National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 1.2013

NCCN.org

NCCN Guidelines for Patients™ available at www.nccn.com

Continue

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Panel Members
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

*David S. Ettinger, MD/Chair †
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

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

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

Andrew C. Chang, MD ¶
University of Michigan Comprehensive Cancer Center

*Richard T. Cheney, MD ≠
Roswell Park Cancer Institute

Lucian R. Chirieac, MD ≠
Dana-Farber/Brigham and Women's Cancer Center

Thomas A. D'Amico, MD ¶
Duke Cancer Institute

Todd L. Demmy, MD ¶
Roswell Park Cancer Institute

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

Frederic W. Grannis, Jr., MD ¶
City of Hope Comprehensive Cancer Center

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

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

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

*Ritsuko Komaki, MD §
The University of Texas MD Anderson Cancer Center

*Feng-Ming (Spring) Kong, MD, PhD, MPH §
University of Michigan Comprehensive Cancer Center

*Mark G. Kris, MD †
Memorial Sloan-Kettering Cancer Center

Lee M. Krug, MD †
Memorial Sloan-Kettering Cancer Center

Rudy P. Lackner, MD ¶
UNMC Eppley Cancer Center at The Nebraska Medical Center

Inga T. Lennes, MD †
Massachusetts General Hospital Cancer Center

*Billy W. Loo, Jr., MD, PhD §
Stanford Cancer Institute

Renato Martins, MD, MPH †
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Gregory A. Otterson, MD †
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

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

Mary C. Pinder-Schenck, MD †
Moffitt Cancer Center

Katherine M. Pisters, MD †
The University of Texas MD Anderson Cancer Center

Karen Reckamp, MD, MS † ‡
City of Hope Comprehensive Cancer Center

Gregory J. Riely, MD, PhD †
Memorial Sloan-Kettering Cancer Center

Eric Rohren, MD, PhD ф
The University of Texas MD Anderson Cancer Center

Theresa A. Shapiro, MD, PhD ¥
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Scott J. Swanson, MD ¶
Dana-Farber/Brigham and Women's Cancer Center

Kurt Tauer, MD
University of Tennessee Cancer Institute

*Douglas E. Wood, MD ¶
Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance

Stephen C. Yang, MD ¶
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

NCCN
Kristina Gregory, RN, MSN
Miranda Hughes, PhD

† Medical oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
≠ Pathology
‡ Hematology/Hematology oncology
ф Diagnostic/Interventional radiology
¥ Patient advocate
*Writing Committee Member

Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Table of Contents
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

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

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

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

See NCCN Categories of Evidence and Consensus

NCCN Guidelines for Patients™ available at www.nccn.com

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

PREV-1
- Last bullet deleted and replaced with this bullet: Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the NCCN Guidelines for Lung Cancer Screening).

DIAG-1 through DIAG-A 2 of 2
- New section added addressing the diagnostic evaluation of nodules suspicious of lung cancer.

NSCL-1
- Initial Evaluation, sub-bullet added under "Smoking cessation advice, counseling, and pharmacotherapy": "Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange. http://www.ahrq.gov/clinic/tobacco/5steps.htm."
- Footnote "b" added: Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.
- New clinical stage added for "multiple lung cancers."
- Stage IV (M1b) Disseminated metastases: deleted "Workup as clinically indicated."

NSCL-2
- Pretreatment evaluation
  - Mediastinoscopy and/or EBUS/EUS changed to "Pathologic mediastinal lymph node evaluation." (also applies to NSCL-4)
  - Footnote "g" added: "Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy." (also applies to NSCL-4)
  - PET/CT scan: "if not previously done" added. (also applies to NSCL-4, NSCL-6, and NSCL-10 through NSCL-12)
  - Footnote "h" modified: "Positive PET/CT scan findings *for distant disease* need pathologic or other radiologic confirmation. (also applies to NSCL-4, NSCL-6, NSCL-7, and NSCL-10 through NSCL-12)

NSCL-3
- Stage IIIA modified: T1-3, N2; T3 ~~[>7 cm]~~, N1.
- Footnote "l" added: "Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative."
- Footnote "o" modified: "High-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, *and incomplete lymph node sampling* (Nx).

NSCL-5
- The following footnotes were deleted and incorporated into the Principles of Radiation Therapy section:
  - Footnote "o": "In the preoperative chemoradiation setting, a total dose of 45-50 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease, although preoperative chemoradiotherapy should be avoided if a pneumonectomy is required, to avoid postoperative pulmonary toxicity.
  - Footnote "q": In the definitive chemoradiation setting, a total dose of 60 to 70 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.
  - Footnote "r": Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-318.
  - Footnote "s" modified: "If full-dose chemotherapy not given concurrently with RT as initial treatment, give additional 4 cycles of full-dose chemotherapy." (also applies to NSCL-10, and NSCL-11)

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-5 (continued)
- **Footnote "t" added: "Consider RT boost if chemoradiation given as initial treatment."**

NSCL-6
- **Separate pulmonary nodules: Mediastinoscopy replaced with "Pathologic mediastinal lymph node evaluation."**

NSCL-7
- **"No progression" changed to No *apparent* progression.**

NSCL-8
- **Separate pulmonary nodules**
  - **Nodal status added after surgery to be consistent with NSCL-7.**
  - **Surgery, N2, margins positive: "+ chemotherapy" added to ~~concurrent~~ Chemoradiation.**
  - **Footnote "n" added: "The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections."**
- **Stage IIIA modified, (~~T3, N1;~~ T4, N0-1) Unresectable: "Definitive" added to concurrent chemoradiation. Additional chemotherapy deleted.**

NSCL-8 and NSCL-9
- **New section added addressing "Multiple lung cancers."**

NSCL-10
- **N3 negative: link changed from NSCL-2 to NSCL-7.**
- **N3 positive: "Definitive" added to concurrent chemoradiation. Additional chemotherapy deleted.**

NSCL-11
- **Ipsilateral mediastinal node positive and Contralateral mediastinal node positive: "Definitive" added to concurrent chemoradiation. Additional chemotherapy deleted.**

NSCL-12
- **Mediastinoscopy replaced with "Pathologic mediastinal lymph node evaluation."**
- **Footnote "g" added: "Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy."**
- **T1-2, N0-1; T3, N0 after initial treatment: all category 2B designations removed (SABR, chemotherapy, chemotherapy following surgery, and surgery following chemotherapy).**
- **Foonote "aa" modified: "Patients with N2 disease have a poor prognosis and systemic therapy *should* ~~may~~ be considered."**

NSCL-13
- **Surveillance: "for routine follow-up" removed after "PET or brain MRI is not indicated."**

NSCL-14
- **Locoregional recurrence: Resectable recurrence, "SABR" added as an option.**
- **Locoregional recurrence: SVC obstruction, stent clarified as "SVC stent."**

NSCL-15
- **Evaluation of Metastatic Disease modified, "Establish histologic subtype *with adequate tissue for molecular testing."***

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-15 (continued)

- Adenocarcinoma, Large Cell, NSCLC NOS
  - Footnote "cc" added, "If ROS1 mutation status known and positive, may treat with crizotinib. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870."
  - Testing results modified: "EGFR mutation or ALK negative ~~or unknown~~."
- Squamous cell carcinoma, testing recommendation modified: EGFR mutation and ALK testing are not routinely recommended *except in never smokers and small biopsy specimens.*
  - Footnote "ee" added: "Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther Published on-line August 14, 2012."

NSCL-16

- Continuation maintenance chemotherapy:
  - Bevacizumab + pemetrexed added with category 2A recommendation and the following footnote "kk": "If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen."
  - Pemetrexed changed from a "category 2A" recommendation to a "category 1" recommendation.
- "Observation" changed to "close observation." (also applies to NSCL-18)
- Footnote "ll": abstract reference updated with publication. (also applies to NSCL-18)

NSCL-17

- Adenocarcinoma, large cell, NSCLC NOS; EGFR mutation discovered during first-line chemotherapy: "May add erlotinib to current chemotherapy" changed to a "category 2A" recommendation from a "category 2B" recommendation.
- Therapy added for progression on erlotinib.
  - "Symptomatic, brain, isolated lesion: Consider local therapy and continue erlotinib."
  - "Symptomatic, brain, multiple lesions: Consider WBRT and continue erlotinib."
  - "Symptomatic, systemic, isolated lesion: Consider local therapy and continue erlotinib."
  - "Symptomatic, systemic, multiple lesions: Consider systemic therapy ± erlotinib."
  - "Asymptomatic: Continue erlotinib."
  - Footnote "qq" added: "Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression."
  - Footnote "rr" added: "Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI."

NSCL-A 1 of 4

- Pathologic evaluation
  - Bullet 1 modified: The purpose of pathologic evaluation is to ~~precisely~~ classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC, including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis. Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to ~~a growing~~ an increasing number of ~~targeted therapies~~ *drugable targets*, primarily tyrosine kinase inhibitors (TKIs) (see *Molecular Diagnostic Studies* in this section).

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-A 1 of 4 (continued)

- **Pathologic evaluation: bullet 6 modified, ~~Judicious~~ *Limited* use of ~~ancillary~~ IHC studies in small tissue samples is *strongly* recommended, thereby preserving *critical* tumor tissue for molecular studies, particularly in patients with advanced-stage disease. *A limited panel of p63 and TTF-1 should suffice for most diagnostic problems.***

NSCL-A 2 of 4

- **Immunohistochemical Staining, bullet 3, sub-bullet 4 modified: The panel of TTF-1 and p63 *(or alternatively p40)* may be useful in refining the diagnosis ~~in small biopsy specimens~~ *to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens* previously ~~generically~~ classified as NSCLC, *not otherwise specified (NOS)*.**

NSCL-A 3 of 4

- **Molecular Diagnostic Studies in Lung Cancer, EGFR, and KRAS**
  - **Sub-bullet 2 modified: There is a significant association between EGFR mutations—especially exon 19 deletion and exon 21 ~~mutation~~ (L858R) and exon 18 (G719X) *mutations*—and ~~response~~ *sensitivity* to TKIs.**
  - **Sub-bullet 3 added: "The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs."**
  - **Sub-bullet 7 modified: *Primary* resistance to TKI therapy is associated with KRAS mutation. *Acquired resistance is associated* ~~and~~ with second-*site* ~~ary acquired~~ ~~EGFR~~ mutations *within the EGFR kinase domain, amplification of alternative kinases (such as MET), histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).* ~~such as T790M.~~**
- **Molecular Diagnostic Studies in Lung Cancer, ALK (EML4-ALK changed to *ALK* throughout section)**
  - **Sub-bullet 1 modified: Anaplastic lymphoma kinase (ALK) gene rearrangements, ~~in a subset of anaplastic large cell lymphomas (ALCL), have been recognized for over 15 years.~~ *represent* the fusion between *ALK and various partner genes, including* echinoderm microtubule-associated protein-like 4 (EML4). ~~and~~ ALK *fusions* have ~~recently~~ been identified in a subset of patients with NSCLC. ~~EML4-ALK NSCLC~~ *and* represent a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.[26] Crizotinib is an oral ALK inhibitor that ~~was recently~~ is approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement (ie, ALK positive).**
  - **Sub-bullet 3 modified: The current standard method for detecting ~~EML4-~~ALK NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged anaplastic large cell lymphomas (ALCL), is applicable for the diagnosis of ALK-rearranged lung adenocarcinomas. The IHC tests used to diagnose ALK-rearranged ALCLs in clinical laboratories worldwide are inadequate for the detection of ~~the majority of~~ *most* ALK-rearranged lung adenocarcinomas. This *inadequacy is because of* ~~is due to~~ the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs. A molecular diagnostic test that uses FISH was recently approved by the FDA to determine which patients with lung adenocarcinoma are ALK positive.**

NSCL-B

- **Extensive revisions to the Principles of Radiation Therapy section.**

NSCL-C

- **The following regimens were added for Concurrent Chemotherapy/RT:**

"Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT (nonsquamous)"

"Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT (nonsquamous)"

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-C (continued)

- **Reference "c" added: Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120-3125.**
- **Reference "d" added: Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. Clin Lung Cancer 2009;10:193-198.**

NSCL-D 1 of 4

- **Headings added to improve the clarity and readability of this section.**
- **Evaluation**
  - **Bullet 1 modified: Determination of resectability, *surgical staging, and pulmonary resection* should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
  - **Bullet 2 added: "CT and PET used for staging should be within 60 days before proceeding with surgical evaluation."**
  - **Bullet 3 modified: Resection~~, including wedge resection,~~ is *the* preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, and stereotactic ablative RT [SABR]). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk patients, a multidisciplinary evaluation (including a radiation oncologist) is recommended.**
  - **Bullet 4 removed, as it has been combined with bullet 1: Surgical staging and pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
  - **Last bullet added: "In current smokers who stop smoking, consider waiting 4 weeks before surgery to maximize outcomes after surgery."**
- **Resection**
  - **Bullet 2 modified: In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (*decreased* pain, *reduced* hospital length of stay, *more rapid* return to function, *fewer complications*) without compromise of cancer outcomes.**
  - **Bullet 4 modified: T3 (~~extension~~*invasion*) and T4 local ~~invasion~~*extension* tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.**

NSCL-D 2 of 4

- **Margins and Nodal Assessment**
  - **Bullet 2 modified: N1 and N2 node resection and mapping ~~(ATS map)~~ *should be a routine component of lung cancer resections - a* minimum of three N2 stations sampled or complete lymph node dissection.**
  - **Bullet 4 modified: Complete resection requires free resection margins, systematic node dissection or sampling, ~~no extracapsular nodal extension of the tumor,~~ and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, ~~extracapsular nodal extension,~~ unremoved positive lymph nodes, or positive pleural or pericardial effusions. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.**

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-D 2 of 4 (continued)

- **Margins and Nodal Assessment**
  - **Last bullet modified: ~~Consider referral to medical oncologist for resected stage IB, and~~ Consider referral to radiation oncologist for resected stage IIIA.**
- **Role of Surgery in Patients With Stage IIIA (N2) NSCLC**
  - **The first section was modified as follows:**

    The role of surgery in patients with pathologically documented N2 disease remains controversial.[1] ~~This population is heterogeneous. On one side of the spectrum we have a patient with negative pre-operative evaluation of the mediastinum, found to have involvement of a single station at the time of surgery.[1] On the other side we have patients with multiple pathologically proven malignant lymph node (LNs) greater than 3 cm. Most would consider the first patient a candidate for resection, while the majority would recommend definitive chemoradiotherapy, without surgery for the second. The goal of this text is to review concepts in the therapy of patients with stage IIIA (N2) NSCLC, based on the review of available evidence by the panel members of the NCCN guidelines committee. The panel recognizes that there are~~ Two randomized trials ~~that have~~ evaluated the role of surgery in this population ~~and that both did not~~ *but neither* show*ed* an overall survival benefit with the use of surgery.[2,3] However, *this population is heterogeneous and* ~~we~~ *the panel* believe*s* that these trials ~~do~~ *did* not sufficiently evaluate the nuances present with the heterogeneity of N2 disease and the likely oncologic benefit of surgery in specific clinical situations.
  - **Bullet 2, sentence added: "If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option."**
  - **Bullet 4 modified: The presence of N2 positive lymph nodes substantially increases the likelihood of positive N3 lymph nodes. Pathologic evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS ~~have provided~~ *are* additional techniques for *minimally invasive* pathologic mediastinal staging that are complementary to mediastinoscopy. Even when these modalities are employed, it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral lymph node involvement prior to a final treatment decision.**

NSCL-D 3 of 4

- **Role of Surgery in Patients With Stage IIIA (N2) NSCLC**
  - **Bullet 1 modified: ~~It may be preferable to sample mediastinal lymph nodes by EBUS/EUS prior to initiating therapy, preserving mediastinoscopy and mediastinal lymph node dissection until the planned surgical resection.~~ *Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (± EUS) in the initial pre-treatment evaluation and to reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.***
  - **Bullet 3 deleted, as it has been combined with bullet 1 on this page: "Radiographic methods have poor positive and negative predictive values in the evaluation of the mediastinum after neoadjuvant therapy. Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (+/- EUS) in the initial pre-treatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy."**
  - **Bullet 6 modified: When neoadjuvant chemoradiotherapy is used with doses lower than ~~the ones considered~~ *those used for* standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. *Treatment* breaks of more than 1 week are considered unacceptable.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013 Updates
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

Updates in the 1.2013 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2012 version include:

NSCL-D 3 of 4 (continued)

- **Role of Surgery in Patients With Stage IIIA (N2) NSCLC**
  - **Bullet 7, sentence added: "If a surgeon or center is uncertain about the feasibility or safety of resection after definitive doses of radiation, consider obtaining an additional surgical opinion from a high-volume specialized center. These operations may also benefit from additional considerations of soft tissue flap coverage in the radiation field resection."**
  - **Last bullet, sentence added: "In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy." Reference 17 added.**

NSCL-E

- **Modified title of page to "Chemotherapy Regimens for *Neoadjuvant* and Adjuvant Chemotherapy."**
- **Deleted headings of "Published Chemotherapy Regimens" and "Other Acceptable Cisplatin-based Regimens."**
- **Clarified number of cycles as "4 cycles" for the cisplatin/gemcitabine and cisplatin/docetaxel regimens.**
- **Footnote deleted: "These regimens can be used as neoadjuvant chemotherapy. They are to be given for 3 cycles prior to localized therapy. See Discussion for further information and references."**

NSCL-F 1 of 3

- **First-line therapy**
  - **Bullet 3 modified: Erlotinib is ~~indicated~~ *recommended* as a first-line therapy in patients with EGFR mutation.**
  - **Previous bullet 9 removed: In locally advanced NSCLC, concurrent chemotherapy and thoracic irradiation is superior to radiation alone and sequential chemotherapy followed by radiation.**
  - **Bullet 9 modified: Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, o*r albumin-bound paclitaxel*.**

NSCL-F 2 of 3

- **Continuation maintenance**
  - **Sub-bullet 3 added: "Continuation of bevacizumab + pemetrexed after 4 to 6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma."**
- **Switch maintenance**
  - **Sub-bullet 4 modified: Close ~~follow-up~~ *surveillance* of patients without therapy is a reasonable alternative to switch maintenance.**

NSCL-F 3 of 3

- **Reference 21 added: "Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. J Clin Oncol 2012:30:2055-2062."**

NSCL-G

- **"Herpes zoster vaccine" added as an annual immunization in long-term follow-up.**
- **Cancer screening recommendations: text removed and links to Guidelines remain.**

ST-2

- **Table 2 added to the Guidelines "Anatomic Stage and Prognostic Groups."**

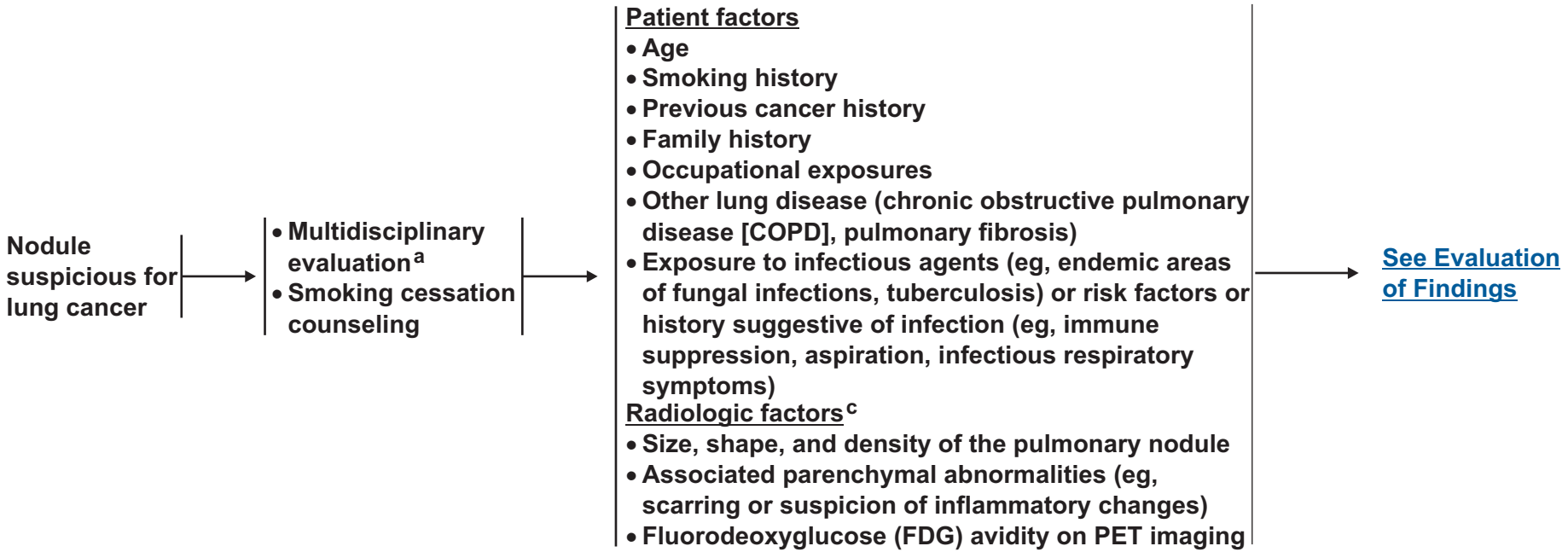
LUNG CANCER PREVENTION AND SCREENING

- **Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85% to 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products, and other tobacco control measures.**
- **Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life, and reduced survival.**
- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from second-hand smoke exposure associated with living with a smoker (http://surgeongeneral.gov/library/reports/smokeexposure/fullreport.pdf). Every person should be informed of the health consequences, addictive nature, and mortal threat posed by tobacco consumption and exposure to tobacco smoke, and effective legislative, executive, administrative, or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke (www.who.int/tobacco/framework/final_text/en/).**
- **Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (www.ahrq.gov/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.**
- **Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.**
- **Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the NCCN Guidelines for Lung Cancer Screening).**

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.

CLINICAL PRESENTATION

RISK ASSESSMENT[b]

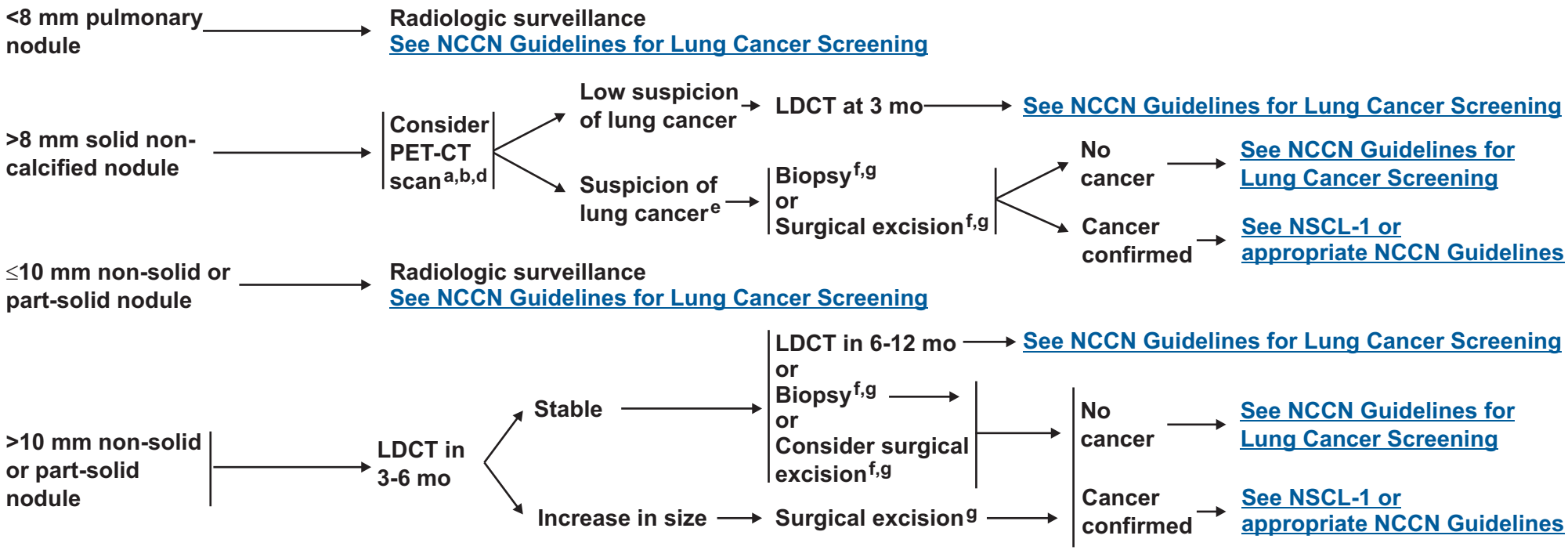


[a] Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

[b] Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

[c] See Principles of Diagnostic Evaluation (DIAG-A 1 of 2).

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.



[a] Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

[b] Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

[c] See Principles of Diagnostic Evaluation (DIAG-A 1 of 2).

[d] A positive PET result is defined as a standard uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

[e] Patients with a suspicion of lung cancer after PET-CT require histologic confirmation before any nonsurgical therapy.

[f] The choice of biopsy or surgical excision should be based on the clinical suspicion of lung cancer, location of lesion (feasibility for surgical identification and resection by minimally invasive video-assisted thoracic surgery [VATS]), and patient preferences.

[g] Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.

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

PRINCIPLES OF DIAGNOSTIC EVALUATION

- **Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.**
  - **A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.**
  - **A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by FNA.**
  - **A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.**
  - **If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection or needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.**
- **Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.**
  - **Bronchoscopy is required before surgical resection (see NSCL-2).**
  - **A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.**
  - **A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).**
- **Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (see NSCL-2).**
  - **Patients should preferably undergo invasive mediastinal staging as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure.**
  - **A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.**
  - **Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.**
- **In patients with suspected NSCLC, many techniques are available for tissue diagnosis.**
  - **Diagnostic tools that should be routinely available include:**
    - **Sputum cytology**
    - **Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)**
    - **Image-guided transthoracic needle aspiration (TTNA)**
    - **Thoracentesis**
    - **Mediastinoscopy**
    - **Video-assisted thoracic surgery (VATS) and open surgical biopsy**
  - **Diagnostic tools that provide important additional strategies for biopsy include:**
    - **Endobronchial ultrasound (EBUS)–guided biopsy**
    - **Navigational bronchoscopy**

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

PRINCIPLES OF DIAGNOSTIC EVALUATION

- **The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.**
  - **Factors to be considered in choosing the optimal diagnostic step include:**
    - **Anticipated diagnostic yield (sensitivity)**
    - **Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (that is, true negative)**
    - **Adequate volume of tissue specimen for diagnosis and molecular testing**
    - **Invasiveness and risk of procedure**
    - **Efficiency of evaluation**
      - **Access and timeliness of procedure**
      - **Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (that is, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion).**
    - **Technologies and expertise available**
  - **Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation may also benefit from involvement of a pulmonologist with experience in advanced bronchoscopic techniques for diagnosis, depending on local expertise.**
  - **The least invasive biopsy with the highest yield is preferred as the first diagnostic study.**
    - **Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.**
    - **Patients with peripheral (outer one-third) nodules should have navigational bronchoscopy, radial EBUS, or TTNA**
    - **Patients with suspected nodal disease should be biopsied by EBUS, navigational bronchoscopy, or mediastinoscopy.**
      - **Esophageal ultrasound (EUS)–guided biopsy provides additional access to station 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.**
      - **TTNA and anterior mediastinotomy (that is, Chamberlain procedure) provide additional access to anterior mediastinal (station 5 and 6) lymph nodes if these are clinically suspicious.**
    - **Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.**
    - **Patients suspected of having a solitary site of metastatic disease should preferably have tissue confirmation of that site if feasible.**
    - **Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.**
    - **Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.**

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.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2013
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion

PATHOLOGIC DIAGNOSIS OF NSCLC

Non-Small Cell Lung Cancer (NSCLC)

INITIAL EVALUATION

- Pathology review[a]
- H&P (include performance status + weight loss)
- CT chest and upper abdomen, including adrenals
- CBC, platelets
- Chemistry profile
- Smoking cessation advice, counseling, and pharmacotherapy
  - Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange http://www.ahrq.gov/clinic/tobacco/5steps.htm
- Supportive Care[b]

CLINICAL STAGE

Stage IA, peripheral[c] (T1ab, N0) Mediastinal CT negative (lymph nodes <1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage I, peripheral[c] (T2a, N0); central[c] (T1ab-T2a, N0); Stage II (T1ab-T2ab, N1; T2b, N0); stage IIB (T3, N0)[d] Mediastinal CT negative (lymph nodes <1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage IIB[e] (T3 invasion, N0); Stage IIIA[e] (T4 extension, N0-1; T3, N1)	See Pretreatment Evaluation (NSCL-4)
Stage IIIA[e] (T1-3, N2)	See Pretreatment Evaluation (NSCL-6)
Separate pulmonary nodule(s) (Stage IIB, IIIA, IV)	See Pretreatment Evaluation (NSCL-6)
Multiple lung cancers	See Pretreatment Evaluation (NSCL-8)
Stage IIIB[e] (T1-3, N3) mediastinal CT positive Contralateral (lymph nodes ≥1 cm) or palpable supraclavicular lymph nodes	See Pretreatment Evaluation (NSCL-10)
Stage IIIB[e] (T4 extension, N2-3) on CT	See Pretreatment Evaluation (NSCL-11)
Stage IV (M1a) (pleural or pericardial effusion)	See Pretreatment Evaluation (NSCL-11)
Stage IV (M1b) Solitary metastasis with resectable lung lesion	See Pretreatment Evaluation (NSCL-12)
Stage IV (M1b) Disseminated metastases	See Systemic Therapy (NSCL-15)

[a] See Principles of Pathologic Review (NSCL-A).

