National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Small Cell Lung Cancer

Version 1.2011

NCCN.org

Continue

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 1.2011 Panel Members
Small Cell Lung Cancer

NCCN Guidelines Index
SCLC Table of Contents
Staging, Discussion, References

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

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

Paul Bogner, MD ≠
Roswell Park Cancer Institute

Hossein Borghaei, DO, MS † ‡
Fox Chase Cancer Center

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

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

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

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

Apar Kishor P. Ganti, MD †
UNMC Eppley Cancer Center at the Nebraska Medical Center

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

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

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

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

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

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

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

Harvey B. Niell, MD † Þ ‡
University of Tennessee Cancer Institute

Janis O'Malley, MD ф
University of Alabama at Birmingham Comprehensive Cancer Center

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

Neal Ready, MD, PhD †
Duke Comprehensive Cancer Center

Charles M. Rudin, MD, PhD † Þ
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Charles C. Williams, Jr., MD †
H. Lee Moffitt Cancer Center and Research Institute

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

NCCN Guidelines Panel Disclosures

Continue

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

National Comprehensive Cancer Network®

NCCN Guidelines™ Version 1.2011 Table of Contents
Small Cell Lung Cancer

NCCN Small Cell Lung Cancer Panel Members
Summary of the Guidelines Updates
Small Cell Lung Cancer:
- Initial Evaluation and Staging (SCL-1)
- Limited Stage, Workup and Treatment (SCL-2)
- Extensive Stage, Workup and Treatment (SCL-4)
- Response Assessment after Initial Therapy (SCL-5)
- Surveillance (SCL-5)
- Subsequent Therapy and Palliative Therapy (SCL-6)
- Principles of Surgical Resection (SCL-A)
- Principles of Chemotherapy (SCL-B)
- Principles of Radiation Therapy (SCL-C)
- Principles of Supportive Care (SCL-D)

Lung Neuroendocrine Tumors:
- Workup and Primary Treatment (LNT-1)
  - High-grade neuroendocrine carcinoma (large cell neuroendocarcinoma)
  - Intermediate-grade neuroendocrine carcinoma (atypical carcinoid)
  - Low-grade neuroendocrine carcinoma (typical carcinoid)
  - Combined SCLC and NSCLC

For help using these documents, please click here

Staging
Discussion
References

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

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

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

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

See NCCN Categories of Evidence and Consensus

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 1.2011 Updates
Small Cell Lung Cancer

NCCN Guidelines Index
SCLC Table of Contents
Staging, Discussion, References

Updates in Version 1.2011 of the NCCN Small Cell Lung Cancer Guidelines from Version 1.2010 include:

SCL-1

- Chest/liver/adrenal CT was clarified by adding "with IV contrast whenever possible."
- TNM stage groupings added to limited stage and extensive stage.

SCL-2

- "Mediastinoscopy or surgical or endoscopic mediastinal staging" changed to "Pathologic mediastinal staging" with a footnote "Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy." (also applies to SCL-3)

SCL-5

- Chest/liver/adrenal CT was clarified by adding "with IV contrast whenever possible."
- Qualifier "after 2 y follow-up" removed from "New pulmonary nodule."

SCL-6

- "Continue until maximal benefit or refractory to therapy or development of unacceptable toxicity" changed to "Continue until *two cycles beyond best response or progression of disease* or development of unacceptable toxicity."

SCL-B 1 of 2

- The recommended cycles were changed from 4 cycles to a "maximum of 4-6 cycles."
- The chemotherapy regimen of cyclophosphamide/doxorubicin/vincristine (CAV) was removed as an option in primary therapy for extensive disease.
- Topotecan was clarified as PO or IV.

SCL-C 1 of 2

- Radiotherapy for limited disease:

  Bullet 1 - the following sentence was added: "If bid fractionation is utilized, there should be at least a 6 hour inter-fraction interval to allow for repair of normal tissue."

  Bullet 3 - Radiation target volumes should be defined on the CT scan obtained at the time of radiotherapy planning, *following ICRU definitions (Reports 50 and 62). Radiation doses should be calculated with inhomogeneity corrections*.

  Bullet 4 - Three-dimensional conformal radiation techniques *or IMRT* are preferred *(category 1). If IMRT is utilized, four- dimensional imaging should also be performed to assure tumor movement of less than 1 cm is achievable.*
- New information was added for Normal Tissue Constraints and Prophylactic Cranial Radiotherapy.

SCL-C 2 of 2

- References 6, and 8-11 are new to the page.

LNT-1

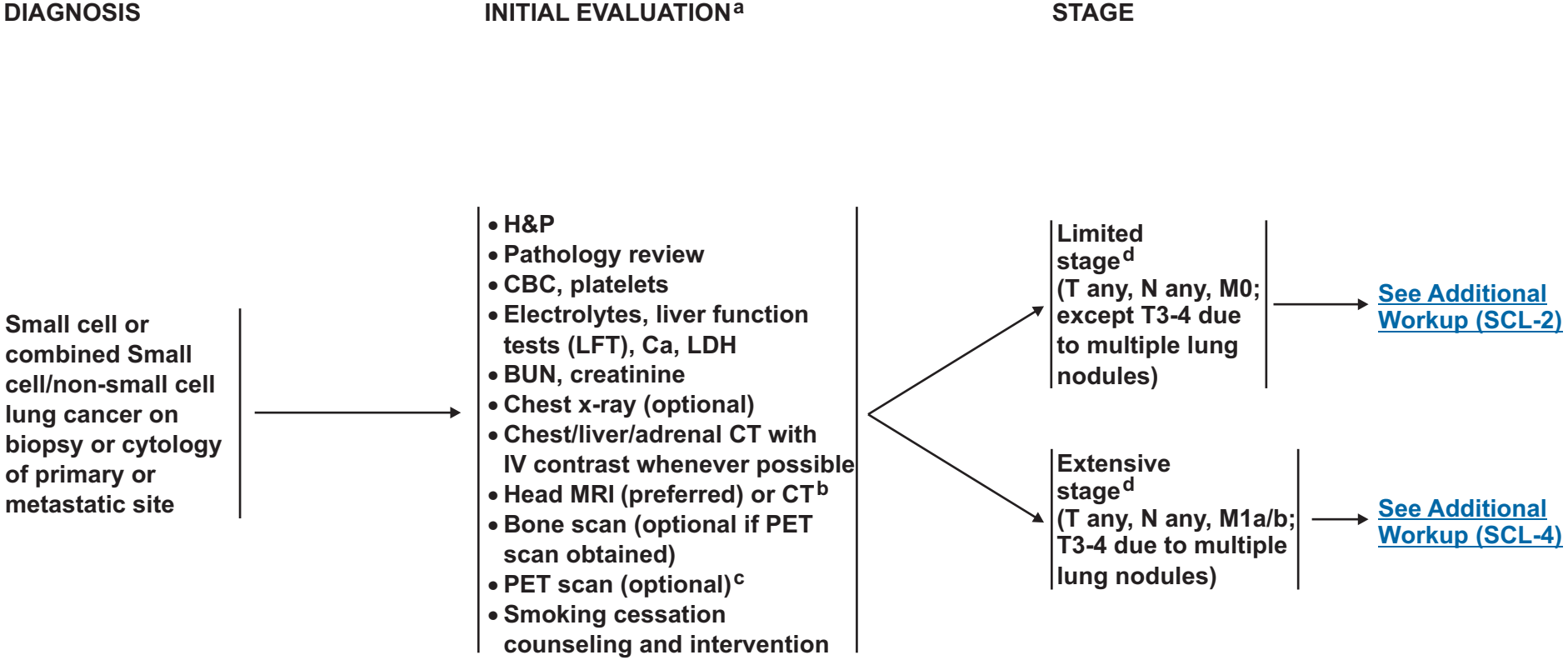
- A new footnote, "Wedge resection for peripheral low-grade neuroendocrine carcinoma (category 2B)" was added to "Lobectomy or other anatomic resection."

ST-1

- Staging tables updated to reflect the 7th Edition of the AJCC Staging Manual.

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

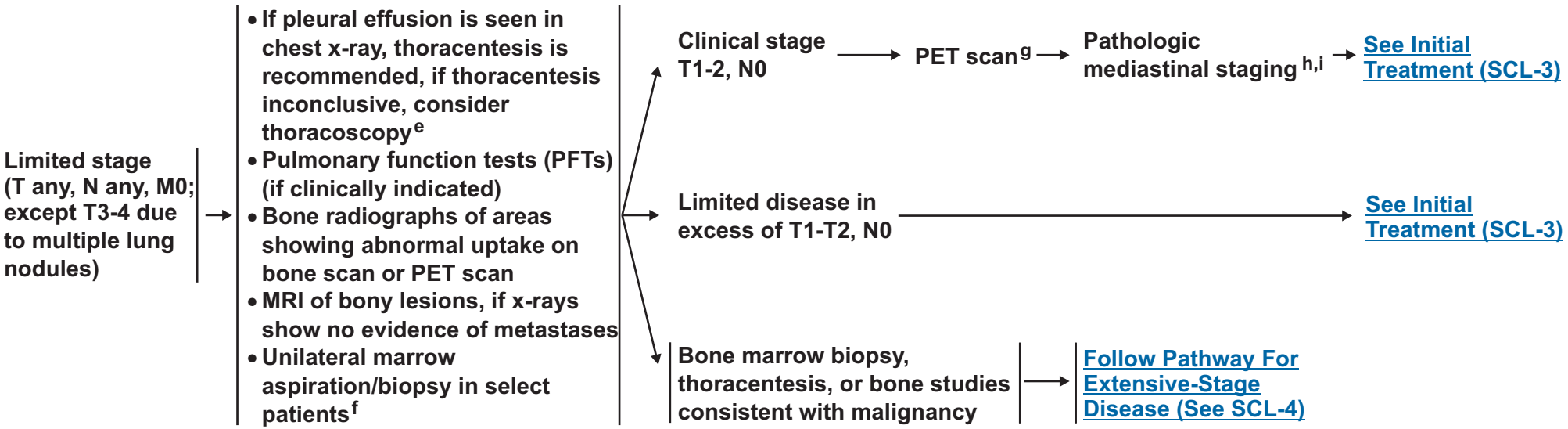


[a] If extensive stage is established, further testing for staging is optional.
[b] Head MRI is more sensitive than CT for identifying brain metastases and is preferred over CT.
[c] PET scan can be used as part of the initial evaluation, in addition to the other recommended studies.
[d] See Staging on page ST-1.

