National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Non-Small Cell Lung Cancer

V.2.2009

Continue

www.nccn.org

NCCN Non-Small Cell Lung Cancer Panel Members

* 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

* Gerold Bepler, MD, PhD †
H. Lee Moffitt Cancer Center & Research Institute

Matthew G. Blum, MD ¶
Robert H. Lurie Comprehensive Cancer Center of Northwestern University

Andrew 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 Comprehensive Cancer Center

Todd L. Demmy, MD ¶
Roswell Park Cancer Institute

Steven J. Feigenberg, MD §
Fox Chase Cancer Center

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

Frederic W. Grannis, Jr., MD ¶
City of Hope

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

Mohammad Jahanzeb, MD †
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

David H. Johnson, MD †
Vanderbilt-Ingram Cancer Center

Anne Kessinger, MD †
UNMC Eppley Cancer Center at The Nebraska Medical Center

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

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

Quynh-Thu Le, MD §
Stanford Comprehensive Cancer Center

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

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

Raymond U. Osarogiagbon, MD
St. Jude Children's Research Hospital/University of Tennessee Cancer Institute

Gregory A. Otterson, MD †
Arthur G. James Cancer Hospital & Richard J. Solove Research Institute at The Ohio State University

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

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

Karen Reckamp, MD, MS †
City of Hope

Francisco Robert, MD †
University of Alabama at Birmingham Comprehensive Cancer Center

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

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

Continue

† Medical Oncology
¶ Surgery/Surgical oncology
§ Radiation oncology/Radiotherapy
≠ Pathology
‡ Hematology/Hematology oncology
*Writing Committee Member

NCCN Guidelines Panel Disclosures

Table of Contents

For help using these documents, please click here

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

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

Click here to find a clinical trial at an NCCN Center

Summary of the Guidelines updates

The 2.2009 version of the Non-small Cell Lung Cancer Guidelines represents the addition of the Discussion section correspondent to the changes in the algorithm.

Summary of the changes in the 1.2009 version of the Non-small Cell Lung Cancer guidelines from the 2.2008 version include:

PREV-1
- The sentence was added, "Available data are conflicting and, thus, conclusive data from ongoing national trials are necessary to define the benefits and risks associated with screening for lung cancer with low dose CT."
- Additional references were added in footnotes 4 and 5.

NSCL-2
- PET scan was changed to "PET/CT scan" throughout the guidelines.
- Brain MRI, "nonsquamous histology" was removed.

NSCL-4:
- Stage was clarified as Stage IIIA, IIIB (T3-4, N1)

NSCL-6
- Footnote q, "mediastinotomy and CT-guided FNA" was added to methods of evaluation.

NSCL-7
- For T1-2, N2 nodes positive, adjuvant therapy, progression was separated into "local" and "systemic disease."
- For T3, N2 nodes positive, definitive concurrent chemoradiation, excellent response, was clarified as "reassess" surgical resection.

NSCL-9
- "Endobronchial ultrasound (EBUS) biopsy" was added as a pretreatment evaluation.

NSCL-10
- Stage IIIB, "EBUS biopsy" was added as a pretreatment evaluation.

NSCL-12
- A category 2B designation was added to the H&P and chest CT in the Surveillance section. Footnote "t" was added with a link to the new Cancer Survivorship page.

NSCL-13
- For performance status (PS) 0-1 patients who meet criteria, "cetuximab/vinorelbine/cisplatin" and "cisplatin/pemetrexed" were added as a first-line treatment options. For PS 2 patients, "cetuximab/vinorelbine/cisplatin" was added as an option.
- Footnote "y" defining criteria for cetuximab was added. Footnote "z" defining criteria for pemetrexed/cisplatin was added.

NSCL-14
- Pemetrexed maintenance was added as a treatment option for nonsquamous histology with a category 2B designation.

NSCL-C
- Principles of Radiation Therapy - this section was revised and updated.
- "Dose Volume Constraints for the Thorax" table is new to this section.

NSCL-D 1 of 2

Chemotherapy Regimens for Adjuvant Therapy:
- "Chemotherapy Regimens for patients with comorbidities or not able to tolerate cisplatin", the following regimens were removed:
  - Gemcitabine/Carboplatin
  - Docetaxel/Carboplatin
  - Gemcitabine/Docetaxel

NSCL-D 2 of 2
- Concurrent chemotherapy/RT followed by chemotherapy -first regimen with docetaxel, "x 3 doses every 3 weeks" was added to docetaxel for clarification.

NSCL-E 1 of 2

First-line therapy
- The second and third bullets are new supplying additional information regarding the cetuximab and pemetrexed regimens added to first-line therapy.
- The fourth bullet was modified to clarify that a third cytotoxic drug does not increase survival. The exceptions are bevacizumab and cetuximab.
- The last bullet was modified to include a category 2B designation. A sentence was added that patients with a KRAS mutation should be considered for therapy other than erlotinib.

NSCL-E 2 of 2
- "Albumin-bound paclitaxel" and "cetuximab" were added to list for systemic therapy for advanced or metastatic disease.

NSCL-F
- Cancer survivorship care guidelines were added.

LUNG CANCER PREVENTION AND SCREENING

- **Lung cancer is a unique disease in that the etiologic agent is an industry. More than 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.**

- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/00_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 secondhand smoke exposure associated with living with a smoker (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.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/clinic/cpgsix.htm) 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.**

- **At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Available data[1-5] are conflicting and, thus, conclusive data from ongoing national trials are necessary to define the benefits and risks associated with screening for lung cancer with low dose CT. The panel recommends that high risk individuals participate in a clinical trial evaluating CT screening. If a trial is not available or the high risk individual is not eligible for participation in a trial, then the individual should go to a center of excellence with expertise (in radiology, pathology, cytology, thoracic surgery, and general expertise in lung cancer treatment) to discuss the potential risks and benefits before having a screening CT.[2] If a screening strategy is used, then the I-ELCAP screening protocol should be followed. http://www.ielcap.org/professionals/docs/ielcap.pdf**

[1]Henschke CI, Yakelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
[2]Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-961.
[3]McMahon PM, Kong CY, Johnson BF, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT Screening Study. Radiology 2008;248:278-287.
[4]Jett JR, Midthun DE. Commentary: CT screening for lung cancer--caveat emptor. Oncologist 2008;13(4):439-444.
[5]Mulshine JL. Commentary: lung cancer screening--progress or peril. Oncologist 2008;13(4):435-438.

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.

Non-Small Cell Lung Cancer

Guidelines Index
NSCL Table of Contents
Staging, Discussion, References

PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

CLINICAL STAGE

Non-Small Cell Lung Cancer (NSCLC) →

- Pathology review[a]
- H&P (include performance status + weight loss)
- CT chest and upper abdomen, including adrenals
- CBC, platelets
- Chemistry profile
- Smoking cessation counseling

Clinical stage	
Stage I, peripheral[b] T1,N0 Mediastinal CT negative (lymph nodes < 1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage I, peripheral T2, N0, central[b] T1-2, N0 and stage II, T1-2, N1 Mediastinal CT negative (lymph nodes < 1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage IIB,[c] T3, N0, Stage IIIA, IIIB T3-4, N1 by CT or bronchoscopy	See Pretreatment Evaluation (NSCL-4)
Stage IIIA,[c] T1-3, N2, mediastinal CT positive Ipsilateral (lymph nodes ≥ 1 cm)	See Pretreatment Evaluation (NSCL-6)
Stage IIIB,[c] T4, N0-1 (possibly resectable)	See Pretreatment Evaluation (NSCL-6)
Stage IIIB,[c] T1-3, N3, mediastinal CT positive Contralateral (lymph nodes ≥ 1 cm) or palpable supraclavicular lymph nodes	See Pretreatment Evaluation (NSCL-9)
Stage IIIB,[c] T4, N2-3 on CT	See Pretreatment Evaluation (NSCL-10)
Stage IIIB,[c] T4 (pleural or pericardial effusion)	See Pretreatment Evaluation (NSCL-10)
Stage IV, M1 Solitary metastasis with resectable lung lesion	See Pretreatment Evaluation (NSCL-11)
Stage IV, M1 Disseminated metastases	See Pretreatment Evaluation (NSCL-11)
Occult TX, N0, M0	See Evaluation (NSCL-16)
Second lung primary	See Evaluation (NSCL-16)

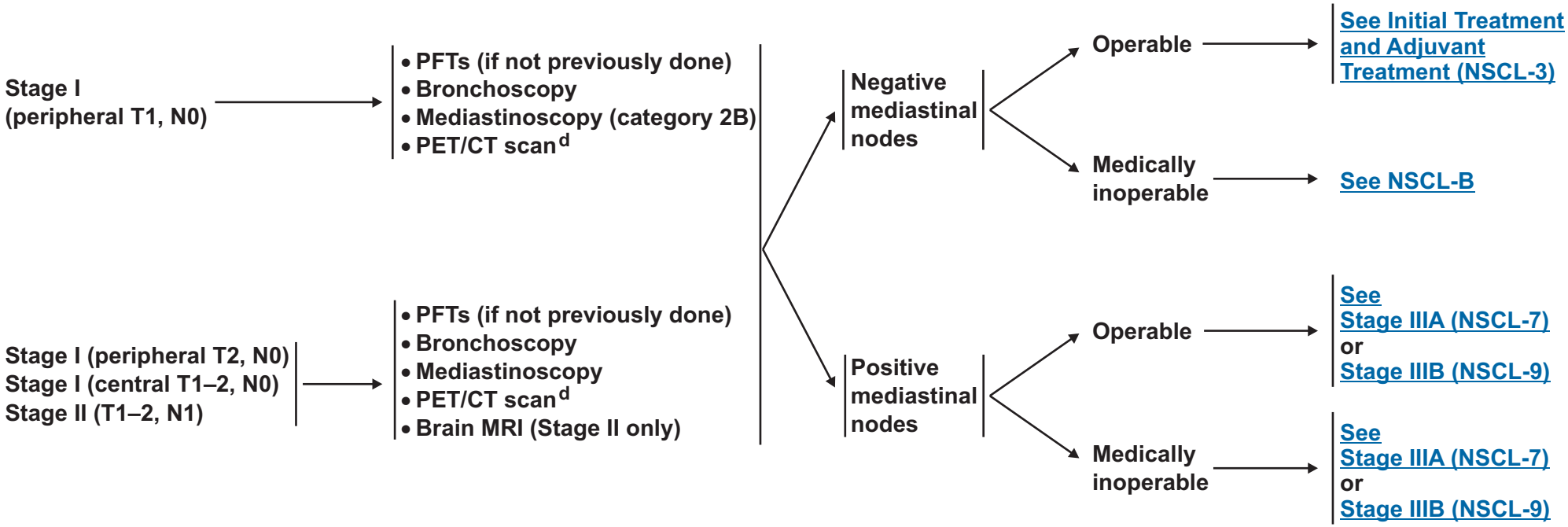
[a] See Principles of Pathologic Review (NSCL-A).