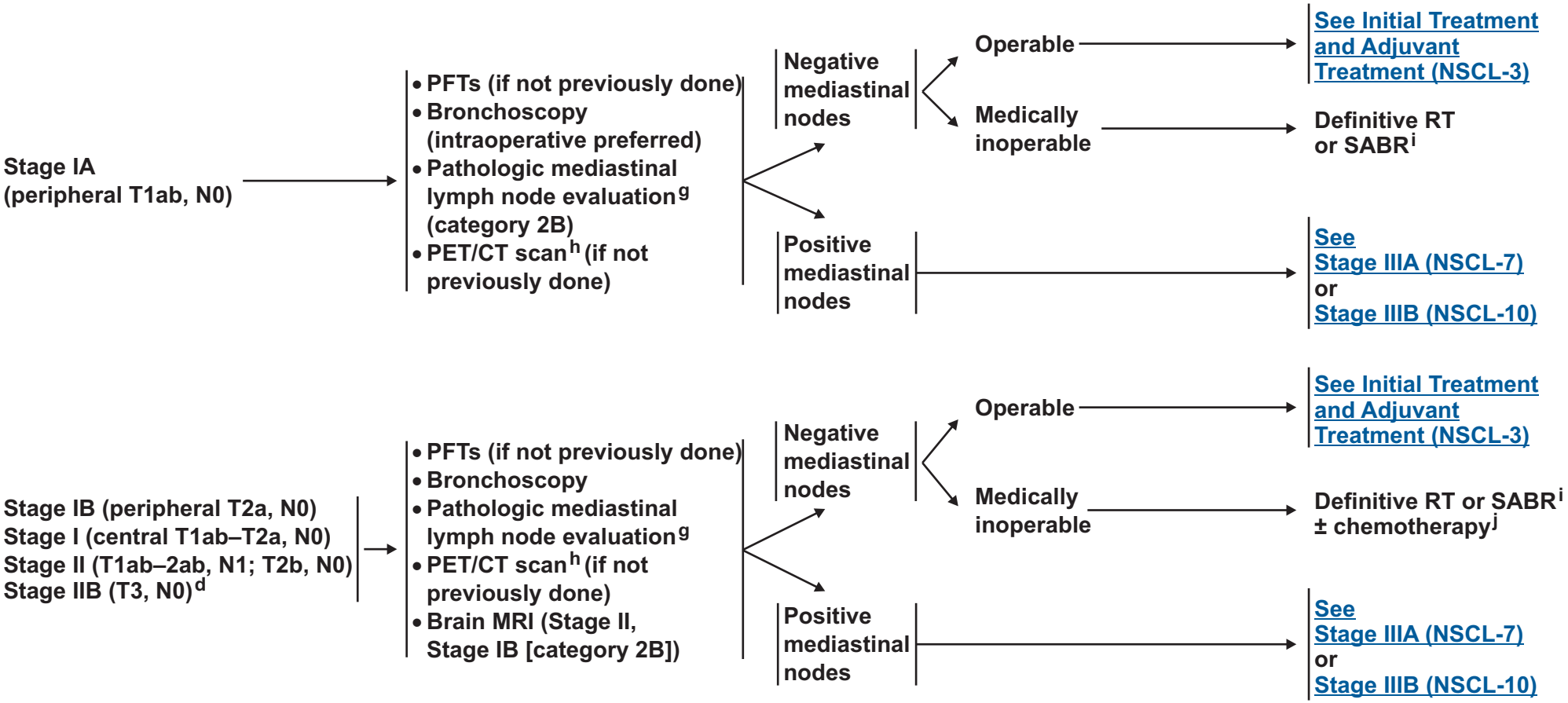
[b] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[c] Based on the CT of the chest: Peripheral = outer third of lung. Central = inner two thirds of lung.

[d] T3, N0 related to size or satellite nodules.

[e] For patients considered to have stage IIB and stage III tumors, where more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.

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.

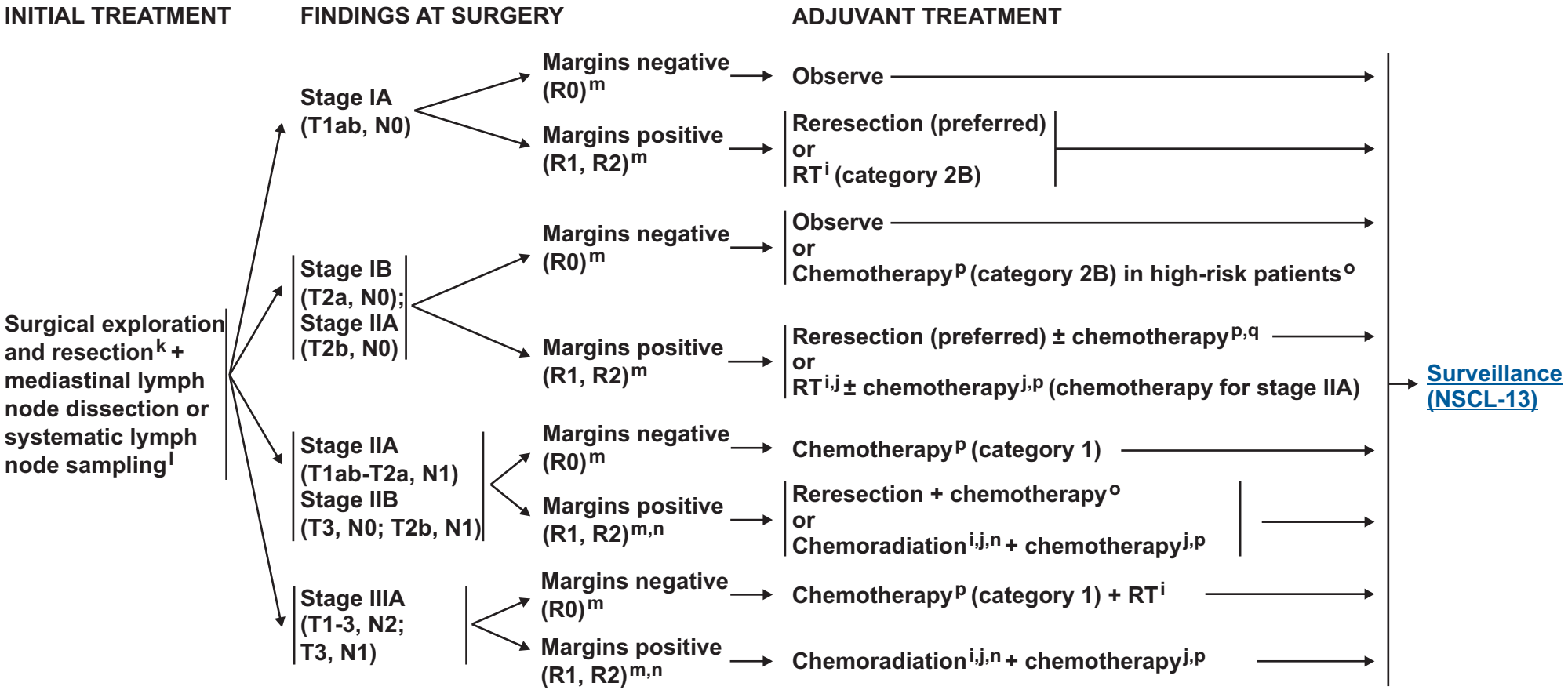


[d] T3, N0 related to size or satellite nodules.
[f] Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.
[g] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[i] See Principles of Radiation Therapy (NSCL-B).
[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

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.

NCCN Guidelines Version 1.2013
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[i] See Principles of Radiation Therapy (NSCL-B).

[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

[k] See Principles of Surgical Therapy (NSCL-D).

[l] Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

[m] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

[n] The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections.

[o] High-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy. (See Principles of Surgical Therapy, NSCL-D)

[p] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

[q] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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.

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

CLINICAL EVALUATION

Stage IIB (T3 invasion, N0)
Stage IIIA (T4 extension, N0-1; T3, N1)

- **PFTs (if not previously done)**
- **Bronchoscopy**
- **Pathologic mediastinal lymph node evaluation[g]**
- **Brain MRI**
- **MRI of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels**
- **PET/CT scan[h] (if not previously done)**

Superior sulcus tumor → **See Treatment (NSCL-5)**

Chest wall → **See Treatment (NSCL-5)**

Proximal airway or mediastinum → **See Treatment (NSCL-5)**

Unresectable disease → **See Treatment (NSCL-5)**

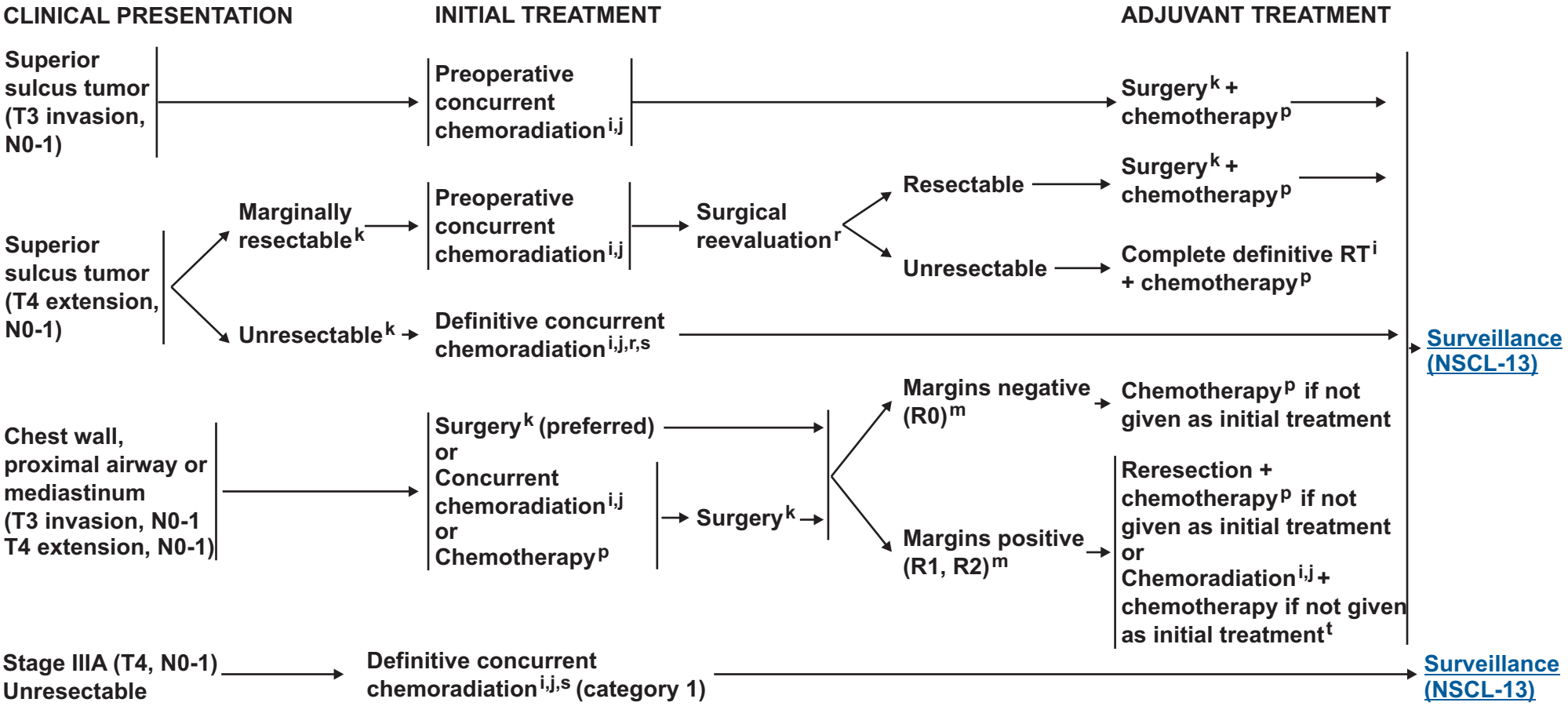
Metastatic disease → **See Treatment for Metastasis solitary site (NSCL-12) or distant disease (NSCL-14)**

[g]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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.

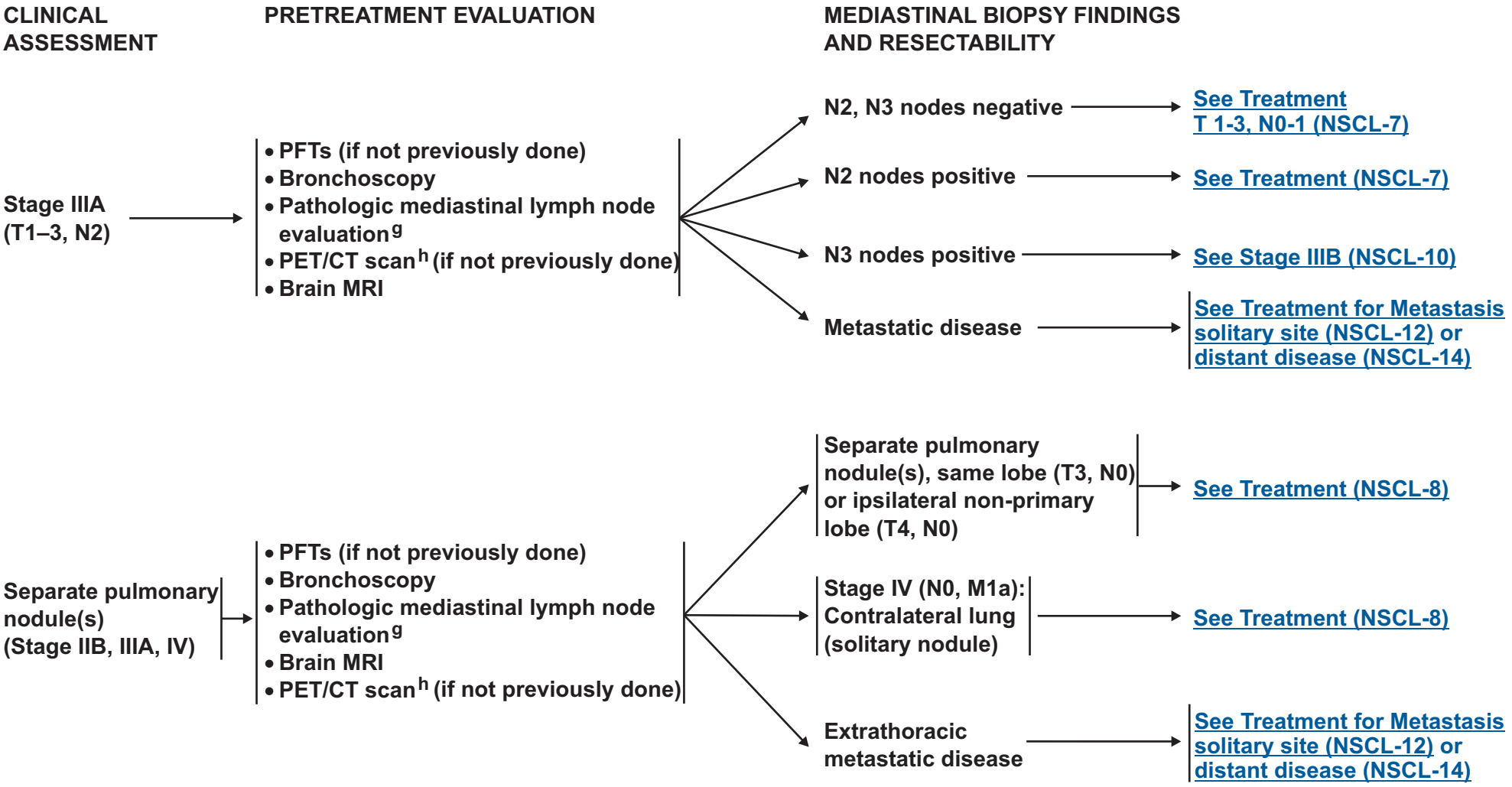
NCCN Guidelines Version 1.2013
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[i] See Principles of Radiation Therapy (NSCL-B).
[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).
[k] See Principles of Surgical Therapy (NSCL-D).
[m] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[p] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).
[r] RT should continue to definitive dose without interruption if patient is not a surgical candidate.
[s] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 4 cycles of full-dose chemotherapy.
[t] Consider RT boost if chemoradiation is given as initial treatment.

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.



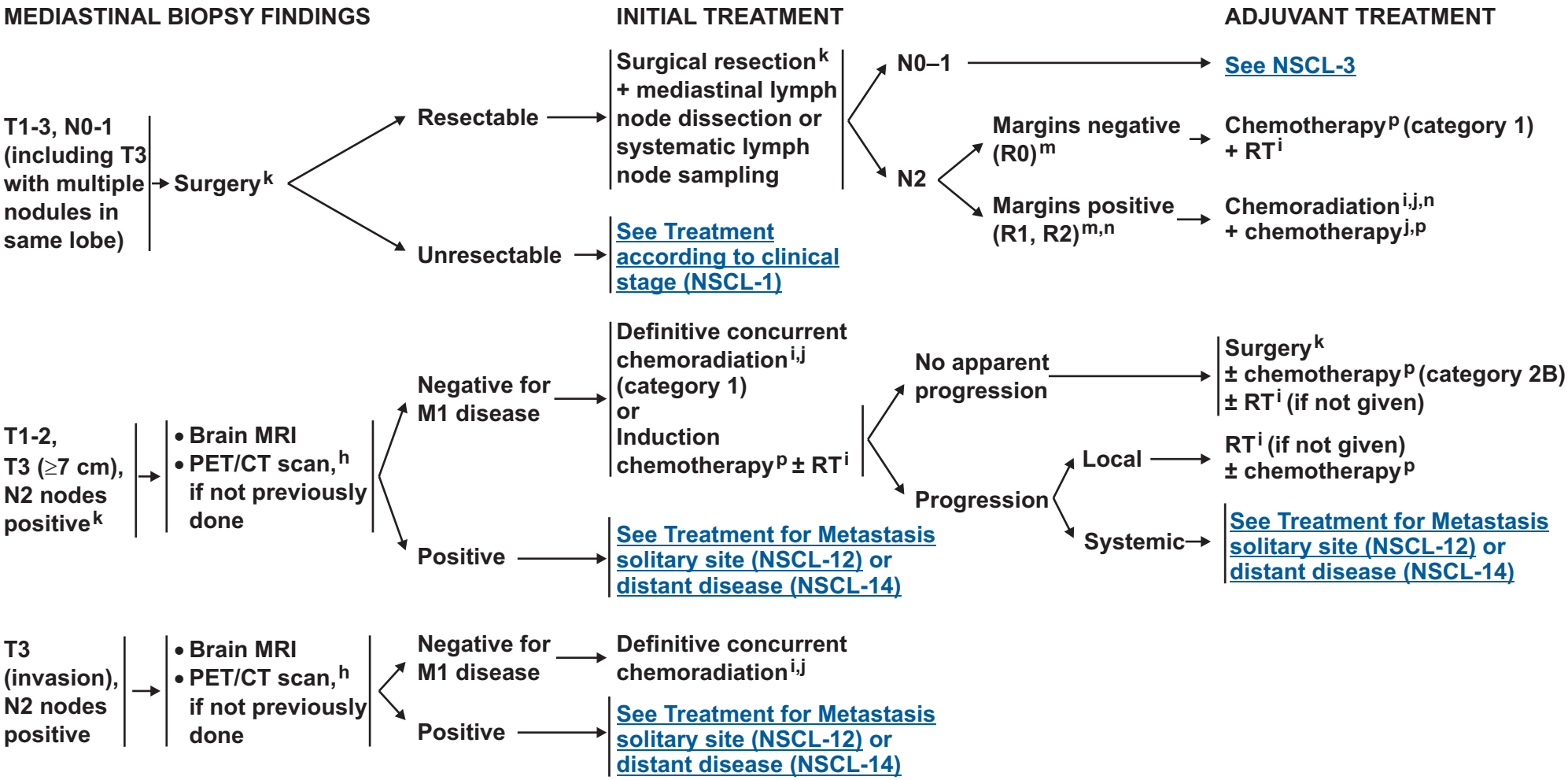
[g] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

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.

NCCN Guidelines Version 1.2013
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[i] See Principles of Radiation Therapy (NSCL-B).

[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

[k] See Principles of Surgical Therapy (NSCL-D).

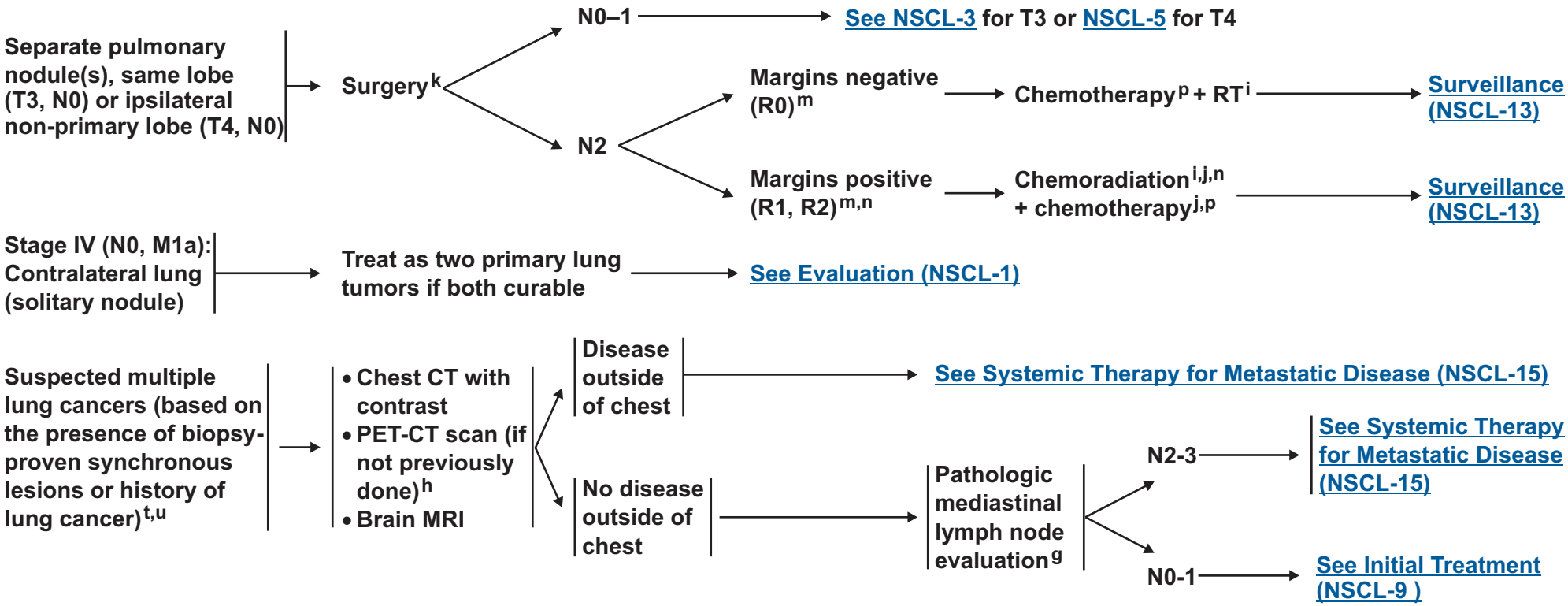
[m] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

[n] The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections.

[p] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

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.

CLINICAL PRESENTATION



[g] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

[i] See Principles of Radiation Therapy (NSCL-B).

[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

[k] See Principles of Surgical Therapy (NSCL-D).

[m] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

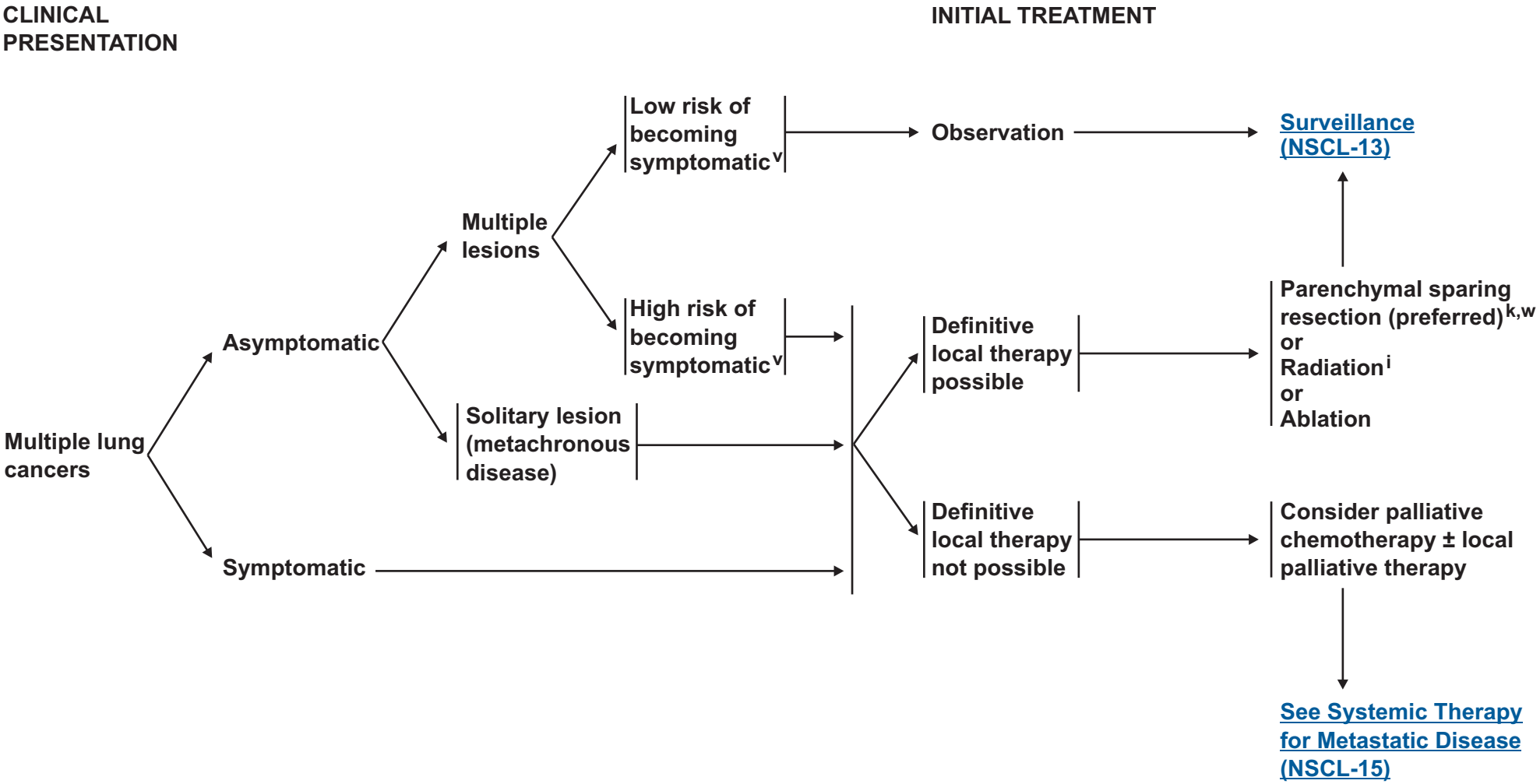
[n] The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections.

[p] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-E).

[t] Lesions with different cell types (eg, squamous cell carcinoma and adenocarcinoma) may be different primary tumors. This analysis may be limited by small biopsy samples. However, lesions of the same cell type are not necessarily metastases.

[u] For guidance regarding the evaluation, workup, and management of subsolid pulmonary nodules, please see the diagnostic evaluation of a nodule suspicious for lung cancer (DIAG-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.



[i] See Principles of Radiation Therapy (NSCL-B).

[k] See Principles of Surgical Therapy (NSCL-D).

[v] Lesions at low risk of becoming symptomatic can be observed. However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms, treatment should be considered.

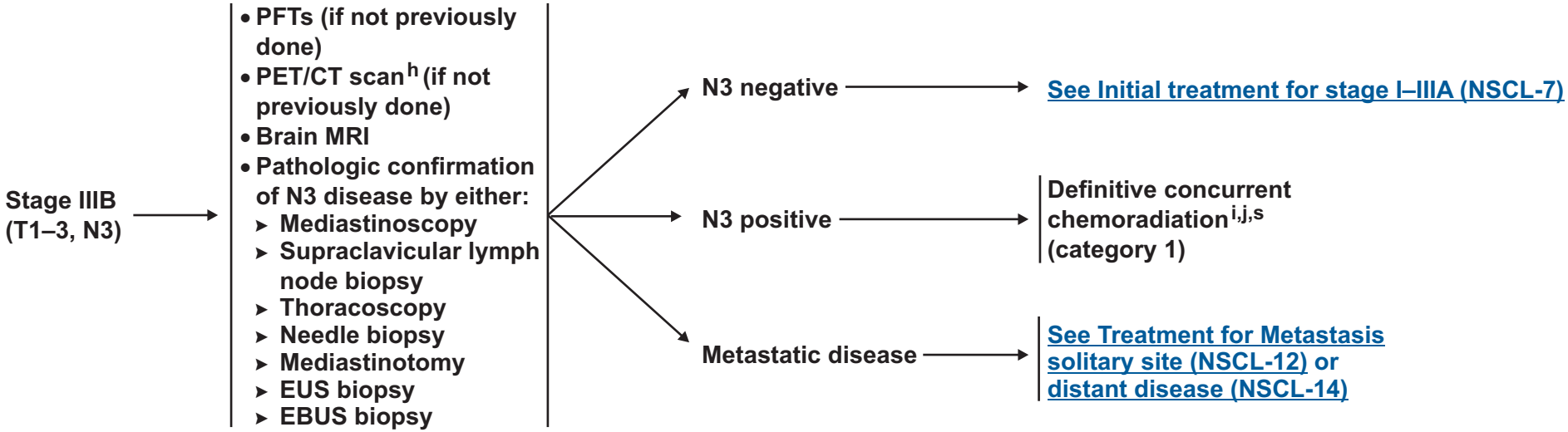
[w] Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning.

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.

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

[i] See Principles of Radiation Therapy (NSCL-B).