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



[e] Most pleural effusions in patients with lung cancer are due to cancer; however, if the effusion is too small to allow image-guided sampling, then the effusion should not be considered in staging. If 3 cytological examinations of pleural fluid are negative for cancer, fluid is not bloody and not an exudate and clinical judgment suggests that the effusion is not directly related to the cancer, then the effusion should not be considered evidence of extensive stage disease.

[f] Selection criteria include: nucleated RBCs on peripheral blood smear, neutropenia, or thrombocytopenia.

[g] PET scan to identify distant disease and to guide mediastinal evaluation, if not previously done.

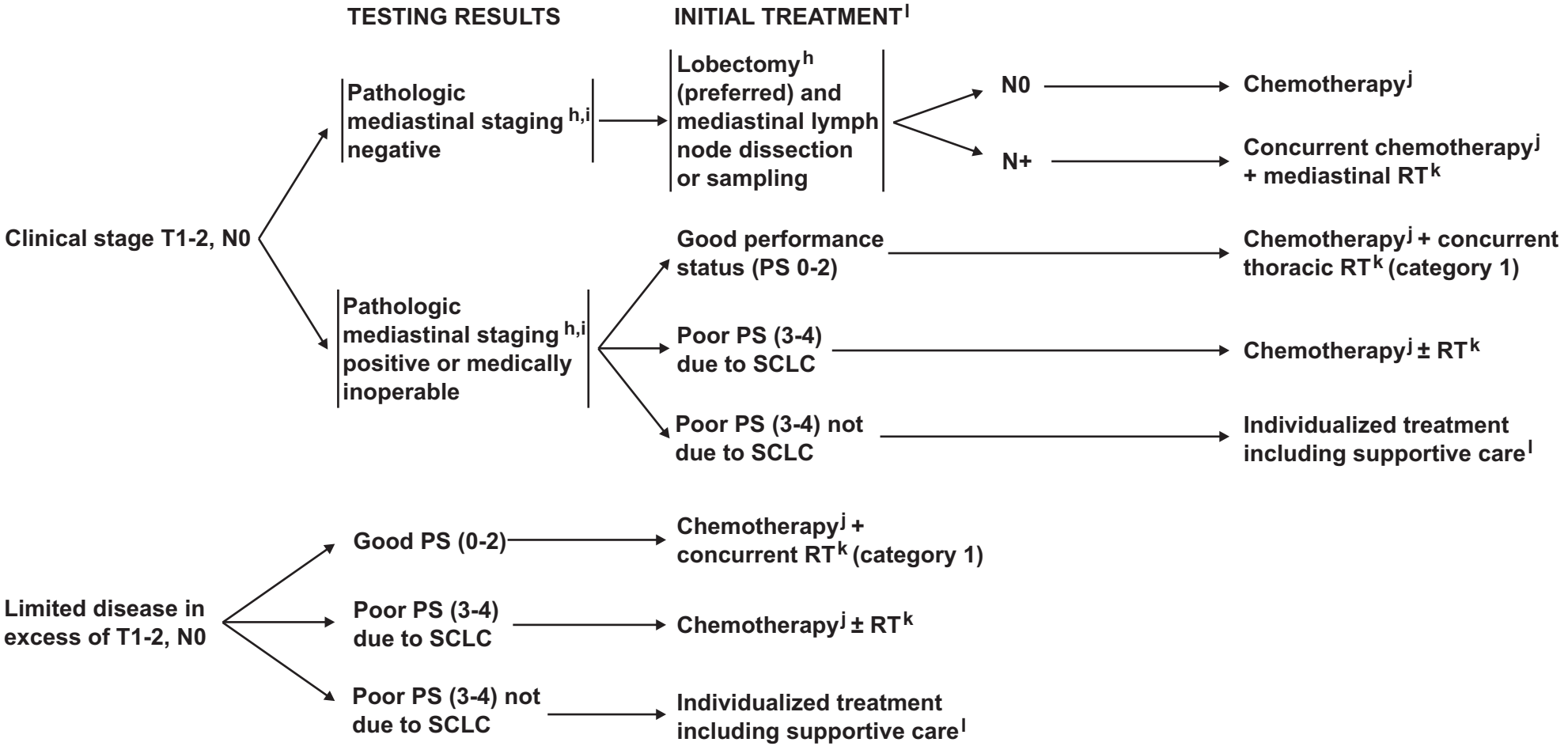
[h] See Principles of Surgical Resection (SCL-A).

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

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



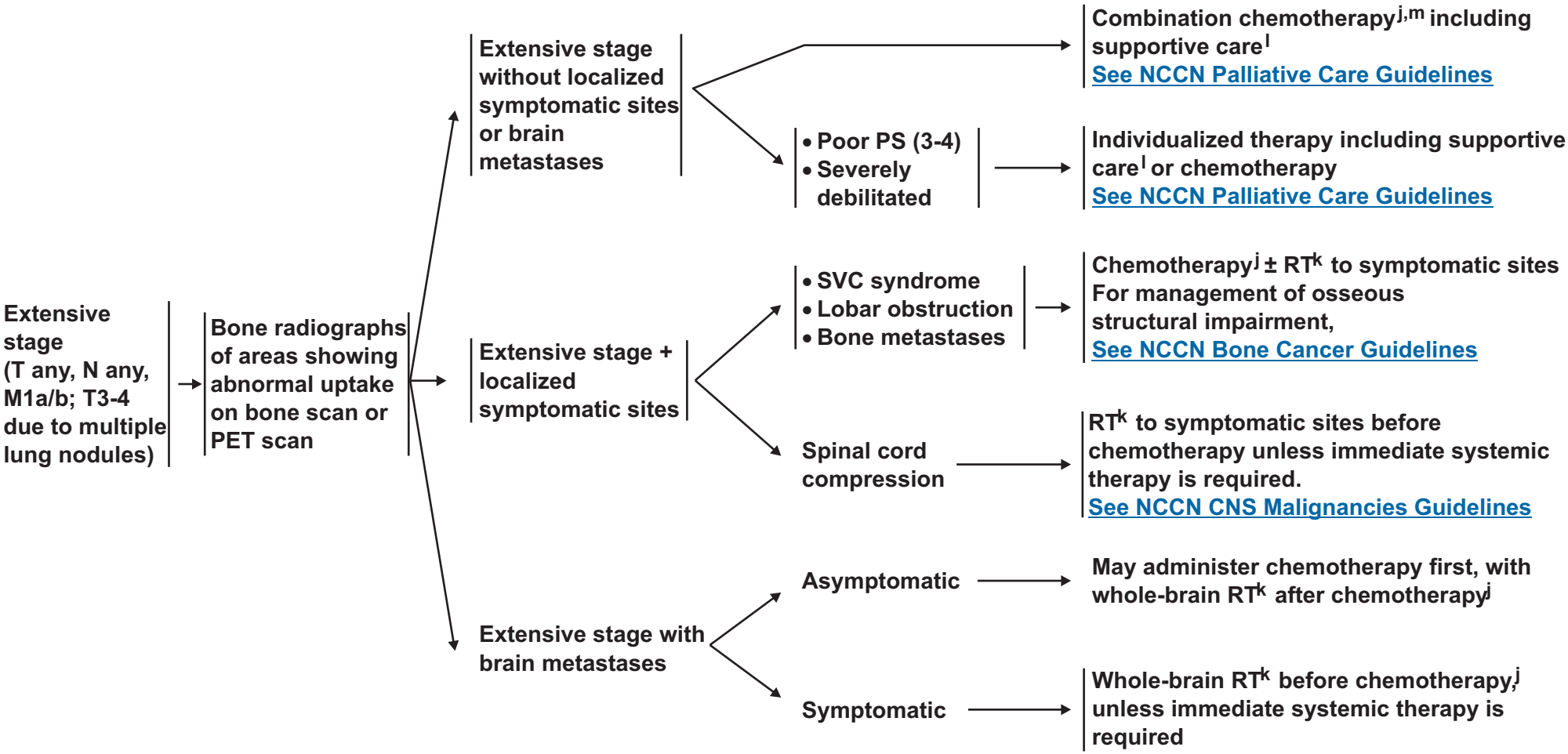
[h] See Principles of Surgical Resection (SCL-A).
[i] Mediastinal staging procedures include mediastinoscopy, mediastinotomy, endobronchial or esophageal ultrasound-guided biopsy, and video-assisted thoracoscopy. If endoscopic lymph node biopsy is positive, additional mediastinal staging is not required.
[j] See Principles of Chemotherapy (SCL-B).
[k] See Principles of Radiation Therapy (SCL-C).
[l] See Principles of Supportive Care (SCL-D).

