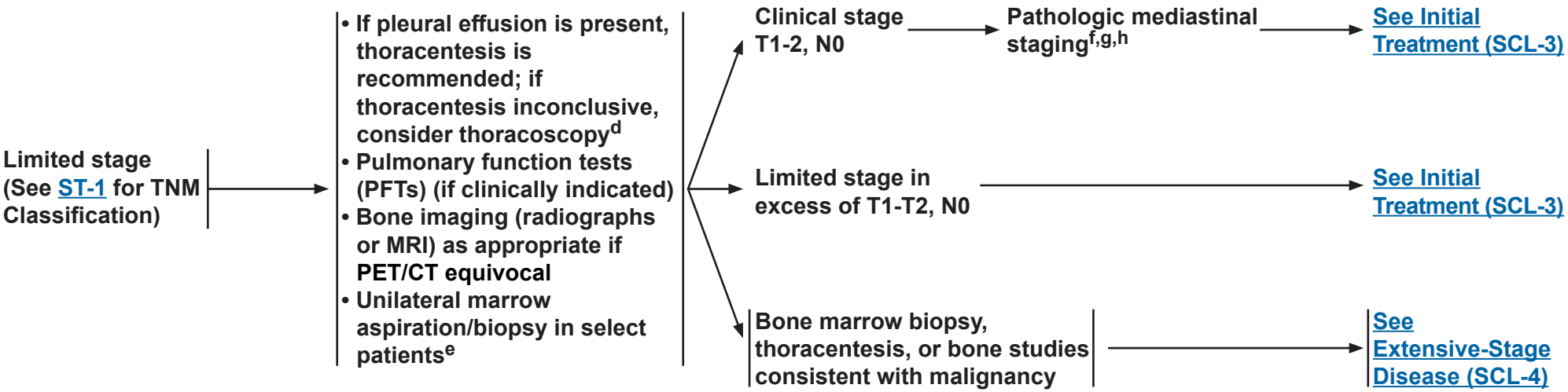


[a]If extensive stage is established, further staging evaluation is optional. However, brain imaging, MRI (preferred), or CT with contrast should be obtained in all patients.
[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[c]If PET/CT is not available,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

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



[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 suggestive of bone marrow infiltration.
[f]See Principles of Surgical Resection (SCL-A).
[g]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]Pathologic mediastinal staging is not required if the patient is not a candidate for surgical resection or if non-surgical treatment is pursued.

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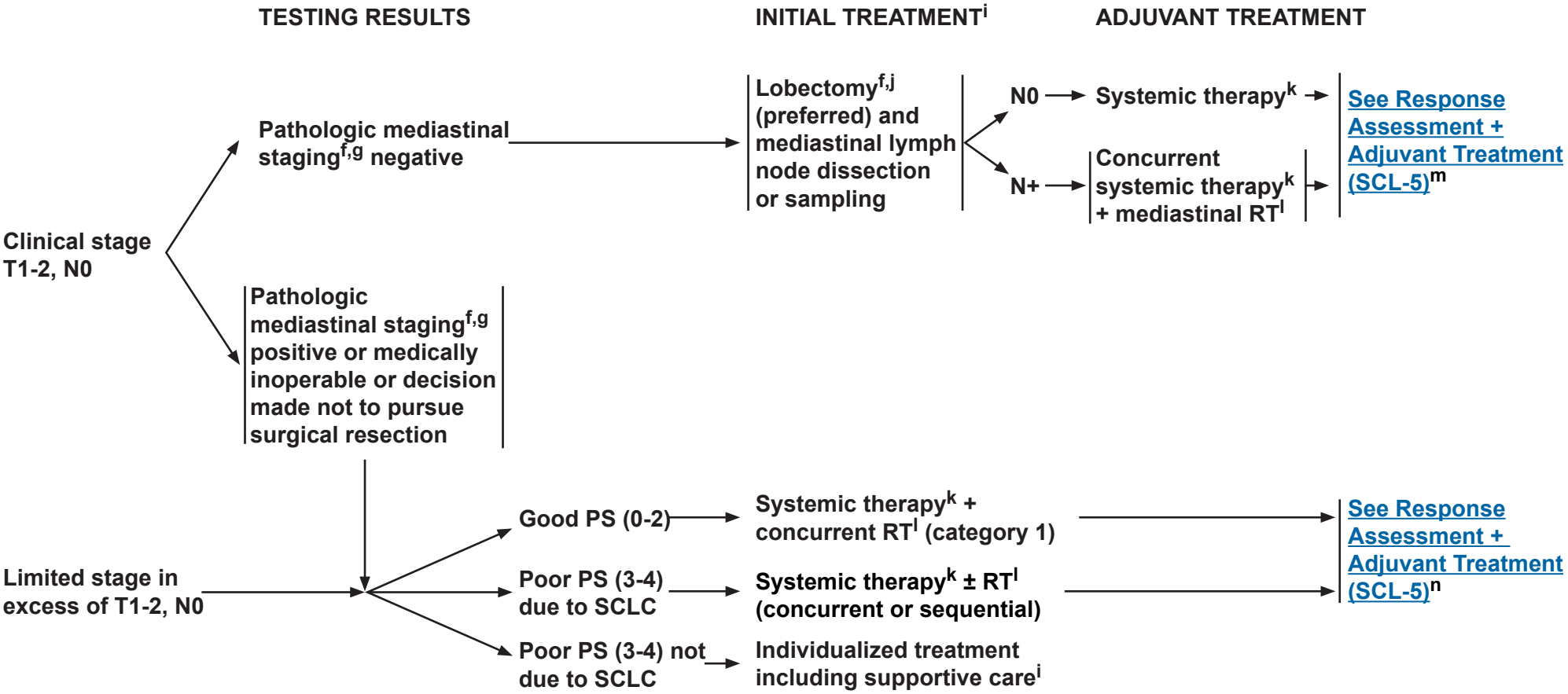

[f] See Principles of Surgical Resection (SCL-A).
[g] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.
[i] See Principles of Supportive Care (SCL-B).
[j] Select patients may be treated with systemic therapy/RT as an alternative to surgical resection.
[k] See Principles of Systemic Therapy (SCL-C).
[l] See Principles of Radiation Therapy (SCL-D).
[m] For patients receiving adjuvant therapy, response assessment should occur only after completion of initial therapy (SCL-5); do not repeat scans to assess response during adjuvant treatment.
[n] For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy (SCL-5); do not repeat scans to assess response during initial treatment. For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by CT chest/liver/adrenal with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy (SCL-5).