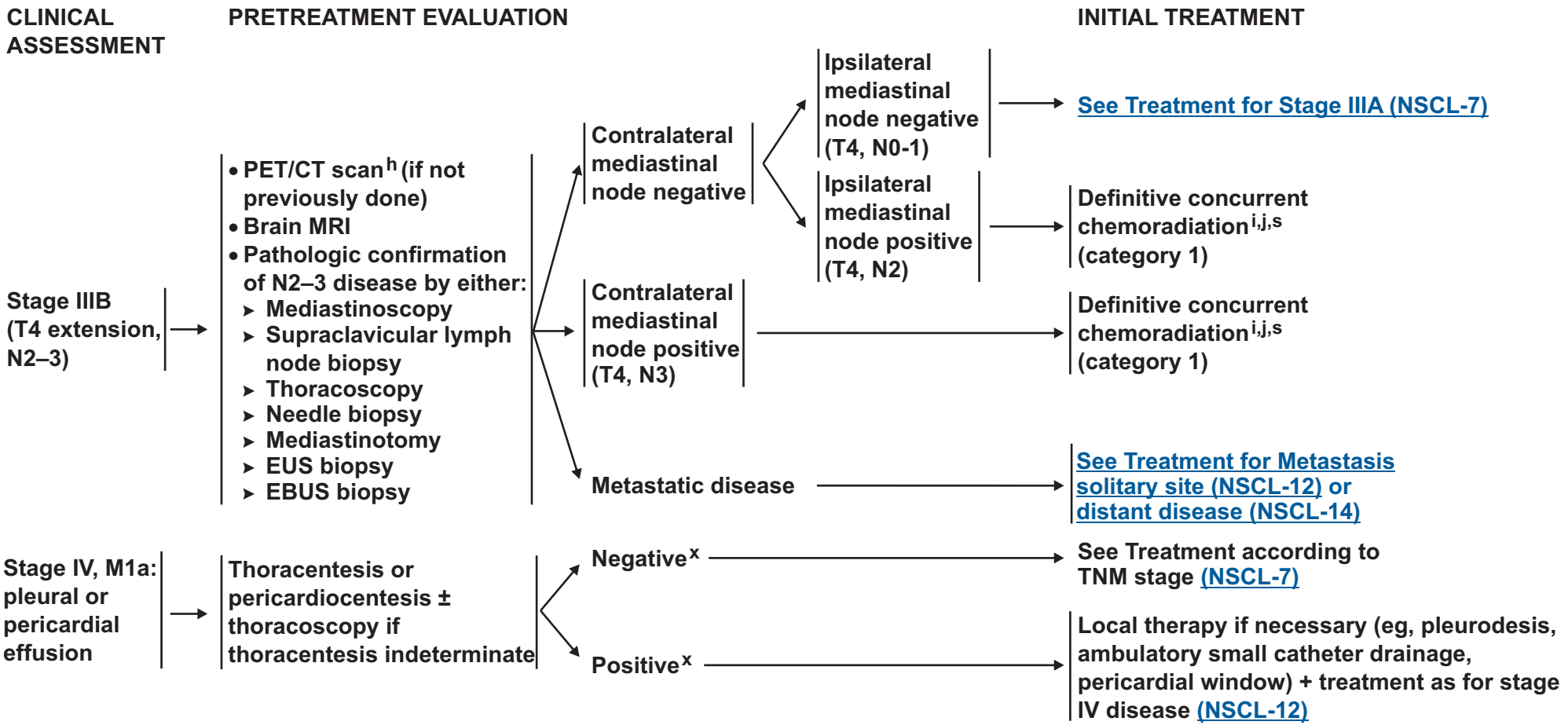
[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

[s] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 4 cycles of full-dose chemotherapy.

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.

NCCN Guidelines Version 1.2013
Non-Small Cell Lung Cancer

NCCN Guidelines Index
NSCLC Table of Contents
Discussion



[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

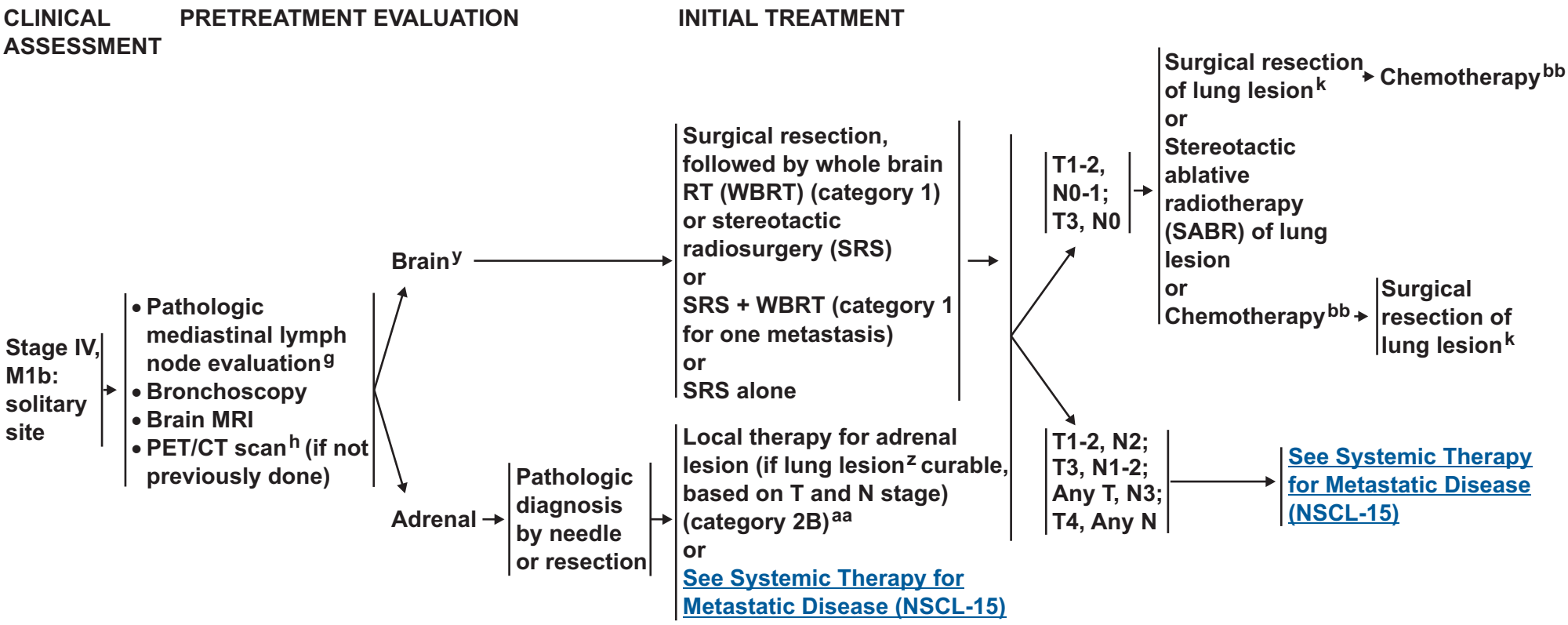
[i] See Principles of Radiation Therapy (NSCL-B).

[j] See Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

[s] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 4 cycles of full-dose chemotherapy.

[x] While most pleural effusions associated with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.

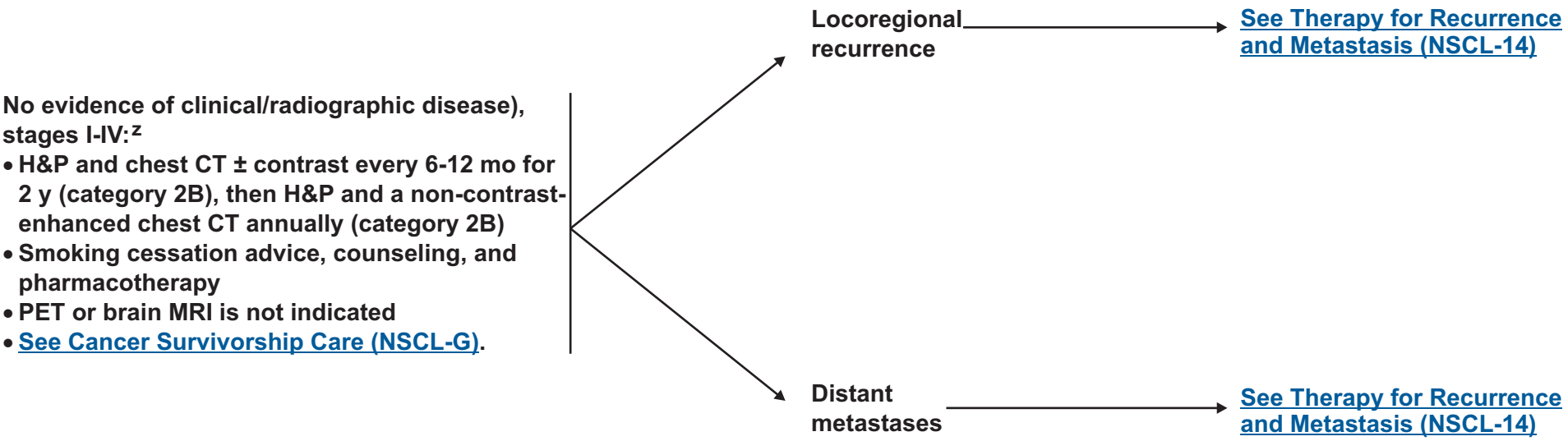
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[g] Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h] Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k] See Principles of Surgical Therapy (NSCL-D).
[y] See NCCN Guidelines for Central Nervous System Cancers.
[z] May include adrenalectomy or RT (including SABR).
[aa] Patients with N2 disease have a poor prognosis and systemic therapy should be considered.
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

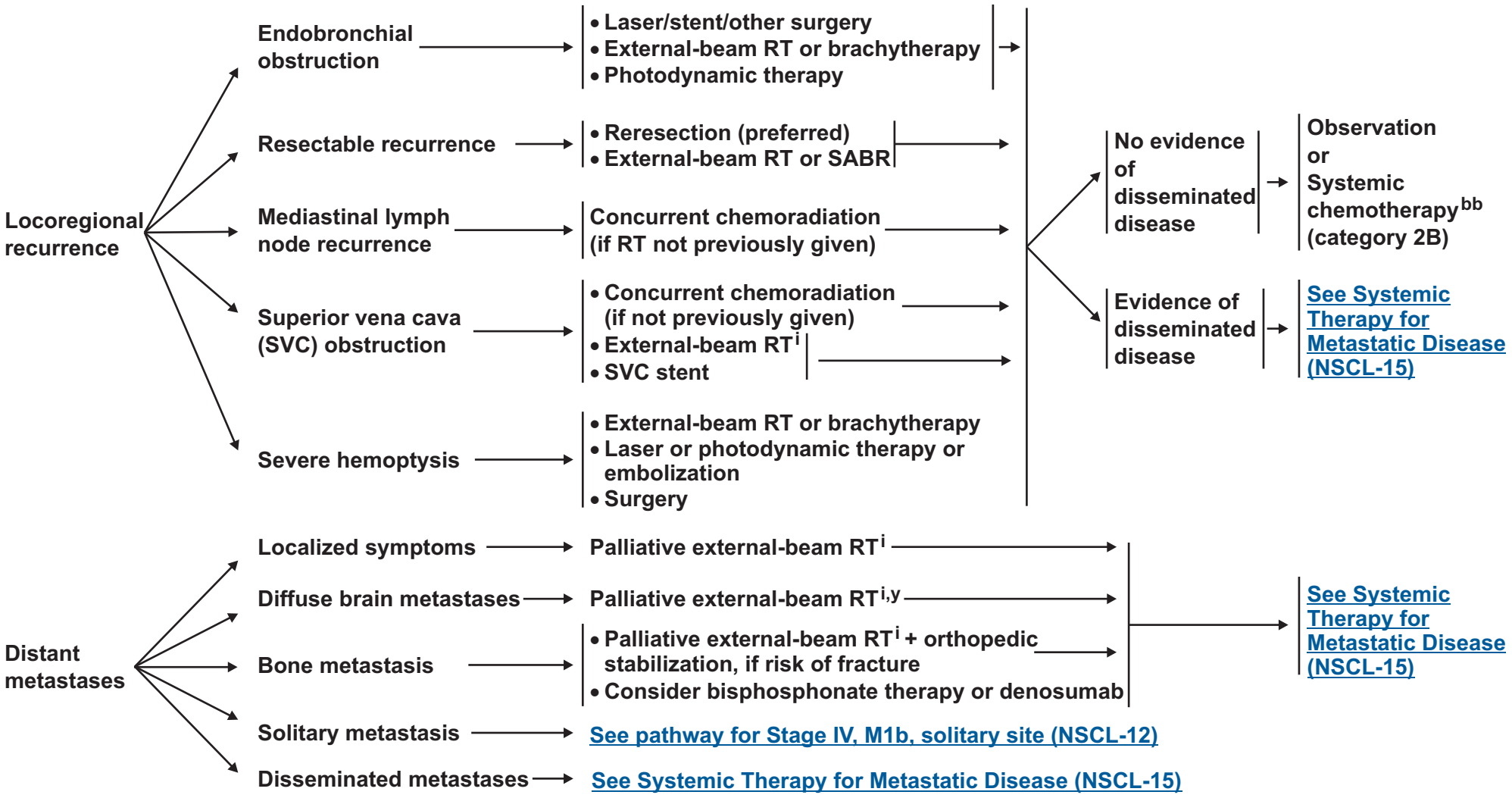
Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SURVEILLANCE



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.

THERAPY FOR RECURRENCE AND METASTASIS

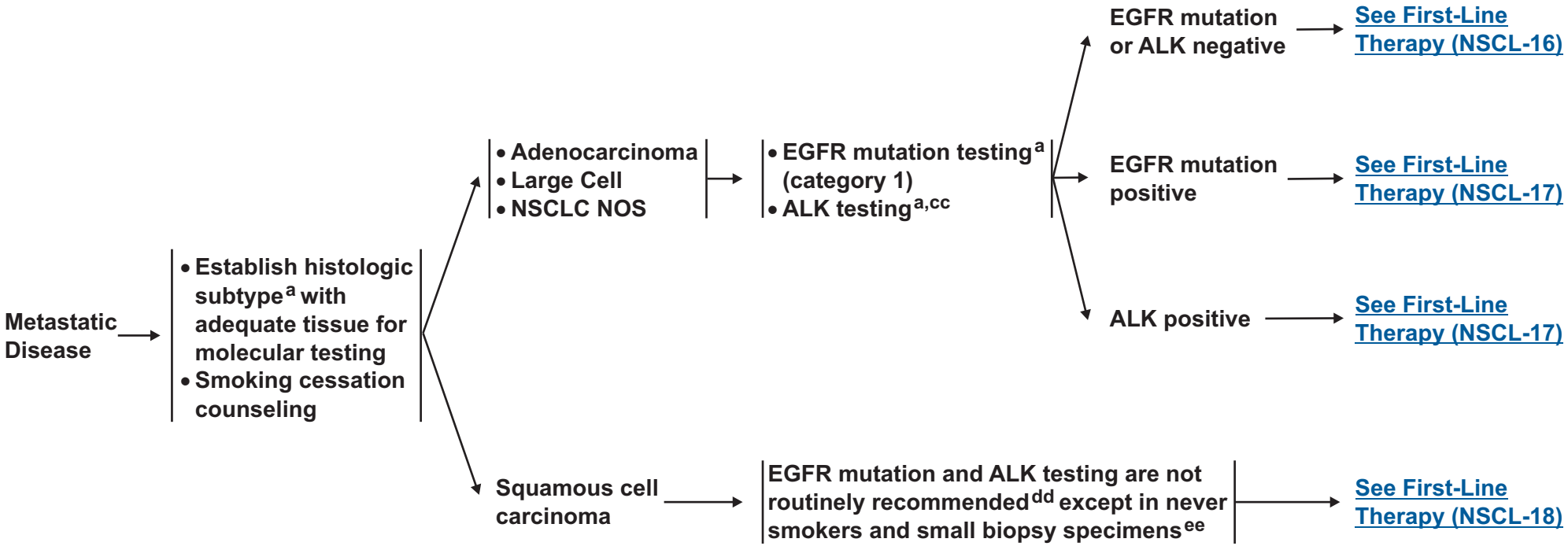


[i] See Principles of Radiation Therapy (NSCL-B).
[y] See NCCN CNS Guidelines.
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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.

SYSTEMIC THERAPY FOR METASTATIC DISEASE

HISTOLOGIC SUBTYPE



[a] See Principles of Pathologic Review (NSCL-A).

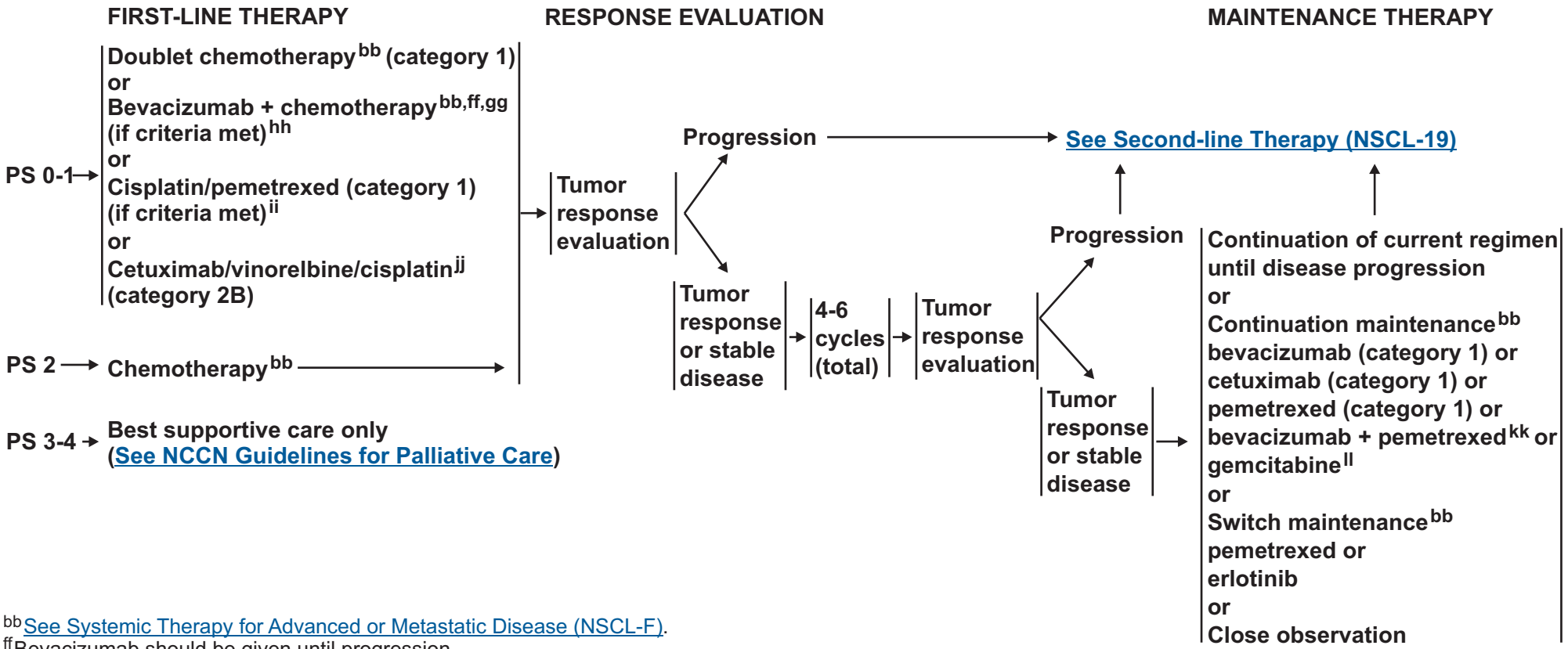
[cc] If ROS1 mutation status is known and positive, may treat with crizotinib. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

[dd] In patients with squamous cell carcinoma, the observed incidence is 2.7% with a confidence that the true incidence of mutations is less than 3.6% in patients with squamous cell carcinoma. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.

[ee] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther Published on-line August 14, 2012.

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.

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION AND ALK NEGATIVE



bb See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

ff Bevacizumab should be given until progression.

gg Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

hh Criteria for treatment with bevacizumab + chemotherapy: non-squamous NSCLC, and no recent history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

ii There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients who do not have squamous histology, in comparison to cisplatin/gemcitabine. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage NSCLC. J Clin Oncol 2008;26:3543-3551.

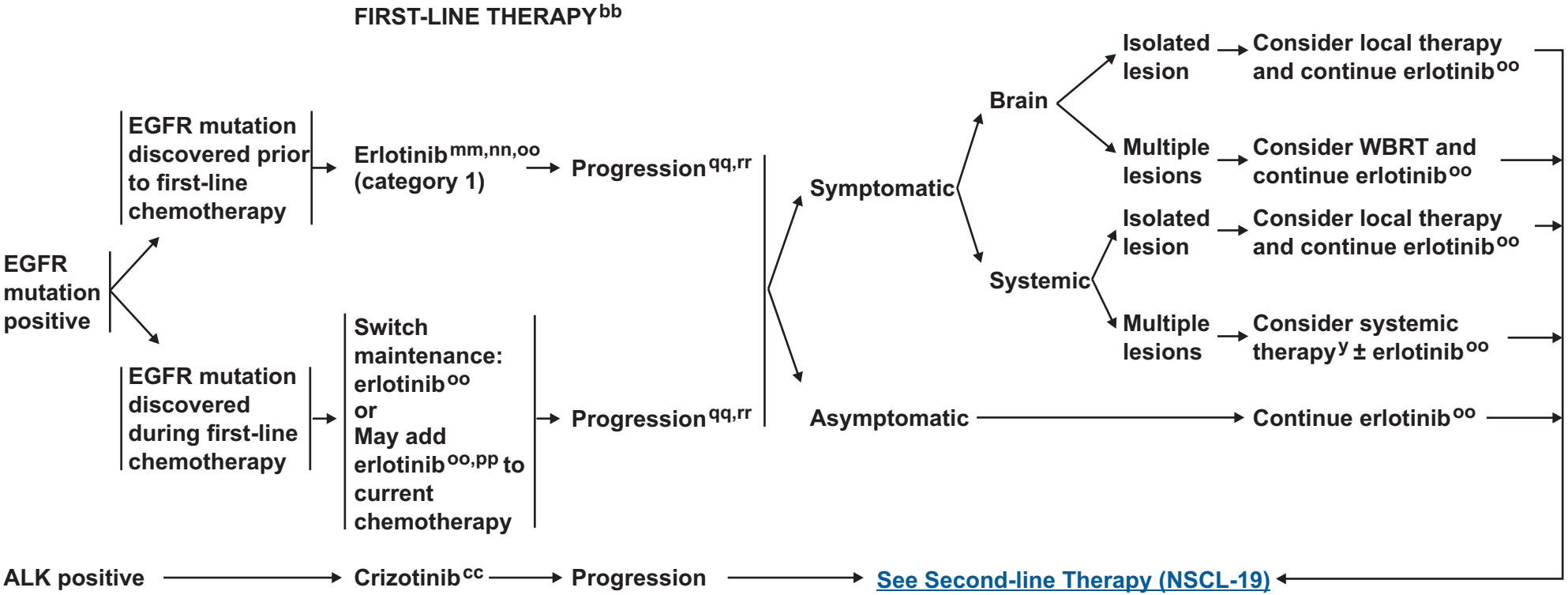
jj Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open label randomised phase III trial. Lancet 2009;373:1525-1531.

kk If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

ll Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524.

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.

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION OR ALK POSITIVE



bb See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

cc If ROS1 mutation status is known and positive, may treat with crizotinib. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

mm Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-2388. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-128.

nn For performance status 0-4.

oo In areas of the world where gefitinib is available, it may be used in place of erlotinib.

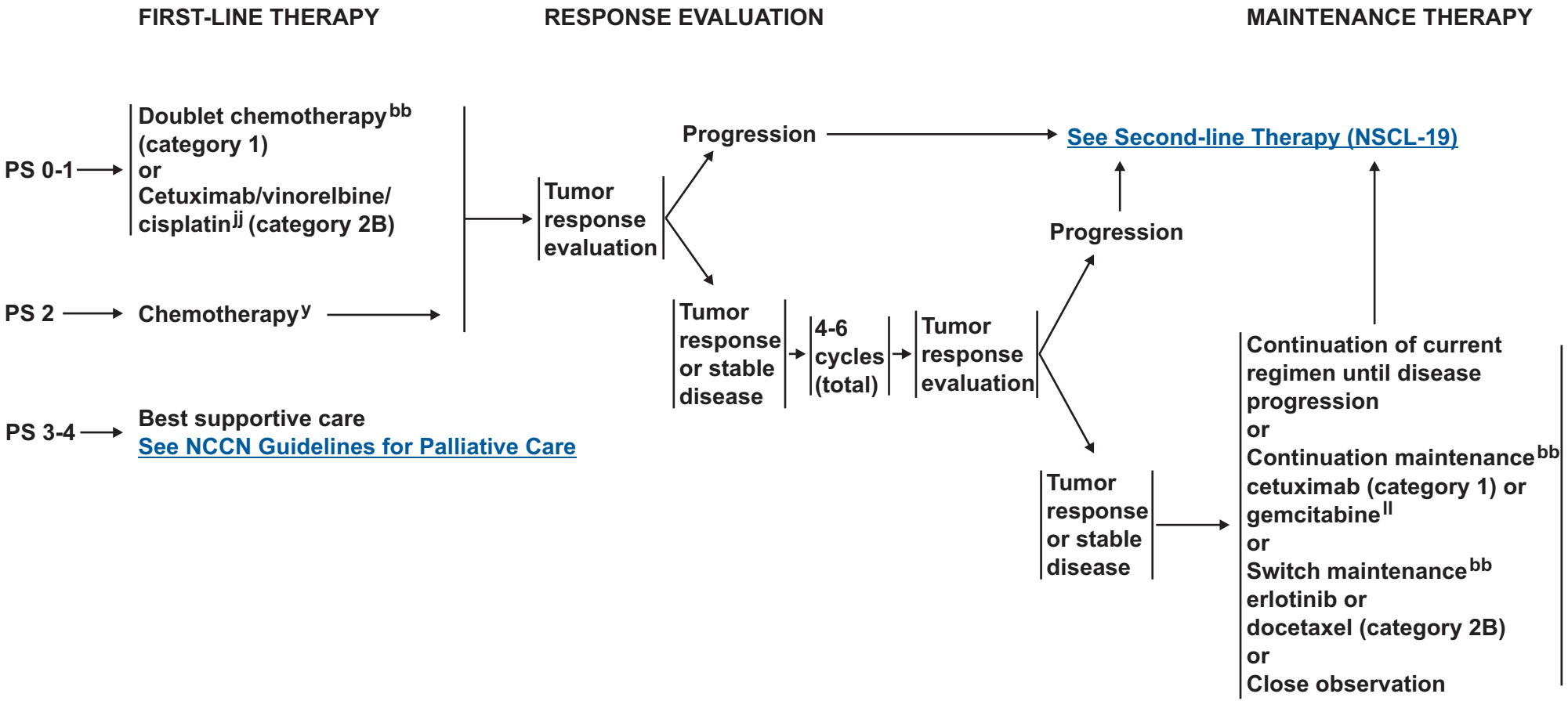
pp Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.

qq Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression.

rr Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

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.

SQUAMOUS CELL CARCINOMA



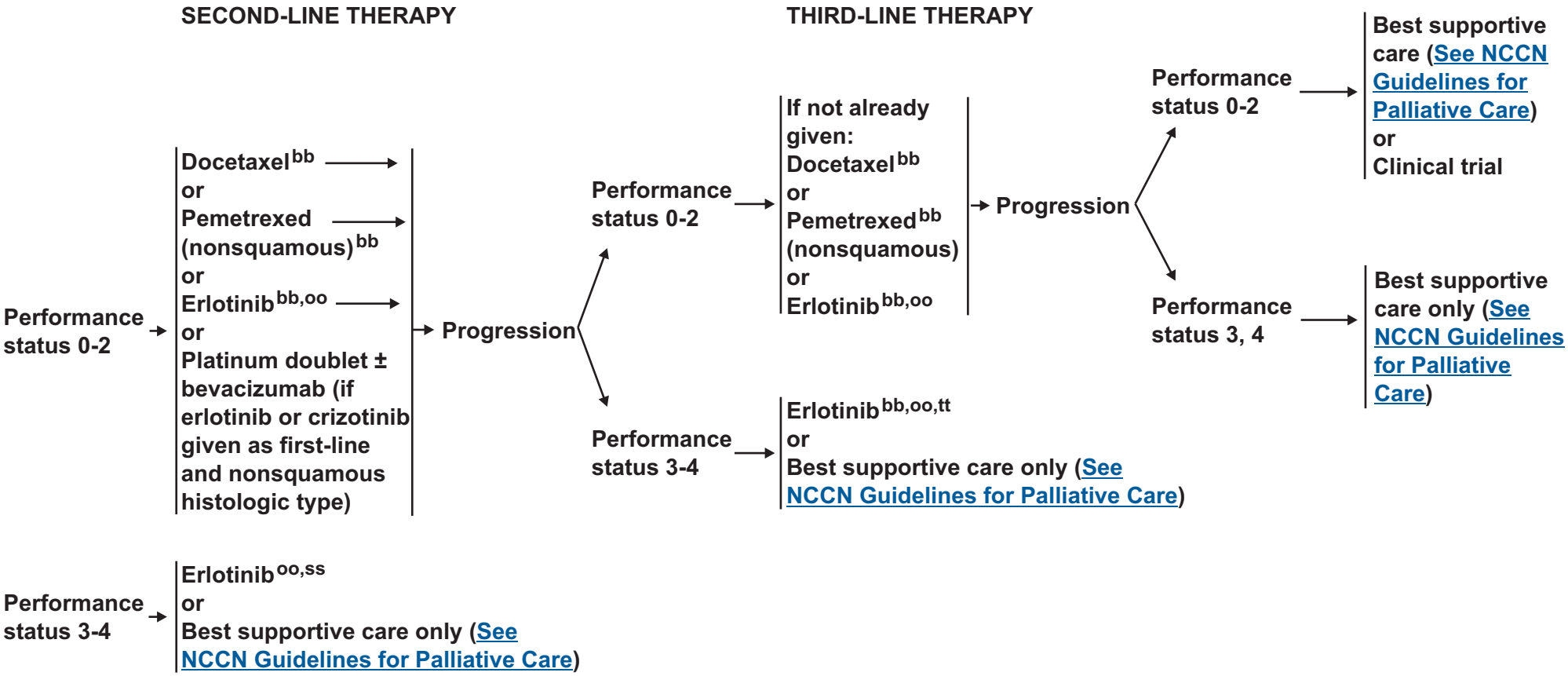
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

[jj] Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open label randomised phase III trial. Lancet 2009;373:1525-1531.

[ll] Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524.

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.

ADENOCARCINOMA, LARGE CELL, NSCLC NOS, or SQUAMOUS CELL CARCINOMA



[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[oo] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ss] Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

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

PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC,[1] including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis.[2,3] Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to an increasing number of drugable targets, primarily tyrosine kinase inhibitors (TKIs) (see *Molecular Diagnostic Studies* in this section).[4,5]
- The WHO tumor classification system has historically provided the foundation for the classification of lung tumors, including histologic types, clinical features, staging considerations, and the molecular, genetic, and epidemiologic aspects of lung cancer.[6,7]
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung with squamous morphology, neuroendocrine differentiation, and other variant carcinomas. The recently published classification of adenocarcinoma should be used for this tumor subtype in resection specimens and small biopsies.[8] Use of bronchioloalveolar carcinoma (BAC) terminology is strongly discouraged.
- The generic term "non-small cell lung cancer (NSCLC)" should be avoided as a single diagnostic term. In small biopsies of poorly differentiated carcinomas where immunohistochemistry (IHC) is used, the following terms are acceptable: "NSCLC favor adenocarcinoma" or "NSCLC favor squamous cell carcinoma."[8] Mutational testing (eg, epidermal growth factor receptor [EGFR]) should be performed in this setting.
- Although formalin-fixed paraffin-embedded tumor may be used for most molecular analyses, acquisition of fresh cryopreserved tumor tissue for advanced molecular studies should be considered.
- Limited use of IHC studies in small tissue samples is strongly recommended, thereby preserving critical tumor tissue for molecular studies, particularly in patients with advanced-stage disease. A limited panel of p63 and TTF-1 should suffice for most diagnostic problems.[8]

Adenocarcinoma Classification[8]

- Adenocarcinoma in situ (AIS; formerly BAC): ≤3 cm nodule, lepidic growth, mucinous, non-mucinous, or mixed mucinous/non-mucinous types.
- Minimally invasive adenocarcinoma (MIA): ≤3 cm nodule with ≤5 mm of invasion, lepidic growth, mucinous, non-mucinous, or mixed mucinous/non-mucinous types.
- Invasive adenocarcinoma, predominant growth pattern: lepidic >5 mm of invasion, acinar, papillary, micropapillary, or solid with mucin
- Invasive adenocarcinoma variants: mucinous adenocarcinoma, colloid, fetal, and enteric morphologies.