See Response Assessment + Adjuvant Treatment (SCL-5)

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



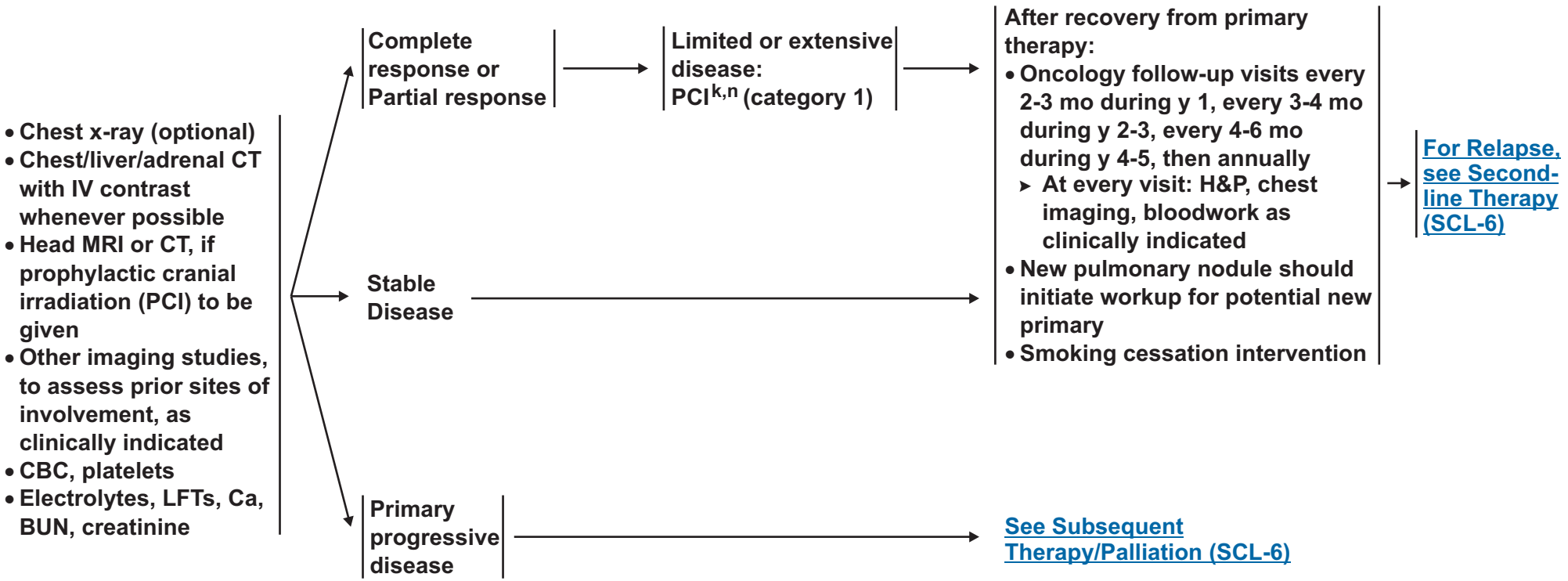
[j] See Principles of Chemotherapy (SCL-B).
[k] See Principles of Radiation Therapy (SCL-C).
[l] See Principles of Supportive Care (SCL-D).
[m] Sequential radiotherapy to thorax in selected patients with low-bulk metastatic disease and CR or near CR after systemic therapy.

See Response Assessment + Adjuvant Treatment (SCL-5)

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.



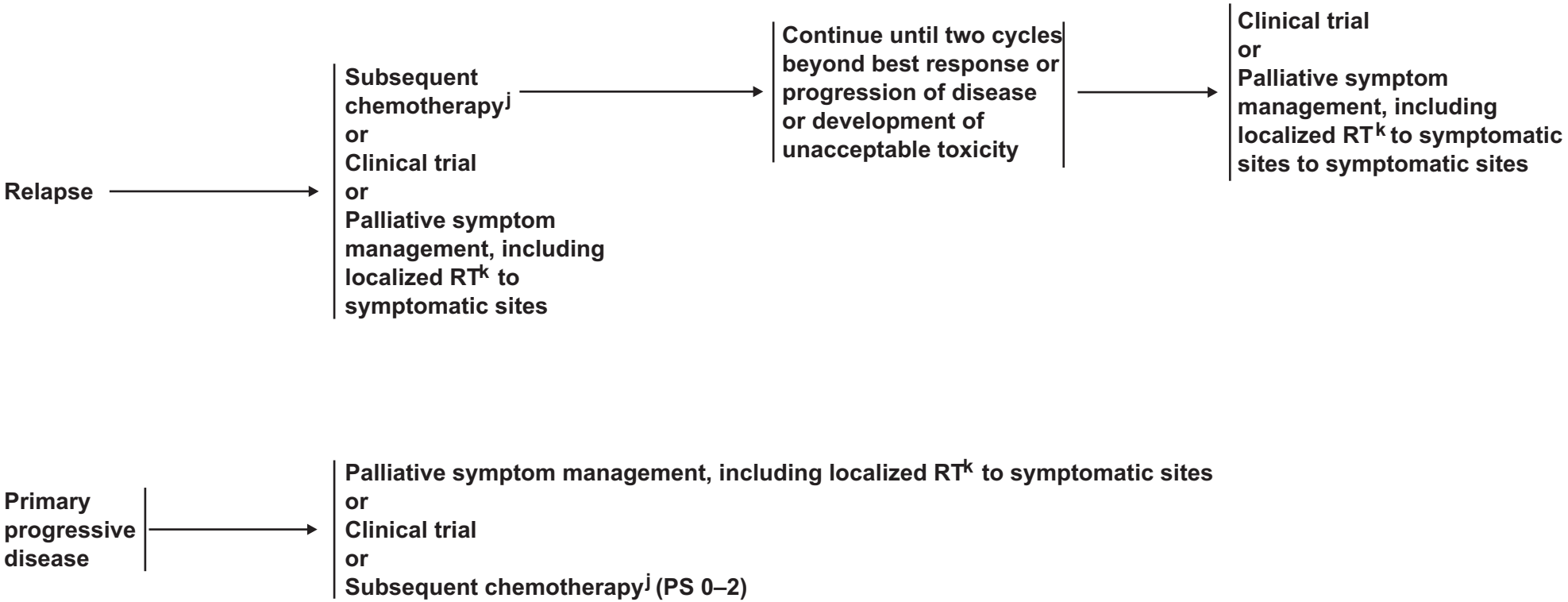
[k] See Principles of Radiation Therapy (SCL-C).
[n] Not recommended in patients with poor performance status or impaired mental function.

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PROGRESSIVE DISEASE **SUBSEQUENT THERAPY/PALLIATION**



[k] See Principles of Radiation Therapy (SCL-C).
[j] See Principles of Chemotherapy (SCL-B).

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF SURGICAL RESECTION

- **Stage I SCLC is diagnosed in less than 5% of patients with SCLC.**
- **Patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery.[1]**
- **Patients with SCLC that is clinical stage I (T1-2, N0) after standard staging evaluation (including CT of the chest and upper abdomen, bone scan, brain imaging, and PET imaging) may be considered for surgical resection.**
  - **Prior to resection, all patients should undergo mediastinoscopy or other surgical mediastinal staging to rule out occult nodal disease. This may also include an endoscopic staging procedure.**
  - **Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy. Patients without nodal metastases should be treated with chemotherapy alone. Patients with nodal metastases should be treated with postoperative concurrent chemotherapy and mediastinal radiation therapy.**
- **Because prophylactic cranial irradiation (PCI) can improve both disease-free and overall survival in patients with SCLC in complete remission, PCI should be considered after adjuvant chemotherapy in patients who have undergone a complete resection.[2]**

[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.

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF CHEMOTHERAPY*

Chemotherapy as primary therapy:

- **Limited stage (maximum of 4-6 cycles):**
  - **Cisplatin 60 mg/m^2 day 1 and etoposide 120 mg/m^2 days 1, 2, 3[1]**
  - **Cisplatin 80 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[2]**
  - **Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[3]**
  - **During chemotherapy + RT, cisplatin/etoposide is recommended (category 1)**

- **Extensive stage (maximum of 4-6 cycles):**
  - **Cisplatin 75 mg/m^2 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[3]**
  - **Cisplatin 80 mg/m^2 day 1 and etoposide 80 mg/m^2 days 1, 2, 3[4]**
  - **Cisplatin 25 mg/m^2 days 1, 2, 3 and etoposide 100 mg/m^2 days 1, 2, 3[5]**
  - **Carboplatin AUC 5-6 day 1 and etoposide 100 mg/m^2 days 1, 2, 3[6]**
  - **Cisplatin 60 mg/m^2 on day 1 and irinotecan 60 mg/m^2 on days 1, 8, 15[7]**
  - **Cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 on days 1, 8 every 21 days[8]**
  - **Carboplatin AUC 5 day 1 and Irinotecan 50 mg/m^2 on days 1, 8, and 15[9]**

Subsequent chemotherapy:

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

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

See References on SCL-B 2 of 2

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

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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]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.

[4]Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-does and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol 1994;12(10):2022-2034.

[5]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.

[6]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.

[7]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.

[8]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.

[9]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.

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF RADIATION THERAPY

Radiotherapy for limited disease:

- **Radiotherapy should be delivered as either 1.5 Gy bid (twice daily) to a total dose of 45 Gy (category 1), or 2 Gy once daily to 60-70 Gy.[1-6] If bid fractionation is utilized, there should be at least a 6 hour inter-fraction interval to allow for repair of normal tissue.**
- **Radiotherapy should start concurrent with chemotherapy, cycle 1 or 2. (Category 1)**
- **Radiation target volumes should be defined on the CT scan obtained at the time of radiotherapy planning, following ICRU definitions (Reports 50 and 62).[7-9] Radiation doses should be calculated with inhomogeneity corrections.**
- **Three-dimensional conformal radiation techniques or IMRT are preferred (category 1). If IMRT is utilized, four-dimensional imaging should also be performed to assure tumor movement of less than 1 cm is achievable.**

Normal Tissue Constraints:[10-11]

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

Prophylactic Cranial Radiotherapy:

- **Parallel opposed fields should be utilized to encompass the whole brain. The field edges should be at least 1 cm from the outer skull margin. The recommended dose is 25 Gy in 10 fractions or 30 Gy in 15 fractions.[12-13]**

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF RADIATION THERAPY
References

[1] Turisi AT 3rd, Kim K, Blum R, et al. Twice daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. N Engl J Med 1999;340(4):265-271.
[2] Schild SE, Bonner JA, Shanahan TG, et al. Long-term results of a phase III trial comparing once-daily radiotherapy with twice-daily radiotherapy in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004;59(4):943-951.
[3] Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys 2003;56(2):355-359.
[4] Roof KS, Fidias P, Lymch TJ, et al. Radiation dose escalation in limited-stage small cell lung cancer. Int J Radiat Oncol Biol Phys 2003;57(3):701-8.
[5] Bogart JA, Herndon JE, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys 2004;59(2):460-468.
[6] Yuen AR, Zou G, Turrisi AT, et al. Similar Outcome of elderly patients in Intergroup Trial 0096: Cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. Cancer 2000;89(9):1953-1960.
[7] Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. J Clin Oncol 1994;12(3):496-502.
[8] The International Commission on Radiation Units and Measurement (ICRU) Report #50: Prescribing, Recording, and Reporting Photon Beam Therapy: Library of Congress Cataloging-in-Publication Data. 1993.
[9] The International Commission on Radiation Units and Measurements Prescribing, Recording and Reporting Photon Beam Therapy: Supplement to ICRU Report 50, Library of Congress Cataloging-in-Publicaiton Data. 1999.
[10] Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-215.
[11] Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother. Oncol 2009;91:dd282-7.
[12] 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.
[13] Slotman B, Faivre-Finn C, Kramer G, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. N Engl J Med 2007;357:664-672.