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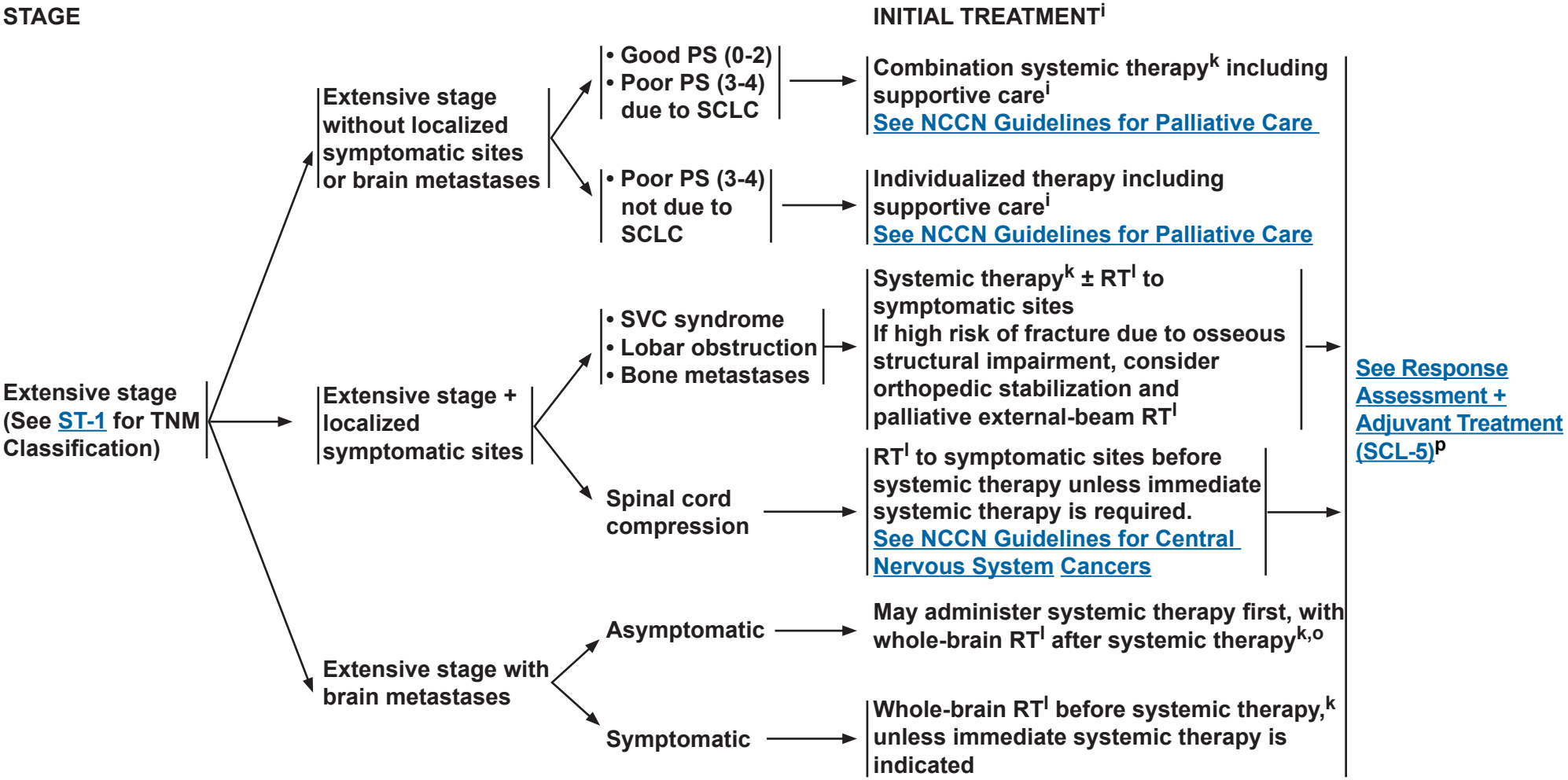

[i] See Principles of Supportive Care (SCL-B).
[k] See Principles of Systemic Therapy (SCL-C).
[l] See Principles of Radiation Therapy (SCL-D).
[o] For patients with asymptomatic brain metastases receiving systemic therapy before whole-brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy (SCL-5).
[p] During systemic therapy, response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy (SCL-5).