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

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 4)

Immunohistochemical Staining

- Although the concordance is generally good between the histologic subtype and the immunophenotype seen in small biopsies compared with surgical resection specimens, caution is advised in attempting to subtype small biopsies with limited material or cases with an ambiguous immunophenotype.
- IHC should be used to differentiate primary pulmonary adenocarcinoma from the following—squamous cell carcinoma, large cell carcinoma, metastatic carcinoma, and malignant mesothelioma—and to determine whether neuroendocrine differentiation is present.[9-11]
- Primary pulmonary adenocarcinoma
  - An appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to the lung.[12]
  - TTF-1 is a homeodomain-containing nuclear transcription protein of the Nkx2 gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid. TTF-1 immunoreactivity is seen in primary pulmonary adenocarcinoma in the majority (70%-100%) of non-mucinous adenocarcinomas subtypes.[13] Metastatic adenocarcinoma to the lung is virtually always negative for TTF-1 except in metastatic thyroid malignancies, in which case thyroglobulin is also positive.
  - Napsin A—an aspartic proteinase expressed in normal type II pneumocytes and in proximal and distal renal tubules—appears to be expressed in >80% of lung adenocarcinomas and may be a useful adjunct to TTF-1.[12]
  - The panel of TTF-1 and p63 (or alternatively p40) may be useful in refining the diagnosis to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens previously classified as NSCLC, not otherwise specified (NOS).[8]
- Neuroendocrine differentiation
  - CD56, chromogranin, and synaptophysin are used to identify neuroendocrine tumors.
- Malignant mesothelioma versus pulmonary adenocarcinoma
  - The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) is made by using a panel of markers, including 2 with known immunopositivity in mesothelioma (but negative in adenocarcinoma) and 2 with known positivity in adenocarcinoma (but negative in mesothelioma).[11]
    - Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma).[14,15]
  - Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (negative in mesothelioma).[8,11]

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

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

Molecular Diagnostic Studies in Lung Cancer

- **EGFR and KRAS**
  - EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents a critical biological determinant for proper therapy selection in patients with lung cancer.
  - There is a significant association between EGFR mutations—especially exon 19 deletion and exon 21 (L858R) and exon 18 (G719X) mutations—and sensitivity to TKIs.[16-19]
  - The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.[20,21]
  - EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.[22]
  - KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy.[23]
  - The prevalence of EGFR mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher EGFR mutation frequency in non-smokers, women, and non-mucinous cancers. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.[24] The most common EGFR mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations are more common in non-mucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.
  - Primary resistance to TKI therapy is associated with KRAS mutation. Acquired resistance is associated with second-site mutations within the EGFR kinase domain, amplification of alternative kinases (such as MET), histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).
- **ALK**
  - Anaplastic lymphoma kinase (ALK) gene rearrangements represent the fusion between ALK and various partner genes, including echinoderm microtubule-associated protein-like 4 (EML4).[25] ALK fusions have been identified in a subset of patients with NSCLC and represent a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.[26] Crizotinib is an oral ALK inhibitor that is approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement (ie, ALK positive).
  - ALK NSCLC occurs most commonly in a unique subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor EGFR mutations.[27,28] However, for the most part, ALK translocations and EGFR mutations are mutually exclusive.[27, 29-31] ALK translocations tend to occur in younger patients and in those with more advanced NSCLC, though this relationship has not been reported for EGFR mutant NSCLC.[31,32]
  - The current standard method for detecting ALK NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged anaplastic large cell lymphomas (ALCL), is applicable for the diagnosis of ALK-rearranged lung adenocarcinomas. The IHC tests used to diagnose ALK-rearranged ALCLs in clinical laboratories worldwide are inadequate for the detection of most ALK-rearranged lung adenocarcinomas.[33,34] This inadequacy is because of the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs. A molecular diagnostic test that uses FISH was recently approved by the FDA to determine which patients with lung adenocarcinoma are ALK positive.

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

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

[1] Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.
[2] Fossella FV, Putnam JB, Komaki R, eds. Lung Cancer. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.
[3] Schrump DS, Carter D, Kelsey CR, et al. Non-small cell lung cancer. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, et al., eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins; 2011.
[4] Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:423-429.
[5] Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005;23:5900-5909.
[6] Travis WD. Pathology and genetics of tumours of the lung, pleura, thymus and heart Lyon: IARC Press; 2004.
[7] Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-1068.
[8] Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-285.
[9] Rekhtman N, Ang DC, Sima CS, et al. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol 2011;24:1348-1359.
[10] Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Am J Surg Pathol 2011;35:15-25.
[11] Husain AN, Colby T, Ordonez N, et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma: 2012 Update of the Consensus Statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2012 Aug 28. [Epub ahead of print]
[12] Jagirdar J. Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. Arch Pathol Lab Med 2008;132:384-396.
[13] Goldstein NS, Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001;116:319-325.
[14] Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-380.
[15] Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. Am J Cancer Res 2011;1:14-24.
[16] Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
[17] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500.
[18] Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98.
[19] Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-495.
[20] Lund-Iverson M, Kleinber L, Fjellbirkeland L, Helland A, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. J Thorac Oncol 2012;7:1471-1413.
[21] Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small cell lung cancer: preclinical data and clinical implications. Lancet Oncol 2012;13:e23-31.
[22] Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res 2006;12:7232-7241.
[23] Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-262.
[24] Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. J Mol Diagn 2007;9:320-326.
[25] Cataldo KA, Jalal SM, Law ME, et al. Detection of t(2;5) in anaplastic large cell lymphoma: comparison of immunohistochemical studies, FISH, and RT-PCR in paraffin-embedded tissue. Am J Surg Pathol 1999;23:1386-1392.
[26] Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-1703.
[27] Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-4253.
[28] Koivunen JP, Kim J, Lee J, et al. Mutations in the LKB1 tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. Br J Cancer 2008;99:245-252.
[29] Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008;14:4275-4283.
[30] Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-19897.
[31] Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol 2009;22:508-515.
[32] Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-1733.
[33] Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-5223.
[34] Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. Clin Cancer Res 2010;16:1561-1571.

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

PRINCIPLES OF RADIATION THERAPY (1 of 9)

General Principles (see Table 1. Commonly Used Abbreviations in Radiation Therapy)

- Determination of the appropriateness of radiation therapy (RT) should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.
- RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with NSCLC.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technological standard is CT-planned 3D-CRT.[1]
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET-CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy. Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.[2-4]
- Centers using advanced technologies should implement and document modality-specific quality assurance measures. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies. Useful references include the ACR-ASTRO Practice Guidelines for Radiation Oncology (http://www.acr.org/~/media/ACR/Documents/PGTS/toc.pdf).

Early-Stage NSCLC (Stage I)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable and who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.[5-10]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy, eg, ≥ age 75, poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.[10-12] A prospective randomized cooperative group trial of sublobar resection versus SABR is ongoing.
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are alternatives.[13-14]
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC* below).

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II and stage III is concurrent chemoRT.[15-17] http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf) RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemoRT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.[18,19] http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf

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

PRINCIPLES OF RADIATION THERAPY (2 of 9)

Locally Advanced NSCLC (Stage II-IIIB) **(continued)**

- **Accelerated RT regimens may be beneficial, particularly if not concurrent with chemotherapy (ie, in a sequential or RT-only approach).[20,21]**
- **RT has a role before or after surgery.**
  http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf
  - **Preoperative concurrent chemoRT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[22] and is recommended for resectable superior sulcus tumors.[23-24]**
  - **Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.[25,26]**
  - **The determination of resectability in trimodality therapy should be made prior to initiation of all treatment.**
  - **In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.[27,28] Although, the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients[29-31] and is recommended for positive resection margins.**
  - **PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.[32]**

Advanced/Metastatic NSCLC (Stage IV)

- **RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction).**
- **Definitive local therapy to isolated or limited metastatic sites (oligometastases) (including but not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease. Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[33-35]**
- **See the NCCN Guidelines for CNS Cancers regarding RT for brain metastases.**

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints (See Tables 2-5 on NSCL-B 6 of 9 and NSCLB 7 of 9)

- **ICRU Reports 62 and 83 detail the current definitions of target volumes for 3D-RT and IMRT. GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a set-up margin for positioning and mechanical variability.**
  http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx
- **PTV margin can be decreased by immobilization, motion management, and IGRT techniques.**
- **Consistent delineation of normal structures is critical for evaluating plans for safety. The RTOG consensus lung contouring atlas is a useful resource. http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx**
- **Commonly used prescription doses and normal tissue dose constraints are summarized in Tables 2-5. These are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.[37,38] Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.[39-43]**

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

PRINCIPLES OF RADIATION THERAPY (3 of 9)

Node-negative early-stage SABR

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[44] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.[44,45] For centrally located tumors (defined as within 2 cm of the proximal bronchial tree), 4-10 fraction risk-adapted SABR regimens appear to be effective and safe,[45,46] while 54-60 Gy in 3 fractions is unsafe and should be avoided.[47] The dose for 5-fraction regimens is being studied prospectively in RTOG 0813.
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.[48]
- Prescription doses incompletely describe the actual delivered doses, which also depend strongly on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.[49,50] All of these must be considered when interpreting or emulating ~~a~~ regimens from prior studies.

Locally advanced stage/conventionally fractionated RT

- IFI omitting ENI allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in PET-CT staged patients.[51-55] One randomized trial found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[56] IFI is reasonable in order to optimize definitive dosing to the tumor.
- The most commonly prescribed doses for definitive RT are 60-70 Gy in 2 Gy fractions. Doses of at least 60 Gy should be given.[57] Dose escalation in RT alone,[58] sequential chemoRT,[59] or concurrent chemoRT[60] is associated with better survival in non-randomized comparisons. Doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected.[61-64] The final results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy are pending, but preliminarily, 74 Gy was not associated with improved overall survival at 1 year.[65]
- Doses of 45 to 50 Gy in 1.8 to 2 Gy fractions are standard preoperative doses. Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,[66-69] but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high-dose RT.
- In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.[70] Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.[29,30] Lung dose constraints should be more conservative as tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.[71]

Advanced stage/palliative RT

- The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment,[72-75] and are preferred for patients with poor performance status and/or shorter life expectancy. When higher doses (>30 Gy) are warranted, 3D-CRT should be used to reduce normal tissue irradiation.

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

PRINCIPLES OF RADIATION THERAPY (4 of 9)

Radiation Therapy Simulation, Planning, and Delivery

- Simulation should be performed using CT scans obtained in the RT treatment position with appropriate immobilization devices. IV contrast with or without oral contrast is recommended for better target/organ delineation whenever possible in patients with central tumors or nodal disease. Because IV contrast can affect tissue heterogeneity correction calculations, density masking or use of a pre-contrast scan may be needed when intense enhancement is present.
- PET/CT significantly improves targeting accuracy,[76] especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.[77] Given the potential for rapid progression of NSCLC,[78,79] PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal is to obtain PET/CT in the treatment position.
- Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or, ideally, 4D-CT.
- Photon beam energy should be individualized based on the anatomic location of the tumors and beam paths. In general, photon energies between 4 to 10 MV are recommended for beams passing through low-density lung tissue before entering the tumor. When there is no air gap before the beam enters the tumor (such as for some large mediastinal tumors or tumors attached to chest wall), higher energies may improve the dose distribution, especially when using a smaller number of fixed beam angles.
- Tissue heterogeneity correction and accurate dose calculation algorithms that account for build-up and lateral electron scatter effects in heterogeneous density tissues are recommended. Heterogeneity correction with simple pencil beam algorithms is not recommended.[50]
- Respiratory motion should be managed when motion is excessive. This includes (but is not limited to) forced shallow breathing with abdominal compression, accelerator beam gating with the respiratory cycle, dynamic tumor tracking, active breathing control (ABC), or coaching/biofeedback techniques. If motion is minimal or the ITV is small, motion-encompassing targeting is appropriate. A useful resource for implementation of respiratory motion management is the report of AAPM Task Group 76.[80]
- IGRT—including (but not limited to) orthogonal pair planar imaging and volumetric imaging (such as CBCT or CT on rails)—is recommended when using SABR and 3D-CRT/IMRT with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques.

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

PRINCIPLES OF RADIATION THERAPY (5 of 9)

Table 1. Commonly Used Abbreviations in Radiation Therapy

RT	Radiation Therapy or Radiotherapy
2D-RT	2-Dimensional RT
3D-CRT	3-Dimensional Conformal RT
4D-CT	4-Dimensional Computed Tomography
AAPM	American Association of Physicists in Medicine
ABC	Active Breathing Control
ACR	American College of Radiology
ASTRO	American Society for Radiation Oncology
BED	Biologically Effective Dose
CBCT	Cone-Beam CT
CTV*	Clinical Target Volume
DVH	Dose-Volume Histogram
ENI	Elective Nodal Irradiation
GTV*	Gross Tumor Volume
ICRU	International Commission on Radiation Units and Measurements
IFI	Involved Field Irradiation
IGRT	Image-Guided RT
IMRT	Intensity-Modulated RT
ITV*	Internal Target Volume
MLD	Mean Lung Dose
OAR	Organ at Risk
OBI	On-Board Imaging
PORT	Postoperative RT
PTV*	Planning Target Volume
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RTOG	Radiation Therapy Oncology Group
SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
V20	% Volume of an OAR receiving ≥20 Gy
VMAT	Volumetric Modulated Arc Therapy

*Refer to ICRU Report 83 for detailed definitions.

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

PRINCIPLES OF RADIATION THERAPY (6 of 9)

Table 2. Commonly Used Doses for SABR

Total Dose	# Fractions	Example Indications
25-34 Gy	1	Peripheral, small (<2 cm) tumors, esp. >1 cm from chest wall
45-60 Gy	3	Peripheral tumors and >1 cm from chest wall
48-50 Gy	4	Central or peripheral tumors <4-5 cm, esp. <1 cm from chest wall
50-55 Gy	5	Central or peripheral tumors, esp. <1 cm from chest wall
60-70 Gy	8-10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal Cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial Plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great Vessels	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
Stomach	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

*Based on constraints used in recent and ongoing RTOG SABR trials (RTOG 0618, 0813, & 0915).

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

PRINCIPLES OF RADIATION THERAPY (7 of 9)

Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

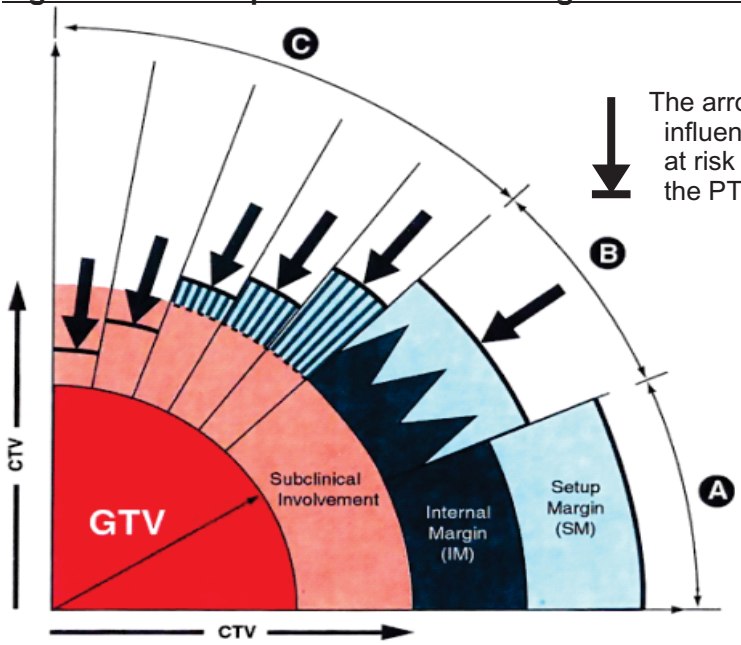
Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60-74 Gy	2 Gy	6-7.5 weeks
Preoperative RT	45-50 Gy	1.8-2 Gy	5 weeks
Postoperative RT			
• Negative margins	50-54 Gy	1.8-2 Gy	5-6 weeks
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy	6 weeks
• Gross residual tumor	60-70 Gy	2 Gy	6-7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30-45 Gy	3 Gy	2-3 weeks
• Bone metastases with soft tissue mass	20-30 Gy	4-3 Gy	1-2 weeks
• Bone metastases without soft tissue mass	8-30 Gy	8-3 Gy	1 day-2 weeks
• Brain metastases	CNS GLs	CNS GLs	CNS GLs
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1-2 weeks
• Any metastasis in patients with poor PS	8-20 Gy	8-4 Gy	1 day-1 week

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30-35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; MLD ≤20 Gy
Heart	V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose
Brachial plexus	Max ≤66 Gy

Vxx = % of the whole OAR receiving ≥xx Gy.

Figure 1. ICRU Report 62 Schema of Target Volume Definitions



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

PRINCIPLES OF RADIATION THERAPY - References (8 of 9)

[1]Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. J Clin Oncol 2011;29:2305-2311.
[2]Liao ZX, Komaki RR, Thames HD, et al. Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non-Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010; 76:775-781.
[3]Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for nonsmall cell lung cancer. Cancer 2011; 117:3004-3013.
[4]Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III nonsmall cell lung cancer. Cancer 2011;117:4707-4713.
[5]Timmerman R, Paulus R, Galvin J, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. JAMA 2010; 303:1070-1076.
[6]Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009; 27:3290-3296.
[7]Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-1358.
[8]Grutters JPC, Kessels AGH, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol 2010; 95:32-40.
[9]Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010; 28:5153-5159.
[10]Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-1070.
[11]Grills IS, Mangona VS, Welsh R, et al. Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non-Small-Cell Lung Cancer. J Clin Oncol 2010;28:928-935.
[12]Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. J Thorac Cardiovasc Surg 2010; 140:377-386.
[13]Bogart JA, Hodgson L, Seagren SL, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. J Clin Oncol 2010; 28:202-206.
[14]Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2007; 68:103-110.
[15]Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010; 28:2181-2190.
[16]O'Rourke N, Roqué I Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. Cochrane Database Syst Rev 2010:CD002140.
[17]Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011;103:1452-1460.
[18]Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. Chest 2000; 117:358-364.
[19]Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 1996; 88:1210-1215.
[20]Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). Radiother Oncol 2011;100:76-85.
[21]Mauguen A, Le Péchoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. J Clin Oncol 2012;30:2788-2797.
[22]Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009; 374:379-386.
[23]Kunitoh H, Kato H, Tsuboi M, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. J Clin Oncol 2008; 26:644-649.
[24]Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007; 25:313-318.
[25]Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer. Lancet Oncol 2008;9:607-608.
[26]Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Biol Phys 2009;75:1462-1467.
[27]Douillard J-Y, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008; 72:695-701.
[28]Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006; 24:2998-3006.
[29]Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol 2007; 2:287-292.
[30]Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J Clin Oncol 2005; 23:3480-3487.
[31]Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000; 343:1217-1222.
[32]Burdett S, Stewart L, Group PM-a. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. Lung Cancer 2005; 47:81-83.
[33]Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. Am J Clin Oncol 2010; 33:157-163.
[34]Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. J Clin Oncol 2009; 27:1579-1584.
[35]Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. Clin Cancer Res 2008; 14:5255-5259.
[36]Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442-1457.
[37]Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 2007; 17:108-120.
[38]Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. Semin Radiat Oncol 2008; 18:215-222.
[39]Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010; 76:S10-19.
[40]Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010; 76:S70-76.
[41]Werner-Wasik M, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys 2010; 76:S86-93.
[42]Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010; 76:S77-85.
[43]Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys 2010; 76:S42-49.
[44]Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007; 2:S94-100.
[45]Lagerwaard FJ, Haasbeek CJA, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008; 70:685-692.

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

PRINCIPLES OF RADIATION THERAPY - References (9 of 9)

[46] Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008; 72:967-971.
[47] Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006; 24:4833-4839.
[48] Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009; 75:677-682.
[49] Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009; 73:1235-1242.
[50] Liu MB, Eclov NC, Trakul N, et al. Clinical impact of dose overestimation by effective path length calculation in stereotactic ablative radiation therapy of lung tumors. Practical Radiation Oncology 2012 In press.
[51] Belderbos JS, Kepka L, Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2008;72:335-342..
[52] Bradley J, Bae K, Choi N, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of radiation therapy oncology group (RTOG) 0515. Int J Radiat Oncol Biol Phys 2012;82:435-441.
[53] Sanuki-Fujimoto N, Sumi M, Ito Y, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. Radiother Oncol 2009; 91:433-437.
[54] Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. Radiat Oncol 2009; 4:5-11.
[55] Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007; 25:5557-5561.
[56] Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. Am J Clin Oncol 2007; 30:239-244.
[57] Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. Cancer 1987; 59:1874-1881.
[58] Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 2005; 63:324-333.
[59] Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004; 60:741-747.
[60] Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved Outcomes for Locally Advanced Non-Small Cell Lung Carcinoma Treated with Chemoradiation: An Analysis of the radiation therapy oncology group. Int J Radiat Oncol Biol Phys 2012;82:425-434.
[61] Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006; 65:1106-1111.
[62] Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. J Clin Oncol 2008; 26:2457-2463.
[63] Stinchcombe TE, Lee CB, Moore DT, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel in unresectable stage IIIA/B non-small cell lung cancer. J Thorac Oncol 2008; 3:1279-1285.
[64] Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol 2010; 28:2475-2480.
[65] Bradley JD, Paulus R, Komaki R, et al. A Randomized Phase III Comparison of Standard-Dose (60 Gy) Versus High-dose (74 Gy) Conformal Chemoradiotherapy +/- Cetuximab for Stage IIIA/IIIB Non-Small Cell Lung Cancer: Preliminary Findings on Radiation Dose in RTOG 0617 [abstract]. Proceedings ASTRO 2011 Abstract LBA2.
[66] Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. Eur J Cardiothorac Surg 2009; 35:718-723; discussion 723.
[67] Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. J Thorac Cardiovasc Surg 2005; 129:1250-1257.
[68] Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004; 78:1200-1205.
[69] Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. Int J Radiat Oncol Biol Phys 2012;84:456-463.
[70] Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006; 65:1097-1105.
[71] Spoelstra FOB, Senan S, Le Péchoux C, et al. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. Int J Radiat Oncol Biol Phys 2010; 76:1106-1113.
[72] Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007; 25:1423-1436.
[73] Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. Int J Radiat Oncol Biol Phys 2011; 79:965-976.
[74] Cross CK, Berman S, Buswell L, et al. Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2004; 58:1098-1105.
[75] Medical Research Council Lung Cancer Working Party. A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. Br J Canc 1992; 65:934-941.
[76] MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiother Oncol 2009; 91:85-94.
[77] Ung YC, Gu C-S, Cline K, et al. An Ontario Clinical Oncology Group (OCOG) randomized trial (PET START) of FDG PET/CT in patients with stage 3 non-small cell lung cancer (NSCLC): impact of PET on radiation treatment volumes [Abstract]. J Thorac Oncol 2011; 6:S428.
[78] Everitt S, Herschtal A, Callahan J, et al. High rates of tumor growth and disease progression detected on serial pretreatment fluorodeoxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. Cancer 2010;116:5030-5037.
[79] Mohammed N, Kestin LL, Grills IS, et al. Rapid disease progression with delay in treatment of non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011; 79:466-472.
[80] AAPM Task Group 76. The Management of Respiratory Motion in Radiation Oncology. AAPM Report No. 91 2006.

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.

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens*

- **Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1-5, 29-33; concurrent thoracic RT[a] (preferred)****
- **Cisplatin 100 mg/m^2 days 1, 29; vinblastine 5 mg/m^2/weekly x 5; concurrent thoracic RT[b] (preferred)**
- **Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)**
- **Cisplatin 75 mg/m^2 on day 1, pemetrexed 500 mg/m^2 on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d] (nonsquamous)**

Sequential Chemotherapy/RT Regimens

- **Cisplatin 100 mg/m^2 on day 1, 29; vinblastine 5 mg/m^2/weekly on days 1, 8, 15, 22, 29; followed by RT[b]**
- **Paclitaxel 200 mg/m^2 every 3 weeks over 3 hours, 2 cycles; carboplatin AUC 6, 2 cycles followed by thoracic RT[e]**

Concurrent Chemotherapy/RT Followed by Chemotherapy

- **Cisplatin 50 mg/m^2 on days 1, 8, 29, 36; etoposide 50 mg/m^2 days 1-5, 29-33; concurrent thoracic RT followed by cisplatin 50 mg/m^2 and etoposide 50 mg/m^2 x 2 additional cycles (category 2B)[a]**
- **Paclitaxel 45-50 mg/m^{2}weekly; carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m^2 and carboplatin AUC 6[e] (category 2B)**

*There are data that support full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

**This regimen can be used as neoadjuvant chemoradiotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 3 cycles of full-dose platinum therapy after local treatment is completed.

[a] Albain KS, Crowley JJ, Turrisi AT III, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: A Southwest Oncology Group Phase II Study, SWOG 9019. J Clin Oncol 2002;20:3454-3460.

[b] Curran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452-1460.

[c] Govindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120-3125.

[d] Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. Clin Lung Cancer 2009;10:193-198.

[e] Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol. 2005;23:5883-5891.

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

PRINCIPLES OF SURGICAL THERAPY (1 of 4)

Evaluation

- Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.
- CT and PET used for staging should be within 60 days before proceeding with surgical evaluation.
- Resection is the preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, and SABR. Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk patients, a multidisciplinary evaluation (including a radiation oncologist) is recommended.
- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (eg, multidisciplinary clinic and/or tumor board).
- In current smokers who stop smoking, consider waiting 4 weeks before surgery to maximize outcomes after surgery.

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - Peripheral nodule[1] ≤2 cm with at least one of the following:
    - Pure AIS histology
    - Nodule has ≥50% ground glass appearance on CT
    - Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS is a reasonable and acceptable approach for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.
- In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.
- Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.
- T3 (invasion) and T4 local extension tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.

Margins and Nodal Assessment (see NSCL-D 2 of 4)

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC (see NSCL-D 2 of 4 through NSCL-D 4 of 4)

[1] Peripheral is defined as the outer one third of the lung parenchyma.

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

PRINCIPLES OF SURGICAL THERAPY (2 of 4)

Margins and Nodal Assessment

- Surgical pathologic correlation is critical to assess apparent close or positive margins, as these may not represent true margins or may not truly represent areas of risk for local recurrence (eg, medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed, or pleural margin adjacent to aorta when no attachment to aorta is present).
- N1 and N2 node resection and mapping should be a routine component of lung cancer resections - a minimum of three N2 stations sampled or complete lymph node dissection.
- Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease.
- Complete resection requires free resection margins, systematic node dissection or sampling, and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, unremoved positive lymph nodes, or positive pleural or pericardial effusions. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.
- Patients with pathologic stage II or greater should be referred to medical oncology for evaluation.
- Consider referral to a radiation oncologist for resected stage IIIA.

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC

The role of surgery in patients with pathologically documented N2 disease remains controversial.[1] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[2,3] However, this population is heterogeneous and the panel believes that these trials did not sufficiently evaluate the nuances present with the heterogeneity of N2 disease and the likely oncologic benefit of surgery in specific clinical situations.

- The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. (NSCL-1, NSCL-2, and NSCL-6)
- Patients with occult positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal lymph node dissection. If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option.
- The determination of the role of surgery in a patient with N2 positive lymph nodes should be made prior to the initiation of any therapy by a multidisciplinary team, including a board-certified thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.[4]
- The presence of N2 positive lymph nodes substantially increases the likelihood of positive N3 lymph nodes. Pathologic evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS are additional techniques for minimally invasive pathologic mediastinal staging that are complementary to mediastinoscopy. Even when these modalities are employed it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral lymph node involvement prior to a final treatment decision.

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC continued on NSCL-D 3 of 4 through NSCL-D 4 of 4)

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

PRINCIPLES OF SURGICAL THERAPY (3 of 4)

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC

- Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (± EUS) in the initial pretreatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.[5]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,6,7]
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[7,8]
- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[5,9] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[10] However, that is achieved at the expense of higher rates of acute toxicity and increased cost.
- When neoadjuvant chemoradiotherapy is used with doses lower than those used for standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Treatment breaks of more than 1 week are considered unacceptable.
- When timely surgical evaluation is not available, the strategy of neoadjuvant chemoradiotherapy should not be used. Another option in individual cases, and with the agreement of the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.[11,12] If a surgeon or center is uncertain about the feasibility or safety of resection after definitive doses of radiation, consider obtaining an additional surgical opinion from a high-volume specialized center. These operations may also benefit from additional considerations of soft tissue flap coverage in the radiation field resection.
- Data from a large multi-institutional trial indicate that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality.[2] However, it is not clear if this is also true with neoadjuvant chemotherapy alone. Further, many groups have challenged that cooperative group finding with single institution experiences demonstrating safety of pneumonectomy after induction therapy.[13-16] In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy.[17]

A questionnaire was submitted to the NCCN institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

a) Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
b) Would consider surgery with more than one N2 lymph node station involved, as long as no lymph node was bigger than 3 cm: (47.6%)
c) Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%)
d) Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
e) Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%)

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

PRINCIPLES OF SURGICAL THERAPY (4 of 4)

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC - References

[1]Martins RG, D'Amico TA, Loo BW Jr, et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. J Natl Compr Canc Netw 2012;10:599-613.

[2]Albain K, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. Lancet 2009;374:379-386.

[3]van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-450.

[4]Farjah F, Flum DR, Varghese TK Jr, et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;87:995-1006.

[5]Thomas M, Rübe C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008;9:607-608.

[6]Andre F, Grunenwald D, Pignon J, et al. Survival of patients with resected N2 non–small-cell lung Cancer: Evidence for a subclassification and implications. J Clin Oncol 2000;18:2981-2989.

[7]Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433-439.

[8]Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann Thorac Surg 2000;70:1826-1831.

[9]Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;75:1462-1467.

[10]de Cabanyes Candela S, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. J Thorac Oncol 2010;5:389-398.