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

PRINCIPLES OF SUPPORTIVE CARE

- **Smoking cessation counseling**
- **Granulocyte colony-stimulating factor (GCSF) or granulocyte-macrophage colony-stimulating factor (GMCSF) during RT is not recommended (category 1 for GMSCF).**
  See the NCCN Myeloid Growth Factor Guidelines
- **Syndrome of inappropriate antidiuretic hormone**
  - **Fluid restriction**
  - **Saline infusion for symptomatic patients**
  - **Demeclocycline**
  - **Antineoplastic therapy**
- **Cushing's syndrome**
  - **Consider ketoconazole**
  - **Try to control before initiation of antineoplastic therapy**
- **Leptomeningeal disease**
  See NCCN Carcinomatous/Lymphomatous Meningitis Guidelines
- **Pain Management: See NCCN Adult Cancer Pain Guidelines**
- **Nausea/Vomiting: See NCCN Antiemesis Guidelines**
- **Psychosocial distress: See NCCN Distress Management Guidelines**
- **See NCCN Palliative Care Guidelines as indicated**

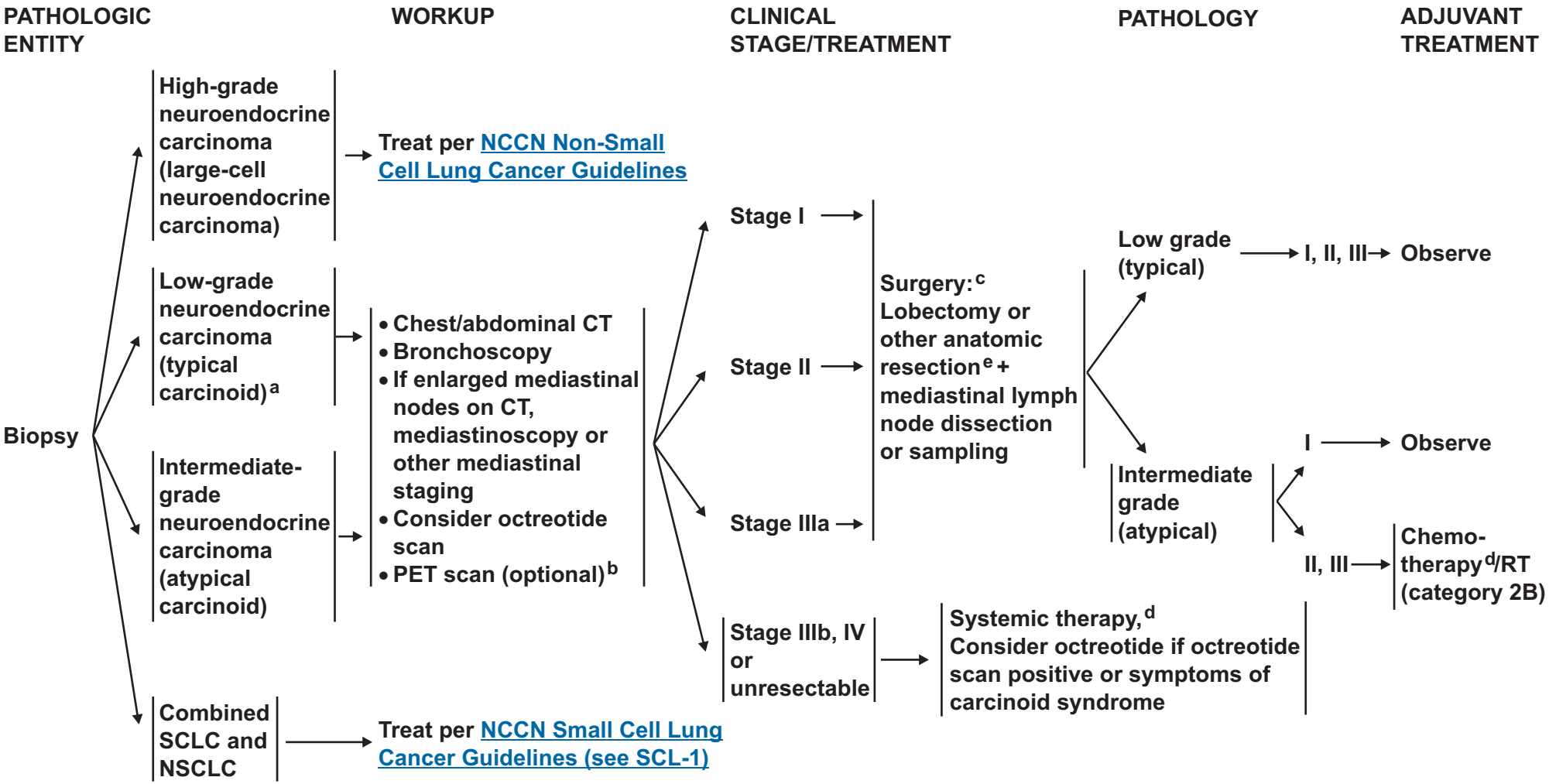
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

NCCN Guidelines™ Version 1.2011
Lung Neuroendocrine Tumors

NCCN Guidelines Index
SCLC Table of Contents
Staging, Discussion, References



[a] Management of endocrine symptoms as indicated (See the Carcinoid Tumors section in the NCCN Neuroendocrine Tumors Guidelines)
[b] PET scan is undergoing evaluation in clinical trials and should only be considered as a supplement and not a replacement to other studies.
[c] For Stage III, typical: RT recommended if surgery is not feasible.
For Stage III, atypical: Chemotherapy/RT is recommended if surgery is not feasible.
[d] There is no substantial evidence for a commonly used regimen. Cisplatin/etoposide is a regimen commonly used at NCCN institutions.
[e] Wedge resection for peripheral low-grade neuroendocrine carcinoma (category 2B).

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

Version 1.2011, 07/25/10 © National Comprehensive Cancer Network, Inc. 2010, All rights reserved. The NCCN Guidelines™ and this illustration may not be reproduced in any form without the express written permission of NCCN®.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Table 1 **- Definition of small cell lung cancer consists of two stages:**
(1) Limited-stage disease: disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field.
(2) Extensive-stage disease: disease beyond ipsilateral hemithorax which may include malignant pleural or pericardial effusion or hematogenous metastases.

Table 2 **- Definitions of TNM**

T Primary Tumor

TX Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy

T0 No evidence of primary tumor

Tis Carcinoma in situ

T1 Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*

- T1a Tumor 2 cm or less in greatest dimension
- T1b Tumor more than 2 cm but 3 cm or less in greatest dimension

T2 Tumor with any of the following features of size or extent:

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

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

T3 Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

N Regional Lymph Nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes including involvement by direct extension

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)

N3 Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

M Distant Metastasis

M0 No distant metastasis

M1 Distant metastasis

- M1a Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion**
- M1b Distant metastasis

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

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

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 and 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.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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

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 and 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.

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/03/09

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Discussion update in progress

Overview

Small cell lung cancer (SCLC) accounts for 16% of all lung cancers. In 2009, approximately 35,110 new cases of SCLC will be diagnosed in the United States.[1] Nearly all cases of SCLC are attributable to cigarette smoking. When compared with non-small cell lung cancer, SCLC generally has a more rapid doubling time, a higher growth fraction, and earlier development of widespread metastases. Most patients with SCLC present with hematogenous metastases, while only about one third of patients present with limited disease confined to the chest. SCLC is highly sensitive to initial chemotherapy and radiotherapy; however, most patients eventually die from recurrent disease.[2,3] In patients with limited-stage SCLC, the goal of treatment with chemotherapy plus thoracic radiotherapy is to achieve a cure. In patients with extensive-stage disease, chemotherapy alone can palliate symptoms and prolong survival in most patients, but long-term survival is rare.[4] Surgery is appropriate for the few patients (2%-5%) with surgically resectable stage I SCLC.

Smoking cessation should be strongly encouraged (1-800-QUIT NOW—the national access number to State-based quitline services) (http://www.smokefree.gov/). Patients who smoke have increased toxicity during treatment and shorter survival.[5] Programs using behavioral counseling combined with Food and Drug Administration (FDA)-approved medications that promote smoking cessation can be very useful (http://www.surgeongeneral.gov/tobacco/index.html).

Pathology

SCLC is a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli.[6] The cells are round, oval, or spindle shaped, and nuclear molding is prominent. The mitotic count is high. Up to 30% of autopsies in patients with SCLC reveal areas of non-small cell carcinoma differentiation, which are less commonly detected in specimens from previously untreated patients. This finding has led to the proposal that pulmonary carcinogenesis occurs in a pluripotent stem cell capable of differentiation along several pathways.

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.[7-9] Both pulmonary and extrapulmonary small cell carcinomas have a similar clinical and biologic behavior, leading to a high potential for widespread metastases. However, unlike SCLC, malignant cells from patients with extrapulmonary small cell carcinoma do not exhibit macromolecular 3p deletions, which suggests a different pathogenesis.[10]

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and thyroid transcription factor 1 (TTF1). Most SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM; CD56), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from non-small cell lung cancer, because approximately 10% of non-small cell lung cancers will be immunoreactive for at least one of these neuroendocrine markers.[11]

Clinical Manifestations, Staging, and Prognostic Factors

SCLC typically presents as a large hilar mass and bulky mediastinal lymphadenopathy that cause cough and dyspnea. Frequently, patients present with symptoms of widespread metastatic disease, such as weight loss, debility, bone pain, and neurologic compromise. Presentation as a solitary peripheral nodule without central adenopathy is uncommon, and, in this situation, fine-needle aspiration may not adequately differentiate small cell carcinoma from low-grade (typical carcinoid), intermediate-grade (atypical carcinoid), or high-grade (large-cell) neuroendocrine carcinoma.