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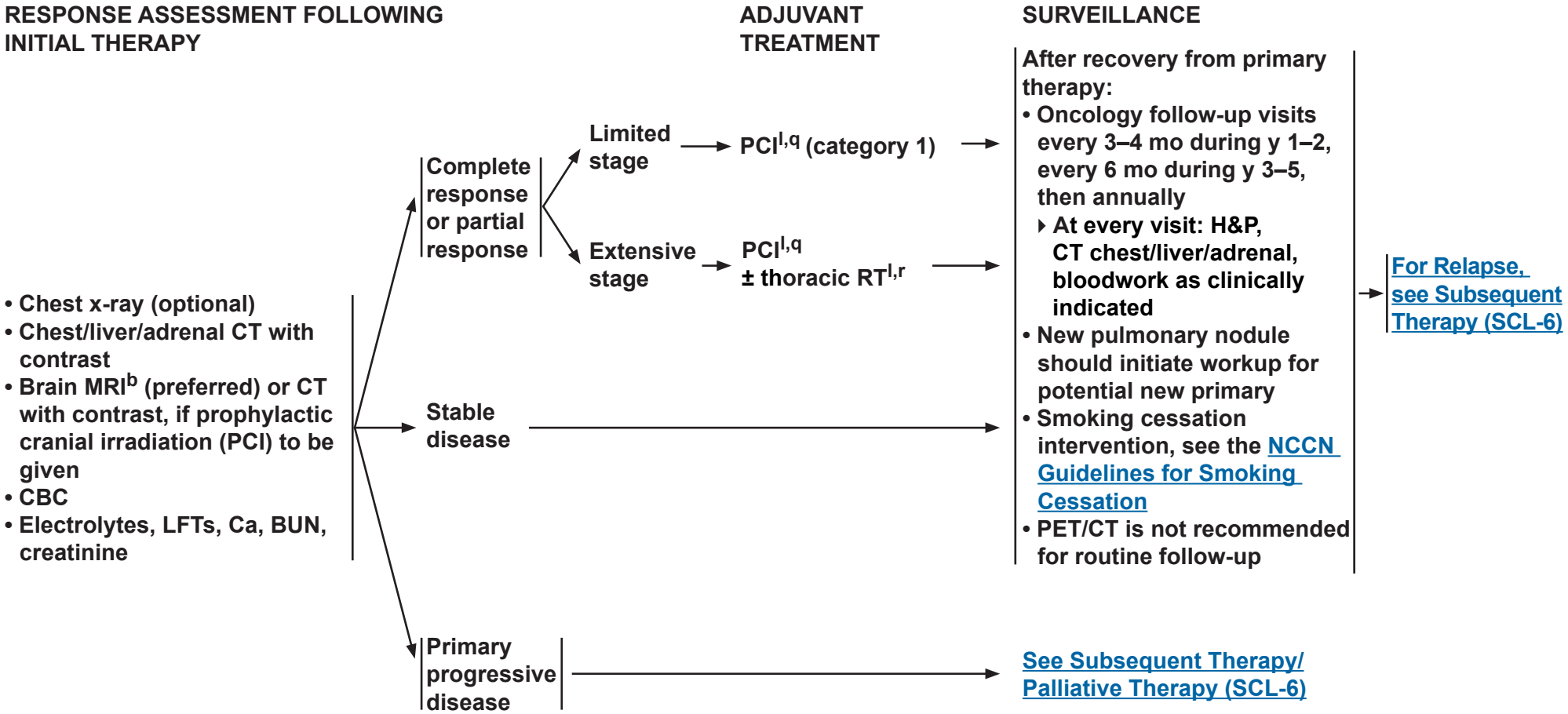

[b]Brain MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[l]See Principles of Radiation Therapy (SCL-D).
[q]Not recommended in patients with poor performance status or impaired neurocognitive function.
[r]Sequential radiotherapy to thorax in selected patients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

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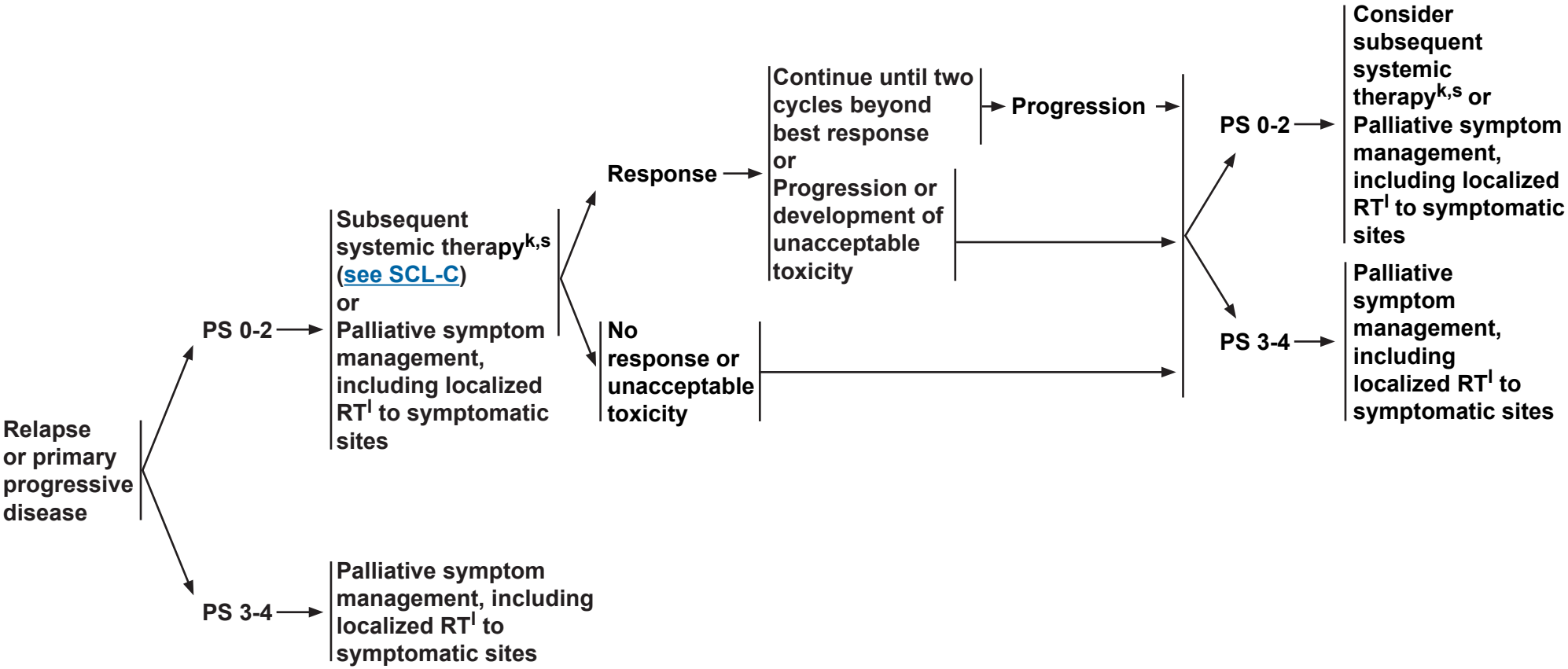
PROGRESSIVE DISEASE **SUBSEQUENT THERAPY/PALLIATIVE THERAPY**



[k]See Principles of Systemic Therapy (SCL-C).
[l]See Principles of Radiation Therapy (SCL-D).
[s]Response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy.