[b] Based on the CT of the chest:
Peripheral = outer half of lung.
Central = inner half of lung.

[c] 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.

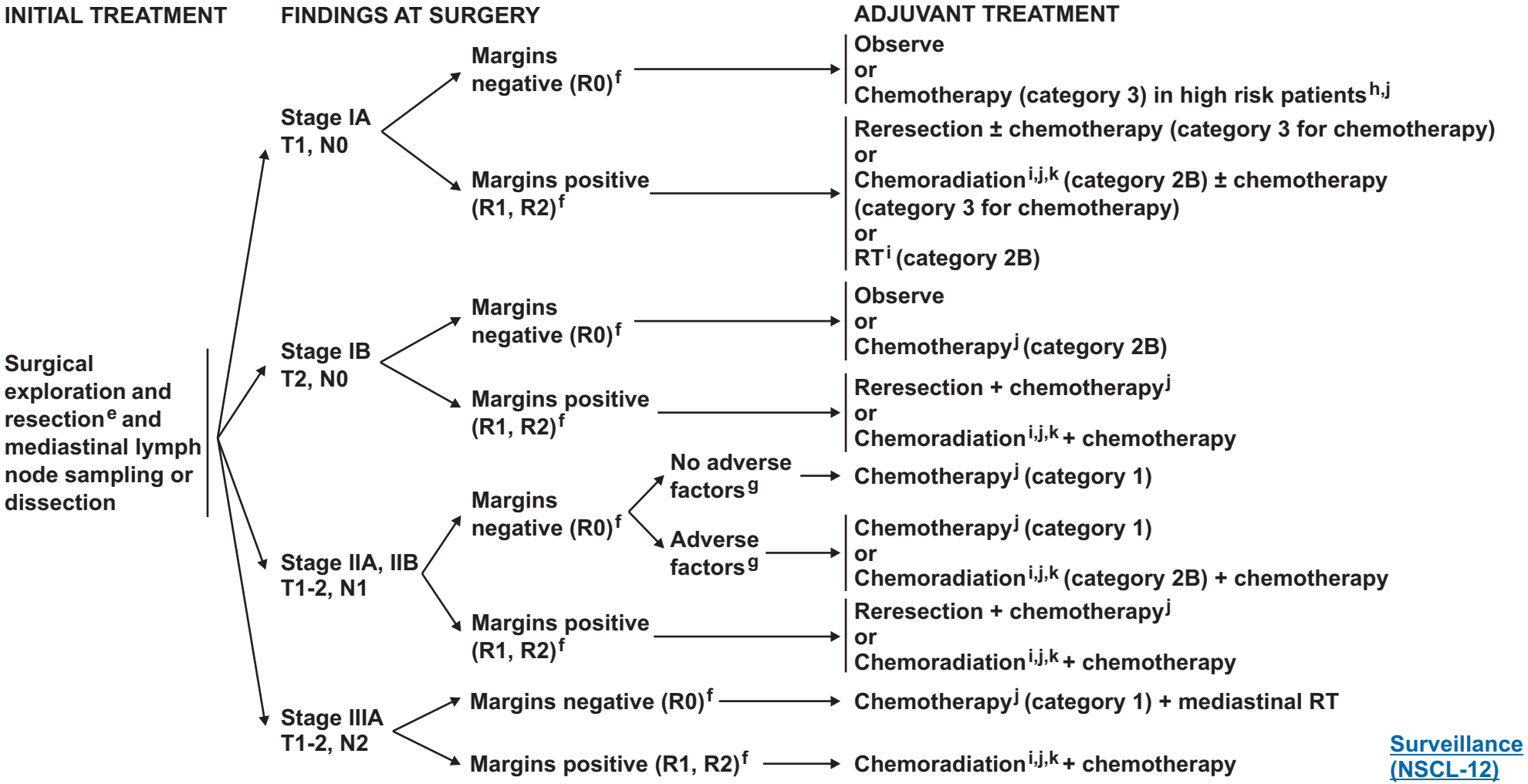
CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION**



[d]Positive PET/CT scan findings 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.

Non-Small Cell Lung Cancer



Surveillance (NSCL-12)

[e] See Principles of Surgical Resection (NSCL-B).

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

[g] Adverse factors include: inadequate mediastinal lymph node dissection, extracapsular spread, multiple positive hilar nodes, close margins.

[h] High risk patients are defined by poorly differentiated tumor, vascular invasion, wedge resection, minimal margins.

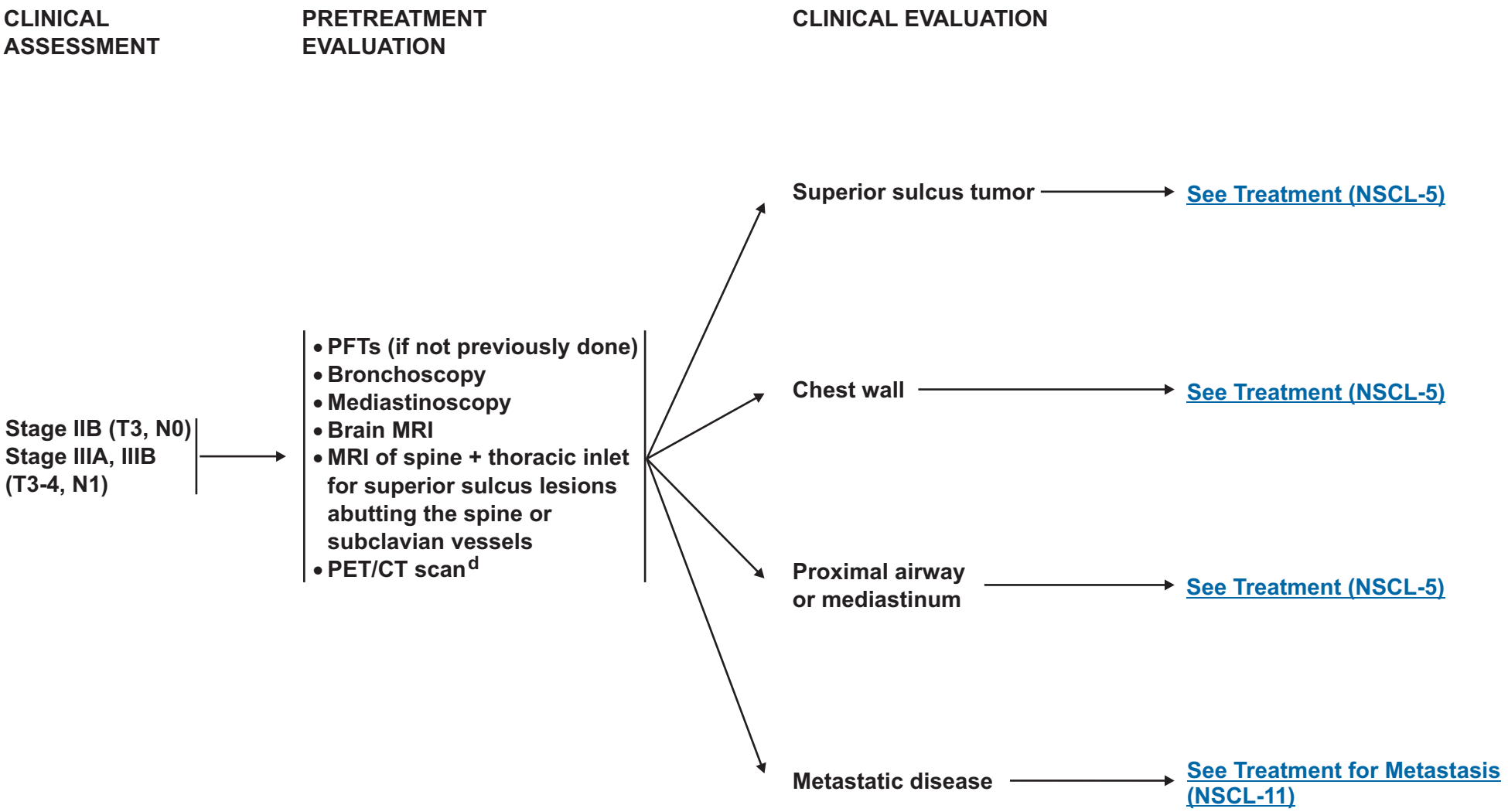
[i] See Principles of Radiation Therapy (NSCL-C).

[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

[k] For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT ± 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.