[11]Bauman JE, Mulligan MS, Martins RG, et al. Salvage Lung Resection After Definitive Radiation (>59 Gy) for Non-Small Cell Lung Cancer: Surgical and Oncologic Outcomes. Ann Thorac Surg 2008;86:1632-1639.

[12]Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary Resection After Curative Intent Radiotherapy (>59 Gy) and Concurrent Chemotherapy in Non–Small-Cell Lung Cancer. Ann Thorac Surg 2004;78:1200-1205.

[13]Evans NR 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. J Thorac Cardiovasc Surg 2010;139:991-996.

[14]Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy—Influence of preoperative induction therapy. J Thorac Cardiovasc Surg 2009;138:289-294.

[15]Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! Eur J Cardiothorac Surg 2007;31:181-185.

[16]Weder W, Collaud S, Eberhardt WEE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non–small-cell lung cancer. J Thorac Cardiovasc Surg 2010;139:1424-1430.

[17]Shah AA, Berry M, Tzao C, et al. Induction chemoradiotherapy is not superior to induction chemotherapy alone in stage IIIA lung cancer: a systematic review and meta-analysis. Ann Thorac Surg 2012;93:1807-1812.

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.

CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- **Cisplatin 50 mg/m^2 days 1 and 8; vinorelbine 25 mg/m^2 days 1, 8, 15, 22, every 28 days for 4 cycles**[a]
- **Cisplatin 100 mg/m^2 on day 1; vinorelbine 30 mg/m^2 days 1, 8, 15, 22; every 28 days for 4 cycles**[b,c]
- **Cisplatin 75-80 mg/m^2 day 1; vinorelbine 25-30 mg/m^2 days 1 + 8, every 21 days for 4 cycles**
- **Cisplatin 100 mg/m^2 on day 1; etoposide 100 mg/m^2 days 1-3, every 28 days for 4 cycles**[b]
- **Cisplatin 80 mg/m^2 on days 1, 22, 43, 64; vinblastine 4 mg/m^2 days 1, 8, 15, 22 then every 2 wks after day 43, every 21 days for 4 cycles**[b]
- **Cisplatin 75 mg/m^2 on day 1; gemcitabine 1250 mg/m^2 on days 1, 8, every 21 days for 4 cycles**
- **Cisplatin 75 mg/m^2; docetaxel 75 mg/m^2 every 21 days for 4 cycles**[d]
- **Pemetrexed 500 mg/m^2 on day 1; cisplatin 75 mg/m^2 on day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype) every 21 days for 4 cycles**

Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin

Paclitaxel 200 mg/m^2 on day 1, carboplatin AUC 6 on day 1, every 21 days[e]

[a] Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. N Engl J Med 2005;352:2589-2597.

[b] Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-360.

[c] Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-727.

[d] Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024.

[e] Strauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-5051.

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.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 3)

ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status, and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate (≈ 25%-35%), time to progression (4-6 mo), median survival (8-10 mo), 1 y survival rate (30%-40%) and 2 y survival rate (10%-15%) in fit patients.
- Unfit of any age (performance status 3-4) do not benefit from cytotoxic treatment, except erlotinib for EGFR mutation-positive patients.

First-line therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Cetuximab + vinorelbine/cisplatin is an option for patients with performance status 0-1 (category 2B).
- Erlotinib is recommended as a first-line therapy in patients with EGFR mutation.
- Crizotinib is indicated as a first-line therapy in patients who are ALK positive.
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival.
- Single-agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).

See Maintenance Chemotherapy, Second- and Third-line therapy NSCL-F (2 of 3)

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.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 OF 3)

Maintenance Therapy

Continuation maintenance refers to the use of at least one of the agents given in first line, beyond 4-6 cycles, in the absence of disease progression. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen, in the absence of disease progression, after 4-6 cycles of initial therapy.

- **Continuation Maintenance: Bevacizumab and cetuximab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.**
  - **Continuation of bevacizumab after 4-6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).**
  - **Continuation of cetuximab after 4-6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).**
  - **Continuation of pemetrexed after 4-6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).**
  - **Continuation of bevacizumab + pemetrexed after 4-6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.**
  - **Continuation of gemcitabine after 4-6 cycles of platinum-doublet chemotherapy.**
- **Switch Maintenance: Two recent studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4-6 cycles of therapy.**
  - **Initiation of pemetrexed after 4-6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma.**
  - **Initiation of erlotinib after 4-6 cycles of first-line platinum-doublet chemotherapy.**
  - **Initiation of docetaxel after 4-6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).**
- **Close surveillance of patients without therapy is a reasonable alternative to maintenance.**

Second-line therapy

- **In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, or erlotinib are established second-line agents.**
  - **Docetaxel is superior to vinorelbine or ifosfamide.**
  - **Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.**
  - **Erlotinib is superior to best supportive care.**

Third-line therapy

- **Erlotinib is superior to best supportive care.**

Continuation After Disease Progression

- **With the exception of erlotinib in patients with EGFR sensitizing mutations who have experienced objective regressions with erlotinib, no agent should be continued after disease progression has been documented. (refer to discussion section)**

See Specific Systemic Agents on page NSCL-F (3 of 3)

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.

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 OF 3)

Agents listed below are used in the treatment of patients with NSCLC. Most are used in combination, while others are used as monotherapy (eg, maintenance or second-line therapy).

- **Cisplatin**[1-9]
- **Carboplatin**[4,6-11]
- **Paclitaxel**[1,4,6,8-11]
- **Docetaxel**[5,7,8,12,13]
- **Vinorelbine**[7,9,10]
- **Gemcitabine**[3,5,6,8,9,13]
- **Etoposide**[4]
- **Irinotecan**[9]
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**[12]
- **Pemetrexed**[14,15]
- **Erlotinib**[16]
- **Bevacizumab**[17]
- **Cetuximab**[18]
- **Albumin-bound paclitaxel**[19-21 †]
- **Crizotinib**[22]

[1] Bonomi P, Kim K, Fairclough D, et al. Comparison of survival and quality of life in advanced non-small cell lung cancer patients treated with two dose levels of paclitaxel combined with cisplatin versus etoposide with cisplatin:results of an Eastern Cooperative Oncology Group trial. J Clin Oncol 2000;18:623-631.

[2] Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small cell lung cancer: A Southwest Oncology Group Study. J Clin Oncol 1998;16:2459-2465.

[3] Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 1999;17:12-18.

[4] Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005;16:1069-1075.

[5] Sandler AB, Nemunaitis J, Denham C, et al. Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small cell lung cancer. J Clin Oncol 2000;18:122-130.

[6] Smit EF, van Meerbeeck JP, Lianes P, et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group-EORTC 08975. J Clin Oncol 2003;21:3909-3917.

[7] Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21(16):3016-3024.

[8] Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. N Engl J Med 2002;346:92-98.

[9] Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323.

[10] Kelly K, Crowley J, Bunn PA, et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small cell lung cancer: A Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-3218.

[11] Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008;26:468-473.

[12] Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362.

[13] Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610.

[14] Hanna NH, Sheperd FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

[15] Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage NSCLC. J Clin Oncol 2008;26:3543-3551.

[16] Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.

[17] Sandler AB, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 2006;355:2542-2550.

[18] Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open label randomised phase III trial. Lancet 2009;373:1525-1531.

[19] Green M, Manikhas G, Orlov S, et al. Abraxane®, a novel Cremophor® -free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006;17:1263-1268.

[20] Rizvi N, Riely G, Azzoli, C, et al. Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel As Initial Chemotherapy in Patients With Stage IV Non–Small-Cell Lung Cancer. J Clin Oncol 2008;26:639-643.

[21] Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. J Clin Oncol 2012:30:2055-2062.

[22] Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011;12:1004-1012.

† Albumin-bound paclitaxel may be substituted for either paclitaxel or docetaxel in patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or for patients where the standard premedications (dexamethasone, H2 blockers, H1 blockers) are contraindicated.

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.

CANCER SURVIVORSHIP CARE

NSCLC Long-term Follow-up Care

- **Cancer Surveillance**
  - **H&P and a chest CT scan ± contrast every 6-12 months for 2 years, then H&P and a non-contrast-enhanced chest CT scan annually**
  - **Smoking status assessment at each visit; counseling and referral for cessation as needed.**
- **Immunizations**
  - **Annual influenza vaccination, herpes zoster vaccine**
  - **Pneumococcal vaccination with revaccination as appropriate**

Counseling Regarding Health Promotion and Wellness[1]

- **Maintain a healthy weight**
- **Adopt a physically active lifestyle (Regular physical activity: 30 minutes of moderate-intensity physical activity on most days of the week)**
- **Consume a healthy diet with emphasis on plant sources**
- **Limit consumption of alcohol if one consumes alcoholic beverages**

Additional Health Monitoring

- **Routine blood pressure, cholesterol, and glucose monitoring**
- **Bone health: Bone density testing as appropriate**
- **Dental health: Routine dental examinations**
- **Routine sun protection**

Resources

- **National Cancer Institute Facing Forward: Life After Cancer Treatment**
  http://www.cancer.gov/cancertopics/life-after-treatment/allpages

Cancer Screening Recommendations[2,3]

These recommendations are for average-risk individuals and high-risk patients should be individualized.

- **Colorectal Cancer:**
  See NCCN Guidelines for Colorectal Cancer Screening
- **Prostate Cancer:**
  See NCCN Guidelines for Prostate Cancer Early Detection
- **Breast Cancer:**
  See NCCN Guidelines for Breast Cancer Screening
- **Cervical Cancer:**
  See NCCN Guidelines for Cervical Cancer Screening

[1] ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention: http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED (Accessed November 30, 2012)

[2] Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed November 30, 2012)

[3] American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 30, 2012)

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.

Table 1. Definitions for T, N, M*

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 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)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features:[b] Involves main bronchus, ≥ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a] 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 in 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
MX	Distant metastasis cannot be assessed
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[c]
M1b	Distant metastasis

[a] 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 T1.

[b] T2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm

[c] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (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 T1, T2, T3, or T4.

*Used with permission. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. J Thorac Oncol 2007;2:706-714.

Table 2. Anatomic Stage and Prognostic Groups

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0

Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N1	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	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+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Table 3. Descriptors, T and M Categories, and Stage Grouping*

6th Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (<2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (<5-7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 extension	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the sixth edition for a particular TNM category.

*Used with permission. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumors. J Thorac Oncol 2007;2:706-714.

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 04/30/12

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

Overview

Lung cancer is the leading cause of cancer death in the United States. An estimated 221,000 new cases (115,000 in men and 106,000 in women) of lung and bronchial cancer will be diagnosed in 2011, and 156,900 deaths (85,600 in men and 71,300 in women) are estimated to occur due to the disease.[1] Only about 15.6% of all lung cancer patients are alive 5 years or more after diagnosis (http://seer.cancer.gov/statfacts/html/lungb.html). Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for more than 85%-90% of all lung cancer-related deaths (http://www.surgeongeneral.gov/library/smokingconsequences/).[2-4] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[3,5] The risk of lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking (ie, pack-years of smoking history). Exposed nonsmokers also have an increased relative risk (RR=1.24) of developing lung cancer from “secondhand smoke” (http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf).[5-8]

Radon gas, a radioactive gas that is produced by the decay of radium 226, also appears to cause lung cancer (http://www.surgeongeneral.gov/pressreleases/sg01132005.html).[9-12] The U.S. Environmental Protection Agency (EPA) estimates that radon is the main cause of lung cancer in nonsmokers; however, secondhand smoke may also be a factor (http://www.epa.gov/radon/healthrisks.html).

Asbestos, a mineral compound that breaks into small airborne shards, is a known carcinogen that increases the risk of lung cancer in people exposed to airborne fibers, especially in individuals who smoke. It is estimated that about 3% to 4% of lung cancers are caused by asbestos exposure.[13] In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (ie, bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds).[14,15] The International Agency for Research on Cancer (IARC) lists several agents known to cause lung cancer, including arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.[16,17] Asbestos also causes malignant pleural mesothelioma.

It is not clear whether hormone replacement therapy (HRT) affects the risk of lung cancer in women. More than 20 studies have been published, but the results have been inconsistent. In a large randomized controlled study,[18] no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT; however, the risk of death from non-small cell lung cancer (NSCLC) was increased.[18]

Prevention and Screening

Approximately 85%-90% of cases of lung cancer are caused by cigarette smoking.[2] Active smoking and secondhand smoke both cause lung cancer (see Reports from the Surgeon General, which are the next 2 links). There is a causal relationship between active smoking and lung cancer and also with other cancers (such as esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, ovarian

cancer, colorectal, and cervical cancers) as well as other diseases and conditions (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf).

Smoking harms nearly every organ in the body. Those who live with someone who smokes have a 20% to 30% increased risk for lung cancer (http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer (http://www.surgeongeneral.gov/tobacco/tobaqrg.htm). Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA [Food and Drug Administration]) can be very useful (see *Treating Tobacco Use and Dependence: 2008 Update*, which is published by the Agency for Healthcare Research and Quality [AHRQ]) (http://www.ahrq.gov/clinic/tobacco/tobaqrg.htm#Findings).

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline. Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[19-21] However, almost 30% of patients had nausea while using varenicline.[22] The effectiveness of varenicline for preventing relapse has not been clearly established.[23] The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm). Varenicline has also been associated with other disorders (eg, visual disturbances, movement disorders, unconsciousness, cardiovascular disorders) and, therefore, is banned in truck and bus drivers, pilots, and air traffic controllers.[24] Bupropion is also associated with serious adverse events (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm169986.htm). Nicotine replacement has fewer adverse effects than varenicline or bupropion.[25] However, in spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[25]

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.[26,27] Because localized cancer can be managed curatively and because survival in other solid tumors (eg, breast, cervix, colon, and prostate) appears to be increased by screening and early detection, lung cancer would be an appropriate candidate for a population-based screening approach. Pilot trials of spiral (helical) low-dose computed tomography (CT) in lung cancer screening were promising with a frequency of stage I detectable lung cancer in more than 80% of newly diagnosed cases.[28-30]

The National Lung Screening Trial (NLST, ACRIN Protocol A6654) was a randomized, controlled study involving more than 53,000 current or former heavy smokers; this trial assessed the risks and benefits of low-dose helical CT scans compared with chest x-rays for detecting lung cancer.[31] Recent published results from the NLST show that screening high-risk patients with low-dose helical CT decreases the mortality rate from lung cancer by 20% when compared with chest x-ray.[32] High-risk patients were either current or former smokers with a 30-pack year smoking history (former smokers had quit 15 years ago),

were 55-74 years old, and had no evidence of lung cancer.[33,34] Additional information on NLST can be found at http://www.cancer.gov/nlst. An NCCN panel is developing a new guideline for lung cancer screening.

The International Early Lung Cancer Action Program (I-ELCAP) has been assessing whether annual screening by low-dose helical CT scan increases the detection of early stage lung cancer in patients at risk for cancer. Data from I-ELCAP showed that stage I lung cancer can be detected using annual low-dose CT screening. The 10-year survival rate was 92% for stage I patients whose cancers were promptly removed; however, all stage I patients who chose not to be treated died within 5 years.[35] Additional information on I-ELCAP can be found at http://www.ielcap.org/index.htm. Screening can increase the diagnosis of early stage lung cancers. Recent data from the NLST show that screening decreases the mortality rate.[32]

Classification and Prognostic Factors

The World Health Organization (WHO) divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC (discussed in this guideline) and small cell lung cancer (SCLC). NSCLC accounts for more than 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring cell type in nonsmokers. An international panel recently revised the classification of lung adenocarcinoma (see next section on “Pathologic Evaluation of Lung Cancer”).[36] Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early stage disease at diagnosis, good performance status ([PS] Eastern Cooperative Oncology Group 0, 1, or 2), no significant weight loss (not more than 5%), and female gender.[37]

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the histologic type of the lung cancer, determine the extent of invasion, determine whether it is primary lung cancer or metastatic cancer, establish the cancer involvement status of the surgical margins (ie, positive or negative margins), and do molecular diagnostic studies to determine whether certain gene mutations are present (eg, epidermal growth factor receptor [EGFR] mutations). Data show that targeted therapy is potentially very effective in patients with specific gene mutations or rearrangements (see sections on “EGFR Mutations” and “EML4-ALK Gene Rearrangements” in this Discussion).[38-42] Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy. In addition, the mediastinal lymph nodes are systematically sampled to assess the staging and therapeutic options.

Lobectomy or pneumonectomy specimens are evaluated intraoperatively to determine the surgical resection margin status, diagnose incidental nodules discovered at the time of surgery, or evaluate the regional lymph nodes. Postoperative evaluation provides the pathology characteristics necessary for the classification of tumor type, staging, and prognostic factors. The surgical pathology report should include the histologic classification published by the WHO for carcinomas of the lung.[43] However, the classification for lung adenocarcinoma was recently revised by an international panel (see next section).[36] The new classification requires immunohistochemical, histochemical, and molecular studies. In addition, the revised

classification recommends that use of general categories (eg, NSCLC) should be minimized, because more effective treatment can be selected when the histology is known.

Adenocarcinoma

Recently, the classification for adenocarcinoma was revised; the categories of bronchioloalveolar carcinoma (BAC) or mixed subtype adenocarcinoma are no longer used.[36] If necessary, the term "former BAC" is used. The new categories include 1) adenocarcinoma in situ (AIS) (formerly BAC), which is a preinvasive lesion; 2) minimally invasive adenocarcinoma (MIA); 3) invasive adenocarcinoma (includes formerly nonmucinous BAC); and 4) variants of invasive adenocarcinoma (includes formerly mucinous BAC). Both AIS and MIA are associated with excellent survival if they are resected. The international panel and NCCN recommend that all patients with adenocarcinoma be tested for the EGFR mutation; the NCCN panel also recommends that these patients be tested for the ALK gene rearrangement.

Immunohistochemical Staining

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung (eg, breast, prostate, colorectal), to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the NCCN NSCLC algorithm (see "Principles of Pathologic Review"). Although cytology can be used to distinguish adenocarcinomas from squamous cell carcinomas, immunohistochemistry is also useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens.[36,44] Squamous cell carcinomas are often TTF-1 negative, p63 positive, and cytokeratin 5/6 positive, whereas adenocarcinomas are usually TTF-1 positive. Thus, a panel of these 3 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[44] Other markers (eg, high molecular weight cytokeratin [34ßE12], napsin A, mucicarmine) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[45,46]

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma.[47] The stains that are positive for adenocarcinoma, include CEA (carcinoembryonic antigen), B72.3, Ber-EP4, MOC31, and TTF-1; these stains are negative for mesothelioma.[48] Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin),[49] and cytokeratin 5/6.[47] A panel of 4 markers can be used to distinguish mesothelioma from adenocarcinoma—2 are positive in mesothelioma and 2 are positive in adenocarcinoma but negative in mesothelioma—including calretinin, cytokeratin 5/6 (or WT-1), CEA, and MOC-31 (or B72.3, Ber-EP4, or BG-8).[47,50]

TTF-1 is a transcription factor that regulates tissue-specific expression of surfactant apoprotein A (SPA), surfactant apoprotein B (SPB), surfactant apoprotein C (SPC), Clara cell antigen, and T1α. TTF-1 is very important in distinguishing primary from metastatic adenocarcinoma, because most primary carcinomas are TTF-1 positive. TTF-1 is typically negative for squamous cell carcinoma.[44] However, TTF-1 is positive in tumors from patients with thyroid cancer.[51] In addition, thyroglobulin is present in tumors from patients with thyroid cancer, while it is negative in lung cancer tumors. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- whereas metastatic adenocarcinoma of the colorectum is usually CK7- and CK20+. CDX-2 is a marker for metastatic gastrointestinal malignancies that can be used to differentiate them from primary lung tumors. All typical and atypical carcinoid tumors are positive for chromogranin and

synaptophysin, whereas small cell lung carcinoma is negative in 25% of the cases.

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC.[52] However, many patients with SCLC have characteristic CT and clinical findings (eg, massive lymphadenectomy, mediastinal invasion). Most SCLCs are immunoreactive for TTF-1; they are typically negative for CK34βE12 and p63.[53,54] Many SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs are immunoreactive for at least one of these neuroendocrine markers.[55] Recent data suggest that microRNAs (miRNA) expression can be used to distinguish SCLC from NSCLC.[56]

Staging

The international staging system for lung cancer has been revised and adopted by the American Joint Committee on Cancer (AJCC) and by the Union Internationale Contre le Cancer.[57-60] Recently, the lung cancer staging system was revised by the International Association of the Study of Lung Cancer (IASLC)[61,62] and is available from the AJCC (7th edition).These NCCN guidelines use the revised AJCC (7th edition) staging.[63] The revised stage grouping is summarized in the staging tables. The descriptors of the TNM classification scheme are summarized in the staging tables.

The TNM staging revisions (AJCC 7th edition) became effective for all new cases diagnosed after January 1, 2010.[63] With the new staging, locally advanced disease is now stage III; advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging: for example, wet IIIB (ie, malignant pleural effusions) is upstaged to stage IV.[64,65] These new changes reflect the prognosis of patients with these different tumors. Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (eg, thoracotomy, examination of lymph nodes using mediastinoscopy).[57]

For 1999-2007, the overall 5-year relative survival rate for lung cancer was 15.6% (from 17 SEER [Surveillance, Epidemiology, and End Results] geographic areas in the United States). Of lung and bronchial cancer cases, 15% were diagnosed while the cancer was still confined to the primary site (localized stage); 22% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 56% were diagnosed after the cancer had already metastasized (distant stage); and for the remaining 7%, the staging information was unknown. The corresponding 5-year relative survival rates were: 52% for localized, 24% for regional, 3.6% for distant, and 8.1% for unstaged (http://seer.cancer.gov/statfacts/html/lungb.html). However, these data include small cell lung cancer, which has a poorer prognosis.

Five-year survival after lobectomy for pathologic stage I NSCLC ranges from 45% to 65%, depending on whether the patient has stage 1A or 1B disease and on the location of the tumor.[66] Another study in stage I patients (n=19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; however, for untreated stage I NSNCL, 5-year overall survival was only 6%.[67] Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Prognostic and Predictive Biomarkers

Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, the evidence is strongest for epidermal growth factor receptor (EGFR), the 5′ endonuclease of the nucleotide excision repair complex (ERCC1), the k-ras oncogene, the regulatory subunit of ribonucleotide reductase (RRM1), and the EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]). A *prognostic* biomarker is a biomolecule that is indicative of patient survival independent of the treatment received; that is, the biomolecule is an indicator of the innate tumor aggressiveness. A *predictive* biomarker is a biomolecule that is indicative of therapeutic efficacy; that is, there is an interaction between the biomolecule and therapy on patients' outcome.

The presence of the EGFR exon 19 deletion (LREA) or exon 21 L858R mutation does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.[68] However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitors (EGFR-TKI) therapy.[69,70] High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.[71,72] High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy.[72,73] The presence of K-ras mutations is prognostic of poor survival for patients with NSCLC when compared to absence of K-ras mutations, independent of therapy.[74] K-ras mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.[69,75] High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression, independent of therapy.[76,77] Low levels of RRM1 expression are also predictive of better response to chemotherapy.[73,78-80] The EML4-ALK fusion oncogene (ie, ALK gene rearrangement) is a new predictive biomarker that has been identified in a small subset of patients with NSCLC (see the section on "EML4-ALK Gene Rearrangements").

Testing for EGFR mutations and ALK gene rearrangements is recommended in the NCCN NSCLC guidelines for select patients (eg, those with adenocarcinoma) so that patients with these genetic abnormalities can receive effective treatment (eg, erlotinib, crizotinib). Patients with adenocarcinoma may have other genetic abnormalities.[81,82] Mutation screening assays for detecting multiple biomarkers (eg, SNaPshot Multiplex System) have been developed that can detect more than 100 point mutations, including EGFR (http://www.mycancergenome.org/molecular-pathology/).[83] However, these systems do not detect ALK gene rearrangements, because they are not point mutations. ALK gene rearrangements are detected using fluorescence in situ hybridization (FISH) (see the section on "EML4-ALK Gene Rearrangements" in this Discussion). Ongoing research is assessing whether other biomarkers (eg, BRAF) may be useful therapeutic targets.[84]

EGFR Mutations

EGFR is a transmembrane receptor that is detectable in approximately 80%-85% of patients with NSCLC, and the levels of expression vary widely on a continual scale. The most commonly found EGFR mutations in patients with NSCLC are deletions in exon 19 (E19del [LREA deletion] in 45% of patients) and a mutation in exon 21 (L858R in 40%). Both mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small molecule TKIs, erlotinib and gefitinib. These drug-sensitive mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian

patients.[85] Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).[86] The T790M mutation is associated with resistance to TKI therapy and has been reported in about 50% of patients with disease progression.[87-89]

DNA mutational analysis is the preferred method to assess for EGFR status, although fluorescence in situ hybridization ([FISH] to determine gene copy number) and immunohistochemistry (to determine level of expression) have been used.[90-92] Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18-21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.[85,91,93-95] The multiplex mutation screening assay (SNaPshot Multiplex System) can detect more than 100 point mutations, including EGFR.[83] It may be better to assess EGFR mutation status on the primary tumor before therapy and not on the metastasis, although no consensus has been reached.

The prognostic effect of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—is not clear, because most reports are limited to patients receiving active therapy. A retrospective study of patients treated with first-line chemotherapy with or without erlotinib found that the median overall survival for all patients with mutations (N=11) was significantly better (>20 months, *P*<.001) than overall survival for patients without mutations (N=45, 10 months).[40] It has been reported that in patients with EGFR mutations who receive TKIs, those with E19del (LREA deletion) have increased survival when compared with L858R mutations; those with wild-type EGFR have poorer outcomes.[96]

The predictive effects of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib or gefitinib. The initial retrospective reports suggested that approximately 90% of patients with a tumor response to these drugs had mutations, whereas unresponsive patients did not have mutations.[97,98] Subsequent retrospective studies have demonstrated an objective response rate of approximately 80% with a median progression-free survival of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and an EGFR mutation.[69] A prospective study has demonstrated that the objective response rate in North American patients with non-squamous cell histology and EGFR mutations (53% E19del [LREA deletion], 26% L858R, 21% other mutations) is 55% with a median progression-free survival of 9.2 months.[70] In patients treated with first-line chemotherapy with or without erlotinib, EGFR mutations were predictive of a better response in patients receiving erlotinib (53% in patients with mutations versus 18% in those without mutations).[40] The response rates in the group of patients receiving only chemotherapy were 21% for those with mutations and 27% for those without mutations.

In contrast, recent data suggest that erlotinib alone (instead of standard first-line chemotherapy) should be used as first-line systemic therapy in patients with EGFR mutations proven before use of first-line therapy.[99-103] Data show that PFS is improved with use of TKI inhibitors in patients with EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.

EML4-ALK Gene Rearrangements

It is estimated that 2%-7% of patients have EML4-ALK gene rearrangements, about 10,000 patients in the United States.[42] These patients are resistant to EGFR TKIs but are similar to those with EGFR mutations (ie, adenocarcinoma, nonsmokers or light smokers) except

they are often younger and male.[82] In addition, ALK rearrangements are found in patients with adenocarcinoma but are usually not been found in squamous cell or large cell carcinoma.[82] Thus, ALK rearrangement testing is not routinely recommended for patients with squamous cell or large cell carcinoma. In these selected populations, estimates are that about 30% of patients will have EML4-ALK rearrangements.[82] EGFR mutations and EML4-ALK rearrangements are generally mutually exclusive.[104] Thus, erlotinib (or gefitinib) may not be effective as second-line therapy in patients with ALK rearrangements who relapse on crizotinib.[81,82] Recently, a molecular diagnostic test (using fluorescence in situ hybridization [FISH]) was approved by the FDA for detecting ALK. A FISH probe set (for ALK-rearranged anaplastic large cell lymphomas) appears to be better than immunohistochemistry tests for detecting EML4-ALK rearrangements.[105-107]

Crizotinib (an inhibitor of ALK and MET tyrosine kinases) was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK gene rearrangement (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/202570s003lbl.pdf).[108-110] Recently, crizotinib has been shown to yield very high response rates (> 80%) and to improve survival when used in patients with advanced NSCLC who have EML4-ALK rearrangements and have progressed on previous therapy.[42,111] Crizotinib is orally active with few side effects (eg, elevations in aminotransferases). However, a few patients have had life-threatening pneumonitis; crizotinib is discontinued in these patients.[108] Patients have responded rapidly to crizotinib, although many have developed resistance to crizotinib after about 1 year.[112] However, other EMLK4-ALK inhibitors are in development.[113-116] A randomized phase III trial (PROFILE-1007) is comparing crizotinib with standard second-line chemotherapy.

ERCC1 Level of Expression

ERCC1 is the 5' endonuclease of the nucleotide excision repair complex. It is found in all tumor cells, and its level of expression varies widely. In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, *ERCC1* mRNA levels were prognostic of survival.[71,72] Multiple translational investigations have provided evidence for the predictive use of ERCC1 levels to assess the efficacy of platinum-based chemotherapies in NSCLC; high levels are associated with resistance, while low levels are associated with sensitivity.[72,79,80]

K-ras Mutations

K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, K-ras is constitutively active, able to transform immortalized cells, and promote cell proliferation and survival. Current data suggest that approximately 25% of adenocarcinomas in a North American population have K-ras mutations.[40,69,75] K-ras mutation prevalence is associated with cigarette smoking.[117] K-ras mutational status is prognostic of survival. Patients with K-ras mutations appear to have a shorter survival than patients with wild-type K-ras.[74,75,118] K-ras mutational status is also predictive of therapeutic efficacy from EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.[40,69] The addition of erlotinib to chemotherapy in patients with K-ras mutations may adversely interfere with chemotherapeutic efficacy.[40]

RRM1 Level of Expression

RRM1 is the gene that encodes the regulatory subunit of ribonucleotide reductase, and it is crucial for production of deoxynucleotides from nucleotides.[119,120] RRM1 is found in all tumor cells, and its level of expression varies widely over a continuous range.

In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, *RRM1* mRNA levels were prognostic of survival. Patients whose tumors had high levels (N=39, relative *RRM1* expression above the cohort median of 12.2) lived significantly longer than patients whose tumors had low levels (N=38, relative expression below 12.2).[76] Patients with high tumoral RRM1 expression had a median overall survival of greater than 120 months compared to 60.2 months for patients with low RRM1 expression.[77] In a randomized phase III clinical trial, Bepler and colleagues reported that in situ RRM1 protein levels (in tumor specimens collected prospectively) were significantly and inversely correlated with disease response to gemcitabine or carboplatin/gemcitabine (*P*=.001, *r* =-0.41); that is, response was better in patients with low levels of RRM1 expression.[79,80]

Treatment Approaches

Surgery, radiation therapy (RT), and chemotherapy are the 3 modalities commonly used to treat patients with NSCLC. They can be used either alone or in combination depending on the disease status. In the following sections, the clinical trials are described that have led to the standard treatments.