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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 systemic therapy. Patients without nodal metastases should be treated with systemic therapy alone. Patients with nodal metastases should be treated with postoperative concurrent systemic therapy and mediastinal radiation therapy (RT).**
- **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 systemic therapy in patients who have undergone a complete resection.[2] PCI is not recommended in patients with poor performance status or impaired neurocognitive functioning.[3,4,5]**

[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.
[5]Yang CE, Chan DY, Speicher PJ, et al. Role of adjuvant therapy in a population based cohort of patients with early-stage small-cell lung cancer. J Clin Oncol 2016;34:1057-1064.

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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 Smoking Cessation**

- **Granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using 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 SYSTEMIC THERAPY* (1 of 3)

Systemic therapy as primary or adjuvant therapy:

- **Limited stage (maximum of 4–6 cycles):**
  - **Cisplatin 60 mg/m² day 1 and etoposide 120 mg/m² days 1, 2, 3[1]**
  - **Cisplatin 80 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[2]**
  - **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[3]**
  - **During systemic therapy + RT, cisplatin/etoposide is recommended (category 1).**
  - **The use of myeloid growth factors is not recommended during concurrent systemic therapy plus radiotherapy (category 1 for not using GM-CSF).****

- **Extensive stage (maximum of 4–6 cycles):**
  - **Carboplatin AUC 5–6 day 1 and etoposide 100 mg/m² days 1, 2, 3[4]**
  - **Cisplatin 75 mg/m² day 1 and etoposide 100 mg/m² days 1, 2, 3[5]**
  - **Cisplatin 80 mg/m² day 1 and etoposide 80 mg/m² days 1, 2, 3[6]**
  - **Cisplatin 25 mg/m² days 1, 2, 3 and etoposide 100 mg/m² days 1, 2, 3[7]**
  - **Carboplatin AUC 5 day 1 and irinotecan 50 mg/m² days 1, 8, 15[8]**
  - **Cisplatin 60 mg/m² day 1 and irinotecan 60 mg/m² days 1, 8, 15[9]**
  - **Cisplatin 30 mg/m² and irinotecan 65 mg/m² days 1, 8[10]**

Subsequent systemic therapy:

- **Clinical trial preferred.**

- **Relapse ≤6 mo, PS 0-2:**
  - **topotecan PO or IV[11-13]**
  - **irinotecan[14]**
  - **paclitaxel[15,16]**
  - **docetaxel[17]**
  - **temozolomide[18,19]**
  - **nivolumab ± ipilimumab[20]**
  - **vinorelbine[21,22]**
  - **oral etoposide[23,24]**
  - **gemcitabine[25,26]**
  - **cyclophosphamide/doxorubicin/vincristine (CAV)[11]**
  - **bendamustine (category 2B)[27]**

- **Relapse >6 mo: original regimen[28,29]**

Consider dose reduction or growth factor support for patients with PS 2

Response Assessment SCL-C 2 of 3

References on SCL-C 3 of 3

*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 SYSTEMIC THERAPY (2 of 3)

Response assessment

- **Limited-stage**
  - **For patients receiving adjuvant therapy, response assessment should occur only after completion of initial therapy; do not repeat scans to assess response during adjuvant treatment.**
  - **For patients receiving systemic therapy + concurrent RT, response assessment should occur only after completion of initial therapy; do not repeat scans to assess response during initial treatment.**
  - **For patients receiving systemic therapy alone or sequential systemic therapy followed by RT, response assessment by CT chest/liver/adrenal with contrast should occur after every 2 cycles of systemic therapy and at completion of therapy.**

- **Extensive-stage**
  - **During systemic therapy, response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy and at completion of therapy.**
  - **For patients with asymptomatic brain metastases receiving systemic therapy before whole-brain RT, brain MRI (preferred) or CT with contrast should be repeated after every 2 cycles of systemic therapy and at completion of therapy.**

- **Subsequent systemic therapy**
  - **Response assessment by CT chest/liver/adrenal with contrast should occur after every 2–3 cycles of systemic therapy.**

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PRINCIPLES OF SYSTEMIC THERAPY (3 of 3)

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]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.
[5]Spigel DR, Townley PM, Waterhouse DM, et al. Randomized phase II study of bevacizumab in combination with chemotherapy in previously untreated extensive-stage small-cell lung cancer: results from the SALUTE trial. J Clin Oncol 2011;29:2215-2222.
[6]Niell HB, Herndon JE, Miller AA, et al. Randomized phase III Intergroup trial of etoposide and cisplatin with or without paclitaxel and granulocyte-colony stimulating factor in patients with extensive-stage small-cell lung cancer: Cancer and Leukemia Group B trial 9732. J Clin Oncol 2005;23:3752-3759.
[7]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.
[8]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.
[9]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.
[10]Hanna N, Bunn Jr. PA, Langer C, et al. Randomized phase III trial comparing irinotecan/cisplatin with etoposide/cisplatin in patients with previously untreated extensive-stage disease small-cell lung cancer. J Clin Oncol 2006;24(13):2038-2043.
[11]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.
[12]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.
[13]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.
[14]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.
[15]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.
[16]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.
[17]Smyth JF, Smith IE, Sessa C, et al. Activity of docetaxel (Taxotere) in small cell lung cancer. Eur J Cancer 1994; 30A:1058-1060.
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PRINCIPLES OF RADIATION THERAPY

General Principles:

- General principles of 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) 4D-CT 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/quality-safety/appropriateness-criteria

Limited Stage:

- Timing: RT concurrent with systemic therapy is standard and preferred to sequential chemo/RT.[1] RT should start early, with cycle 1 or 2 of systemic therapy (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 systemic therapy before RT, the gross tumor volume (GTV) can be limited to the post-induction systemic therapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-systemic therapy 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 is beneficial for selected patients with extensive-stage SCLC that responds to systemic therapy. 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] The Dutch CREST randomized trial of modest-dose thoracic RT in patients with extensive stage SCLC that responded to systemic therapy demonstrated significantly improved two-year overall survival and six-month progression-free survival, although the protocol-defined primary endpoint of one-year overall survival was not significantly improved.[21]

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-stage SCLC who have a good response to initial therapy, PCI decreases brain metastases and increases overall survival (category 1).[22,23] In patients with extensive-stage SCLC that has responded to systemic therapy, PCI decreases brain metastases. However, while a randomized trial conducted by the EORTC found improved overall survival with PCI,[24] preliminary results from a Japanese randomized trial found no improved overall survival in patients who had MRI to confirm absence of brain metastases.[25] In patients not receiving PCI, surveillance for metastases by brain imaging should be considered.
- The preferred dose for PCI to the whole brain is 25 Gy in 10 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.[26,27]
- 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).[27] Concurrent systemic therapy 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.[28,29] 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 uncontrolled extracranial disease.[30,31]
- Recommended dose for WBRT is 30 Gy in 10 daily fractions.

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

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PRINCIPLES OF RADIATION THERAPY
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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

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.

Table of Contents

Overview

Neuroendocrine tumors account for approximately 20% of lung cancers; most (approximately 14%) are small cell lung cancer (SCLC).[1,2] In 2017, an estimated 31,000 new cases of SCLC will occur in the United States.[3] Nearly all cases of SCLC are attributable to cigarette smoking.[4] 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] Management of SCLC and other lung neuroendocrine tumors (LNTs) is described in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for SCLC and for LNTs, which include the algorithms and this supporting Discussion text (see the NCCN Guidelines® for SCLC and *Lung Neuroendocrine Tumors* in the NCCN Guidelines for Neuroendocrine Tumors, available at NCCN.org). The *Summary of the Guidelines Updates* section in the algorithm describes the most recent revisions, which have been incorporated into this revised Discussion (see the NCCN Guidelines for SCLC). For the 2017 update for SCLC, nivolumab and nivolumab with ipilimumab were added as new options for second-line and beyond (ie, subsequent) systemic therapy;[5] new imaging guidelines for response assessment after systemic therapy were also added in addition to other changes as outlined in the summary updates. The NCCN Guidelines for SCLC were originally published 20 years ago and have been subsequently updated at least once every year (see NCCN.org).[6]

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.[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] Note that the definitions for limited-stage and extensive-stage SCLC incorporate TNM staging (see the NCCN Guidelines for SCLC and *Staging* in this Discussion). Surgery is only appropriate for a 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 in patients with SCLC and other high-grade neuroendocrine carcinomas (see the NCCN Guidelines for Smoking Cessation, available at NCCN.org).[12] 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.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for SCLC, an electronic search of the PubMed database was performed to obtain key literature in SCLC—published between April 1, 2015 and May 1, 2016—using the following search term: *small cell lung cancer*. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 1; Clinical Trial, Phase 2; Clinical Trial,

Phase 3; Clinical Trial, Phase 4; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 253 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these NCCN Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available on the NCCN webpage.

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 (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).[15] Although low-dose CT screening can detect early-stage non-small cell lung cancer (NSCLC), it does not seem to be useful for detecting early-stage SCLC.[14-16] Low-dose CT screening is probably not useful 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.[17] 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 carcinoma (LCNEC) (which is also a high-grade neuroendocrine carcinoma) (see *Lung Neuroendocrine Tumors* in the NCCN Guidelines for Neuroendocrine Tumors available at NCCN.org).[18,19]

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC.[20-22] 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.[23,24] 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.[25]

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.[26,27] In patients with SCLC, SIADH occurs more

frequently than Cushing syndrome. Cancer treatment and/or supportive care may also cause hyponatremia (eg, cisplatin, opiates).[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 SCLC).[28-30] ADH levels and hyponatremia usually improve after successful treatment for SCLC.

Pathology

SCLC is a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.[18,31] 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.[18] 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.[32,33] Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases.

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor–1 (TTF-1).[18] Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin.[18] 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.[34]

Staging

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).[7,35] Historically, contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy were 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.[7,35,36] Approximately 66% of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. The AJCC is currently revising the TNM staging system for SCLC; new staging guidelines will be published in late 2016.[37] The SCLC panel will continue to use the combined VA/TNM system for staging SCLC after publication of the 8th edition of the AJCC Cancer Staging Manual.

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 in the NCCN Guidelines for SCLC).[38-41] This TNM staging system is applicable to both NSCLC and SCLC based on studies that showed the prognostic significance of the various stage designations in both diseases.[38,40] In the combined approach for staging SCLC, *limited-stage* SCLC is defined as stage I to III (T any, N any, M0) that can be safely treated

with definitive radiation therapy, excluding 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 (see Table 1 in the NCCN Guidelines for SCLC). *Extensive-stage* SCLC is defined as stage IV (T any, N any, M1a/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.

The VA Lung Study Group's 2-stage classification scheme is also used to define the extent of disease in patients with SCLC: 1) limited-stage disease is disease confined to the ipsilateral hemithorax, which can be safely encompassed within a radiation field; and 2) extensive-stage disease is disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.[42] 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.[35] 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 therapy 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).[36] However, once a patient has been found to have extensive-stage disease, further staging is optional, except for brain imaging.[7] Unilateral bone marrow aspirates and biopsies may be indicated in select patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia suggestive of bone marrow infiltration and with 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.[7,35] A bone scan can be performed if PET/CT is equivocal or not available.