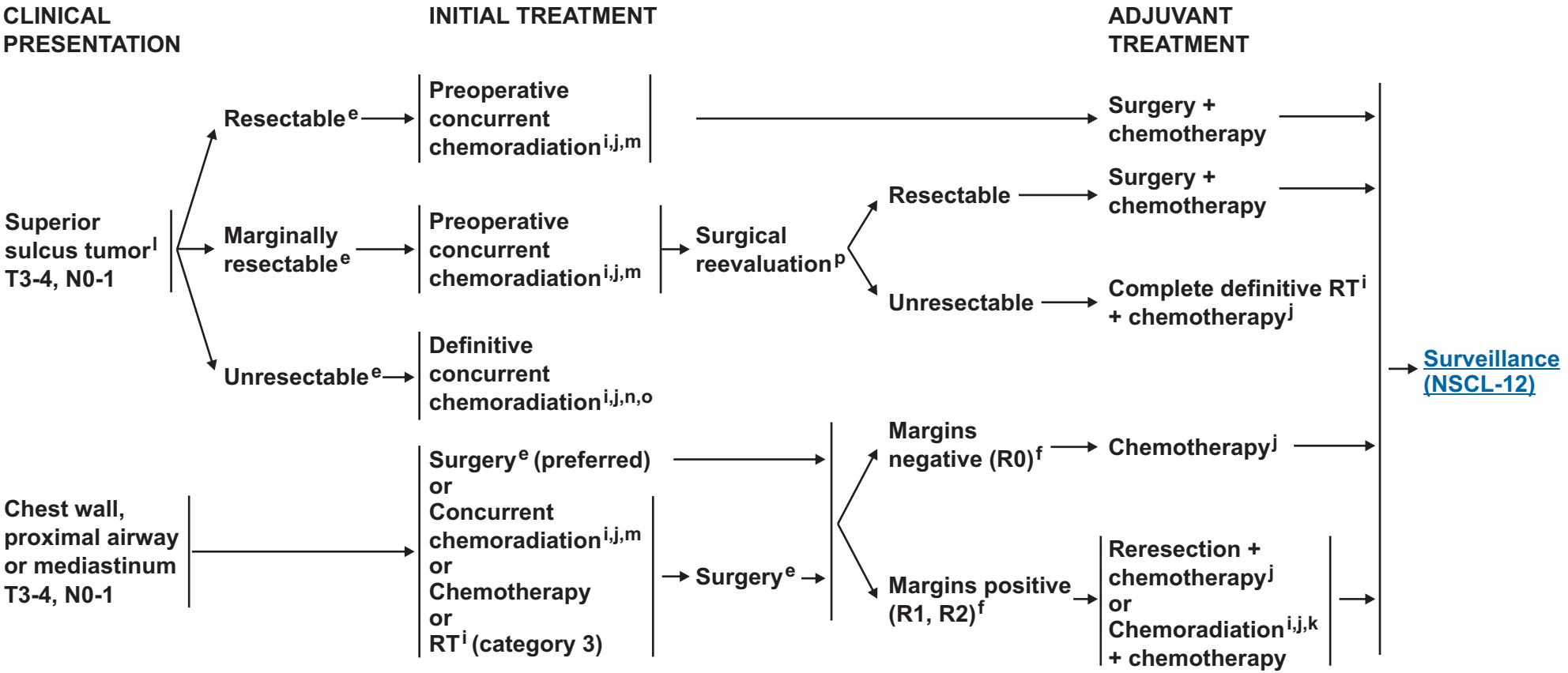
Non-Small Cell Lung Cancer



[d] Positive PET/CT scan findings 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.

Non-Small Cell Lung Cancer



[e] See Principles of Surgical Resection (NSCL-B).

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

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

[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

[k] For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT ± chemotherapy.

[l] It is difficult to distinguish between T3 and T4 superior sulcus tumors.

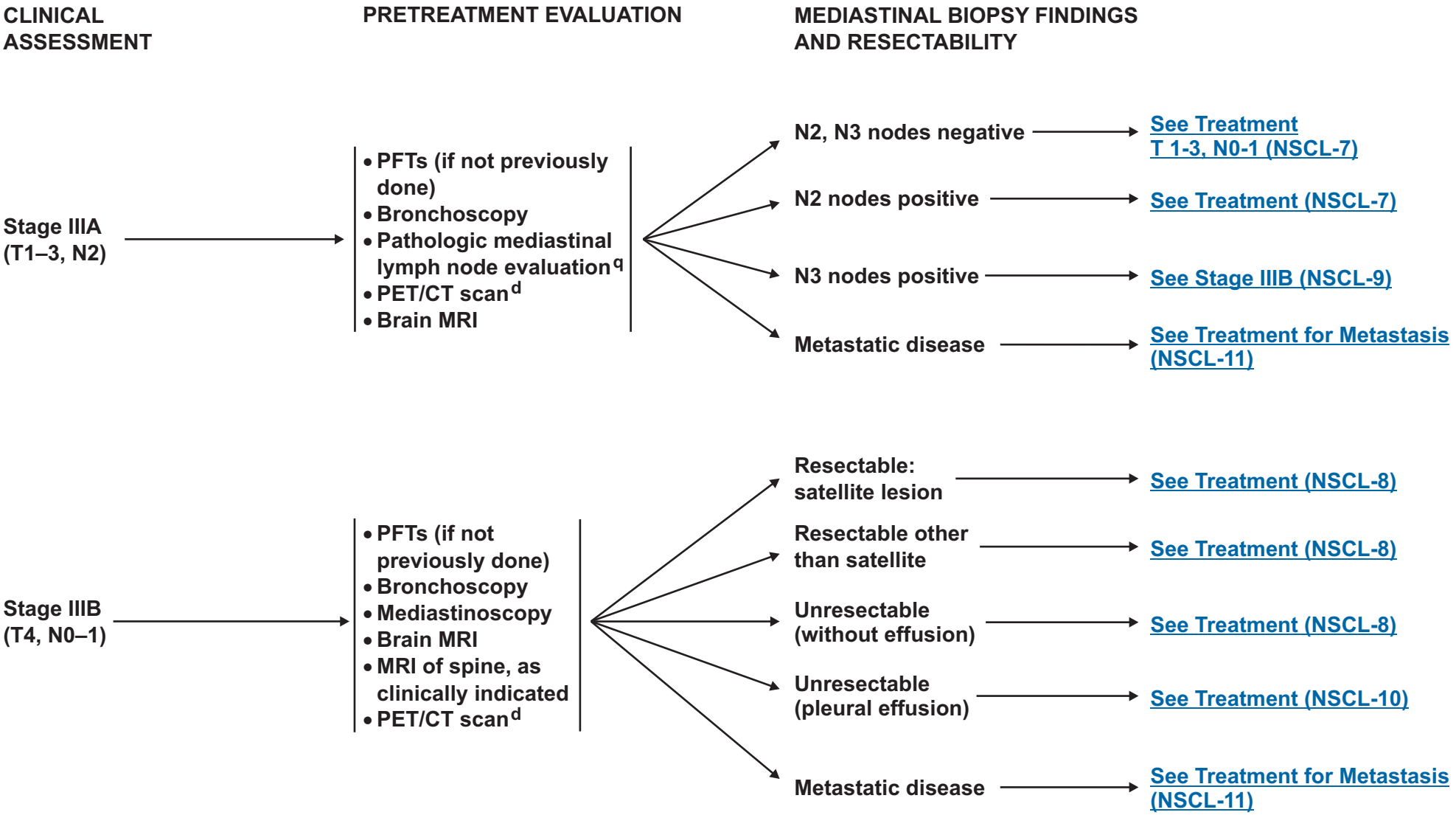
[m] In the preoperative chemoradiation setting, a total dose of 45-50 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease, although preoperative chemoradiotherapy should be avoided if a pneumonectomy is required to avoid post-operative pulmonary toxicity.

[n] RT should continue to definitive dose without interruption if patient is not a surgical candidate.

[o] In the definitive chemoradiation setting, a total dose of 60-74 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.

[p] 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 the Southwest Oncology Group trial 9416 (Intergroup trial 0160). J Thorac Cardiovasc Surg 2001;121(3):472-483.

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.