Surgery

In general, for patients with stage I or stage II disease, surgery provides the best chance for cure. However, thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated.

The “Principles of Surgical Therapy” are summarized here. Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who should participate in multidisciplinary clinics and/or Tumor Boards for lung cancer patients. Patients with pathologic stage II or greater disease should be referred to medical oncology for evaluation. For patients with resected stage IB, consider referral to medical oncologist. For resected stage IIIA, consider referral to radiation oncologist. If stereotactic ablative radiotherapy (SABR), traditionally known as stereotactic body RT (SBRT), is considered for high-risk patients, a multidisciplinary evaluation is recommended (including a radiation oncologist). Treatment delays, because of poor coordination among specialists, should be avoided.

The surgical procedure used depends on the extent of disease and on the cardiopulmonary reserve of the patient. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; lobectomy or pneumonectomy should be done if physiologically feasible.[121,122] Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the NCCN NSCLC algorithm (see “Principles of Surgical Therapy”).[123,124] Resection (including wedge resection) is preferred over ablation.[122] Wide wedge resection may improve outcomes.[125] However, it is controversial whether lung-sparing surgeries, such as segmentectomy and wedge resection, are useful in patients with severely reduced pulmonary function who are otherwise not candidates for surgery.[122,126,127] SABR may be more appropriate for these patients (see section on “Stereotactic Radiotherapy” in this Discussion).[128]

Lymph Node Dissection

The American College of Surgeons Oncology Group randomized trial (ACOSOG Z0030) compared systematic mediastinal lymph node

sampling versus complete lymphadenectomy during pulmonary resection in patients with N0 (no demonstrable metastasis to regional lymph nodes) or N1 (metastasis to lymph nodes in the ipsilateral peribronchial and/or hilar region, including direct extension) NSCLC disease. In patients with early stage disease who had negative nodes by systematic lymph node dissection, complete mediastinal lymph node dissection did not improve survival.[129-131] Thus, systematic lymph node sampling is appropriate during pulmonary resection; one or more nodes should be sampled from all mediastinal stations. For right-sided cancers, an adequate mediastinal lymphadenectomy should include stations 2R, 4R, 7, 8, and 9. For left- sided cancers, stations 4L, 5, 6, 7, 8, and 9 should be sampled.[132,133] Patients should have N1 and N2 node resection and mapping (American Thoracic Society [ATS] map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection. Note that the IASCL (International Association for the Study of Lung Cancer) has proposed a new lymph node map.[134] Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because it would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients: 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features. Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins either 1) 2 cm or more, or 2) the size of the nodule or more.

Stage IIIA N2 Disease

The role of surgery in patients with pathologically documented stage IIIA (N2) disease is summarized here. Before treatment, it is essential to carefully evaluate for N2 disease using radiologic and invasive staging (ie, endobronchial ultrasound-guided procedures, mediastinoscopy, thoracoscopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team (which should include a board-certified thoracic surgeon).[135] Randomized controlled trials suggest that surgery does not increase survival in these patients.[136,137] However, one of these trials (EORTC) only enrolled unresectable patients.[137] Most clinicians agree that resection is appropriate for patients with a negative preoperative mediastinum and with a single positive node (< 3 cm) found at thoracotomy.[138] Neoadjuvant therapy is recommended for select patients. In N2 patients, 50% of the NCCN institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.[139] Clinicians also agree that resection is not appropriate for patients with multiple pathologically proven malignant lymph nodes greater than 3 cm; definitive chemoradiotherapy is recommended for these patients.

The NCCN panel believes that surgery may be appropriate for select patients with N2 disease, especially those who respond to induction chemotherapy.[140] However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.[136,140-146] Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.[140,147]

Thoracoscopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also referred to as thoracoscopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.[148,149] Published studies suggest that thoracoscopic lobectomy has several advantages over the standard thoracotomy (or pleurotomy).[150-154] Acute and chronic pain associated with thoracoscopic lobectomy is minimal; thus, this

procedure requires shorter length of hospitalization.[155,156] Thoracoscopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[157-161] Recent analyses show that thoracoscopic lobectomy is associated with less morbidity than lobectomy by thoracotomy.[162,163]

In stage I NSCLC patients who had thorascopic lobectomy with lymph node dissection, the 5-year survival rate, long-term survival, and local recurrence were comparable to those achieved by routine open lung resection.[164-166] Thoracoscopic lobectomy has also been shown to improve discharge independence in older populations and in high-risk patients as well.[167,168] Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[169,170] Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy is included in the NCCN NSCLC algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as standard principles of thoracic surgery are not compromised (see “Principles of Surgical Therapy”).

Radiation Therapy

General Principles

Radiation therapy can be used as 1) adjuvant therapy for patients with resectable NSCLC who have no contraindications for surgery; 2) the primary local treatment (ie, definitive RT or SABR for patients with medically inoperable or unresectable NSCLC); and/or 3) palliative therapy for patients with incurable NSCLC. Treatment recommendations should be made by a multidisciplinary team. The NCCN NSCLC algorithm contains a “Principles of RT” section, which includes the following: 1) general principles for early stage, locally advanced, and advanced lung cancer; and 2) target volumes, prescription doses, and normal tissue dose constraints for early stage, locally advanced, and advanced lung cancer; and 3) radiation simulation, planning and delivery.[171-176] These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery (SRS) for brain metastases are also discussed in this section. The abbreviations for RT are described in the NCCN NSCLC algorithm (see Table 1).

SABR is recommended for early stage NSCLC patients (ie, stage I) who are medically inoperable, older patients, or those who refuse surgery. Definitive chemoradiation is recommended for patients with locally advanced (ie, stage II-III) disease who are medically inoperable.[177] For patients with advanced lung cancer (ie, stage IV) with extensive metastases, palliative RT can be used for primary or distant sites. The RT recommendations for stages I-IV are described in “Principles of RT” section in the NCCN NSCLC algorithm (see ”General Principles”).

To avoid postoperative pulmonary toxicity, some clinicians feel that preoperative chemoradiotherapy should be avoided, if pneumonectomy would be required; however, this is a controversial issue.[136,178,179] Surgery in a field that has had 60 Gy is difficult, because the landmarks disappear with high doses of radiation. Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 Gy, especially patients who have received RT doses of more than 60 Gy (ie, patients who have received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. Radiation therapy should continue to definitive dose without interruption if the patient is not a surgical candidate.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints

The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in "Principles of RT" section in the NCCN NSCLC algorithm (see Table 4).[172,174,180-183] After surgery, lung tolerance to RT is much less than for patients with intact lungs. Thus, every effort should be made to minimize the [postoperative] dose of RT. Although the dose volume constraints for normal lungs are a useful guide (see Table 5), more conservative constraints should be used for postoperative RT. For definitive RT, the commonly prescribed dose is 60-70 Gy.[184] The use of higher RT doses is discussed in "Principles of RT" section in the NCCN NSCLC algorithm (see "Locally Advanced Stage/Conventionally Fractionated RT").[185-190] The role of high-dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).[190,191]

For treatment volume consideration, planning target volume (PTV) should be defined using the ICRU-50 and ICRU-62 (International Commission on Radiation Units and Measurements Reports 50 and 62) guidelines, based on gross tumor volume (GTV), plus clinical target volume (CTV) margins for microscopic diseases, internal target volume (ITV) margins for target motion, and margins for daily set-up errors.[192,193] Additional volume considerations are described in the NCCN NSCLC algorithm.

It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the spinal cord, lungs, heart, esophagus, and brachial plexus to minimize normal tissue toxicity (see Table 5).[194] These limits are mainly empirical.[195-202] For patients receiving postoperative RT, more strict DVH parameters should be considered for lung.

Radiation Simulation, Planning, and Delivery

Treatment planning should be based on CT scans obtained in the treatment position. IV contrast CT scans are recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal diseases. PET/CT is recommended for select patients (ie, those with significant atelectasis, when IV contrast is contraindicated). PET-CT can significantly improve the target accuracy.[203] In the "Principles of RT" section of the NCCN NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or intensity modulated radiotherapy (IMRT) (see "Simulation, Planning and Delivery").[204-209] Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the AAPM Task Group 76 guideline, are described in the "Principles of RT" section of the NCCN NSCLC algorithm (see "Simulation, Planning and Delivery").[210]

Stereotactic Ablative Radiotherapy (SABR)

SABR (traditionally known as SBRT), uses short courses of very high dose RT that are precisely delivered to the target.[211-213] Studies have shown that SABR is very useful for patients with inoperable stage I NSCLC or for those who refuse surgery.[214,215] With conventional treatment, 3-year survival is only about 20%-35% in these patients.[216] There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SABR.[217,218] In patients with stage I NSCLC, SABR provides a significantly longer 5-year survival than 3-D conformal RT.[209] SABR yields median survival of 32 months and 3-year overall survival of about 43% in patients with stage I disease; patients with T1 tumors survive longer than those with T2 tumors (39 versus 25 months).[219] Randomized clinical trials are currently comparing SABR to surgery.[211,220] SABR can also be used for patients with limited lung metastases and for palliative therapy.[221,222]

Studies also suggest that SABR can be used for bone, liver, and brain metastases.[211] A recent study reported that SABR increased survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment.[223] SABR is discussed the "Principles of RT" section of the NCCN NSCLC algorithm; fractionation regimens and normal tissue constraints are also provided (see Tables 2 and 3; "Early Stage Lung Cancer [Stage I]").[215,219,224-230] Decisions about whether to recommend SABR should be based on multidisciplinary discussion.

Radiofrequency Ablation

Studies suggest that radiofrequency ablation (RFA) may be an option for node-negative patients who either refuse surgery or cannot tolerate surgery because of poor PS, significant cardiovascular risk, poor pulmonary function, and/or comorbidities. Optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm; RFA can be used for previously irradiated tissue and for palliation.[231] A study with RFA in 33 patients with NSCLC yielded overall survival of 70% (95% CI, 51%–83%) at 1 year and 48% (30%-65%) at 2 years. A 2-year overall survival of 75% (45%–92%) was reported in patients with stage I NSCLC (n=13) who received RFA.[232] The procedure specific 30-day mortality rate is reported to be 2.6%.[233]

Whole Brain RT and Stereotactic Radiosurgery (SRS)

Many patients with NSCLC have brain metastases (30%-50%), which substantially affect their quality of life.[234] Surgery followed by whole brain RT is recommended (category 1) for select patients (those with good PS) with a single brain metastasis.[235-238] SRS is another option after surgical resection, although there are only a few retrospective case series supporting this option.[235] Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with or without whole brain RT.[234,239,240] Note that recent data suggest that erlotinib may be useful to manage brain metastases.[241,242]

Decisions about whether to recommend surgery, whole brain RT, SRS, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.[235,243] Treatment should be individualized for patients with recurrent or progressive brain lesions.[244]

There have been concerns that whole brain RT adversely affects neurocognition. However, a study in 208 patients with brain metastases found that patients who responded (with tumor shrinkage) after whole brain radiation had improved neurocognitive function and that tumor progression affects neurocognition more than whole brain radiation.[245] In 132 patients with 1-4 brain metastases who received SRS with or without whole brain RT, survival was similar in both groups.[240] In a subset of 92 of these patients who received SRS with or without whole brain RT, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function.[246] However, a study in 58 patients found that patients who received SRS plus whole brain radiation had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SRS alone.[247] Some have suggested that using resection with SRS (instead of resection with whole brain RT) will decrease neurocognitive problems.[248]

Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) does not appear to improve survival in patients with NSCLC; however, it may be considered in individual patients. Although it closed early because of poor accrual, a randomized phase III trial (RTOG 0214) of PCI for patients with stage III NSCLC showed that the incidence of brain metastases was decreased in patients who received PCI (18% versus 7.7%); however,

overall survival was not improved.[249] Impaired memory (immediate and delayed recall) was reported in these patients receiving PCI.[250]

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease who are medically fit and can tolerate surgery. However, SABR can be considered for patients with stage I disease who are unresectable or refuse surgery (see section on "Stereotactic Ablative Radiotherapy" in this Discussion). In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early stage disease.[251-253] Concurrent chemoradiation is superior to sequential therapy for patients with unresectable stage III disease.[254-257]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.[258-262] Of interest, recent data show that early palliative care combined with standard care improves quality of life, mood, and survival in patients with metastatic NSCLC, even though these patients had less aggressive therapy when compared with those receiving standard care alone.[263] Surgery is rarely done for patients with stage IV disease. However, surgical resection of a solitary brain metastasis may improve survival in selected patients with stage IV disease.[264] Surgical resection of a solitary metastasis located in sites other than the brain remains controversial; however, SRS or SABR may be useful in these settings. The trials supporting the recommendations for combined modality therapy are discussed in this section.

Surgery Followed by Chemotherapy: Trial Data

In the NCCN guidelines for stage IA disease, adjuvant chemotherapy is not recommended based on the following trials. Adjuvant chemotherapy is only recommended for high-risk margin-negative stage IB disease. Recommended chemotherapy regimens for adjuvant therapy are provided in the NCCN NSCLC algorithm (see "Chemotherapy Regimens for Adjuvant Therapy").

The International Adjuvant Lung Cancer Trial (IALT) reported a statistically significant survival benefit with cisplatin-based adjuvant therapy in patients with completely resected stage I, II, or III NSCLC.[251] The study included 1867 patients with surgically resected lung cancer who were randomly assigned either to cisplatin-based adjuvant chemotherapy or to observation, with a median follow-up duration of 56 months. A significantly higher survival rate (45% versus 40% at 5 years; hazard ratio for death, 0.86; 95% confidence interval [CI], 0.76 to 0.98; *P*<.03) and disease-free survival rate (39% versus 34% at 5 years; hazard ratio, 0.83; 95% CI, 0.74 to 0.94; *P*<.003) were observed for patients assigned to chemotherapy when compared with observation. IALT data suggest that cisplatin-based adjuvant chemotherapy improves survival 5 years after treatment in patients with completely resected NSCLC. However, after 7.5 years of followup, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.[265] But, data show that adjuvant chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA (Adjuvant Navelbine International Trialist Association) trial compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in early stage NSCLC. In the JBR.10 trial, 482 patients (ECOG PS of 0-1) with completely resected stage IB (T2, N0) or stage II (T1, N1, or T2, N1) NSCLC were randomly assigned either to vinorelbine plus cisplatin or to observation.[252] Adjuvant chemotherapy significantly prolonged overall survival (94 versus 73 months, hazard ratio for death, 0.69, *P*=.04) and relapse-free survival (not reached versus 47 months, hazard ratio for recurrence, 0.60; *P*<.001) when compared with observation alone. The 5-year survival rates were 69% and 54%, respectively (*P*=.03).

However, recent updated data from JBR.10 after 9 years of followup show that when compared with observation alone, adjuvant chemotherapy is beneficial for stage II but not for stage IB patients.[266] In stage II patients receiving adjuvant chemotherapy, median survival is 6.8 versus 3.6 years in those who were only observed. Of note, patients receiving chemotherapy did not have an increased death rate.

In the ANITA trial, 840 patients with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned either to adjuvant vinorelbine plus cisplatin or to observation.[253] Grade 3/4 toxicities were manageable in the chemotherapy group; however, 7 toxic deaths were reported. After median follow-up of 76 months, median survival was 66 months in the chemotherapy group and 44 months in the observation group.[253] Adjuvant chemotherapy significantly improved (8.6%) the 5-year overall survival in patients with completely resected stage II and IIIA disease, although no benefit was observed in stage I. Some clinicians consider vinorelbine/cisplatin to be the preferred regimen for completely resected early stage NSCLC based on the number of trials and the amount of use.[267]

A meta-analysis in 4,584 patients (the Lung Adjuvant Cisplatin Evaluation) found that postoperative cisplatin-based chemotherapy increased survival over 5 years (absolute benefit of 5.4%); there was no difference among the chemotherapy regimens (vinorelbine, etoposide, others).[268] A subgroup analysis found that cisplatin/vinorelbine also increased survival.[267] The benefit was greater in patients with stage II and III disease and good PS. A recent analysis found that postoperative adjuvant chemotherapy benefited elderly patients up to 80 years old.[269]

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;[270] updated results have been reported.[271,272] In this trial, 344 patients were randomly assigned either to paclitaxel and carboplatin or to observation (within 4-8 weeks of resection) with a median follow-up duration of 54 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 4 years was not significantly different, although 3-year survival was significant (79% versus 70%, *P*=.045).[271,272] The original results from CALBG suggested that the paclitaxel and carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors 4 cm or more). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin.[273] However, it is important to note that the CALGB trial was underpowered for stage 1B patients.[274]

Chemoradiation: Trial Data

The major controversies in NSCLC relate to the management of patients with stage IIIA disease. All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used in treating stage III disease. The ongoing debate centers on which modalities to use and in what sequence.[275-279] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[275,276,278,279] However, concurrent chemoradiation is superior to sequential therapy.[254-257] Concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. Patient selection affects not only the response to therapy but also how well the patient tolerates therapy.

Concurrent chemoradiation regimens used for initial treatment include cisplatin/etoposide (preferred), cisplatin/vinblastine (preferred), and carboplatin/paclitaxel (category 2B).[254,256,280,281] A randomized controlled trial in 203 unresectable patients with either stage IIIA or IIIB NSCLC assessed induction chemotherapy followed by either radiotherapy alone

or chemoradiation using paclitaxel; median survival was 14.1 months versus 18.7 months (*P*=.091), respectively.[282]

Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS, benefit from chemotherapy, usually with a platinum-based regimen.[260,261,283] Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, vinblastine, etoposide, pemetrexed, and gemcitabine. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, cisplatin/pemetrexed, and docetaxel/cisplatin.[273,284-287] Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.[288,289] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;[284,290-292] gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.[293-295] In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor.

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel for patients 1) who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or 2) in whom the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.[296,297]

Targeted Therapies

Specific targeted therapies have been developed for the treatment of advanced lung cancer.[298,299] Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor of EGFR; crizotinib is a small molecule inhibitor that targets ALK and MET. Cetuximab is a monoclonal antibody that targets EGFR.

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. The Eastern Cooperative Oncology Group (ECOG) recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase II-III clinical trials (ECOG 4599).[300] To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC and no recent history of hemoptysis. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab. For patients with nonsquamous NSCLC and PS 0-1 who are EGFR mutation negative or unknown, bevacizumab in combination with chemotherapy is one of the recommended options.

Erlotinib was approved by the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib is also recommended as first-line therapy in patients with advanced, recurrent, or metastatic nonsquamous NSCLC who have known active EGFR mutation or gene amplification regardless of their PS.[40,301-303] This recommendation is based on the results of a phase III randomized trial (Iressa Pan-Asia study [IPASS]) in which patients with EGFR mutations who received gefitinib had increased progression-free survival (24.9% versus 6.7%), response rate (71.2% versus 47.3%) and quality of life with fewer side

effects (eg, neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).[302] Gefitinib is not readily available in the United States, so erlotinib is often used. Erlotinib is an orally active agent that is very well tolerated by most patients.

An analysis of 5 clinical trials in mainly Western patients (n = 223) with advanced NSCLC (stage IIIB or IV) found that patients with EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.[96] The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced nonsquamous NSCLC.[304] Survival was increased in patients with wild type EGFR who received first-line chemotherapy compared with those who receive erlotinib first followed by second-line chemotherapy (10.8 versus 7.7 months). The recent OPTIMAL trial found that progression-free survival was increased in patients with EGFR mutations who receiving erlotinib.[101,102] The American Society of Clinical Oncology recommends that patients be tested for whether they have an EGFR mutation.[305] However, the NCCN and ESMO guidelines specify that only patients with nonsquamous histology (eg, adenocarcinoma) be assessed for EGFR mutations.[306] Patients with squamous cell carcinoma are unlikely to have EGFR mutations.

Crizotinib was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. The approval is based on an ongoing phase II trial that showed dramatic response rates (> 80%) in patients who had previously progressed.[108,109] Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough.

A large phase III randomized trial (FLEX) assessed cisplatin/vinorelbine with or without cetuximab for patients with advanced NSCLC (most patients had stage IV disease).[307] Adding cetuximab slightly increased overall survival (11.3 versus 10.1 months, *P* = .04). Cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC, regardless of histology. However, the cetuximab/cisplatin/vinorelbine regimen has a category 2B recommendation in the NCCN guidelines because the benefits are very slight, it is a difficult regimen to administer, and because patients have poorer tolerance for this regimen when compared with other regimens (eg, almost 40% of patients have grade 4 neutropenia). Patients may also have comorbid conditions that prevent them from receiving cisplatin (eg, poor kidney function). Some clinicians feel that although the FLEX trial results were statistically significant they were not clinically significant.

Maintenance Therapy

Maintenance therapy refers to systemic therapy that may be given for patients with advanced NSCLC after 4-6 cycles of first-line chemotherapy. However, patients are only candidates for maintenance therapy if they have responded to their previous treatment (ie, tumor response) or have stable disease and their tumors have not progressed. *Continuation maintenance* therapy refers to the use of at least one of the agents that was given in the first-line regimen. *Switch maintenance* therapy refers to the initiation of a different agent that was not included as part of the first-line regimen. Selection of appropriate maintenance therapy depends on several factors (eg, histologic type, performance status).

For continuation maintenance therapy, targeted agents (which were initially given in combination with conventional chemotherapy) may be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. Bevacizumab (category 1) may be continued beyond 4-6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab) in

patients with nonsquamous histology.[300,308,309] Pemetrexed may also be given as continuation maintenance therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown).[308] A recent phase III randomized trial (PARAMOUNT) found that continuation therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 versus 2.8 months); overall survival data are not available yet.[310] Cetuximab (category 1) may be continued beyond 4-6 cycles of initial therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown) or those with squamous histology (ie, cisplatin, vinorelbine, and cetuximab therapy).[307]

Use of continuation maintenance therapy depends on several factors such as whether the patient had minimal toxicity during treatment. A drug "vacation" may be more appropriate for some patients. Some clinicians feel that continuation maintenance therapy is only appropriate for select patients, because it has not been shown to improve overall survival or quality of life.[311-313] In addition, maintenance therapy has not been shown to be superior to second-line therapy, which is initiated at disease progression. There are no randomized trials supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.[311] However, some clinicians feel that if the patient is responding to the cytotoxic chemotherapy then it should be continued.

A recent phase III randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Data show that continuation maintenance therapy with gemcitabine increased progression-free survival to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).[314] Another phase III randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.[315] The data showed a slight difference in progression-free survival but no difference in overall survival. Thus, the NCCN guidelines recommend using gemcitabine as continuation maintenance therapy.

For switch maintenance therapy, 2 recent phase III randomized trials have shown a benefit in progression-free survival and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4-6 cycles) in patients without disease progression.[316,317] Switch maintenance therapy with pemetrexed may be initiated in patients with histologies other than squamous cell carcinoma who are EGFR mutation negative (or with unknown mutation status).[317] The FDA has approved maintenance therapy with pemetrexed (http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021462s029s030s032lbl.pdf).[318] Likewise, switch maintenance therapy with erlotinib may be initiated in patients with or without EGFR mutations or with squamous cell carcinoma.[314,316] Both erlotinib and pemetrexed have a category 2A recommendation for switch maintenance therapy in the NCCN NSCLC algorithm. A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.[319] However, switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN guidelines because many patients in the delayed chemotherapy arm did not receive docetaxel.

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.[320] The data showed that erlotinib alone was associated with fewer side effects in patients with EGFR mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to switch to maintenance therapy with erlotinib in patients found to have EGFR mutations during chemotherapy. The FDA has approved

maintenance therapy with erlotinib (http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021743s14s16lbl.pdf).[321]

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC. The clinical stage is initially determined from disease history (ie, cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests. The panel also recommends that smoking cessation counseling be made available to patients (http://www.smokefree.gov/). Based on the initial evaluation, the clinical stage is determined and the patient is assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. Although PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease), CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.[322-324]

Mediastinoscopy is the gold standard for evaluating mediastinal nodes. Thus, mediastinoscopy is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high (based on tumor size and location). Therefore, mediastinoscopy is appropriate for patients with T2-T3 lesions even if the PET/CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive PET/CT scan. In contrast, because of the low prior probability of lymph node involvement in patients with peripheral T1ab, N0 lesions,[325] some NCCN institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2a, central T1ab, or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy and/or endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) is recommended (see the next section).

Dillemans and colleagues have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT.[326] This strategy resulted in a 16% incidence of positive N2 nodes discovered only at the time of thoracotomy. For identifying N2 disease, chest CT scans had sensitivity and specificity rates of 69% and 71%, respectively. However, using both the chest CT scan plus mediastinoscopy was significantly more accurate (89% versus 71%) than using the chest CT scan alone for identifying N2 disease. When using CT scans, node positivity is based on the size of the lymph nodes. Therefore, the CT scan will miss small metastases that do not result in node enlargement. To address this issue, Arita and colleagues specifically examined lung cancer metastases to normal size mediastinal lymph nodes in 90 patients and found an incidence of 16% (14/90) false-negative chest CT scans with histologic identification of occult N2 or N3 disease.[327]

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I, stage II, and stage IIIA tumors. However, in patients who present with a solitary pulmonary nodule where the suspicion of

malignancy is high, surgical resection without prior invasive testing may be reasonable.

Other Imaging Studies

As previously mentioned, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.[322] PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN guideline panel reviewed the diagnostic performance of CT and PET scans. Panel members assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.[328] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported. Seely and coworkers reported on the number of metastatic lymph nodes discovered on routine mediastinoscopy and chest CT scan in patients with the most favorable tumors (ie, T1 cancer).[329] This study revealed a 21% incidence of identifying N2 or N3 nodes in patients who clinically appeared to have stage IA tumors. The positive predictive value of chest CT scan was only 43% per patient, and the negative predictive value was 92%.

Because they detect tumor physiology, as opposed to anatomy, PET scans may be more sensitive than CT scans. Moreover, if postobstructive pneumonitis is present, there is little correlation between the size of the mediastinal lymph nodes and tumor involvement.[330] Chin and colleagues found that PET, when used to stage the mediastinal nodes, was 78% sensitive and 81% specific with a negative predictive value of 89%.[331] Kernstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[332,333] The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% versus 65%). PET/CT has been shown to be useful in restaging patients after adjuvant therapy.[334,335]

The NCCN panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, for example, in identifying stage I (peripheral and central T1-2, N0), stage II, stage III, and stage IV diseases.[336,337] However, PET/CT is even more sensitive and is recommended by NCCN.[338-340] When patients with early stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.[338] However, positive PET/CT scans findings need pathologic or other radiologic confirmation (eg, MRI of bone). If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Precisely how PET/CT scans will fit into the overall staging and surveillance of NSCLC will become clearer as newer studies mature.

Transesophageal EUS-FNA and EBUS-TBNA have proven useful to stage patients or to diagnose mediastinal lesions; these techniques can be used instead of invasive staging procedures in select patients.[341] When compared with CT and PET, EBUS-TBNA has a high sensitivity and specificity for staging mediastinal and hilar lymph nodes in patients with lung cancer.[342] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[343,344] However, in patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[344,345]

The routine use of bone scans (to exclude bone metastases) is not recommended. Brain magnetic resonance imaging (MRI) (to rule out asymptomatic brain metastases) is recommended for patients with stage II, III, and IV disease to rule out metastatic disease if aggressive combined-modality therapy is being considered.[346]

Initial Therapy

It is strongly recommended that determination of tumor resectability be made by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.

Stage I, Stage II, and Stage IIIA Disease

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2, N1) tumors are generally candidates for surgical resection and mediastinal lymph node dissection. In some instances, positive mediastinal nodes (N2) are discovered at surgery; in this setting, an additional assessment of staging and tumor resectability must be made, and the treatment (ie, inclusion of systematic mediastinal lymph node dissection) must be modified accordingly. Therefore, the NCCN NSCLC algorithm includes 2 different tracks for T1–3, N2 disease: 1) T1–3, N2 disease discovered unexpectedly at surgical exploration; and 2) T1–3, N2 disease confirmed before thoracotomy. In the second case, an initial brain MRI and PET/CT scan (if not previously done) are recommended to rule out metastatic disease.

For patients with clinical stage IIB (T3, N0) and stage IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0-1) and stage IIIA (T4, N0-1) tumors, treatment options are organized according to the location of the tumor (ie, the superior sulcus, chest wall, and proximal airway or mediastinum). For each location, a thoracic surgeon needs to determine whether the tumor is resectable.

For patients with resectable tumors (T3 invasion, N0-1) in the superior sulcus, the panel suggests concurrent chemoradiation therapy followed by surgical resection and chemotherapy. Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.[180,182,347-350] The overall 5-year survival rate is approximately 40%.[180] Patients with marginally resectable superior sulcus tumors should undergo concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T4 extension, N0-1) in the superior sulcus, definitive concurrent chemoradiation is recommended followed by chemotherapy if full-dose chemotherapy was not given initially.[281,351] Note that “Principles of RT” is in the NCCN NSCLC algorithm. In addition, the NCCN NSCLC algorithm also provides recommendations for chemotherapy (see “Chemotherapy Regimens for Adjuvant Therapy,” “Chemotherapy Regimens Used with Radiation Therapy,” and “Systemic Therapy for Advanced or Metastatic Disease”).

Surgical resection is the preferred treatment option for patients with tumors of the chest wall, proximal airway, or mediastinum (T3-4, N0-1). Other treatment options include chemotherapy or concurrent chemoradiation before surgical resection.

For patients with stage IIIA disease and positive mediastinal nodes (T1-3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation. Patients with negative mediastinal biopsy findings are candidates for surgery, with additional assessment of resectability at the time of thoracotomy. For those patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the surgery. Those individuals found to have unresectable lesions should be treated according to pathologic stage. For patients with (T1-2 or T3) node-positive disease, an additional brain MRI and PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the panel recommends that the patient be

treated with definitive concurrent chemoradiation therapy.[255] Induction chemotherapy with (or without) RT is another option for patients with T1-3, N2 disease.[137] Recommended therapy for metastatic disease is described in the NCCN NSCLC algorithm.

When a lung metastasis is present, it usually occurs in patients with other systemic metastases; the prognosis is poor. Therefore, many of these patients are not candidates for surgery; however, systemic therapy is recommended. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery.[352] Patients with separate pulmonary nodule(s) in the same lobe or ipsilateral non-primary lobe without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.[353] Intrapulmonary metastases have been downstaged in the recent TNM revised staging (ie, AJCC 7th edition).[65,353,354] After surgery, concurrent chemoradiation (if tolerated) is recommended for those with positive margins and chemotherapy is recommended for those with negative margins.