PET scans can increase staging accuracy in patients with SCLC, because SCLC is a highly metabolic disease.[43-45] PET/CT is superior to PET alone.[45] 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.[36] 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, available at NCCN.org).[46] 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.[36,44,47] 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.[7] However, mediastinal staging is not required if the patient is not a candidate for surgical resection 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).[48,49]

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. The effusion should be excluded as a staging element if: 1) multiple cytopathologic examinations of the pleural fluid are negative for cancer; 2) the fluid is not bloody and not an exudate; and 3) clinical judgment suggests that the effusion is not directly related to the cancer. Pericardial effusions are classified using the same criteria.

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.[50,51]

Treatment

Systemic Therapy

For all patients with SCLC, chemotherapy is an essential component of appropriate treatment. Adjuvant chemotherapy is recommended for those who have undergone surgical resection. For patients with limited-stage SCLC in excess of T1-2, N0 and good PS (0–2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1).[9,52,53] 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 Systemic Therapy* in the NCCN Guidelines for SCLC). In patients with extensive-stage 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 SCLC).[10,54]

For the 2017 update, the NCCN Panel added new recommendations for response assessment during and after therapy in patients with limited-stage or extensive-stage SCLC. After adjuvant chemotherapy alone or chemotherapy with concurrent RT for patients with limited-stage disease, response assessment using CT with contrast of the chest, liver, and adrenal gland should occur only after completion of initial therapy; repeating scans during therapy is not recommended. For

systemic therapy alone or sequential systemic therapy followed by RT in patients with limited-stage disease, response assessment using CT with contrast of the chest, liver, and adrenal gland should occur after every 2 cycles of systemic therapy and again at completion of therapy. During systemic therapy for patients with extensive-stage disease, response assessment using CT with contrast of the chest, liver, and adrenal gland should occur after every 2 to 3 cycles of chemotherapy and again at completion of therapy. Scanning for brain metastases is also recommended in patients with extensive-stage disease who have asymptomatic brain metastases and are receiving systemic therapy before whole-brain RT; brain MRI (preferred) or brain CT with contrast should occur after every 2 cycles of chemotherapy and again at completion of therapy.

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC. Etoposide and cisplatin (EP) is the most commonly used initial combination chemotherapy regimen (see *Principles of Systemic Therapy* in the NCCN Guidelines for SCLC).[55] This combination replaced alkylator/anthracycline-based regimens based on its superiority in both efficacy and toxicity in the limited-stage setting.[56] EP plus concurrent thoracic radiotherapy is the recommended therapy for patients with limited-stage disease in excess of T1-2, N0 (category 1).[52,53,57,58]

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 (category 1 for not using GM-CSF) in patients undergoing concurrent chemoradiation.[60] In clinical practice, carboplatin is frequently substituted for cisplatin to reduce the risk of emesis, neuropathy, and nephropathy.[61] However, the use of carboplatin carries a greater risk of myelosuppression.[62] Small randomized trials have suggested similar efficacy of cisplatin and carboplatin in patients with SCLC as did a retrospective analysis in patients with extensive-stage disease.[61,63,64] A meta-analysis of individual patient data from 4 randomized studies compared cisplatin-based versus carboplatin-based regimens in patients with SCLC.[65] 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 initially appeared to be better than EP. A small phase 3 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).[66] In addition, the 2-year survival was 19.5% in the irinotecan plus cisplatin group versus 5.2% in the EP group.[66] However, 2 subsequent large phase 3 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.[67,68]

A phase 3 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 is an option in the NCCN Guidelines for patients with extensive-stage disease. A 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 data from individual patients. 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 either limited-stage or extensive-stage 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. 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.[52,53] 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 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-stage 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 2 trials but did not improve survival and was associated with unacceptable toxicity in a subsequent phase 3 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 carries a greater risk of cumulative toxicity.[78] A meta-analysis reported that maintenance chemotherapy did not prolong overall survival.[79]

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.[80] However, randomized trials have failed to show improved PFS or overall survival with this approach.[81,82]

Multidrug cyclic weekly therapy was designed to increase dose intensity. Early phase 2 results of this approach were promising, although favorable patient selection was of some concern.[83,84] Nevertheless, no survival benefits were documented in randomized trials, and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.[85-88] The role of higher-dose therapy for patients with SCLC remains controversial. Higher complete and partial response rates, and modestly longer median survival times, have been observed in patients receiving high doses when compared with those given conventional doses of the same agents.[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 rate or survival.[90-93] In addition, a meta-analysis of trials that compared standard versus dose-intense variations of the cyclophosphamide, doxorubicin, and vincristine (CAV) 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 (eg, granulocyte-macrophage colony-stimulating factor [GM-CSF], 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] maintenance of dose intensity with growth factors does not prolong disease-free or overall survival.[96,97] Thus, the routine use of growth factors at the initiation of systemic therapy is not recommended.

The benefits of antiangiogenic therapy are being evaluated in SCLC. In patients with limited-stage SCLC, a phase 2 study of irinotecan, carboplatin, and bevacizumab with concurrent radiotherapy followed by maintenance bevacizumab was terminated early because of an unacceptable incidence of tracheoesophageal fistulae. In extensive-stage SCLC, phase 2 trials of platinum-based chemotherapy plus bevacizumab have yielded promising response and survival data.[98-101] However, at least one randomized trial has demonstrated no survival benefit for the addition of bevacizumab to standard chemotherapy.[102] Other randomized phase 3 trials are ongoing in patients with extensive-stage SCLC.[103] Currently, the NCCN Panel does not recommend use of bevacizumab in patients with SCLC.