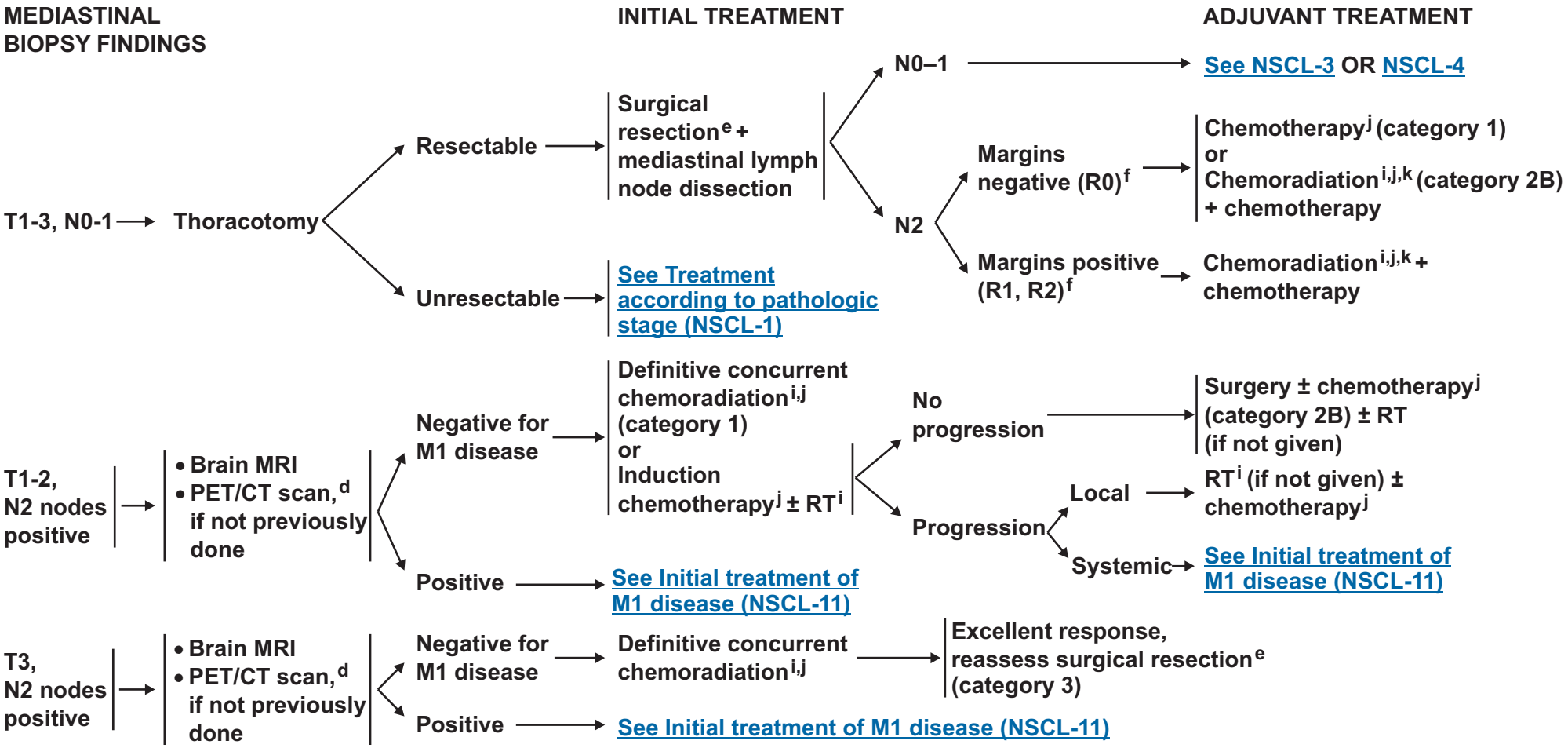


[d] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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.

Non-Small Cell Lung Cancer



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

[e] See Principles of Surgical Resection (NSCL-B).

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

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

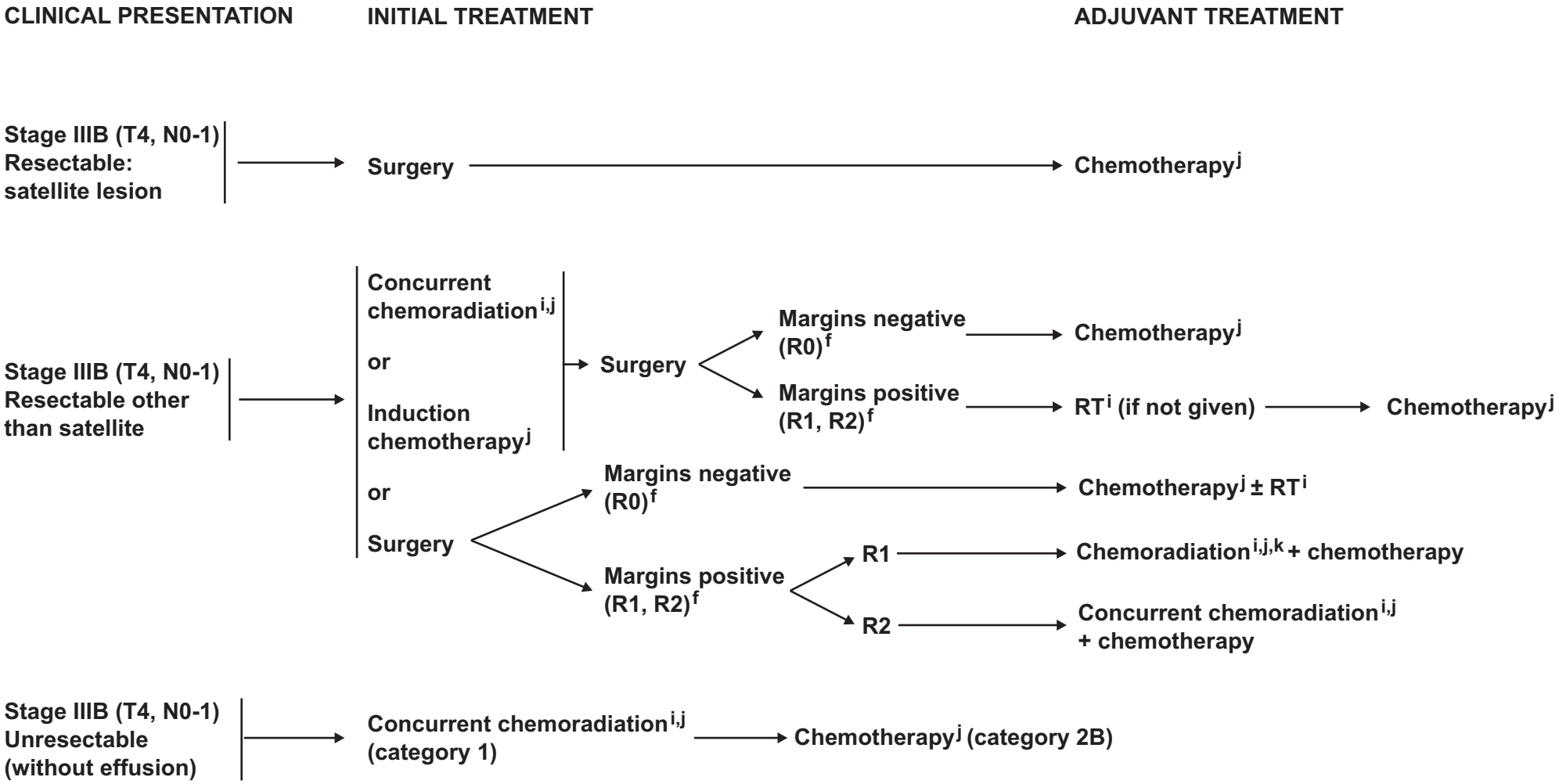
[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

[k] For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT ± chemotherapy.

Surveillance (NSCL-12)

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.

Non-Small Cell Lung Cancer



[f]R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[i]See Principles of Radiation Therapy (NSCL-C).
[j]See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).
[k]For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT ± chemotherapy.

Surveillance (NSCL-12)

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

Stage IIIB (T1–3, N3) →

- PFTs (if not previously done)
- PET/CT scan[d]
- Brain MRI
- Pathologic confirmation of N3 disease by either:
  - Mediastinoscopy
  - Supraclavicular lymph node biopsy
  - Thoracoscopy
  - Needle biopsy
  - Mediastinotomy
  - Endoscopic ultrasound (EUS) biopsy
  - Endobronchial ultrasound (EBUS) biopsy

→ **N3 negative** → See Initial treatment for stage I–IIIA (NSCL-1)

→ **N3 positive** → Concurrent chemoradiation[i,j] (category 1) → Consolidation chemotherapy[j] (category 2B)

→ **Metastatic disease** → See Treatment for Metastasis (NSCL-11)

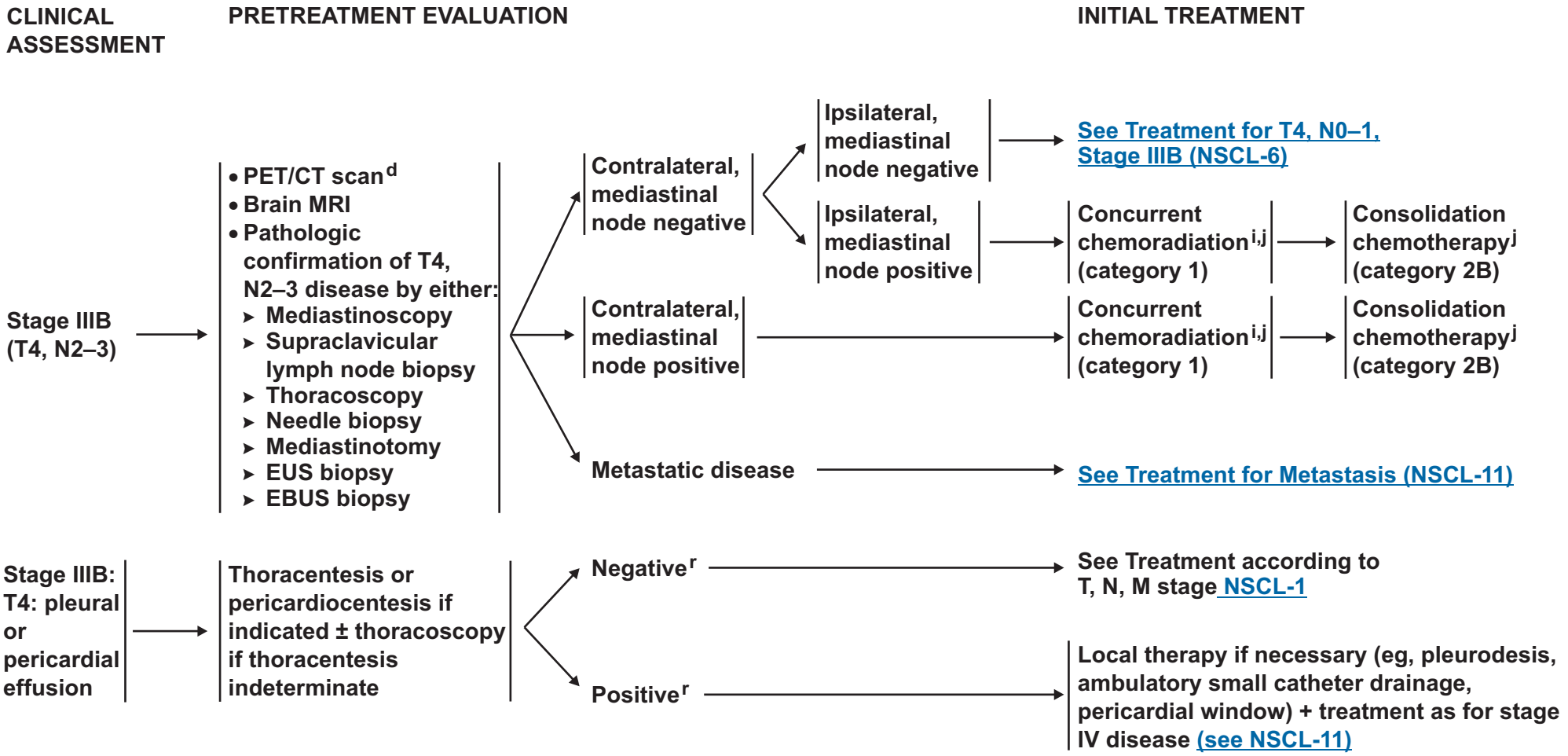
[d] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

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.