Many neurologic and endocrine paraneoplastic syndromes are associated with SCLC. Neurologic syndromes include Lambert-Eaton myasthenic syndrome, encephalomyelitis, and sensory neuropathy. The Lambert-Eaton syndrome presents with proximal leg weakness and is caused by antibodies directed against the voltage-gated calcium channels.[12] 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.[13,14] SCLC cells also can produce numerous polypeptide hormones, including adrenocorticotropic hormone (ACTH) and vasopressin (ADH), which cause Cushing's syndrome and hyponatremia of malignancy, respectively.[15,16]

The Veteran's Administration Lung Group 2-stage classification scheme is routinely used to define the extent of disease in patients with SCLC as shown in Table 1: (1) *limited-stage disease* is defined as disease confined to the ipsilateral hemithorax, which can be safely encompassed within a tolerable radiation field; and (2) *extensive-stage disease* is defined as disease beyond the ipsilateral hemithorax, including malignant pleural or pericardial effusion or hematogenous metastases.[17] Contralateral mediastinal and ipsilateral supraclavicular lymphadenopathy are generally classified as limited-stage disease, while contralateral hilar and supraclavicular lymphadenopathy usually are classified as extensive-stage disease. Approximately two thirds of patients present with overt hematogenous metastases, which commonly involve the contralateral lung, liver, adrenal glands, brain, bones, and/or bone marrow. Table 2 provides the definitions for TNM that are used for SCLC. A new lung cancer staging system has been proposed by the International Association of the Study of Lung Cancer (IASLC).[18-20] The revised staging will be published by the American Joint Commission for Cancer (AJCC) (7th ed) in November 2009.

All SCLC patients, even those with radiographically limited-stage disease, require systemic chemotherapy. Therefore, staging provides a therapeutic guideline for chest radiotherapy, which is indicated for patients with limited-stage disease. Full staging includes a history and physical examination; computed tomography (CT) scan including the chest, liver, and adrenal glands; a magnetic resonance imaging (MRI) scan (preferred) or CT scan of the head; and a bone scan (optional if PET scan is obtained). A chest radiograph is optional. Unilateral or bilateral bone marrow aspirates and biopsies may be indicated in

Discussion Update in Progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

patients with nucleated red blood cells on peripheral blood smear, neutropenia, or thrombocytopenia and no other evidence of metastatic disease. Bone marrow involvement as the only site of extensive-stage disease occurs in less than 5% of patients. A positron emission tomography (PET) scan is optional but can be used as part of the initial evaluation in addition to the other recommended studies. A PET scan can increase staging accuracy in patients with SCLC; however, it is not adequate for detecting brain metastases.[21]

If a pleural effusion is large enough to be seen by a chest radiograph, then thoracentesis is recommended. If thoracentesis does not show malignant cells, then thoracoscopy can be considered to document pleural involvement, 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) 3 cytopathologic examinations of pleural fluid are negative for cancer; (2) the fluid is not bloody and not an exudate; and (3) clinical judgment suggests that the effusion is not directly related to the cancer.

Staging should not be directed only to sites of symptomatic disease or sites suggested by laboratory tests. Bone scans are positive in up to 30% of patients without bone pain or an abnormal alkaline phosphatase level. A head MRI or CT scan can identify central nervous system (CNS) metastases in 10% to 15% of patients at diagnosis, of which about 30% are asymptomatic. Early treatment of brain metastases results in less chronic neurologic morbidity, arguing for the utility of early diagnosis in asymptomatic patients. Due to the aggressive nature of SCLC, staging should not delay the onset of treatment more than 1 week; otherwise, many patients may become more seriously ill in the interval with a decline in their performance status (PS).

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. In patients with limited-stage disease, good PS (0-2), female gender, age younger than 70 years, normal LDH, and stage I disease are associated with a more favorable prognosis. In patients with extensive-stage disease, normal LDH and a single metastatic site are favorable prognostic factors.[22,23]

Chemotherapy

Chemotherapy is an essential component of appropriate treatment for all patients with SCLC.[4] For those who have undergone successful surgical resection, adjuvant chemotherapy is recommended. For most patients with limited-stage SCLC and good PS (0-2), recommended treatment consists of chemotherapy with concurrent thoracic radiotherapy (category 1).[24,25] For patients with extensive-stage disease, chemotherapy alone is the recommended treatment. In patients with extensive disease and brain metastases, chemotherapy can be given either before or after whole-brain RT depending on whether or not the patient has neurologic symptoms.

Single-agent and combination chemotherapy regimens have been shown to be active in SCLC.[3,26,27] The most commonly used initial combination chemotherapy regimen is etoposide and cisplatin (EP).[4,28,29] This combination supplanted alkylator/anthracycline-based regimens based on superiority in both efficacy and toxicity in the limited-stage setting.[30] Etoposide and cisplatin plus concurrent thoracic radiotherapy is now the recommended therapy for patients with limited-stage disease (category 1).[24,25,31] In combination with thoracic radiotherapy, EP causes an increased risk of esophagitis and pulmonary toxicity. The hematologic toxicity is manageable with dose

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

reductions or growth factor support (see the NCCN Myeloid Growth Factors in Cancer Treatment Guidelines). In clinical practice, carboplatin is frequently substituted for cisplatin in order to reduce the risk of emesis, neuropathy, and nephropathy. However, the use of carboplatin carries a greater risk of myelosuppression.[32] The substitution of carboplatin for cisplatin in patients with limited-stage disease has not been adequately evaluated and should only be done when cisplatin is contraindicated or poorly tolerated.[33,34] The substitution of carboplatin for cisplatin is more acceptable in patients with extensive-stage disease, because there is ample data regarding the therapeutic equivalence of the drugs in this setting.[33,35]

Many other combinations have been evaluated in patients with extensive-stage disease with little consistent evidence of benefit when compared with EP. Combinations of a platinum with irinotecan have raised significant interest. Initially, a small phase III trial performed in Japan reported that patients with extensive-stage SCLC who were treated with irinotecan plus cisplatin achieved a median survival of 12.8 months compared to 9.4 months for patients treated with EP (*P*=.002).[36] In addition, 2-year survival was 19.5% in the irinotecan plus cisplatin group and 5.2% in the EP group.[36] However, 2 subsequent large phase III trials performed in the United States comparing irinotecan plus cisplatin to EP failed to demonstrate a significant difference in response rate or overall survival between the regimens.[37,38]

A randomized phase II trial (n = 70) comparing carboplatin and irinotecan versus carboplatin and etoposide showed a modest improvement in progression-free survival with the irinotecan combination.[39] A recent phase III randomized trial (n = 220) found that median overall survival was slightly improved with irinotecan and carboplatin compared with carboplatin and oral etoposide (8.5 versus 7.1 months, *P*=.04).[40] Therefore, the carboplatin and irinotecan regimen has been added to the guidelines as an option for patients with extensive-stage disease.

In patients with limited-stage disease, response rates of 70% to 90% are expected after treatment with cisplatin and etoposide plus thoracic radiotherapy, while in extensive-stage disease, response rates of 60% to 70% can be achieved with combination chemotherapy alone.[3] Unfortunately, median survival rates are only 14 to 20 months and 9 to 11 months for patients with limited-stage and extensive-stage disease, respectively. After appropriate treatment, the 2-year survival rate is about 40% in patients with limited-stage disease, but less than 5% in those with extensive-stage disease.[41] Thoracic radiotherapy improves the local control rates by 25% in limited-stage disease patients and is associated with improved survival.[24,25,42] Data indicate 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.[42,43]

Many strategies have been evaluated in an effort to improve on the results that have been achieved with standard treatment for extensive-stage SCLC, including the addition of a third agent to standard 2-drug regimens. In 2 trials, the addition of ifosfamide (or cyclophosphamide plus an anthracycline) to EP demonstrated a modest survival advantage for patients with extensive disease.[44,45] However, such findings have not been uniformly observed, and the addition of an alkylating agent with or without an anthracycline significantly increases hematologic toxicity when compared to EP alone.[46] 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.[47] The use of maintenance or consolidation chemotherapy

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

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.[48]

The inability to destroy residual cells, despite the initial chemosensitivity of SCLC, suggests the existence of tumor stem cells that are relatively resistant to cytotoxic therapy. To overcome drug resistance, alternating or sequential combination therapies have been designed to expose the tumor to as many active cytotoxic agents as possible during initial treatment.[49] However, randomized trials have failed to show improved disease-free or overall survival with this approach.[50,51]

Multidrug cyclic weekly therapy was designed to increase dose-intensity. Although patient selection effects were of some concern, early phase II results were promising.[52,53] Nevertheless, no survival benefits were documented in randomized trials and excessive treatment-related mortality was noted with multidrug cyclic weekly regimens.[54-57]

The role of higher-dose therapy for patients with SCLC remains controversial.[58] 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.[59] In general, however, randomized trials comparing conventional doses to an incrementally increased dose-intensity up to 2 times the full conventional dose have not consistently shown an increased response rate or survival.[60-63] In addition, a meta-analysis of trials that compared standard versus dose-intense variations of the 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.[64]

Currently available cytokines (e.g., GM-CSF and G-CSF) can ameliorate chemotherapy-induced myelosuppression and reduce the incidence of febrile neutropenia, but cumulative thrombocytopenia remains dose-limiting. Although trials involving SCLC patients were instrumental in obtaining Food and Drug Administration (FDA) approval for the clinical use of cytokines,[65] there is little evidence to suggest that maintenance of dose intensity with growth factors prolongs disease-free or overall survival.