Although immune checkpoint inhibitors have demonstrated activity in a variety of cancers, including SCLC, a recent phase 3 randomized trial reported that the addition of ipilimumab to etoposide with either cisplatin or carboplatin did not improve either overall survival or PFS in patients with extensive-stage SCLC.[104] 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.[105] Although advanced chronologic age adversely affects tolerance to treatment, the functional status of an individual patient is much more useful than age in guiding clinical decision making (see the NCCN Guidelines for Senior Adult Oncology, available at 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).[106,107] 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).[108,109] A recent retrospective analysis in 8637 elderly patients with limited-stage disease reported that chemoradiation increased survival when compared with chemotherapy alone.[106] Several other strategies have been evaluated in elderly patients with SCLC.[64,110-112] 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.[112] However, targeting carboplatin to an AUC of 5, rather than 6, is more reasonable in this population.[113] 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.[114]

Second-Line and Beyond (Subsequent) Systemic Therapy

Although SCLC is very responsive to initial treatment, most patients relapse with relatively resistant disease.[115,116] These patients have a median survival of only 4 to 5 months when treated with further systemic therapy. Subsequent systemic therapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse.[117] 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%. If patients relapse more than 6 months after first-line treatment, then treatment with their original regimen is recommended.[7,117,118] Response assessment should occur after every 2 to 3 cycles of subsequent systemic therapy using CT with contrast of the chest/liver/adrenal gland. Dose reduction or growth factor support should be considered for patients with PS 2 who are receiving subsequent systemic therapy.

Based on phase 2 trials, recommended subsequent systemic therapy agents for patients who have relapsed 6 months or less after primary therapy include topotecan, irinotecan, paclitaxel, docetaxel, temozolomide, nivolumab with or without ipilimumab, vinorelbine, oral etoposide, gemcitabine, CAV, and bendamustine (category 2A for all agents except for bendamustine, which is a category 2B recommendation) (see *Principles of Systemic Therapy* in the NCCN Guidelines for SCLC).[119-122] These agents are listed in order of preference in the NCCN Guidelines. Ifosfamide was deleted for the 2017 update, because panel members no longer use this agent.

For the 2017 update, the NCCN Panel added recommendations for nivolumab and nivolumab plus ipilimumab (both are category 2A) as options for subsequent therapy for patients who have relapsed 6 months or less after primary therapy. Nivolumab and ipilimumab are novel immunotherapeutic agents that stimulate the immune system and thus have different mechanisms of action when compared with standard cytotoxic chemotherapy.[123] These recommendations are based on a recent phase 1/2 trial in which patients received either nivolumab alone or various doses of nivolumab with ipilimumab for relapsed SCLC.[5] Response rates were 10% (10/98) for nivolumab 3 mg/kg, 23% (14/61) for nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and 19% (10/54) for nivolumab 3 mg/kg plus ipilimumab 1 mg/kg. The responses did not correlate with PD-L1 expression; studies indicate the SCLC has a lower rate of PD-L1 expression than NSCLC.[5] Diarrhea was the most common grade 3 or 4 treatment-related adverse event. The overall frequency of grade 3 or 4 adverse events was about 20%, and fewer than 10% of patients discontinued treatment because of treatment-related adverse events.

Preliminary data suggest that temozolomide may be useful for patients with SCLC, especially those with brain metastases and methylated O^6-methylguanine-DNA methyltransferase (MGMT).[120,124] A recent phase 3 trial (JCOG0605) from Japan in patients with sensitive relapsed SCLC reported that the combination of cisplatin, etoposide, and irinotecan improved survival (median, 18.2 months; 95% CI, 15.7–20.6) when compared with topotecan (12.5 months, 10.8–14.9; hazard ratio [HR], 0.67; 90% CI, 0.51–0.88; *P* = .0079). However, the toxicity of this

approach was significant, and it is not recommended as standard second-line therapy.[125]

A randomized phase 3 trial compared single-agent intravenous topotecan with the combination regimen CAV.[126] Both arms had similar response rates and survival, but intravenous topotecan caused less toxicity. In another phase 3 trial, oral topotecan improved overall survival when compared with best supportive care (26 vs. 14 weeks).[127] Single-agent topotecan is approved by the FDA as subsequent therapy for patients with SCLC who relapse after initial response to chemotherapy. Either oral or intravenous topotecan may be used, because efficacy and toxicity seem to be similar with either route.[127,128]

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.[129] Published studies have yielded conflicting data regarding the usefulness of weekly topotecan in patients with relapsed SCLC, and this approach remains under investigation.[130,131] Amrubicin is an active drug in patients with relapsed or refractory SCLC.[132-135] However, grade 3–4 toxicity, primarily neutropenia, is common.[136,137] A phase 3 trial reported that amrubicin did not improve overall survival as second-line treatment for SCLC when compared to topotecan, except in a subset of patients with refractory disease.[138]

The optimal duration of subsequent systemic therapy 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 systemic therapy should be continued until 2 cycles beyond best response, progression of disease, or development of unacceptable toxicity. Additional subsequent systemic therapy (eg, third line) can be considered if patients are still PS 0-2.

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 SCLC). The American College of Radiology (ACR) Appropriateness Criteria® are a useful resource.[139] The *Principles of Radiation Therapy* in the NSCLC algorithm may also be useful (eg, general principles of radiotherapy, palliative radiotherapy) (see the NCCN Guidelines for NSCLC, available at NCCN.org). This section describes the studies supporting the NCCN recommendations for SCLC. A few reports have suggested that stereotactic ablative radiotherapy (SBRT) might be useful for select patients with limited-stage SCLC; however, there are insufficient data to make a recommendation.[140,141]

Thoracic Radiotherapy

The addition of thoracic radiotherapy has improved survival for patients with limited-stage disease. 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.[52,53] However, achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge.

Timing of Radiation with Chemotherapy

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 3 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 3 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.[142] Several systematic reviews and meta-analyses on the timing of thoracic radiotherapy in limited-stage SCLC have reported that early concurrent radiotherapy results in a small, but significant improvement in overall survival when compared with late concurrent or sequential radiotherapy.[143,144] Another meta-analysis in patients with limited-stage SCLC showed that survival was improved with more rapid completion of the chemo/RT regimen (start of any chemotherapy until the end of radiotherapy [SER]).[145] A recent meta-analysis of individual patient data from 12 trials (2,668 patients) reported that early concurrent chemo/RT increased 5-year overall survival (HR, 0.79; 95% CI, 0.69–0.91), although severe acute esophagitis was also increased, when compared with late concurrent therapy.[146]

Radiation Fractionation

The ECOG/Radiation Therapy Oncology Group compared once-daily to twice-daily radiotherapy with EP.[147] 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 to 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.[147] 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.[148] Another concern regarding hyperfractionation is that twice-daily thoracic radiation is technically challenging for patients with bilateral mediastinal adenopathy.