Non-Small Cell Lung Cancer



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

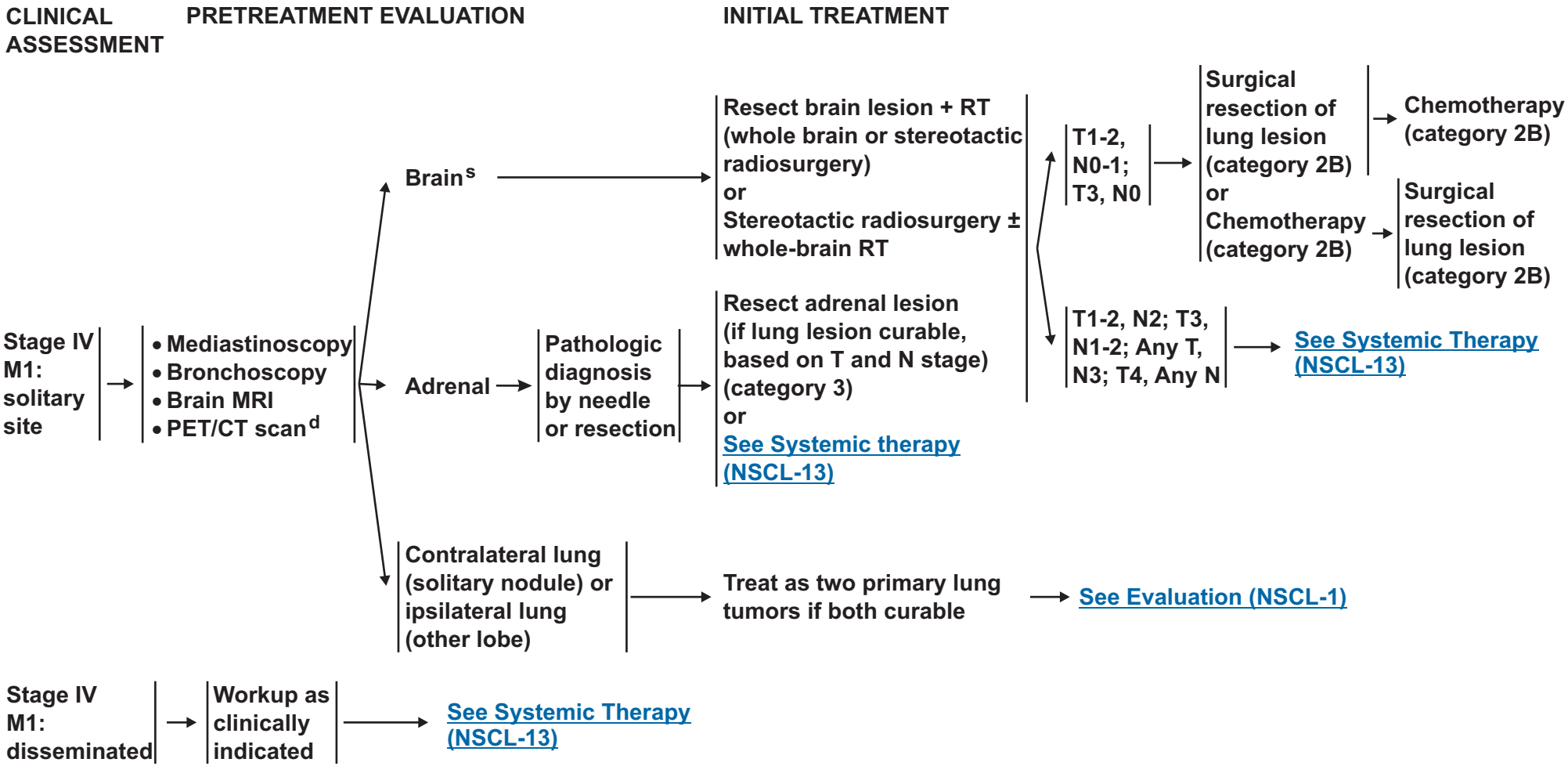
[i] See Principles of Radiation Therapy (NSCL-C).

[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

[r] Most pleural effusions associated with lung cancer are due to tumor. There are 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 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.

Non-Small Cell Lung Cancer



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

[s] See NCCN CNS Guidelines.

Surveillance (NSCL-12)

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.

Non-Small Cell Lung Cancer

SURVEILLANCE

NED, stages I-IV:[t]
- History & physical and a contrast-enhanced chest CT every 4-6 mo for 2 y (category 2B), then H&P and a non-contrast-enhanced chest CT annually (category 2B)
- Smoking cessation counseling

Locoregional recurrence

- Endobronchial obstruction → Laser/stent/other surgery; Brachytherapy; External-beam RT; Photodynamic therapy
- Resectable recurrence → Reresection; External-beam RT
- Mediastinal lymph node recurrence → Concurrent chemoradiation (if RT not previously given)
- Superior vena cava (SVC) obstruction → External-beam RT; Stent
- Severe hemoptysis → External-beam RT; Brachytherapy; Laser; Photodynamic therapy; Embolization; Surgery

Distant metastases

- Localized symptoms → Palliative external-beam RT
- Diffuse brain metastases → Palliative external-beam RT
- Bone metastasis → Palliative external-beam RT + orthopedic stabilization, if risk of fracture; Consider bisphosphonate therapy
- Solitary metastasis → See pathway for Stage IV, M1, solitary site (NSCL-11)
- Disseminated metastases → See Systemic Therapy (NSCL-13)

THERAPY FOR RECURRENCE AND METASTASIS

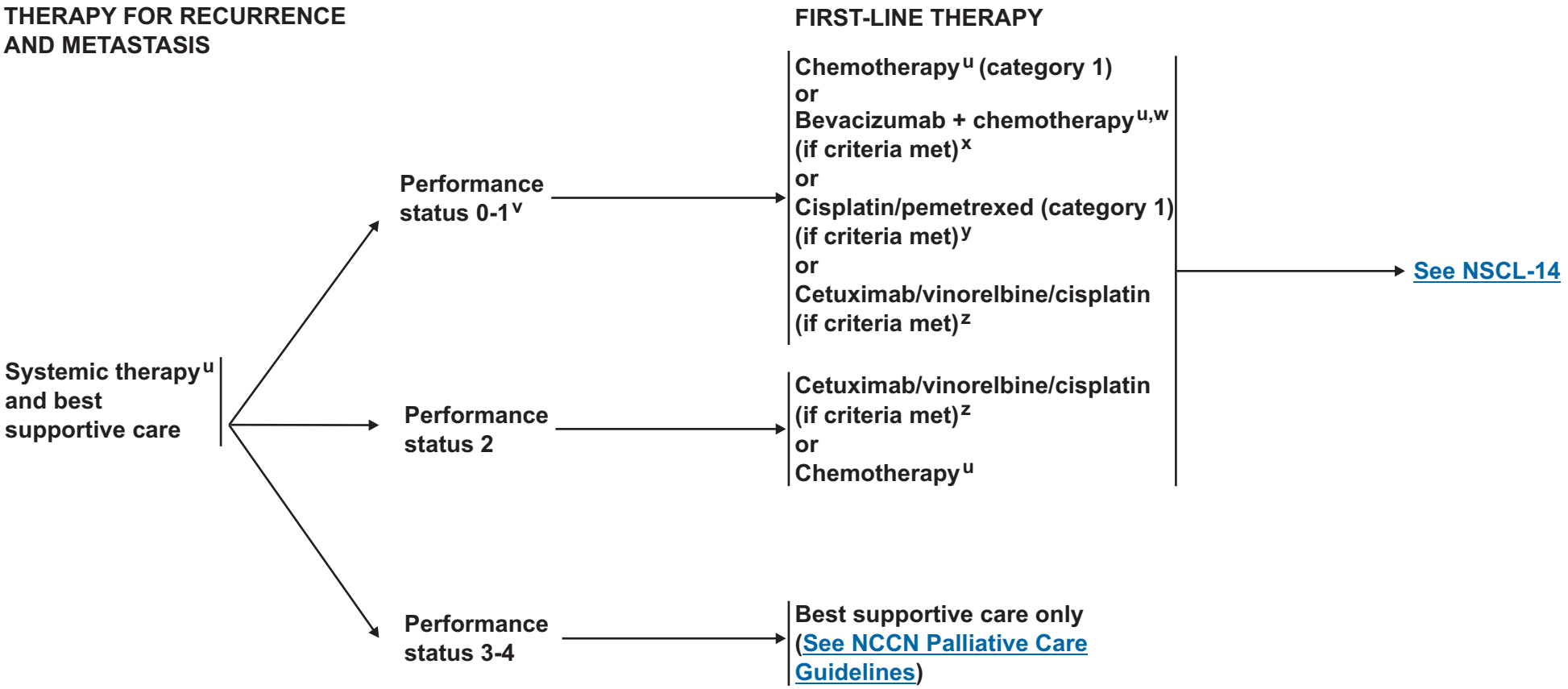
- No evidence of disseminated disease → Observation or Systemic chemotherapy (category 2B)
- Evidence of disseminated disease → See Systemic therapy and best supportive care (NSCL-13)

Palliative external-beam RT → See Systemic therapy and best supportive care (NSCL-13)

[t] See Cancer Survivorship Care (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.

Non-Small Cell Lung Cancer



[u] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-E).