Maintenance therapy with bevacizumab (phase II trial) was associated with tracheoesophageal fistulae in patients with limited-stage SCLC who had received bevacizumab, irinotecan, carboplatin, and concurrent RT(http://www.fda.gov/downloads/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/UCM153953.pdf). Note that 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 generally failed to yield significant advantages when compared to standard approaches.

Elderly Patients

The incidence of lung cancer increases with age; 66% of patients with lung cancer are 65 years or older. However, elderly patients are under-represented in clinical trials.[66] Although advanced chronological age does adversely affect tolerance to treatment, an individual patient's functional status is much more useful than age in guiding clinical decision making (see the NCCN Senior Adult Oncology Guidelines). If an older person is functional in terms of the ability to perform activities of daily living, he/she should be treated with standard combination

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

chemotherapy (and radiotherapy, if indicated). However, myelosuppression, fatigue, and lower organ reserves are encountered more frequently in elderly patients.

Greater anticipation of the needs and support systems of elderly patients is recommended. However, elderly patients have similar prognoses when compared with younger patients. Randomized trials have indicated that less intensive treatment (e.g., single-agent etoposide) is inferior to combination chemotherapy (e.g., platinum plus etoposide) in elderly patients with good PS (0-2).[67,68] Several other strategies have been evaluated in elderly patients with SCLC.[34,35,69,70] The use of 4 cycles of carboplatin plus etoposide appears to yield favorable results, because the AUC (area-under-the-curve) dosing of carboplatin takes into account the declining renal function of the aging patient.[34] However, some patients may not tolerate a dose of carboplatin with an AUC as high as 6.[71] The utility of short-course, full-intensity chemotherapy has also been explored in elderly or infirm patients, and the results with only 2 cycles of chemotherapy appear to be quite acceptable.[72] However, none of these newer approaches have been directly compared with standard therapy.

Salvage Therapy

Most patients with SCLC will relapse or progress after initial treatment; these patients have a median survival of only 4 to 5 months when treated with further chemotherapy. Second-line (i.e., subsequent) chemotherapy provides significant palliation in many patients, although the likelihood of response is highly dependent on the time from initial therapy to relapse. If this interval is less than 3 months, response to most agents or regimens is poor (10% or less), indicating refractory SCLC. If greater than 3 months has elapsed, expected response rates are approximately 25%.

In phase II trials, active subsequent agents include docetaxel, oral etoposide, gemcitabine, ifosfamide, irinotecan, paclitaxel, topotecan, and vinorelbine.[29,73-75] In a randomized phase III trial, single-agent topotecan was compared to the combination regimen CAV (cyclophosphamide, doxorubicin [Adriamycin], and vincristine).[76] Both arms had similar response rates and survival, but topotecan caused less toxicity and is now recommended as the subsequent agent for patients with relapsed SCLC (category 1 for relapse > 2-3 months up to 6 months).[77] Single-agent topotecan is approved by the U.S. FDA as subsequent therapy for patients with SCLC who initially respond to chemotherapy but then progress after 2-3 months.

Recent data from phase II studies suggest that amrubicin, an investigational anthracycline, has promising activity in patients with extensive-stage SCLC that is refractory to or progressing after first-line platinum-based chemotherapy.[78-80] However, grade 3-4 neutropenia is common.[81] Phase II studies have shown that picoplatin may be useful as second-line therapy in patients with refractory extensive-stage disease.[82] Subsequent chemotherapy should be given until patients achieve maximal benefit, become refractory to therapy, or develop unacceptable toxicity. For patients with localized symptomatic sites of disease (such as painful bony lesions, obstructive atelectasis, or brain metastases), radiotherapy can provide excellent palliation. For spinal cord compression, RT can be given to symptomatic sites before chemotherapy unless immediate systemic chemotherapy is required. Chemotherapy with or without radiotherapy is useful for patients with superior vena cava syndrome.[83,84]

Discussion Update in Progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

Radiotherapy

Thoracic Radiotherapy

The addition of thoracic radiotherapy has improved survival for patients with limited-stage disease.[2] Meta-analyses that included more than 2000 patients show that thoracic radiation for limited-stage disease causes a 25% to 30% reduction in local failure and a corresponding 5% to 7% improvement in 2-year survival.[24,25] However, achieving long-term local control using conventional chemoradiotherapy for patients with limited-stage SCLC remains a challenge.

The administration of thoracic radiotherapy requires the assessment of several factors, including the timing of chemotherapy and radiotherapy (concurrent versus sequential versus alternating therapy), timing of radiotherapy (early versus late), volume of the radiation port (original tumor volume versus shrinking field as the tumor responds), dose of radiation, and fractionation of radiotherapy. Based on randomized trials, early, concurrent radiotherapy is recommended along with chemotherapy for patients with limited-stage SCLC. A randomized trial by the Japanese Cooperative Oncology Group assessed sequential versus concurrent thoracic radiotherapy combined with EP for patients with limited-stage disease; they reported that patients treated with concurrent radiotherapy lived longer than those treated with sequential radiotherapy.[85] Another randomized phase III trial by the National Cancer Institute of Canada compared radiotherapy beginning with either cycle 2 or cycle 6 of chemotherapy; they demonstrated that early radiotherapy was associated with improved local and systemic control and with longer survival.[86] A systematic review on the timing of thoracic radiotherapy in limited-stage SCLC determined that early concurrent radiotherapy results in a small, but significant, improvement in overall survival when compared to late concurrent or sequential radiotherapy.[87]

Based on a phase II study by Turrisi et al,[88] the Eastern Cooperative Oncology Group/Radiation Therapy Oncology Group (ECOG/RTOG) compared once a day to twice a day radiotherapy with EP. In this trial, 412 patients with limited-stage SCLC were treated with concurrent chemoradiotherapy using a total dose of 45 Gy delivered either twice a day over 3 weeks or once a day over 5 weeks. The twice-daily schedule produced a survival advantage and a higher incidence of grade 3-4 esophagitis. Median survival was 23 versus 19 months (*P*=.04), and 5-year survival was 26% versus 16% in the twice-daily and once-daily radiotherapy arms, respectively.[89]

A caveat to these encouraging long-term survival results is that twice-daily fractionation is technically challenging for patients with bilateral mediastinal adenopathy. In addition, the once-a-day therapy was not delivered at its maximum tolerated dose, so it remains unclear if hyperfractionation is superior to once daily chest radiotherapy given to a biologically equivalent dose. Another randomized phase III trial demonstrated no survival difference between once-a-day thoracic radiotherapy to 50.4 Gy with concurrent EP and a split-course of twice-a-day thoracic radiotherapy to 48 Gy with concurrent EP.[90] However, split-course radiotherapy may be less efficacious because of interval tumor regrowth between courses. Overall, patients selected for combined modality treatment that incorporates twice-a-day radiotherapy must have an excellent PS and good baseline pulmonary function.

For limited-stage disease, the NCCN guidelines recommend that radiation should be delivered concurrently with chemotherapy and should start with the first or second cycle (category 1) at a dose of either 1.5 Gy twice daily to a total dose of 45 Gy, or 1.8 to 2.0 Gy/day to 60 to 70 Gy.[24,87,90-92] Concurrent chemoradiotherapy (category 1) is preferable to sequential therapy in patients with good PS (0-2); 3-

Discussion Update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

dimensional (3D) conformal radiation techniques are preferred, if available. The radiation target volumes should be defined on the CT scan obtained at the time of radiotherapy planning. However, the pre-chemotherapy CT scan should be reviewed to include the originally involved lymph node regions in the treatment fields.[93,94]

Selected patients with low-bulk metastatic disease who have a complete or near complete response after systemic therapy may be considered for sequential thoracic radiotherapy based on a randomized trial that noted improved survival with this approach.[95]

Prophylactic Cranial Irradiation

Intracranial metastases occur in more than 50% of patients with SCLC. Randomized studies have shown that prophylactic cranial irradiation (PCI) is effective in decreasing the incidence of cerebral metastases, but most individual studies did not have sufficient power to demonstrate a meaningful survival advantage.[96] Moreover, late neurologic sequelae have been attributed to radiotherapy, particularly in studies using fractions greater than 3 Gy and/or administering PCI concurrent with chemotherapy. When given after the completion of chemotherapy and at low doses per fractions, PCI may cause less neurological toxicity. Symptomatic brain relapses result in major morbidity, which frequently does not completely resolve with therapeutic cranial irradiation.

A meta-analysis of all randomized PCI trials reported a 25% decrease in the 3-year incidence of brain metastases from 58.6% in the control group to 33.3% in the PCI treated group.[97] Thus, it appears that PCI prevents and does not simply delay the emergence of brain metastases. This meta-analysis also reported a 5.4% increase in 3-year survival in patients treated with PCI from 15.3% in the control group to 20.7% in the PCI group.[97] Although the number of patients in this meta-analysis with extensive-stage disease was small, the observed benefit was similar in both limited- and extensive-stage patients. A recent retrospective study of patients with limited-stage disease also found that PCI increased survival at 2, 5, and 10 years when compared to those who did not receive PCI.[98]

A recent randomized trial assessed PCI versus no PCI in 286 patients with extensive-stage SCLC who had responded to initial chemotherapy. PCI decreased symptomatic brain metastases (14.6% versus 40.4%) and increased the 1-year survival rate (27.1% versus 13.3%) when compared with controls.[99]

A balanced discussion between the patient and physician is necessary before making a decision to administer PCI. PCI is recommended (category 1) for patients with either limited- or extensive-stage disease who attain a complete or partial response. However, PCI is not recommended for patients with poor PS (3-4) or impaired mental function. The recommended dose for PCI is 25 Gy in 10 fractions or 30 Gy in 10-15 fractions.[99,100] PCI should not be given concurrently with systemic chemotherapy because of the increased risk of neurotoxicity. Fatigue, headache, and nausea or vomiting are the most common acute toxic effects after PCI.[100,101]

Surgical Resection of Early-Stage SCLC

Early-stage SCLC is diagnosed in less than 5% of patients with SCLC.[102] Patients with clinically staged disease in excess of T1-2, N0 do not benefit from surgery. The Lung Cancer Study Group conducted the only prospective randomized trial evaluating the role of surgery in SCLC.[103] Patients with limited-stage disease, excluding those with stage I disease, received 5 cycles of chemotherapy with CAV. Patients demonstrating a response to chemotherapy were randomly assigned either to resection plus thoracic radiotherapy or to thoracic radiotherapy

Discussion Update in Progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

alone. The survival of patients on the 2 arms was equivalent, suggesting no benefit to surgery in this setting.