Another randomized phase 3 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.[149] 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.

Radiation for Limited-Stage SCLC

For limited-stage disease in excess of T1-2, N0, 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.[147] 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

SCLC).[150-152] The minimum standard for thoracic irradiation is CT-planned 3-D conformal radiotherapy. More advanced technologies may also be used when needed (eg, 4D-CT) (see *Principles of Radiation Therapy* in the NCCN Guidelines for SCLC). 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).[153,154] However, the pre-chemotherapy PET/CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.[152,155]

The normal tissue constraints used for NSCLC are appropriate for SCLC when using similar radiotherapy doses (see the NCCN Guidelines for NSCLC, available at NCCN.org). 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 SCLC).[156-158] Intensity-modulated radiation therapy (IMRT) may be considered in select patients (see *Principles of Radiation Therapy* in the NCCN Guidelines for SCLC and the NCCN Guidelines for NSCLC).[159-163]

Thoracic Radiation for Extensive-Stage SCLC

Based on the results of a randomized trial by Jeremic et al,[164] the addition of sequential thoracic radiotherapy may be considered in select patients with low-bulk metastatic extensive-stage 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.[164] The investigators found that the addition of radiotherapy resulted in improved median overall survival (17 vs. 11 months). In patients with extensive-stage SCLC who responded to chemotherapy, a phase 3 trial by Slotman et al (Dutch CREST trial) reported that the addition of sequential thoracic radiotherapy did not improve the primary endpoint of 1-year overall survival (33% vs. 28%, $P = .066$), but a secondary analysis did find improvement in 2-year overall survival (13% vs. 3%, $P = .004$) when compared with patients who did not receive sequential thoracic radiotherapy.[165]

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.[166] A meta-analysis of all randomized PCI trials (using data from individual patients) 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.[167] 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.[167] Although the number of patients with extensive-stage disease was small in this meta-analysis, the observed benefit was similar in patients with both limited- and extensive-stage disease.

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.[168] 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.[169] Preliminary data from a Japanese phase 3 trial suggest that PCI did not

improve survival in patients with extensive-stage disease who had MRI to confirm that they did not have brain metastases.[170]

Late neurologic sequelae have been attributed to PCI, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrently with chemotherapy.[171,172] Thus, PCI is not recommended for patients with poor PS (3–4) or impaired neurocognitive function.[173,174] Older age (>60 years) has also been associated with chronic neurotoxicity.[175] When given after the completion of chemotherapy and at a low dose per fraction, PCI may cause less neurologic toxicity.

Before the decision is made to administer PCI, a balanced discussion between the patient and physician is necessary.[176] PCI is a category 1 recommendation for patients with limited-stage disease who attain a complete or partial response; PCI is a category 2A recommendation for patients with extensive-stage disease.[169,173] PCI is also recommended for all patients who have had a complete resection (see *Principles of Surgical Resection* in the NCCN Guidelines for SCLC). The preferred dose for PCI to the whole brain is 25 Gy in 10 daily fractions (2.5 Gy/fraction), (see *Principles of Radiation Therapy* in the NCCN Guidelines for SCLC).[167,169,177] The NCCN Panel feels that a shorter course of PCI may be appropriate (eg, 20 Gy in 5 fractions) for selected patients with extensive-stage disease.[169] Higher doses (eg, 36 Gy) increased mortality and toxicity when compared with standard doses (25 Gy).[175,177] PCI should not be given concurrently with systemic therapy, and high total radiotherapy dose (>30 Gy) should be avoided because of the increased risk of neurotoxicity.[175] Fatigue, headache, and nausea/vomiting are the most common acute toxic effects after PCI.[174,177] After the acute toxicities of initial therapy have resolved, PCI can be administered. For patients not receiving PCI, surveillance for metastases with brain imaging should be considered.

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 SCLC and the NCCN Guidelines for NSCLC, available at NCCN.org).[178-180] 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 SCLC and the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).[181] Although late complications, such as neurocognitive impairment, may occur with whole-brain radiotherapy this is less of an issue in patients with SCLC because long-term survival is rare.[171] The recommended dose for whole-brain radiotherapy is 30 Gy in 10 daily fractions.[181] In patients who develop brain metastases after PCI, stereotactic radiosurgery may be considered.[182]

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 mediastinal staging has confirmed that mediastinal lymph nodes are not involved.[183] Data show that patients with clinically staged disease in excess of T1–2,N0 do not benefit from surgery.[184] Note that only 5% of patients with SCLC have true stage I SCLC.[39]

The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[184] 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.[183,185-189] 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.

Analyses of the SEER database also suggest that surgery may be appropriate for some patients with localized disease.[11,190] 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 to concurrent chemoradiotherapy in patients who are rigorously staged.

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.[191] 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.[173,187,192,193] 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 SCLC). 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 SCLC).[167] For the 2017 update, the NCCN Panel added new recommendations for response assessment after adjuvant therapy. Response assessment using CT with contrast of the chest, liver, and adrenal gland should occur only after completion of initial therapy for patients with limited-stage disease; repeating scans during therapy is not recommended.

Surveillance

The schedule for follow-up examinations is shown in the algorithm (see *Surveillance* in the NCCN Guidelines for SCLC); the frequency of surveillance decreases during subsequent years because of the declining risk of recurrence.[194] 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.[195,196] Smoking cessation should be encouraged for all patients with SCLC, because second primary tumors occur less

commonly in patients who quit smoking (see the NCCN Guidelines for Smoking Cessation, available at NCCN.org).[197-199] Former smokers should be encouraged to remain abstinent.

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