[v] Performance status (PS) 2 patients have greater toxicity and potential for lower benefit than PS 0-1 patients.

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

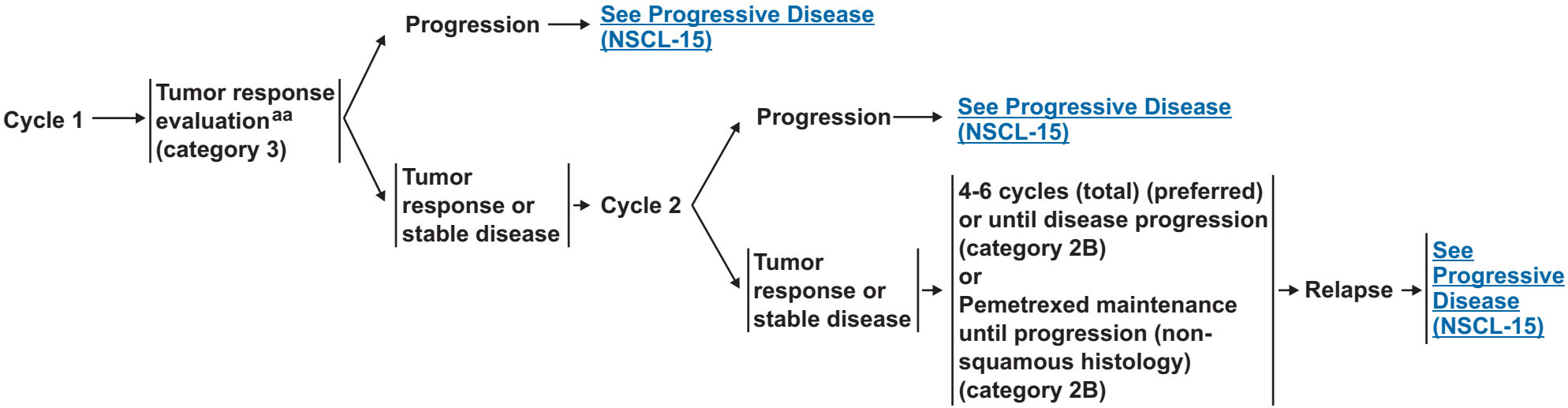
[x] Criteria for treatment with bevacizumab + chemotherapy: non-squamous NSCLC, no history of hemoptysis, no untreated CNS metastases. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.

[y] There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous 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(21):3543-3551.

[z] Criteria for treatment with cetuximab: NSCLC IIIB(pleural effusion)/IV, EGFR expression by immunohistochemistry (≥ 1 positive tumor cell), age ≥ 18 years, ECOG PS 0-2, no known brain metastases and no prior chemotherapy, or anti-EFGR therapy. Pirker R, Szczesna A, von Pawel J, et al. FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 26:2008(May 20 suppl;abstr 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.

THERAPY FOR RECURRENCE AND METASTASIS



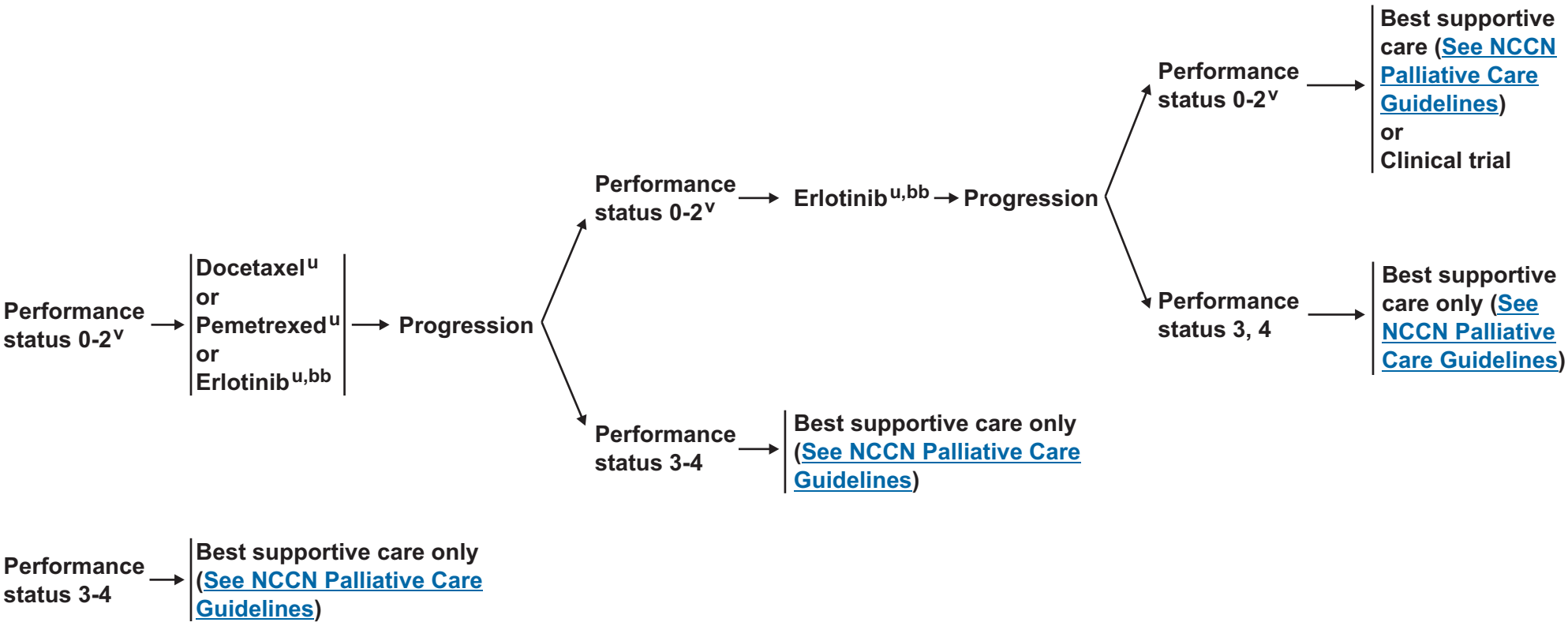
[aa] Some institutions advocate imaging (CT) studies to evaluate tumor progression after the first course.

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.

PROGRESSIVE DISEASE

SECOND-LINE THERAPY

THIRD-LINE THERAPY

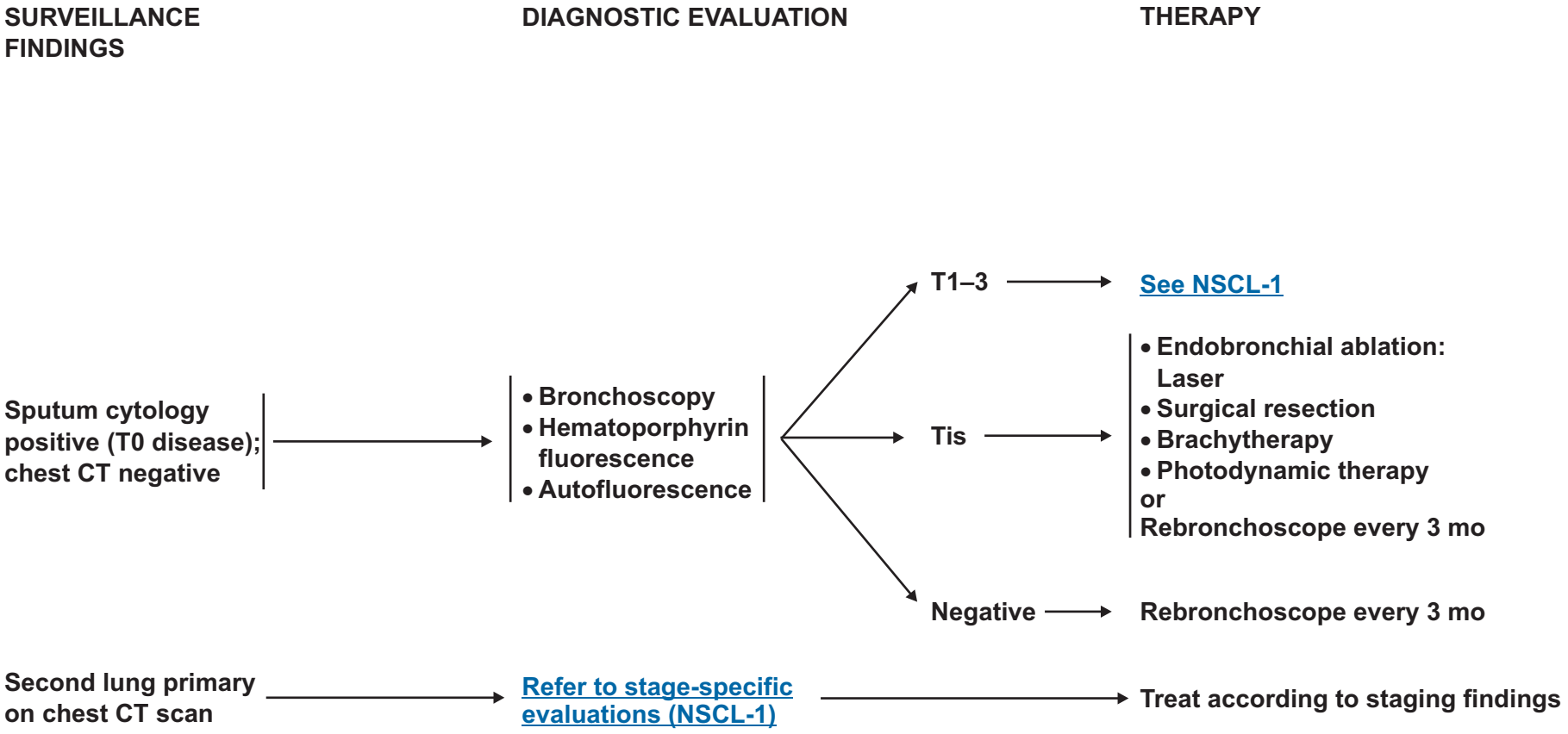


[u] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-E).