Patients with SCLC that has been determined to be clinical stage I (T1-2, N0) after a standard staging evaluation (including CT of the chest and upper abdomen, bone scan, brain imaging, and probably PET imaging) may undergo surgical resection.[104] Before resection, all patients should undergo mediastinoscopy or other surgical or endoscopic mediastinal staging to rule out occult nodal disease.[105] If an endoscopic lymph node biopsy is positive, additional mediastinal staging is not required. Patients who undergo complete resection (preferably by a lobectomy with either mediastinal nodal dissection or sampling) should be treated with postoperative chemotherapy.[106,107] Patients without nodal metastases can be treated with chemotherapy alone, but concurrent chemotherapy and postoperative mediastinal RT are recommended for patients with nodal metastases. Because PCI can improve both disease-free and overall survival in patients with SCLC in complete remission, it is reasonable to administer PCI after adjuvant therapy in patients who have undergone a complete resection.[97]

Management of Patients Not Participating in Clinical Trials

Clinical trials generally represent state-of-the-art treatment for patients with SCLC. Despite recent advances, the standard therapy for SCLC based on prior clinical trials and outlined by the practice guidelines does not yet result in very good outcomes. Thus, participation in clinical trials should be strongly encouraged.

Patients with limited-stage disease who are not enrolled in a clinical trial should be treated with concurrent chemotherapy (cisplatin plus etoposide for 4 cycles) plus early thoracic radiotherapy (category 1).[85]

Chest radiotherapy should begin during cycle 1 or 2 and should consist of either 45 Gy as 1.5 Gy twice daily (category 1) or 1.8 to 2.0 Gy once daily to 60 to 70 Gy.[85,86] PCI is recommended (category 1) for patients who achieve a complete or partial response. Follow-up examinations are recommended every 2 to 3 months during the first year with concomitant chest imaging. If a new pulmonary nodule appears after 2 years, it should be evaluated as a new primary tumor, because second primary tumors are a frequent occurrence in patients who are cured of SCLC.[108]

For patients with extensive-stage disease, standard combination platinum-based chemotherapy is recommended, with subsequent PCI in responding patients. More effective approaches are desperately needed.

Discussion Update in Progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

References

1. Jemal A, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. CA Cancer J Clin. 2009;59:225-249.

2. Simon G, Ginsberg RJ, Ruckdeschel JC. Small-cell lung cancer. Chest Surg Clin N Am. 2001;11:165-188, ix.

3. Simon M, Argiris A, Murren JR. Progress in the therapy of small cell lung cancer. Crit Rev Oncol Hematol. 2004;49:119-133.

4. Johnson BE, Janne PA. Basic treatment considerations using chemotherapy for patients with small cell lung cancer. Hematol Oncol Clin North Am. 2004;18:309-322.

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

6. Travis WD, Colby TV, Corrin B, et al. Histological Typing of Lung and Pleural Tumours. World Health Organization International Histological Classification of Tumours Berlin: Springer-Verlag; 1999.

7. Brenner B, Tang LH, Klimstra DS, Kelsen DP. Small-cell carcinomas of the gastrointestinal tract: a review. J Clin Oncol. 2004;22:2730-2739.

8. Galanis E, Frytak S, Lloyd RV. Extrapulmonary small cell carcinoma. Cancer. 1997;79:1729-1736.

9. Remick SC, Ruckdeschel JC. Extrapulmonary and pulmonary small-cell carcinoma: tumor biology, therapy, and outcome. Med Pediatr Oncol. 1992;20:89-99.

10. Johnson BE, Whang-Peng J, Naylor SL, et al. Retention of chromosome 3 in extrapulmonary small cell cancer shown by molecular and cytogenetic studies. J Natl Cancer Inst. 1989;81:1223-1228.

11. Guinee DG, Jr., Fishback NF, Koss MN, Abbondanzo SL, Travis WD. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. Am J Clin Pathol. 1994;102:406-414.

12. Meriney SD, Hulsizer SC, Lennon VA, Grinnell AD. Lambert-Eaton myasthenic syndrome immunoglobulins react with multiple types of calcium channels in small-cell lung carcinoma. Ann Neurol. 1996;40:739-749.

13. Graus F, Keime-Guibert F, Rene R, et al. Anti-Hu-associated paraneoplastic encephalomyelitis: analysis of 200 patients. Brain. 2001;124:1138-1148.

14. Manley GT, Smitt PS, Dalmau J, Posner JB. Hu antigens: reactivity with Hu antibodies, tumor expression, and major immunogenic sites. Ann Neurol. 1995;38:102-110.

15. Delisle L, Boyer MJ, Warr D, et al. Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. Arch Intern Med. 1993;153:746-752.

16. Johnson BE, Chute JP, Rushin J, et al. A prospective study of patients with lung cancer and hyponatremia of malignancy. Am J Respir Crit Care Med. 1997;156:1669-1678.

17. Micke P, Faldum A, Metz T, et al. Staging small cell lung cancer: Veterans Administration Lung Study Group versus International Association for the Study of Lung Cancer--what limits limited disease? Lung Cancer. 2002;37:271-276.

18. Shepherd FA, Crowley J, Van Houtte P, et al. The International Association for the Study of Lung Cancer lung cancer staging project: proposals regarding the clinical staging of small cell lung cancer in the forthcoming (seventh) edition of the tumor, node, metastasis classification for lung cancer. J Thorac Oncol. 2007;2:1067-1077.

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

19. Ignatius Ou SH, Zell JA. The applicability of the proposed IASLC staging revisions to small cell lung cancer (SCLC) with comparison to the current UICC 6th TNM Edition. J Thorac Oncol. 2009;4:300-310.

20. Vallieres E, Shepherd FA, Crowley J, et al. The IASLC Lung Cancer Staging Project: proposals regarding the relevance of TNM in the pathologic staging of small cell lung cancer in the forthcoming (seventh) edition of the TNM classification for lung cancer. J Thorac Oncol. 2009;4:1049-1059.

21. Podoloff DA, Ball DW, Ben-Josef E, et al. NCCN task force: clinical utility of PET in a variety of tumor types. J Natl Compr Canc Netw. 2009;7 Suppl 2:S1-26.

22. Albain KS, Crowley JJ, LeBlanc M, Livingston RB. Determinants of improved outcome in small-cell lung cancer: an analysis of the 2,580-patient Southwest Oncology Group data base. J Clin Oncol. 1990;8:1563-1574.

23. Yip D, Harper PG. Predictive and prognostic factors in small cell lung cancer: current status. Lung Cancer. 2000;28:173-185.

24. Pignon JP, Arriagada R, Ihde DC, et al. A meta-analysis of thoracic radiotherapy for small-cell lung cancer. N Engl J Med. 1992;327:1618-1624.

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

26. Spira A, Ettinger DS. Multidisciplinary management of lung cancer. N Engl J Med. 2004;350:379-392.

27. Johnson BE. Management of small cell lung cancer. Clin Chest Med. 2002;23:225-239.

28. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. J Clin Oncol. 1985;3:1471-1477.

29. Jackman DM, Johnson BE. Small-cell lung cancer. Lancet. 2005;366:1385-1396.

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

31. Saito H, Takada Y, Ichinose Y, et al. Phase II study of etoposide and cisplatin with concurrent twice-daily thoracic radiotherapy followed by irinotecan and cisplatin in patients with limited-disease small-cell lung cancer: West Japan Thoracic Oncology Group 9902. J Clin Oncol. 2006;24:5247-5252.

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

33. Skarlos DV, Samantas E, Kosmidis P, et al. Randomized comparison of etoposide-cisplatin vs. etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. Ann Oncol. 1994;5:601-607.

34. Okamoto H, Watanabe K, Nishiwaki Y, et al. Phase II study of area under the plasma-concentration-versus-time curve-based carboplatin plus standard-dose intravenous etoposide in elderly patients with small-cell lung cancer. J Clin Oncol. 1999;17:3540-3545.

35. Okamoto H, Watanabe K, Kunikane H, et al. Randomised phase III trial of carboplatin plus etoposide vs split doses of cisplatin plus etoposide in elderly or poor-risk patients with extensive disease small-cell lung cancer: JCOG 9702. Br J Cancer. 2007;97:162-169.

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

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

37. Hanna N, Bunn PA, Jr, 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 10.1200/JCO.2005.04.8595. J Clin Oncol. 2006;24:2038-2043.

38. Natale RB, Lara PN, Chansky K, et al. S0124: A randomized phase III trial comparing irinotecan/cisplatin (IP) with etoposide/cisplatin (EP) in patients (pts) with previously untreated extensive stage small cell lung cancer (E-SCLC). J Clin Oncol (Meeting Abstracts). 2008;26:7512.

39. 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.

40. Hermes A, Bergman B, Bremnes R, et al. Irinotecan plus carboplatin versus oral etoposide plus carboplatin in extensive small-cell lung cancer: a randomized phase III trial. J Clin Oncol. 2008;26:4261-4267.

41. Chute JP, Chen T, Feigal E, Simon R, Johnson BE. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol. 1999;17:1794-1801.

42. Niho S, Kubota K, Yoh K, et al. Clinical outcome of chemoradiation therapy in patients with limited-disease small cell lung cancer with ipsilateral pleural effusion. J Thorac Oncol. 2008;3:723-727.

43. Niho S, Kubota K, Yoh K, et al. Chemoradiation therapy in patients (pts) with small cell lung cancer (SCLC) with pericardial effusion but no distant metastasis. J Clin Oncol (Meeting Abstracts). 2009;27:7555.