For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy.[136,254,281] In patients with synchronous nodules (contralateral lung), the guidelines suggest treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar.

Stage IIIB Disease

Stage IIIB tumors comprise 2 groups including 1) tumors with contralateral mediastinal nodes (T1-3, N3); and 2) tumors with T4 extension and N2-3 disease, which are unresectable. Surgical resection is not recommended in patients with T1-3, N3 disease. However, in patients with suspected N3 disease, the guidelines recommend pathologic confirmation of nodal status.[355,356] In addition, PET/CT scans and brain MRI should also be included in the pretreatment evaluation. If these tests are negative, then treatment options for the appropriate nodal status should be followed. If N3 disease is confirmed, concurrent chemoradiation (category 1) is recommended followed by chemotherapy if full-dose chemotherapy was not given initially.[136,254,281,357,358] For metastatic disease that is confirmed by PET/CT scan and brain MRI, treatment is described in the NCCN NSCLC algorithm.

For patients with T4 extension, N2-3 disease (stage IIIB), surgical resection is not generally recommended. The initial work-up includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0-1) disease. If either the contralateral or ipsilateral mediastinal node is positive, concurrent chemoradiation therapy is recommended (category 1) followed by chemotherapy if full-dose chemotherapy was not given initially.[136,254,281,357-359]

Stage IV Disease

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised AJCC staging (7th edition), T4 with effusion has been reclassified as stage IV, M1a (see Table 3).[65] Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (eg, obstructive pneumonia), an exudate or sanguinous effusion is considered malignant no matter what the results of cytologic

examination. If the pleural effusion is considered negative, the NCCN NSCLC algorithm tracks back to the confirmed T and N stage. However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.[360] In patients with effusions that are positive for malignancy, the tumor is treated as M1a with local therapy (ie, ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease.

Recommendations for patients with distant metastases (ie, stage IV, M1b) depend on the location of the metastases—a solitary nodule in the brain or adrenal—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, PET/CT scan, and brain MRI. The increased sensitivity of PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. However, positive PET/CT scan findings need pathologic or other radiologic confirmation. If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.

Patients with solitary brain metastases may benefit from surgical resection (see the section on “Whole Brain RT and Stereotactic Radiosurgery” in this Discussion).[234,235] The 5-year survival rates with such an approach range from 10% to 20%;[298,361] median survival is about 40 weeks.[238] Follow-up whole brain RT (category 1) or SRS may be used.[236,245,362] SRS alone or followed by whole brain radiation are additional treatment options.[239,240] Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.[363] After their brain lesions are treated, further treatment options for these patients with T1-2, N0-1 NSCLC or for those with T3, N0 then include: 1) surgical resection of the lung lesion followed by chemotherapy (category 2B for chemotherapy); 2) SABR of the lung lesion (category 2B); or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B). Systemic therapy is an option after surgery for patients with higher stage NSCLC.

Adrenal metastases from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. If an adrenal metastasis is found and if the lung lesion is curable, the resection of the adrenal lesion (category 2B) has produced some long-term survivors.[364,365] Some panel members feel that resection of adrenal metastases only makes sense if the synchronous lung disease is stage I or maybe stage II (ie, resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Treatment options for patients with stage IA (T1ab, N0 disease) and with positive surgical margins (R1, R2) include 1) re-resection (preferred); or 2) RT (category 2B). Observation is recommended for patients with T1ab, N0 tumors and with negative surgical margins (R0). Patients with T2ab, N0 tumors with negative surgical margins are usually observed; chemotherapy (category 2B) is recommended as adjuvant treatment for patients with high-risk features (including lung neuroendocrine tumors [but excluding well-differentiated neuroendocrine tumors]), such as poorly differentiated tumor, vascular invasion, wedge resection, minimal margins, tumors greater than 4 cm, visceral pleural involvement, and Nx.[272] If the surgical margins are positive in patients with T2ab, N0 tumors, these patients should have either 1) re-resection (preferred) with or without chemotherapy; or 2) RT with or without chemotherapy (chemotherapy is used for stage IIA).[173,272]

The panel recommends chemotherapy (category 1) for patients with negative surgical margins and stage II disease 1) T1ab-2a, N1; 2) T2b, N1; or 3) T3, N0 disease.[268,366] If surgical margins are positive in these patients, options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with T1-3, N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy. Patients with negative margins may be treated with chemotherapy (category 1) and RT.[268]

Panel members disagreed about the use of chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.[172] In this trial, no difference in survival rates was observed between stage II and stage IIIA patients who had a surgical resection and received either adjuvant radiotherapy alone (median survival = 39 months) or radiotherapy given with concurrent chemotherapy (median survival = 38 months). Because the 5-year survival rate was less than 40%, some NCCN panel members feel that survival rates may increase with newer chemotherapeutic agents and with higher doses of radiation. For example, a phase II trial (RTOG 9705) (n = 88) using concurrent paclitaxel/carboplatin yielded a median survival of 56.3 months with 3-year survival of 61% in patients with resected stage II and IIIA disease.[174] A phase II trial in 42 patients had similar results (5-year survival, 68%) except those with adenocarcinoma had poorer survival (only 28%).[175]

As with stage IB and stage II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in stage III NSCLC patients who have had surgery. In the case of marginally resectable superior sulcus tumors (T4 extension, N0-1), if the lesion converts to a resectable status following concurrent chemoradiation, resection followed by chemotherapy is recommended. If the lesion does not convert (ie, it remains unresectable), the full course of definitive RT followed by chemotherapy is administered as an adjuvant treatment. Among patients with chest wall lesions with T3 invasion-4 extension, N0-1 disease, those that are initially treated with surgery (preferred) may receive chemotherapy alone if the surgical margins are negative; when surgical margins are positive, they may receive either chemoradiation and chemotherapy or re-resection with chemotherapy. A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3-4, N0-1).

For patients with stage IIIA disease and positive mediastinal nodes (T1-3, N2), if there is no disease progression after initial treatment, recommended treatment includes surgery with (or without) chemotherapy (category 2B). In addition, postoperative RT should be given if not used preoperatively. Alternatively, if the disease progresses, patients may be treated with either 1) local therapy using RT (if not given previously) with (or without) chemotherapy, or 2) systemic treatment. In patients with separate pulmonary nodules in the same lobe or ipsilateral lung, surgery is recommended. If the margins are negative, adjuvant chemotherapy is recommended. If the resection margins are positive, concurrent chemoradiation is recommended (if tolerated).

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease obviously present but undetectable at diagnosis. The timing of this chemotherapy varies, with no one clear preference. Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients.

On the basis of clinical studies on adjuvant chemotherapy for NSCLC,[251-253] the panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with gemcitabine, pemetrexed, or docetaxel.[273,284,287] For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used.[273] A recent phase III randomized trial in elderly (70-89 years) patients with advanced NSCLC reported that combined therapy with weekly paclitaxel and monthly carboplatin improved survival when compared with single-agent therapy using either gemcitabine or vinorelbine (10.3 versus 6.2 months).[367,368] A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery.[369-371]

Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[372-375] The S9900 trial, a SWOG (Southwest Oncology Group) study, one of the largest randomized trials examining preoperative chemotherapy in early stage NSCLC, assessed surgery alone compared with surgery plus preoperative paclitaxel and carboplatin in patients with stage IB/IIA and stage IIB/IIIA NSCLC (excluding superior sulcus tumors). Progression-free survival and overall survival were in favor of preoperative chemotherapy.[374,375] All 3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase III studies had small number of patients while the SWOG study was stopped early because of the positive results of the IALT study. However, the induction chemotherapy-surgery approach needs to be compared with induction chemotherapy-RT in large, randomized clinical trials.

Radiation Therapy

NCCN panel members disagreed (category 2B) about using RT alone as adjuvant treatment for T1ab, N0 tumors based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).[376] This study showed that postoperative radiotherapy is detrimental to patients with early stage, completely resected NSCLC and should not be given routinely to such patients. However, the guideline panelists found several flaws in the meta-analysis, including:

- Many patients were treated with cobalt 60 equipment, which delivers an inhomogeneous dose distribution;
- Studies from the 1960s, when there was no adequate staging, were included in the meta-analysis;
- The data analysis lacked detailed timing for postoperative RT;
- Node-negative NSCLC patients were included (these patients routinely do not receive postoperative RT); and
- The meta-analysis included unpublished data.

An assessment of postoperative radiation in 7,465 patients with resected stage II or III NSCLC found that postoperative radiation increased survival in patients with N2 disease but not in those with N1 or N0 disease.[377] Therefore, guidelines from some cancer organizations recommend that postoperative RT should only be given to those with N2 disease.[378] The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.[173] Adjuvant chemotherapy (category 1) with RT is recommended for T1-3, N2 patients with negative margins.

A recent meta-analysis assessed postoperative chemotherapy with or without postoperative RT in patients mainly with stage III disease.[366] In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemoRT. Regimens

included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide. The American College of Radiology (ACR) appropriateness criteria provide specific recommendations for postoperative RT.[379] The adjuvant chemotherapy regimens described in the NCCN algorithm (eg, cisplatin/vinorelbine, carboplatin/paclitaxel, cisplatin/pemetrexed, cisplatin/gemcitabine, cisplatin/docetaxel) may be used with RT.[173,380,381] Chemoradiation regimens cited in the NCCN guidelines may also be used for stage II-III disease.[174,175,254,255,281]

Surveillance

The surveillance guidelines are described in the NCCN NSCLC algorithm. A helical chest CT scan with or without contrast is recommended every 6-12 months postoperatively for 2 years (category 2B); a non-contrast-enhanced chest CT is recommended annually thereafter (category 2B), although the panel disagreed about these recommendations for helical chest CT scans.[28] Information about smoking cessation (eg, advice, counseling, and therapy) should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients (http://www.smokefree.gov/). Recent data show that low-dose CT screening of select patients at high risk for lung cancer (ie, 30 pack years of smoking) increases survival.[32] However, use of low-dose CT for surveillance is not currently recommended for patients who have been previously treated for lung cancer.

The NCCN NSCLC guidelines include an algorithm for long-term followup care of NSCLC survivors (see “Cancer Survivorship Care”). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening.

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the NCCN NSCLC algorithm. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life.[382] After the treatment for the locoregional recurrence, observation or systemic chemotherapy (category 2B for chemotherapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic chemotherapy or best supportive care are recommended. The type of systemic therapy depends on the histologic type, EGFR mutation status, and PS.

Management of distant metastases (eg, localized symptoms; diffuse brain, bone, solitary, or disseminated metastases) is described in the NCCN NSCLC algorithm. For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT.[383] Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis.[384-386] Note that denosumab can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. The FDA has approved the use of zoledronic acid in patients with bone metastases from solid tumors.[387] For patients with recurrent and metastatic disease, the NCCN NSCLC guidelines now recommend that histologic subtype should be determined before therapy so that the best treatment can be selected.[287] EGFR mutation testing is recommended in patients with nonsquamous NSCLC (ie, adenocarcinoma, large cell) or in NSCLC NOS, because erlotinib is recommended for patients who are positive

for EGFR mutations (see section on "EGFR Mutations").[40,100,302,388] As previously mentioned, recent recommendations from an international panel suggest that general categories be avoided (eg, NSCLC), because more effective treatment can be selected when the histology is known.[36] However, very few patients with squamous cell carcinoma have EGFR mutations (< 4%); therefore, routine testing is not recommended in these patients.[389,390]

Treatment recommendations and eligibility criteria for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) are described in the NCCN NSCLC algorithm. Treatment recommendations and eligibility criteria for patients with squamous histology are described in the NCCN NSCLC algorithm. These recommendations are briefly summarized in the following paragraph. Data supporting these recommendations are described in the following section (see next section on "Trial Data").

Cisplatin/pemetrexed is recommended (category 1) for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met.[287] Bevacizumab/chemotherapy is another option for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met.[391] Previously patients with brain metastases were excluded from receiving bevacizumab because of concerns about CNS hemorrhage; however, data suggest that bevacizumab can be used in patients with treated CNS metastases.[392] Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on PS and other factors (see next section on "Trial Data"). Panel members disagreed (category 2B) about using cetuximab with cisplatin and vinorelbine, because data only showed a slight improvement in survival with the addition of cetuximab (11.3 versus 10.1 months, *P* = .04) and because this regimen is generally not used in the United States because of concerns about toxicity with cisplatin.[307] Cisplatin/gemcitabine is an option for patients with squamous cell carcinoma.[287] Another option is cetuximab with cisplatin and vinorelbine, although this is a category 2B recommendation.[307]

Trial Data

In a phase II/III trial (ECOG 4599), 878 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.[300,393] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin demonstrated an improved median survival (12.3 versus 10.3 months, *P*=.003) when compared to patients receiving paclitaxel and carboplatin alone.[300] The overall 1-year and 2-year survival was 51% versus 44% and 23% versus 15%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.[300] However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 25.5% versus 16.8%, grade 5 hemoptysis: 1.2% versus 0% and grade 3 hypertension: 6.8% versus 0.5%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (15 patients) than with paclitaxel and carboplatin (2 patients) (*P* =.001).

A recent analysis of ECOG 4599 found that adenocarcinoma histology was associated with improved survival in patients receiving bevacizumab/paclitaxel/carboplatin compared with chemotherapy alone (14.2 versus 10.3 months).[391] However, a trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab.[394,395]

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine compared with cisplatin plus pemetrexed.[287] Patients with either adenocarcinoma or large cell histology (ie, nonsquamous) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 versus 10.9 months). Patients with squamous cell histology had improved survival with the cisplatin/gemcitabine regimen (10.8 versus 9.4 months). When compared with the cisplatin/gemcitabine regimen, the cisplatin/pemetrexed regimen had significantly lower rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$). Treatment-related deaths were similar for both regimens (cisplatin plus pemetrexed, 9 patients [1.0%); cisplatin plus gemcitabine, 6 patients [0.7%]). A recent analysis of three phase 3 trials confirmed that pemetrexed improves survival for patients with nonsquamous NSCLC in first-line, second-line and maintenance therapy.[396]

In the FLEX trial, 1125 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) were randomly assigned to either 1) cetuximab in combination with vinorelbine and cisplatin; or 2) vinorelbine and cisplatin alone.[307] The response rate was increased with cetuximab (36% versus 29%, P=.012); there was no difference in progression-free survival. Overall survival was slightly better in patients receiving cetuximab (11.3 versus 10.1 months, P=.04). However, there was increased grade 3 or 4 febrile neutropenia in patients receiving cetuximab (22% versus 15%, P<.05); patients also had grade 2 acne-like rash. Treatment-related deaths were similar in both groups (3% versus 2%).

Data show that platinum-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Cisplatin or carboplatin have been proven effective in combination with any of the following agents: docetaxel, etoposide, gemcitabine, paclitaxel, pemetrexed, vinblastine, and vinorelbine.[273,284-287,290,291] Non-platinum regimens are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).[293-295]

Maintenance Therapy

Patients receiving therapy should be evaluated for tumor response with a CT scan. Approximately 25% of patients demonstrate disease progression after the initial cycle of chemotherapy. Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of chemotherapy[397] or until the disease progresses. A meta-analysis suggests that continuing the initial regimen beyond 4-6 cycles is associated with increased progression-free survival; however, patients have more adverse events.[398] Another review suggests that there is no benefit to continuing chemotherapy beyond 4-6 cycles; however, it is important to note that many patients assigned to longer duration of therapy did not receive the planned number of cycles.[311]

For patients with nonsquamous NSCLC who are EGFR mutation negative (or unknown mutation status), continuation maintenance therapy regimens include bevacizumab (category 1), cetuximab (category 1), pemetrexed, or gemcitabine.[300,307,310,314] Switch maintenance therapy regimens for these patients include pemetrexed or erlotinib.[314,316,317] Observation is another option.

For patients with squamous cell histology, cetuximab (category 1) or gemcitabine can be used as a continuation maintenance therapy regimen.[314,316] Switch maintenance therapy for these patients includes erlotinib or docetaxel (category 2B). Observation is another option. A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until

progression.[319] However, switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN guidelines, because many patients in the delayed chemotherapy arm did not receive docetaxel.

A phase III randomized trial (n = 663) assessed the effect of best supportive care with or without maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but had not progressed.[317] In patients with nonsquamous NSCLC, overall survival was increased with pemetrexed when compared with placebo (15.5 versus 10.3 months, *P*=.002).

Continuation of Erlotinib or Gefitinib After Progression: Has Its Time Come?

Patients may continue to derive benefit from erlotinib or gefitinib after disease progression; discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).[399] This strategy mirrors the experience in other oncogene-addicted cancers, particularly *HER2*-amplified breast cancer. In women with *HER2*-amplified breast cancer who have had progression of disease on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy is added to trastuzumab.[400] Data support the continued use of erlotinib or gefitinib in patients with lung adenocarcinoma with *EGFR* mutations after development of acquired resistance to erlotinib or gefitinib when conventional chemotherapy is initiated.

There is accumulating data about how cancers become resistant to EGFR inhibitors. The most common known mechanism is the acquisition of a secondary mutation in EGFR—T790M—that renders the kinase resistant to erlotinib and gefitinib.[401,402] Amplification of the MET oncogene is another validated resistance mechanism. Activation of the IGF-1R pathway has been observed in laboratory models. To overcome all 3 types of resistance, EGFR must still be inhibited. In the case of MET amplification and IGF-IR activation, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely and colleagues demonstrate that when cancers that were once sensitive to EGFR inhibitors start to progress, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.[399] In total, it is likely that continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.

Second-Line and Third-Line Chemotherapy

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, erlotinib, or platinum doublet (with or without bevacizumab) are recommended as second-line chemotherapy regimens for patients with PS of 0-2 and who have experienced disease progression during or after first-line therapy.[403-406] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life; docetaxel may be used for third-line therapy.[403,404] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[405,407] Pemetrexed is recommended in patients with adenocarcinoma or large cell histology (ie, nonsquamous NSCLC) for second-line and third-line therapy.[317] Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.[406] Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with PS of 3-4 who have the EGFR mutation. A platinum doublet with or without bevacizumab is an option for patients with nonsquamous NSCLC (ie, adenocarcinoma,

large cell, NSCLC NOS) who have progressed after first-line therapy with erlotinib or crizotinib.[300]

In a randomized placebo-controlled double-blind trial (NCIC CTG trial), 731 patients (stage IIIB or IV, PS 0-3) were randomly assigned (2:1) to receive either erlotinib or placebo, following failure of first- or second-line chemotherapy.[406] Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (hazard ratio, 0.70; *P*<.001). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (hazard ratio, 0.61, adjusted for stratification categories; *P*<.001). However, 5% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first- or second-line chemotherapy. A randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel.[408] If disease progression occurs after third-line chemotherapy, patients with PS of 0-2 may be treated with best supportive care or be enrolled in a clinical trial.

References

1. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21685461.

2. The Health Consequences of Smoking: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services. Centers for Disease Control and Prevention (US); 2004.

3. Secretan B, Straif K, Baan R, et al. A review of human carcinogens--Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033-1034. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19891056.

4. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976;2:1525-1536. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1009386.

5. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. Int J Epidemiol 2007;36:1048-1059. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17690135.

6. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2006.

7. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980-988. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9365295.

8. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? Br Med J (Clin Res Ed) 1986;293:1217-1222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3096439.

9. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens--part D: radiation. Lancet Oncol 2009;10:751-752. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19655431.

10. Darby S, Hill D, Deo H, et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand J Work Environ Health 2006;32 Suppl 1:1-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16538937.

11. Krewski D, Lubin JH, Zielinski JM, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A 2006;69:533-597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16608828.

12. Schrump DS, Carter D, Kelsey CR, et al. Non-small cell lung cancer. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, et al., eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

13. Omenn GS, Merchant J, Boatman E, et al. Contribution of environmental fibers to respiratory cancer. Environ Health Perspect 1986;70:51-56. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3830113.

14. Fraumeni JF, Jr. Respiratory carcinogenesis: an epidemiologic appraisal. J Natl Cancer Inst 1975;55:1039-1046. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1107567.

15. Janerich DT, Thompson WD, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990;323:632-636. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2385268.

16. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol

2009;10:453-454. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19418618.

17. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med 2005;48:419-431. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16299703.

18. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 2009;374:1243-1251. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19767090.

19. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008;63:717-724. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18263663.

20. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56-63. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16820547.

21. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47-55. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16820546.

22. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. Clin Ther 2009;31:463-491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19393839.

23. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2011:CD006103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21328282.

24. Xi ZX. Preclinical pharmacology, efficacy and safety of varenicline in smoking cessation and clinical utility in high risk patients. Drug Healthc Patient Saf 2010;2010:39-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21278851.

25. Hays JT, Ebbert JO. Adverse effects and tolerability of medications for the treatment of tobacco use and dependence. Drugs 2010;70:2357-2372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21142259.

26. Carney DN. Lung cancer--time to move on from chemotherapy. N Engl J Med 2002;346:126-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11784881.

27. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. J Clin Oncol 1999;17:1794-1801. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561217.

28. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10408484.

29. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screenings. Cancer 2001;92:153-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11443621.

30. Kaneko M, Kusumoto M, Kobayashi T, et al. Computed tomography screening for lung carcinoma in Japan. Cancer 2000;89:2485-2488. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11147632.

31. The National Lung Screening Trial: Overview and Study Design. Radiology 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21045183.

32. Aberle DR, Adams AM, Berg CD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med

2011;365:395-409. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21714641.

33. The national lung screening trial: overview and study design. Radiology 2011;258:243-253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21045183.

34. Aberle DR, Adams AM, Berg CD, et al. Baseline characteristics of participants in the randomized national lung screening trial. J Natl Cancer Inst 2010;102:1771-1779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21119104.

35. Henschke CI, Yankelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-1771. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17065637.

36. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-285. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21252716.

37. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986;4:702-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3701389.

38. Cooper WA, O'Toole S, Boyer M, et al. What's new in non-small cell lung cancer for pathologists: the importance of accurate subtyping, EGFR mutations and ALK rearrangements. Pathology 2011;43:103-115. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21233671.

39. Fossella FV, Putnam JB, Komaki R, eds. Lung Cancer. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.

40. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005;23:5900-5909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16043828.

41. Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:423-429. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17473658.

42. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-1703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20979469.

43. Travis WD. Pathology and genetics of tumours of the lung, pleura, thymus and heart Lyon: IARC Press; 2004.

44. Rekhtman N, Ang DC, Sima CS, et al. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21623384.

45. Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Am J Surg Pathol 2011;35:15-25. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21164283.

46. Terry J, Leung S, Laskin J, et al. Optimal immunohistochemical markers for distinguishing lung adenocarcinomas from squamous cell carcinomas in small tumor samples. Am J Surg Pathol 2010;34:1805-1811. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21107086.

47. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med

2009;133:1317-1331. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19653732.

48. King JE, Thatcher N, Pickering CA, Hasleton PS. Sensitivity and specificity of immunohistochemical markers used in the diagnosis of epithelioid mesothelioma: a detailed systematic analysis using published data. Histopathology 2006;48:223-232. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16430468.

49. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-380. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15891998.

50. Ordonez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. Am J Surg Pathol 2003;27:1031-1051. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12883236.

51. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. Adv Anat Pathol 2000;7:123-127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10721419.

52. Rivera MP, Mehta AC. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:131S-148S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17873165.

53. Tan D, Zander DS. Immunohistochemistry for assessment of pulmonary and pleural neoplasms: a review and update. Int J Clin Exp Pathol 2008;1:19-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18784820.

54. Zhang H, Liu J, Cagle PT, et al. Distinction of pulmonary small cell carcinoma from poorly differentiated squamous cell carcinoma: an immunohistochemical approach. Mod Pathol 2005;18:111-118. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15309021.

55. Guinee DG, Jr., Fishback NF, Koss MN, et al. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. Am J Clin Pathol 1994;102:406-414. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7524299.

56. Du L, Schageman JJ, Irnov, et al. MicroRNA expression distinguishes SCLC from NSCLC lung tumor cells and suggests a possible pathological relationship between SCLCs and NSCLCs. J Exp Clin Cancer Res 2010;29:75. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20624269.

57. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002.

58. Mountain CF. A new international staging system for lung cancer. Chest 1986;89:225S-233S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3514171.

59. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-1717. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9187198.

60. Mountain CF. Staging classification of lung cancer. A critical evaluation. Clin Chest Med 2002;23:103-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11901906.

61. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM Classification of malignant tumours. J Thorac Oncol 2007;2:706-714. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17762336.

62. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260-271. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19584208.

63. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.

64. Rami-Porta R, Bolejack V, Goldstraw P. The new tumor, node, and metastasis staging system. Semin Respir Crit Care Med 2011;32:44-51. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21500123.

65. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. Ann Thorac Cardiovasc Surg 2009;15:4-9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19262443.

66. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients : a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. Cancer 2007;110:1532-1541. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17702091.

67. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-199. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17505036.

68. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med 2005;353:133-144. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16014883.

69. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol 2008;26:1472-1478. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18349398.

70. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442-2449. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18458038.

71. Simon GR, Sharma S, Cantor A, et al. ERCC1 expression is a predictor of survival in resected patients with non-small cell lung cancer. Chest 2005;127:978-983. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15764785.

72. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983-991. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16957145.

73. Bepler G, Kusmartseva I, Sharma S, et al. RRM1 modulated in vitro and in vivo efficacy of gemcitabine and platinum in non-small-cell lung cancer. J Clin Oncol 2006;24:4731-4737. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16966686.

74. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med 1990;323:561-565. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2199829.

75. Tsao MS, Aviel-Ronen S, Ding K, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol 2007;25:5240-5247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18024870.

76. Bepler G, Sharma S, Cantor A, et al. RRM1 and PTEN as prognostic parameters for overall and disease-free survival in patients with non-small-cell lung cancer. J Clin Oncol 2004;22:1878-1885. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15143080.

77. Zheng Z, Chen T, Li X, et al. DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. N Engl J Med 2007;356:800-808. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17314339.

78. Bepler G, Olaussen KA, Vataire AL, et al. ERCC1 and RRM1 in the international adjuvant lung trial by automated quantitative in situ analysis. Am J Pathol 2011;178:69-78. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21224045.

79. Bepler G, Li X, Schell M, et al. Predictive value of RRM1 and ERCC1 protein levels in a prospective community-based trial of gemcitabine/carboplatin (GC) vs gemcitabine (G) alone [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 8033. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/8033.

80. Reynolds C, Obasaju C, Schell MJ, et al. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. J Clin Oncol 2009;27:5808-5815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884554.

81. Shaw AT, Forcione DG, Digumarthy SR, Iafrate AJ. Case records of the Massachusetts General Hospital. Case 21-2011. A 31-year-old man with ALK-positive adenocarcinoma of the lung. N Engl J Med 2011;365:158-167. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21751909.

82. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-4253. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19667264.

83. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. EMBO Mol Med 2010;2:146-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20432502.

84. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 2011;29:2046-2051. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21483012.

85. Hirsch FR, Bunn PA, Jr. EGFR testing in lung cancer is ready for prime time. Lancet Oncol 2009;10:432-433. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19410185.

86. Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res 2006;12:7232-7241. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17189394.

87. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. PLoS Med 2005;2:e73. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15737014.

88. Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. Clin Cancer Res 2006;12:5764-5769. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17020982.

89. Onitsuka T, Uramoto H, Nose N, et al. Acquired resistance to gefitinib: the contribution of mechanisms other than the T790M, MET, and HGF status. Lung Cancer 2010;68:198-203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19589612.

90. Han SW, Kim TY, Jeon YK, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. Clin Cancer Res 2006;12:2538-2544. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16638863.

91. Dacic S. EGFR assays in lung cancer. Adv Anat Pathol 2008;15:241-247. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18580100.

92. Sholl LM, Xiao Y, Joshi V, et al. EGFR mutation is a better predictor of response to tyrosine kinase inhibitors in non-small cell lung carcinoma than FISH, CISH, and immunohistochemistry. Am J Clin Pathol 2010;133:922-934. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20472851.

93. Eberhard DA, Giaccone G, Johnson BE. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung

Cancer Working Group: standardization for use in the clinical trial setting. J Clin Oncol 2008;26:983-994. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18281673.

94. Pao W, Ladanyi M. Epidermal growth factor receptor mutation testing in lung cancer: searching for the ideal method. Clin Cancer Res 2007;13:4954-4955. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17785543.

95. Shepherd FA, Tsao MS. Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an enigma. J Clin Oncol 2010;28:903-905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20100955.

96. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. Clin Cancer Res 2009;15:5267-5273. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671843.

97. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 2004;350:2129-2139. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15118073.

98. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15118125.

99. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-128. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20022809.

100. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-2388. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20573926.

101. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 2011;12:735-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21783417.

102. Zhou C, Wu YL, Chen G, et al. Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomized, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 7520. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7520.

103. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 7503. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7503.

104. Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. Ann Surg Oncol 2010;17:889-897. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20183914.

105. Kim H, Yoo SB, Choe JY, et al. Detection of ALK gene rearrangement in non-small cell lung cancer: a comparison of fluorescence in situ hybridization and chromogenic in situ hybridization with correlation of ALK protein expression. J Thorac Oncol 2011;6:1359-1366. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21587085.

106. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-5223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19671850.

107. Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. Clin Cancer Res 2010;16:1561-1571. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20179225.

108. Crino L, Kim D, Riely GJ, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005 [abstract]. J Clin Oncol 2011;29 (Suppl 15):Abstract 7514. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7514.

109. Camidge DR, Bang Y, Kwak EL, et al. Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 2501. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/2501.

110. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. Curr Opin Investig Drugs 2010;11:1477-1490. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21154129.

111. Shaw AT, Yeap BY, Solomon BJ, et al. Impact of crizotinib on survival in patients with advanced, ALK-positive NSCLC compared with historical controls [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7507.

112. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010;363:1734-1739. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20979473.

113. Katayama R, Khan TM, Benes C, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. Proc Natl Acad Sci U S A 2011;108:7535-7540. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21502504.

114. Sequist LV, Gettinger S, Senzer NN, et al. Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. J Clin Oncol 2010;28:4953-4960. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20940188.

115. Zhang S, Wang F, Keats F. AP26113, a potent ALK inhibitor, overcomes mutations in EML4-ALK that confer resistance to PF-02341066 (PF1066) [abstract]. Presented at the Proceedings of the 101st Annual Meeting of the American Association for Cancer Research; Washington, DC. Abstract LB-298.

116. Cheng M, Ott GR. Anaplastic lymphoma kinase as a therapeutic target in anaplastic large cell lymphoma, non-small cell lung cancer and neuroblastoma. Anticancer Agents Med Chem 2010;10:236-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20406193.

117. Slebos RJ, Hruban RH, Dalesio O, et al. Relationship between K-ras oncogene activation and smoking in adenocarcinoma of the human lung. J Natl Cancer Inst 1991;83:1024-1027. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2072410.