[v] Performance status (PS) 2 patients have greater toxicity and potential for lower benefit than PS 0-1 patients.

[bb] Patients with a performance status of 3 were included in the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) trial BR.21. Erlotinib may be considered for PS 3 patients.

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.



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 2)

Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the lung cancer, determine the extent of invasion, and establish the cancer involvement status of the surgical margins,[1] and determine the molecular abnormalities of lung cancer that may be able to predict for sensitivity and resistance to epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKI).[2,3]
- The World Health Organization (WHO) tumor classification system provides the foundation for tumor diagnosis, patient therapy and epidemiological and clinical studies.[4]
- The surgical pathology report should include the histologic classification published by the WHO for carcinomas of the lung.[5]

Bronchioloalveolar carcinoma (BAC)

- There is increasing attention to BAC due to evidence that EGFR mutation in lung cancer is linked to bronchioloalveolar differentiation.[6,7]
- BAC includes tumors where neoplastic cells spread along pre-existing alveolar structures (lepidic spread).[5]
- Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.[4]
- BAC is divided into three subtypes: mucinous, non-mucinous, and a mixed mucinous and nonmucinous or indeterminate form. Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1), CK7 and lacks CK20. Mucinous BAC may have an aberrant immunophenotype, expressing CK20 and CK7, but reportedly lacking TTF-1 expression.[8]

Immunohistochemical staining

- Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma and to determine the neuroendocrine status of tumors.
- Differentiation between primary pulmonary adenocarcinoma and metastatic adenocarcinoma
  - 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 is important in distinguishing primary from metastatic adenocarcinoma: the majority of primary lung carcinomas is positive for TTF-1 whereas metastatic adenocarcinoma to the lung is virtually always negative.
  - Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum.
  - CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies, that could help distinguish from primary lung tumors. Prostate specific antigen, prostatic acid phosphatase and gross cystic disease fluid protein 15 may identify metastatic adenocarcinoma of prostate and breast origin, respectively.
- Determining neuroendocrine status of tumors
  - Chromogranin and synaptophysin are used to diagnose neuroendocrine tumors of the lung. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin whereas small cell lung cancer is negative in 25% of cases.
- Distinguishing between malignant mesothelioma and lung adenocarcinoma
  - A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) is used routinely.
  - The stains negative in mesothelioma, but positive in adenocarcinoma are CEA, B72.3, Ber-EP4 and MOC31.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40[9,10] and cytokeratin 5/6.

Continued NSCL-A 2 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.

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 2)

Molecular Diagnostic Studies in Lung Cancer

- **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 critical biological factors for proper patient selection.**
- **There is a significant association between EGFR mutations, especially exon 19 deletion, and response to TKIs.[11-14]**
- **K-ras is a critical downstream effector of the EGFR pathway that has been found to be mutated in approximately 15% to 30% of lung adenocarcinomas and to be associated with tobacco smoke exposure. EGFR and k-ras mutations are mutually exclusive in patients with lung cancer.[15]**
- **K-ras mutations are associated with intrinsic TKI resistance, and k-ras gene sequencing could be useful for the selection of patients as candidates for TKI therapy.[16]**

[1] Fosella FV, Putnam JB & Komaki R. Lung Cancer. New York: Springer, 2003.
[2] 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;23:5900-9.
[3] 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;2:423-9.
[4] Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.
[5] Travis WD, World Health Organization. International Agency for Research on Cancer. International Academy of Pathology & International Association for the Study of Lung Cancer. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004.
[6] Jackman DM, Chirieac LR & Janne PA. Bronchioloalveolar carcinoma: A Review of the Epidemiology, Pathology, and Treatment. Seminars in Respiratory and Critical Care Medicine 2005:342-352.
[7] Blons H, Cote JF, Le Corre D, et al. Epidermal growth factor receptor mutation in lung cancer are linked to bronchioloalveolar differentiation. Am J Surg Pathol 2006;30:1309-15.
[8] 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;116:319-25.
[9] Chirieac LR, et al. Modern Pathology 2006;19:305A 1422.
[10] Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-80.
[11] Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
[12] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
[13] 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;12:90-8.
[14] 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;9:485-95.
[15] Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-62.
[16] 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;9:320-6.

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 RESECTION

- The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.
- We recommend that the determination of resectablility be performed by thoracic surgical oncologists who perform lung cancer surgery as a prominent part of their practice.
- Lobectomy or pneumonectomy, if physiologically feasible.
- Limited resection - either segmentectomy (preferred) or wedge resection - if physiologically compromised.
- Video-assisted thoracic surgery (VATS) may be considered as a feasible option for patients that are surgically resectable as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.[1,2]
- N1 and N2 node resection and mapping (minimum of three N2 stations sampled or complete lymph node dissection)
- If determined medically inoperable by thoracic surgeon, clinical stage I and II patients should receive potentially curative RT as their local approach.
- Lung-sparing anatomic resection (sleeve lobectomy) preferred over pneumonectomy, if anatomically appropriate and margin-negative resection achieved.

[1] McKenna RJ Jr. New approaches to the minimally invasive treatment of lung cancer. Cancer J 2005;11(1):73-76.
[2] Demmy TL, Plante A J, Nwogu CE, et al. Discharge independence with minimally invasive lobectomy. Am J Surg 2004;188(6):698-702.

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 5)

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, medical oncologists, pulmonologists, pathologists and diagnostic radiologists.
- Radiation therapy ± chemotherapy should be offered as potentially curative treatment to patients with stage I and II NSCLC who are medically inoperable but of reasonable performance status and life expectancy. SBRT (stereotactic body radiation therapy) can be considered for patients with node negative peripheral lesions that are less than 5 cm in maximal dimension.[1-3] It is essential to confirm cytology or histology of the primary lesion. It is strongly recommended that mediastinal nodal status be verified by EBUS or mediastinoscopy if mediastinal nodes were negative by PET/CT.
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (ie Grade 3 esophagitis, pneumonitis or hematologic toxicities) should be avoided by optimal plan applying for 3D CRT or IMRT to follow recommended dose volume constraints shown in the table below[4-6] Careful patient monitoring and aggressive supportive care are preferable to avoid treatment breaks.
- For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy followed by postoperative radiotherapy is preferred, though the sequencing between radiation and chemotherapy in this setting has not been established.[7-9] Individual cases need to be discussed via a multidisciplinary team. For tumors with positive resection margins post operative concurrent chemoradiotherapy is recommended.
- Treatment planning should be on CT scans obtained in the treatment position. IV contrast for diagnostic or simulation CT should be used for better target and normal tissue delineation whenever possible. PET/CT is preferable to CT alone for the GTV delineation in cases with significant atelectasis.
- In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume and the cone-down fields should cover the post-chemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the post-chemotherapy volume should be used to avoid excessive pulmonary toxicity.
- Modern three-dimensional (3D) conformal radiation therapy techniques should be used on all patients. It is necessary to evaluate the dose volume histogram (DVH) for the lungs, esophagus, heart and spinal cord to minimize normal tissue toxicity (See Dose Volume Constraints for the Thorax NSCL-C 4 of 5). Whenever feasible, respiratory management techniques such as 4-Dimensional (4D) CT and respiratory gating should incorporated in the radiation set up and delivery.
- In general, photon beam energy between 4 to 10 MV is recommended. For large mediastinal tumors or for patient's separation greater than 20 cm, 15 MV or 18 MV energies can also be used. If the tumor is fixed to the vertebral body, located at the superior sulcus or involving bilateral mediastinum, intensity modulated radiotherapy (IMRT) should be considered to avoid over dose to normal tissues.
- Involved field radiation to high dose without elective nodal treatment has been shown to have less toxicity, superior survival and low risk of isolated nodal relapse.[10,11]

For Recommended Radiation Doses see NSCL-C 3 of 5

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 5 of 5

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

PRINCIPLES OF RADIATION THERAPY (2 of 5)

REFERENCES

[1] Lagerwaard FJ, Haasbeek CJ, 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(3):685-692.

[2] Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004, 101:1623-1631.

[3] 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.

[4] Tucker SL, Liu HH, Wang S,et al. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006; 66:754-761.

[5] 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(5):1399-1407. Epub 2006 Sep 25.

[6] Yom SS, Liao Z, Liu HH, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007; 68:94-102.

[7] The Lung Cancer Study Group: N Engl J Med 1986:315:1377-1381.

[8] 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(17):1217-22.

[9] 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 Apr 24. [Epub ahead of print]

[10] 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.

[11] Rosenzweig KE, Sura S, Jackson A, et al. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007; 25: 5543-5561.

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 5)

Recommended Radiation Doses:

Treatment type	Total dose	Fraction size
Preoperative*[1]	45-50 Gy	1.8-2 Gy
Postoperative[2,3]		
• Negative margins	50 Gy	1.8-2 Gy
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy
• Gross residual tumor	up to 70 Gy	1.8-2 Gy
Definitive		
• Without concurrent chemotherapy[4]	up to 77.4 Gy (keep V20 $\leq$ 35%	2-2.15 Gy
• With concurrent chemotherapy[5] (mainly carboplatin + paclitaxel)[5]	up to 74 Gy	2 Gy

*Doses greater than 50 Gy in the preoperative setting have been reported to be safe at selective institutions (Cerfolio et al, Ann Thorac Surgery 2005;80(4):1224; Kwong et al, J Thorac Cardiovasc Surg 2005;129(6):1250; Sonnett et al, Ann Thorac Surg 2004;78(4):1200). However, this is still considered experimental.

For Dose Volume Constraints for the Thorax see NSCL-C 4 of 5

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 5 of 5

[1] 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(3):313-8.

[2] Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II amd IIIA non-small cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J Clin Oncol 2005;23(15):3480-7.

[3] 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(17):1217-22.

[4] 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 cancer. Int J Radiat Oncol Biol Phys 2005;61(2):318-28.