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

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

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

47. Niell HB, Herndon JE, 2nd, 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.

48. Schiller JH, Adak S, Cella D, DeVore RF, 3rd, Johnson DH. Topotecan versus observation after cisplatin plus etoposide in extensive-stage small-cell lung cancer: E7593--a phase III trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2001;19:2114-2122.

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

50. Fukuoka M, Furuse K, Saijo N, et al. Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. J Natl Cancer Inst. 1991;83:855-861.

51. Roth BJ, Johnson DH, Einhorn LH, et al. Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol. 1992;10:282-291.

52. Miles DW, Earl HM, Souhami RL, et al. Intensive weekly chemotherapy for good-prognosis patients with small-cell lung cancer. J Clin Oncol. 1991;9:280-285.

Discussion Update in Progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

53. Murray N GK, Shah A, et al. . Potential for long-term survival in extensive stage small-cell lung cancer (ESCLC) with CODE chemotherapy and radiotherapy [abstract]. . Lung Cancer. 1994;11:99.

54. Sculier JP, Paesmans M, Bureau G, et al. Multiple-drug weekly chemotherapy versus standard combination regimen in small-cell lung cancer: a phase III randomized study conducted by the European Lung Cancer Working Party. J Clin Oncol. 1993;11:1858-1865.

55. Souhami RL, Rudd R, Ruiz de Elvira MC, et al. Randomized trial comparing weekly versus 3-week chemotherapy in small-cell lung cancer: a Cancer Research Campaign trial. J Clin Oncol. 1994;12:1806-1813.

56. Fukuoka M, Masuda N, Negoro S, et al. CODE chemotherapy with and without granulocyte colony-stimulating factor in small-cell lung cancer. Br J Cancer. 1997;75:306-309.

57. Murray N, Livingston RB, Shepherd FA, et al. Randomized study of CODE versus alternating CAV/EP for extensive-stage small-cell lung cancer: an Intergroup Study of the National Cancer Institute of Canada Clinical Trials Group and the Southwest Oncology Group. J Clin Oncol. 1999;17:2300-2308.

58. Teicher BA. Preclinical models for high-dose therapy. In: Armitage JO, Antman KH, eds. High-Dose Cancer Therapy: Pharmacology, Hematopoietins, Stem Cells, 2nd ed. Baltimore: Williams and Wilkins; 1995:14-42.

59. Cohen MH, Creaven PJ, Fossieck BE, Jr., et al. Intensive chemotherapy of small cell bronchogenic carcinoma. Cancer Treat Rep. 1977;61:349-354.

60. Johnson DH, Einhorn LH, Birch R, et al. A randomized comparison of high-dose versus conventional-dose cyclophosphamide, doxorubicin, and vincristine for extensive-stage small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. J Clin Oncol. 1987;5:1731-1738.

61. Ihde DC, Mulshine JL, Kramer BS, et al. Prospective randomized comparison of high-dose and standard-dose etoposide and cisplatin chemotherapy in patients with extensive-stage small-cell lung cancer. J Clin Oncol. 1994;12:2022-2034.

62. Arriagada R, Le Chevalier T, Pignon JP, et al. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. N Engl J Med. 1993;329:1848-1852.

63. Thatcher N, Girling DJ, Hopwood P, Sambrook RJ, Qian W, Stephens RJ. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. J Clin Oncol. 2000;18:395-404.

64. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. J Clin Oncol. 1991;9:499-508.

65. Crawford J, Ozer H, Stoller R, et al. Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. N Engl J Med. 1991;325:164-170.

66. Hurria A, Kris MG. Management of lung cancer in older adults. CA Cancer J Clin. 2003;53:325-341.

67. Girling DJ. Comparison of oral etoposide and standard intravenous multidrug chemotherapy for small-cell lung cancer: a stopped multicentre randomised trial. Medical Research Council Lung Cancer Working Party. Lancet. 1996;348:563-566.

68. Souhami RL, Spiro SG, Rudd RM, et al. Five-day oral etoposide treatment for advanced small-cell lung cancer: randomized comparison with intravenous chemotherapy. J Natl Cancer Inst. 1997;89:577-580.

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

69. Neubauer M, Schwartz J, Caracandas J, et al. Results of a phase II study of weekly paclitaxel plus carboplatin in patients with extensive small-cell lung cancer with eastern cooperative oncology group performance status of 2, or age >= 70 years. J Clin Oncol. 2004;22:1872-1877.

70. Westeel V, Murray N, Gelmon K, et al. New combination of the old drugs for elderly patients with small-cell lung cancer: a phase II study of the PAVE regimen. J Clin Oncol. 1998;16:1940-1947.

71. Matsui K, Masuda N, Yana T, et al. Carboplatin calculated with Chatelut's formula plus etoposide for elderly patients with small-cell lung cancer. Intern Med. 2001;40:603-606.

72. Murray N, Grafton C, Shah A, et al. Abbreviated treatment for elderly, infirm, or noncompliant patients with limited-stage small-cell lung cancer. J Clin Oncol. 1998;16:3323-3328.

73. Ettinger DS. New drugs for chemotherapy-naive patients with extensive-disease small cell lung cancer. Semin Oncol. 2001;28:27-29.

74. Kelly K. New chemotherapy agents for small cell lung cancer. Chest. 2000;117:156S-162S.

75. Masters GA, Declerck L, Blanke C, et al. Phase II trial of gemcitabine in refractory or relapsed small-cell lung cancer: Eastern Cooperative Oncology Group Trial 1597. J Clin Oncol. 2003;21:1550-1555.

76. von Pawel J, Schiller JH, Shepherd FA, et al. Topotecan versus cyclophosphamide, doxorubicin, and vincristine for the treatment of recurrent small-cell lung cancer. J Clin Oncol. 1999;17:658-667.

77. Cheng S, Evans WK, Stys-Norman D, Shepherd FA. Chemotherapy for relapsed small cell lung cancer: a systematic review and practice guideline. J Thorac Oncol. 2007;2:348-354.

78. Inoue A, Sugawara S, Yamazaki K, et al. Randomized phase II trial comparing amrubicin with topotecan in patients with previously treated small-cell lung cancer: North Japan Lung Cancer Study Group Trial 0402. J Clin Oncol. 2008;26:5401-5406.

79. Ettinger DS, Jotte RM, Gupta V, Allen AR, Oliver JW. A phase II trial of single-agent amrubicin (AMR) in patients with extensive disease small cell lung cancer (ED-SCLC) that is refractory or progressive within 90 days of completion of first-line platinum-based chemotherapy. J Clin Oncol (Meeting Abstracts). 2008;26:8041.

80. Onoda S, Masuda N, Seto T, et al. Phase II trial of amrubicin for treatment of refractory or relapsed small-cell lung cancer: Thoracic Oncology Research Group Study 0301. J Clin Oncol. 2006;24:5448-5453.

81. Shimokawa T, Shibuya M, Kitamura K, et al. Retrospective analysis of efficacy and safety of amrubicin in refractory and relapsed small-cell lung cancer. Int J Clin Oncol. 2009;14:63-69.

82. Eckardt JR, Bentsion DL, Lipatov ON, et al. Phase II study of picoplatin as second-line therapy for patients with small-cell lung cancer. J Clin Oncol. 2009;27:2046-2051.

83. Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus: a systematic review. Clin Oncol (R Coll Radiol). 2002;14:338-351.

84. Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. N Engl J Med. 2007;356:1862-1869.

85. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. J Clin Oncol. 2002;20:3054-3060.

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

86. Murray N, Coy P, Pater JL, et al. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1993;11:336-344.

87. Fried DB, Morris DE, Poole C, et al. Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer. J Clin Oncol. 2004;22:4837-4845.

88. Turrisi AT, 3rd, Glover DJ, Mason BA. A preliminary report: concurrent twice-daily radiotherapy plus platinum-etoposide chemotherapy for limited small cell lung cancer. Int J Radiat Oncol Biol Phys. 1988;15:183-187.

89. 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;340:265-271.

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

91. Miller KL, Marks LB, Sibley GS, et al. Routine use of approximately 60 Gy once-daily thoracic irradiation for patients with limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2003;56:355-359.

92. Roof KS, Fidias P, Lynch TJ, Ancukiewicz M, Choi NC. Radiation dose escalation in limited-stage small-cell lung cancer. Int J Radiat Oncol Biol Phys. 2003;57:701-708.

93. Bogart JA, Herndon JE, 2nd, Lyss AP, et al. 70 Gy thoracic radiotherapy is feasible concurrent with chemotherapy for limited-stage small-cell lung cancer: analysis of Cancer and Leukemia Group B study 39808. Int J Radiat Oncol Biol Phys. 2004;59:460-468.

94. Liengswangwong V, Bonner JA, Shaw EG, et al. Limited-stage small-cell lung cancer: patterns of intrathoracic recurrence and the implications for thoracic radiotherapy. J Clin Oncol. 1994;12:496-502.

95. Jeremic B, Shibamoto Y, Nikolic N, et al. Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol. 1999;17:2092-2099.

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

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

98. Patel S, Macdonald OK, Suntharalingam M. Evaluation of the use of prophylactic cranial irradiation in small cell lung cancer. Cancer. 2009;115:842-850.

99. 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.

100. Le Pechoux 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 (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol. 2009;10:467-474.

Discussion update in progress

Printed by Jorge Garc?a on 12/30/2010 8:36:32 PM. For personal use only. Not approved for distribution. Copyright © 2010 National Comprehensive Cancer Network, Inc., All Rights Reserved.

101. Slotman BJ, Mauer ME, Bottomley A, et al. Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups. J Clin Oncol. 2009;27:78-84.

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

103. Lad T, Piantadosi S, Thomas P, Payne D, Ruckdeschel J, Giaccone G. A prospective randomized trial to determine the benefit of surgical resection of residual disease following response of small cell lung cancer to combination chemotherapy. Chest. 1994;106:320S-323S.

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

105. Inoue M, Nakagawa K, Fujiwara K, Fukuhara K, Yasumitsu T. Results of preoperative mediastinoscopy for small cell lung cancer. Ann Thorac Surg. 2000;70:1620-1623.

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

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

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

Discussion update in progress