118. Mitsudomi T, Steinberg SM, Oie HK, et al. ras gene mutations in non-small cell lung cancers are associated with shortened survival irrespective of treatment intent. Cancer Res 1991;51:4999-5002. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1654209.

119. Brissenden JE, Caras I, Thelander L, Francke U. The structural gene for the M1 subunit of ribonucleotide reductase maps to chromosome 11, band p15, in human and to chromosome 7 in mouse.

Exp Cell Res 1988;174:302-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3275546.

120. Pitterle DM, Kim YC, Jolicoeur EM, et al. Lung cancer and the human gene for ribonucleotide reductase subunit M1 (RRM1). Mamm Genome 1999;10:916-922. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10441745.

121. Boffa DJ, Allen MS, Grab JD, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247-254. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18242243.

122. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:234S-242S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17873171.

123. Sienel W, Dango S, Kirschbaum A, et al. Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. Eur J Cardiothorac Surg 2008;33:728-734. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18261918.

124. Sienel W, Stremmel C, Kirschbaum A, et al. Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins--implications for patient selection for segmentectomy. Eur J Cardiothorac Surg 2007;31:522-527; discussion 527-528. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17229574.

125. Narsule CK, Ebright MI, Fernando HC. Sublobar versus lobar resection: current status. Cancer J 2011;17:23-27. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21263263.

126. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-622; discussion 622-613. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7677489.

127. Koike T, Yamato Y, Yoshiya K, et al. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. J Thorac Cardiovasc Surg 2003;125:924-928. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12698157.

128. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. J Clin Oncol 2010;28:928-935. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20065181.

129. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-670. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21335122.

130. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann Thorac Surg 2006;81:1013-1019; discussion 1019-1020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16488712.

131. Allen MS, Darling GE, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: Results of the randomized, prospective ACOSOG Z0030 trial [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7555. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7555.

132. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: results of the randomized, prospective American College of Surgeons Oncology Group Z0030 trial. Chest 2011;139:1124-1129. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20829340.

133. Darling GE, Allen MS, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: Results of the randomized, prospective ACOSOG Z0030 Trial. Chest 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20829340.

134. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. J Thorac Oncol 2009;4:568-577. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19357537.

135. Farjah F, Flum DR, Varghese TK, Jr., et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;87:995-1004; discussion 1005-1006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19324119.

136. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. Lancet 2009;374:379-386. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632716.

137. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-450. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17374834.

138. Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. Ann Thorac Surg 2008;86:362-366; discussion 366-367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18640297.

139. Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;75:1462-1467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19467798.

140. Stefani A, Alifano M, Bobbio A, et al. Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients. J Thorac Cardiovasc Surg 2010;140:356-363. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20381815.

141. Gopal RS, Dubey S, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) on Induction and Adjuvant Therapy for Stage N2 Non-Small-Cell Lung Cancer: expert panel on radiation oncology-lung. Int J Radiat Oncol Biol Phys 2010;78:969-974. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20813465.

142. Evans NR, 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. J Thorac Cardiovasc Surg 2010;139:991-996 e991-992. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20304144.

143. Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy--influence of preoperative induction therapy. J Thorac Cardiovasc Surg 2009;138:289-294. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19619768.

144. Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! Eur J Cardiothorac Surg 2007;31:181-185. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17141515.

145. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg 2010;139:1424-1430. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20416887.

146. Kappers I, van Sandick JW, Burgers SA, et al. Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. Lung Cancer 2010;68:222-227. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19664843.

147. Decaluwe H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433-439. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19502079.

148. Swanson SJ, Batirel HF. Video-assisted thoracic surgery (VATS) resection for lung cancer. Surg Clin North Am 2002;82:541-559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12371584.

149. Mahtabifard A, Fuller CB, McKenna RJ, Jr. Video-assisted thoracic surgery sleeve lobectomy: a case series. Ann Thorac Surg 2008;85:S729-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18222205.

150. Shaw JP, Dembitzer FR, Wisnivesky JP, et al. Video-assisted thoracoscopic lobectomy: state of the art and future directions. Ann Thorac Surg 2008;85:S705-709. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18222201.

151. Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: A meta-analysis and systematic review of controlled trials. Innovations:Technology and Techniques in Cardiothoracic and Vascular Surgery 2007;2:261-292 210.1097/IMI.1090b1013e3181662c3181666a. Available at: http://journals.lww.com/innovjournal/Fulltext/2007/11000/Video_Assisted_Thoracic_Surgery_in_Lung_Cancer.1.aspx.

152. Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. JSLS 2007;11:368-374. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17931521.

153. Whitson BA, Andrade RS, Boettcher A, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. Ann Thorac Surg 2007;83:1965-1970. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17532379.

154. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. Ann Thorac Surg 2008;86:2008-2016; discussion 2016-2008. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19022040.

155. Scott WJ, Allen MS, Darling G, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. J Thorac Cardiovasc Surg 2010;139:976-981; discussion 981-973. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20172539.

156. Atkins BZ, Harpole DH, Jr., Mangum JH, et al. Pulmonary segmentectomy by thoracotomy or thoracoscopy: reduced hospital length of stay with a minimally-invasive approach. Ann Thorac Surg 2007;84:1107-1112; discussion 1112-1103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17888955.

157. Swanson SJ, Herndon JE, 2nd, D'Amico TA, et al. Video-assisted thoracic surgery lobectomy: report of CALGB 39802--a prospective, multi-institution feasibility study. J Clin Oncol 2007;25:4993-4997. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17971599.

158. Ohtsuka T, Nomori H, Horio H, et al. Is major pulmonary resection by video-assisted thoracic surgery an adequate procedure in clinical stage I lung cancer? Chest 2004;125:1742-1746. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15136385.

159. McKenna RJ, Jr. New approaches to the minimally invasive treatment of lung cancer. Cancer J 2005;11:73-76. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15831227.

160. Demmy TL, Nwogu C. Is video-assisted thoracic surgery lobectomy better? Quality of life considerations. Ann Thorac Surg 2008;85:S719-728. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18222204.

161. Cattaneo SM, Park BJ, Wilton AS, et al. Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. Ann Thorac Surg 2008;85:231-235; discussion 235-236. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18154816.

162. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. J Thorac Cardiovasc Surg 2009;138:419-425. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19619789.

163. Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 2010;139:366-378. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20106398.

164. Thomas P, Doddoli C, Yena S, et al. VATS is an adequate oncological operation for stage I non-small cell lung cancer. Eur J Cardiothorac Surg 2002;21:1094-1099. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12048091.

165. Roviaro G, Varoli F, Vergani C, et al. Long-term survival after videothoracoscopic lobectomy for stage I lung cancer. Chest 2004;126:725-732. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15364748.

166. Solaini L, Prusciano F, Bagioni P, Poddie DB. Long-term results of video-assisted thoracic surgery lobectomy for stage I non-small cell lung cancer: a single-centre study of 104 cases. Interact Cardiovasc Thorac Surg 2004;3:57-62. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17670176.

167. Demmy TL, Plante AJ, Nwogu CE, et al. Discharge independence with minimally invasive lobectomy. Am J Surg 2004;188:698-702. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15619486.

168. Demmy TL. VATS lobectomy for frail or complex patients. Chest Meeting Abstracts 2003;124:234S. Available at: http://meeting.chestpubs.org/cgi/reprint/124/4/234S.pdf.

169. Nicastri DG, Wisnivesky JP, Litle VR, et al. Thoracoscopic lobectomy: report on safety, discharge independence, pain, and chemotherapy tolerance. J Thorac Cardiovasc Surg 2008;135:642-647. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18329487.

170. Petersen RP, Pham D, Burfeind WR, et al. Thoracoscopic lobectomy facilitates the delivery of chemotherapy after resection for lung cancer. Ann Thorac Surg 2007;83:1245-1249; discussion 1250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17383320.

171. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. N Engl J Med 1986;315:1377-1381. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2877397.

172. Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000;343:1217-1222. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11071672.

173. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18439766.

174. Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J Clin Oncol 2005;23:3480-3487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15908657.

175. Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol 2007;2:287-292. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17409799.

176. Jaklitsch MT, Herndon JE, 2nd, DeCamp MM, Jr., et al. Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935. J Surg Oncol 2006;94:599-606. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17039491.

177. Gewanter RM, Rosenzweig KE, Chang JY, et al. ACR Appropriateness Criteria: nonsurgical treatment for non-small-cell lung cancer: good performance status/definitive intent. Curr Probl Cancer 2010;34:228-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20541060.

178. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. J Clin Oncol 1995;13:1880-1892. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7636530.

179. Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309) [abstract]. J Clin Oncol 2005;23 (Suppl 16):Abstract 7014. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/7014.

180. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17235046.

181. Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. Eur J Cardiothorac Surg 2009;35:718-723; discussion 723. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19233668.

182. Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. J Thorac Cardiovasc Surg 2005;129:1250-1257. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15942564.

183. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004;78:1200-1205; discussion 1206. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15464470.

184. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005;61:318-328. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15667949.

185. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:324-333. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16168827.

186. Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2007;68:103-110. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17363189.

187. Wang L, Correa CR, Zhao L, et al. The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;73:1383-1390. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18929449.

188. Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. Int J Radiat Oncol Biol Phys 2002;54:348-356. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12243807.

189. Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:1106-1111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16730134.

190. Bradley JD, Moughan J, Graham MV, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. Int J Radiat Oncol Biol Phys 2010;77:367-372. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20457350.

191. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. J Clin Oncol 2010;28:2475-2480. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20368547.

192. ICRU. ICRU Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.

193. ICRU. Prescribing, Recording and Reporting Photon Beam Therapy (Report 62) (Supplement to ICRU Report 50). Bethesda, MD: ICRU; 1999.

194. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20934273.

195. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 2007;17:108-120. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17395041.

196. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-329. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10487552.

197. Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006;65:1075-1086. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16647222.

198. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51:650-659. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11597805.

199. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15703313.

200. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66:1399-1407. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16997503.

201. 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;91:282-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18950881.

202. Hall WH, Guiou M, Lee NY, et al. Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2008;72:1362-1367. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18448267.

203. MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiother Oncol 2009;91:85-94. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19100641.

204. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010;76:775-781. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19515503.

205. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:1087-1096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682145.

206. Cox JD, Sejpal S, Komaki R, al. e. Proton therapy with concurrent chemotherapy can reduce toxicity and allow higher radiation doses in advanced non-small cell lung cancer. J Thorac Oncol 2008;3:S303-S304. Available at: http://journals.lww.com/jto/toc/2008/11001.

207. Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. Chest 2004;126:1198-1203. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15486383.

208. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:107-111. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16458447.

209. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. Radiother Oncol 2010;95:32-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19733410.

210. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. Med Phys 2006;33:3874-3900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17089851.

211. Dahele M, Senan S. The role of stereotactic ablative radiotherapy for early-stage and oligometastatic non-small cell lung cancer: evidence for changing paradigms. Cancer Res Treat 2011;43:75-82. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21811422.

212. Heinzerling JH, Kavanagh B, Timmerman RD. Stereotactic ablative radiation therapy for primary lung tumors. Cancer J 2011;17:28-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21263264.

213. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. Int J Radiat Oncol Biol Phys 2010;76:326-332. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20117285.

214. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: Can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20638194.

215. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-3296. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19414667.

216. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-1076. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20233825.

217. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. Int J Radiat Oncol Biol Phys 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21640503.

218. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. Int J Radiat Oncol Biol Phys 2010;77:1146-1150. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19800181.

219. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-682. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19251380.

220. Das M, Abdelmaksoud MH, Loo BW, Jr., Kothary N. Alternatives to surgery for early stage non-small cell lung cancer-ready for prime time? Curr Treat Options Oncol 2010;11:24-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20577833.

221. Salazar OM, Sandhu TS, Lattin PB, et al. Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. Int J Radiat Oncol Biol Phys 2008;72:707-715. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18455322.

222. Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. Int J Radiat Oncol Biol Phys 2009;74:47-54. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18977095.

223. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. J Clin Oncol 2010;28:5153-5159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041709.

224. Hadziahmetovic M, Loo BW, Timmerman RD, et al. Stereotactic body radiation therapy (stereotactic ablative radiotherapy) for stage I non-small cell lung cancer--updates of radiobiology, techniques, and clinical outcomes. Discov Med 2010;9:411-417. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20515609.

225. Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. Cancer 2006;106:1347-1352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16475150.

226. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-971. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18954709.

227. Takeda A, Sanuki N, Kunieda E, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. Int J Radiat Oncol Biol Phys 2009;73:442-448. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18990507.

228. Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. J Thorac Oncol 2009;4:976-982. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19633473.

229. Jin JY, Kong FM, Chetty IJ, et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. Int J Radiat Oncol Biol Phys 2010;76:782-788. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19577855.

230. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17603311.

231. Decker RH, Tanoue LT, Colasanto JM, et al. Evaluation and definitive management of medically inoperable early stage non-small-cell lung cancer. Part 2: newer treatment modalities. Oncology (Williston Park) 2006;20:899-905; discussion 905-898, 913. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16922260.

232. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). Lancet Oncol 2008;9:621-628. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18565793.

233. Simon CJ, Dupuy DE, DiPetrillo TA, et al. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. Radiology 2007;243:268-275. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17392258.

234. Hu C, Chang EL, Hassenbusch SJ, 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 2006;106:1998-2004. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16572401.

235. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:33-43. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19960230.

236. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:17-32. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19960231.

237. Mintz A, Perry J, Spithoff K, et al. Management of single brain metastasis: a practice guideline. Curr Oncol 2007;14:131-143. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17710205.

238. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990;322:494-500. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2405271.

239. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:45-68. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19960227.

240. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-2491. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16757720.

241. Kim JE, Lee DH, Choi Y, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer 2009;65:351-354. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19157632.

242. Olson JJ, Paleologos NA, Gaspar LE, et al. The role of emerging and investigational therapies for metastatic brain tumors: a systematic

review and evidence-based clinical practice guideline of selected topics. J Neurooncol 2010;96:115-142. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19957013.

243. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:71-83. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19960229.

244. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:85-96. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19957016.

245. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. J Clin Oncol 2007;25:1260-1266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17401015.

246. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys 2007;68:1388-1395. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17674975.

247. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009;10:1037-1044. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19801201.

248. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive sparing during the administration of whole brain radiotherapy and prophylactic cranial irradiation: Current concepts and approaches. J Oncol 2010;2010:198208. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20671962.

249. Gore EM, Bae K, Wong SJ, et al. Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. J Clin Oncol 2011;29:272-278. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135270.

250. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 2011;29:279-286. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21135267.

251. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-360. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14736927.

252. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-2597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15972865.

253. Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-727. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16945766.

254. Curran WJ, Jr., Paulus R, Langer CJ, et al. Sequential vs concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst 2011. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21903745.

255. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181-2190. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20351327.

256. Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92:1213-1223. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11571735.

257. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692-2699. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10561343.

258. Azzoli CG, Temin S, Aliff T, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2011;29:3825-3831. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21900105.

259. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27:6251-6266. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19917871.

260. NSCLC Meta-Analyses Collaborative Group. Chemotherapy in Addition to Supportive Care Improves Survival in Advanced Non-Small-Cell Lung Cancer: A Systematic Review and Meta-Analysis of Individual Patient Data From 16 Randomized Controlled Trials. J Clin Oncol 2008;26:4617-4625. Available at: http://jco.ascopubs.org/cgi/content/abstract/26/28/4617.

261. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993;342:19-21. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8100290.

262. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7580546.

263. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20818875.

264. Magilligan DJ, Jr., Duvernoy C, Malik G, et al. Surgical approach to lung cancer with solitary cerebral metastasis: twenty-five years' experience. Ann Thorac Surg 1986;42:360-364. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3767508.

265. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933916.

266. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28:29-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19933915.

267. Douillard JY, Tribodet H, Aubert D, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol 2010;5:220-228. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20027124.

268. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin

Oncol 2008;26:3552-3559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506026.

269. Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIA lung cancer: observational cohort study. BMJ 2011;343:d4013. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21757436.

270. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633 [abstract]. J Clin Oncol 2004;22 (Suppl 14):Abstract 7019. Available at: http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/7019.

271. Strauss GM, Herndon JE, II, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633 [abstract]. J Clin Oncol 2006;24 (Suppl 18):Abstract 7007. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7007.

272. Strauss GM, Herndon JE, 2nd, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-5051. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18809614.

273. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17079694.

274. Katz A, Saad ED. CALGB 9633: an underpowered trial with a methodologically questionable conclusion. J Clin Oncol 2009;27:2300-2301; author reply 2301-2302. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19332712.

275. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. N Engl J Med 1990;323:940-945. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2169587.

276. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. J Natl Cancer Inst 1991;83:417-423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1847977.

277. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. N Engl J Med 1992;326:524-530. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1310160.

278. Dillman RO, Seagren SL, Herndon J, al. e. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer: Five-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Clin Oncol (Meeting Abstracts) 1993;12:329. Available at:

279. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. J Natl Cancer Inst 1996;88:1210-1215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8780630.

280. Albain KS, Crowley JJ, Turrisi AT, 3rd, et al. Concurrent cisplatin, etoposide, and chest radiotherapy in pathologic stage IIIB non-small-cell lung cancer: a Southwest Oncology Group phase II study, SWOG 9019. J Clin Oncol 2002;20:3454-3460. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12177106.

281. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-

cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005;23:5883-5891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16087941.

282. Huber RM, Flentje M, Schmidt M, et al. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. J Clin Oncol 2006;24:4397-4404. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16983107.

283. Azzoli CG, Baker S, Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2009:JCO.2009.2023.5622. Available at: http://jco.ascopubs.org/cgi/content/abstract/JCO.2009.23.5622v2.

284. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837811.

285. Smit EF, van Meerbeeck JP, Lianes P, et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group--EORTC 08975. J Clin Oncol 2003;21:3909-3917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581415.

286. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15364136.

287. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-3551. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506025.

288. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-3218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11432888.

289. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11784875.

290. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003;98:542-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12879472.

291. Booton R, Lorigan P, Anderson H, et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). Ann Oncol 2006;17:1111-1119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16603599.

292. Gronberg BH, Bremnes RM, Flotten O, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:3217-3224. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433683.

293. Greco FA, Spigel DR, Kuzur ME, et al. Paclitaxel/carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: a phase II/III study of the Minnie

Pearl Cancer Research Network. Clin Lung Cancer 2007;8:483-487. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17922972.

294. Herbst RS, Khuri FR, Lu C, et al. The novel and effective nonplatinum, nontaxane combination of gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: potential for decreased toxicity and combination with biological therapy. Cancer 2002;95:340-353. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12124835.

295. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15741225.

296. Rizvi NA, Riely GJ, Azzoli CG, et al. Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. J Clin Oncol 2008;26:639-643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235124.

297. Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006;17:1263-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16740598.

298. Sandler AB, Johnson DH, Herbst RS. Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer. Clin Cancer Res 2004;10:4258s-4262s. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15217970.

299. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. J Clin Oncol 2005;23:3235-3242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15886311.

300. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-2550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17167137.

301. Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17285735.

302. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19692680.

303. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-1400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224850.

304. Gridelli C, Ciardiello F, Feld R, et al. International multicenter randomized phase III study of first-line erlotinib (E) followed by second-line cisplatin plus gemcitabine (CG) versus first-line CG followed by second-line E in advanced non-small cell lung cancer (aNSCLC): The TORCH trial [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 7508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7508.

305. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. J Clin Oncol 2011;29:2121-2127. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21482992.

306. Felip E, Gridelli C, Baas P, et al. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung Cancer; Lugano 2010. Ann Oncol 2011;22:1507-1519. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21536661.

307. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19410716.

308. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-3289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19433684.

309. Nadler E, Yu E, Ravelo A, et al. Bevacizumab treatment to progression after chemotherapy: outcomes from a U.S. community practice network. Oncologist 2011;16:486-496. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21441299.

310. Paz-Ares LG, De Marinis F, Dediu M, et al. PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 18):Abstract CRA7510. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/18_suppl/CRA7510.

311. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010;28:5116-5123. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041704.

312. Stinchcombe TE, Socinski MA. Treatment paradigms for advanced stage non-small cell lung cancer in the era of multiple lines of therapy. J Thorac Oncol 2009;4:243-250. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19179904.

313. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21041704.

314. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7507.

315. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155-163. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16569462.

316. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-529. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20493771.

317. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-1440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19767093.

318. Cohen MH, Cortazar P, Justice R, Pazdur R. Approval summary: pemetrexed maintenance therapy of advanced/metastatic nonsquamous, non-small cell lung cancer (NSCLC). Oncologist 2010;15:1352-1358. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21148615.

319. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:591-598. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19075278.

320. Janne PA, Wang XF, Socinski MA, et al. Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 7503. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7503.

321. Cohen MH, Johnson JR, Chattopadhyay S, et al. Approval summary: erlotinib maintenance therapy of advanced/metastatic non-small cell lung cancer (NSCLC). Oncologist 2010;15:1344-1351. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21148614.

322. Patterson GA, Ginsberg RJ, Poon PY, et al. A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assessment of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1987;94:679-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3669696.

323. Gonzalez-Stawinski GV, Lemaire A, Merchant F, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg 2003;126:1900-1905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14688703.

324. Tournoy KG, Maddens S, Gosselin R, et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. Thorax 2007;62:696-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17687098.

325. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg 2006;131:822-829; discussion 822-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16580440.

326. Dillemans B, Deneffe G, Verschakelen J, Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer. A study of 569 patients. Eur J Cardiothorac Surg 1994;8:37-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8136168.

327. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. Thorax 1995;50:1267-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8553299.

328. McLoud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 1992;182:319-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1732943.

329. Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. Radiology 1993;186:129-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8416552.

330. Kerr KM, Lamb D, Wathen CG, et al. Pathological assessment of mediastinal lymph nodes in lung cancer: implications for non-invasive mediastinal staging. Thorax 1992;47:337-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1609375.

331. Chin R, Jr., Ward R, Keyes JW, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. Am J Respir Crit Care Med 1995;152:2090-2096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8520780.

332. Kernstine KH, Trapp JF, Croft DR, al e. Comparison of positron emission tomography (PET) and computed tomography (CT) to identify N2 and N3 disease in non small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 1998;17:458. Available at:

333. Kernstine KH, Stanford W, Mullan BF, et al. PET, CT, and MRI with Combidex for mediastinal staging in non-small cell lung carcinoma. Ann Thorac Surg 1999;68:1022-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10510001.

334. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. J Clin Oncol 2006;24:3333-3339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849747.

335. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. J Thorac Cardiovasc Surg 2006;131:1229-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16733150.

336. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10911007.

337. Manente P, Vicario G, Piazza F, et al. Does PET/CT modify the therapeutic approach in medical oncology [abstract]? . J Clin Oncol 2008;26(Suppl 15):Abstract 17525. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/17525.

338. Maziak DE, Darling GE, Inculet RI, et al. Positron emission tomography in staging early lung cancer: a randomized trial. Ann Intern Med 2009;151:221-228, W-248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581636.

339. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571281.

340. De Wever W, Stroobants S, Coolen J, Verschakelen JA. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J 2009;33:201-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19118231.

341. Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy 2005;37:833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16116534.

342. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest 2006;130:710-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16963667.

343. Ernst A, Eberhardt R, Krasnik M, Herth FJ. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. J Thorac Oncol 2009;4:947-950. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19590457.

344. Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. J Thorac Oncol 2009;4:44-48. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19096305.

345. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. Curr Opin Pulm Med 2009;15:334-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19395972.

346. Mayr NA, Hussey DH, Yuh WT. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. AJNR Am J Neuroradiol 1995;16:215-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7755752.

347. Rusch VW, Kraut MJ, Crowley J, al e. Induction chemoradiotherapy and surgical resection for non-small cell lung carcinomas of the superior sulcus (pancoast tumors): Mature results of Southwest Oncology Group trial 9416 (Intergroup trial 0160) [abstract]. Proc Am Soc Clin Oncol 2003 22:Abstract 2548. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=103854.

348. Barnes JB, Johnson SB, Dahiya RS, et al. Concomitant weekly cisplatin and thoracic radiotherapy for Pancoast tumors of the lung: pilot experience of the San Antonio Cancer Institute. Am J Clin Oncol 2002;25:90-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11823705.

349. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Thorac Cardiovasc Surg 2001;121:472-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11241082.

350. Pourel N, Santelmo N, Naafa N, et al. Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response. Eur J Cardiothorac Surg 2008;33:829-836. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18367406.

351. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 2003;21:2004-2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12743155.

352. Nakagawa T, Okumura N, Miyoshi K, et al. Prognostic factors in patients with ipsilateral pulmonary metastasis from non-small cell lung cancer. Eur J Cardiothorac Surg 2005;28:635-639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16126398.

353. Lee JG, Lee CY, Kim DJ, et al. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging assessment. Eur J Cardiothorac Surg 2008;33:480-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18249000.

354. Oliaro A, Filosso PL, Cavallo A, et al. The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system. Eur J Cardiothorac Surg 2008;34:438-443; discussion 443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18502660.

355. Pearson FG, DeLarue NC, Ilves R, et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. J Thorac Cardiovasc Surg 1982;83:1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7054602.

356. Rice TW. Thoracoscopy in the staging of thoracic malignancies. In: Kaiser LR, Daniel TM, eds, eds. Thoracoscopic Surgery. Philadelphia: Lippincott Williams & Wilkins; 1993:153-162.

357. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). Clin Lung Cancer 2006;8:116-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17026812.

358. Mina LA, Neubauer MA, Ansari RH, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023--Updated results [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 7519. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7519.

359. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable

stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023 [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7512. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7512.

360. Decker DA, Dines DE, Payne WS, et al. The significance of a cytologically negative pleural effusion in bronchogenic carcinoma. Chest 1978;74:640-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/216532.

361. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. J Thorac Cardiovasc Surg 1992;103:399-410; discussion 410-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1312184.

362. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2005;63:37-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16111570.

363. Alexander E, 3rd, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7666461.

364. Raviv G, Klein E, Yellin A, et al. Surgical treatment of solitary adrenal metastases from lung carcinoma. J Surg Oncol 1990;43:123-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1689433.

365. Reyes L, Parvez Z, Nemoto T, et al. Adrenalectomy for adrenal metastasis from lung carcinoma. J Surg Oncol 1990;44:32-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2342373.

366. Arriagada R, Auperin A, Burdett S, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-1277. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20338627.

367. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079-1088. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21831418.

368. Quoix EA, Oster J, Westeel V, et al. Weekly paclitaxel combined with monthly carboplatin versus single-agent therapy in patients age 70 to 89: IFCT-0501 randomized phase III study in advanced non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2010;28 (Suppl 18):Abstract 2. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/18_suppl/2.

369. Burkes RL, Ginsberg RJ, Shepherd FA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II Trial. J Clin Oncol 1992;10:580-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1312587.

370. Bonomi P, Faber L. Neoadjuvant chemoradiation therapy in non-small cell lung cancer: The Rush University experience. Lung Cancer 1993;9:383-390. Available at:

371. Rusch VW, Albain KS, Crowley JJ, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. J Thorac Cardiovasc Surg 1993;105:97-104; discussion 104-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8380477.

372. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330:153-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8043059.

373. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994;86:673-680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8158698.

374. Pisters K, Vallieres E, Bunn P, et al. S9900: A phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results [abstract]. J Clin Oncol 2005;23 (Suppl 16):Abstract LBA7012. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA7012.

375. Pisters K, Vallieres E, Bunn PA, Jr., et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7520. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7520.

376. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9690404.

377. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006;24:2998-3006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16769986.

378. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIA resectable non small-cell lung cancer guideline. J Clin Oncol 2007;25:5506-5518. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17954710.

379. Weisenburger TH, Graham MV, Sause WT, et al. Postoperative radiotherapy in non-small cell lung cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215 Suppl:1295-1318. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11037548.

380. Gadgeel SM, Ruckdeschel JC, Patel BB, et al. Phase II study of pemetrexed and cisplatin, with chest radiotherapy followed by docetaxel in patients with stage III non-small cell lung cancer. J Thorac Oncol 2011;6:927-933. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21415776.

381. Kiura K, Ueoka H, Segawa Y, et al. Phase I/II study of docetaxel and cisplatin with concurrent thoracic radiation therapy for locally advanced non-small-cell lung cancer. Br J Cancer 2003;89:795-802. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12942107.

382. Gelb AF, Tashkin DP, Epstein JD, et al. Physiologic characteristics of malignant unilateral main-stem bronchial obstruction. Diagnosis and Nd-YAG laser treatment. Am Rev Respir Dis 1988;138:1382-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2462389.

383. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17416863.

384. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125-1132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21343556.

385. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613-2621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197804.

386. Henry DH, von Moos R, Hungria V, et al. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 9133. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/9133.

387. Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9:2394-2399. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12855610.

388. Sakuma Y, Matsukuma S, Yoshihara M, et al. Distinctive evaluation of nonmucinous and mucinous subtypes of bronchioloalveolar carcinomas in EGFR and K-ras gene-mutation analyses for Japanese lung adenocarcinomas: confirmation of the correlations with histologic subtypes and gene mutations. Am J Clin Pathol 2007;128:100-108. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17580276.

389. Forbes SA, Bhamra G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIC). Curr Protoc Hum Genet 2008;Chapter 10:Unit 10 11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18428421.

390. Lee SY, Kim MJ, Jin G, et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol 2010;5:1734-1740. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20881644.

391. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. J Thorac Oncol 2010;5:1416-1423. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20686429.

392. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. J Clin Oncol 2009;27:5255-5261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19738122.

393. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-2191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169807.

394. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAil. J Clin Oncol 2009;27:1227-1234. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19188680.

395. Mezger J, von Pawel J, Reck M. Bevacizumab (Bv) single-agent maintenance following Bv-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results from an exploratory analysis of the AVAiL study [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract e19001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e19001.

396. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. J Thorac Oncol 2011;6:64-70. Available at: http://www.ncbi.nlm.nih.gov/pubmed/21119545.

397. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002;20:1335-1343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11870177.

398. Soon YY, Stockler MR, Askie LM, Boyer MJ. Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. J Clin Oncol

2009;27:3277-3283. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19470938.

399. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res 2007;13:5150-5155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17785570.

400. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19289619.

401. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer 2009;10:281-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632948.

402. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene 2009;28 Suppl 1:S24-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19680293.

403. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10856094.

404. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-2103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10811675.

405. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15117980.

406. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16014882.

407. Demarinis F, Paul S, Hanna N, et al. Survival update for the phase III study of pemetrexed vs docetaxel in non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2006;24 (Suppl 18):Abstract 7133. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7133.

408. Ramlau R, Gervais R, Krzakowski M, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. J Clin Oncol 2006;24:2800-2807. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682727.