[5] 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 non-small cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92(5):1213-23.

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 5)

Recommended Radiation Dose-Volume to Selected Normal Tissues: [1-3]

	Dose Volume Constraints for the Thorax		
	Radiation Therapy (RT) alone	Chemotherapy/ RT	Chemotherapy/RT/ Operation
Cord	50 Gy	45 Gy	45 Gy
Lung	20 Gy (<40%)	20 Gy (<35%)	20 Gy (<20%) 15 Gy (<30%) 10 Gy (<40%)
Heart	40 Gy (<100%) 50 Gy (<50%)	40 Gy (<50%)	40 Gy (<50%)
Esoph	60 Gy (<50%)	55 Gy (<50%)	
Liver	30 Gy (<40%)		
Kidney	20 Gy (<50% of combined both kidneys or <25% of one side if another kidney is not functional)		

For Recommended Radiation Doses see NSCL-C 3 of 5

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 5 of 5

[1] Tucker SL, Liu HH, Wang S, et al. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006; 66:754-761.

[2] 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.

[3] Yom SS, Liao Z, Liu HH, et al. Initial Evaluation of Treatment-Related Pneumonitis in Advanced-Stage Non-Small Cell Lung Cancer Patients Treated with Concurrent Chemotherapy and Intensity-Modulated Radiation Therapy. Int J Radiat Oncol Biol Phys 2007;68:94-102.

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 5

Dose Volume Data for Radiation Pneumonitis:

	RT ± Induction Chemotherapy		Concurrent Chemoradiation	
Parameter	**Range**	**% Pneumonitis***	**Range**	**% Pneumonitis***
MLD	< 10 10-20 21-30 > 30 ref 1,2	0-10 9-16 24-27 24-44	< 16.5 ≥ 16.5 ref 4,5	11-13 (grade > 2) 36-45 (grade > 2)
V5			≤ 42% > 42% ref 5	3 38
V20	< 20% 20-31% ≥ 32% ref 1,3	0-2 7-15 13-48	≤ 20% 21-25% 26-30% ≥ 31% ref 6	9 18 51 85
V30	≤ 8% > 8% ref 2	6 (all grades) 24 (all grades)		

MLD = mean lung dose
V5 = percentage of lung that received 5 Gy
V20 = percentage of lung that received 20 Gy
V30 = percentage of lung that received 30 Gy

*All % pneumonitis endpoints are grade 2 and higher unless specified otherwise in the table.

[1] Graham MV, Purdy JA, Emani B. et al. Clinical dose-volume histogram for pneumonitis after 3D treatment for non-small cell lung cancer . Int J Radiat Oncol Biol Phys 1999;45(2):323-9.

[2] 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;51:650-9.

[3] 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: predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006;65(4):1075-86.

[4] 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;235:208-15.

[5] 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(5):1399-1407. Epub 2006 Sep 25.

[6] Tsujino K, Hirota S, Endo M ,et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys. 2003 Jan 1;55(1):110-5.

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

CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY (1 OF 2)

Published Chemotherapy Regimens	Schedule
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[a]
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 day 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]

Other Acceptable Cisplatin-based Regimens	Schedule
Cisplatin 80 mg/m^2 on day 1 Gemcitabine 1000 mg/m^2 on days 1, 8	Every 21 days[d]
Cisplatin 75 mg/m^2 Docetaxel 75 mg/m^2	Every 21 days[e]

Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin	Schedule
Paclitaxel 200 mg/m^2 on day 1 Carboplatin AUC 6 on day 1	Every 21 days[d]

See Chemoradiation on page NSCL-D (2 of 2)

[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;350:351-60.
[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(9):719-727.
[d] 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. Epub 2006 Nov 1.
[e] 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(16):3016-24. Epub 2003 Jul 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.

Non-Small Cell Lung Cancer

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY (2 OF 2)

Concurrent Chemotherapy/RT Regimens*
Cisplatin 50 mg/m^2 on day 1, 8, 29, and 36 Etoposide 50 mg/m^2 days 1-5, 29-33 Concurrent thoracic RT (total dose, 61 Gy)[a] (preferred)
Cisplatin 100 mg/m^2 day 1, 29 Vinblastine 5 mg/m^2/weekly x 5 Concurrent thoracic RT 60 Gy[b] (preferred)
Paclitaxel 45-50 mg/m^2 weekly over 1 hour Carboplatin AUC = 2 mg/mL/min over 30 min weekly Concurrent thoracic RT 63 Gy/7 wks/34 fractions[c] (category 2B)

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 with 60 Gy in 30 fractions beginning on day 50[b]
Paclitaxel 200 mg/m^2 every 3 weeks over 3 hours, 2 cycles Carboplatin AUC 6, 2 cycles followed by thoracic RT 63 Gy[c] beginning on day 42

*Randomized data supports full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

Concurrent Chemotherapy/RT Followed by Chemotherapy
Cisplatin 50 mg/m^2 on day 1, 8, 29, 36 Etoposide 50 mg/m^2 days 1-5, 29-33 Concurrent thoracic RT (total dose, 61 Gy)[d] Docetaxel started 4-6 wks after chemoradiation at an initial dose of 75 mg/m^2 x 3 doses every 3 weeks (category 3)
Paclitaxel 45-50 mg/m^2 weekly Carboplatin AUC 2, concurrent thoracic RT 63 Gy followed by 2 cycles of paclitaxel 200 mg/m^2 and carboplatin AUC 6[c] (category 2B)

[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, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemoradiation for patients with unresected stage III NSCLC: RTOG 9410. Proc Am Soc Clin Oncol 2003;22:621 (abstr 2499).

[c] 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(25):5883-5891.

[d] 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(10):2004-2010.

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.

Non-Small Cell Lung Cancer

Guidelines Index
NSCL Table of Contents
Staging, Discussion, References

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 2)

ADVANCED DISEASE:

- Baseline prognostic variables (stage, weight loss, PS, gender) predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control and yields superior quality of life compared to best supportive care.
- 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.
- No specific platinum-based cytotoxic combination is clearly superior.
- Unfit of any age (performance status 3-4) do not benefit from cytotoxic treatment.

First-line therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC.
- Cetuximab + vinorelbine/cisplatin is indicated in PS 0-2 patients with advanced or recurrent NSCLC who meet the criteria for cetuximab treatment.
- There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- Two drug regimens are preferred; a third cytotoxic drug does not increase survival, with the exception of bevacizumab or cetuximab in treatment-naïve PS 0-1 NSCLC.
- Single agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Systemic chemotherapy is not indicated in PS 3 or 4 patients.
- In locally advanced NSCLC, chemoradiation is superior to radiation alone: concurrent chemoradiation appears to be better than sequential chemoradiation.

First-line therapy (continued)

- Cisplatin-based combinations have been proven superior to best supportive care in advanced, incurable disease, with improvement in median survival of 6-12 wks, and a doubling of one-year survival rates (absolute 10-15% improvement).
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, pemetrexed.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel).
- If patient with known activated EGFR mutation or gene amplification or a never smoker, consider use of erlotinib ± chemotherapy (category 2B). If patient has a known KRAS mutation, therapy other than erlotinib should be considered.

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 has been proven superior to BSC, vinorelbine, or ifosfamide with improved survival/QOL.
  - ➤ Pemetrexed has been shown to be equivalent to docetaxel with less toxicity.
  - ➤ Erlotinib has proven superior to BSC with significantly improved survival and delayed time to symptom deterioration.

Third-line therapy

- Erlotinib has proven statistically superior to BSC with respect to survival.

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.

See Specific Systemic Agents on page NSCL-E (2 of 2)

Non-Small Cell Lung Cancer

Guidelines Index
NSCL Table of Contents
Staging, Discussion, References

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

- Cisplatin[1-9]
- Carboplatin[4,6-11]
- Paclitaxel[1,4,6,8-11]
- Docetaxel[5,7,8,12,13]
- Vinorelbine[6-8]
- Gemcitabine[3,5,6,8,9,13]
- Etoposide[4]
- Irinotecan[9]
- Vinblastine
- Mitomycin
- Ifosfamide
- Pemetrexed[14,15]
- Erlotinib[16]
- Bevacizumab[17]
- Cetuximab[18]
- Albumin-bound paclitaxel[19,20] †

[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] Bellani 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(7):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(21):3909-3917.

[7] Fossella F, Periera JR, von Pawel J, et al. Randomized, mutlinational, 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 2006 Nov 1;[Epub ahead of print].

[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, Larocca RV, Rinaldi WJ, et al. A multicenter, phase III randomized trial for stage IIIB/IV NSCLC of weekly paclitaxel and carboplatin vs. standard paclitaxel and carboplatin given every three weeks, followed by weekly paclitaxel. Proc Am Soc Clin Oncol 2004;23:619[abstract 7017].

[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. Epub 2005 Mar 1.

[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(21):3543-3551.

[16] Shepard FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):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, Szczesna A, von Pawel J, et al. FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC). J Clin Oncol 26: 2008 (May 20 suppl; abstr 3).

[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(8):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.

†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

Cancer Survivorship[1]

- In 2000, the prevalence of living cancer survivors with a diagnosis was
  - Breast cancer: 2,197,000
  - Prostate cancer: 1,637,000
  - Colon cancer: >1,000,000
  - Lung cancer: 340,000

NSCLC long term follow-up care

- Cancer Surveillance
  - History and Physical and a contrast-enhanced chest CT scan every 4-6 months for 2 years (category 2B), then H&P and a non-contrast-enhanced chest CT scan annually (category 2B)
  - Smoking status assessment at each visit, counseling and referral for cessation as needed.
- Immunizations
  - Annual Influenza vaccination
  - Pneumococcal vaccination with revaccination as appropriate

Counseling Regarding Health Promotion and Wellness[2]

- 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 you consume 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

[1] Gloeckler Ries LA, Reichman ME, Riedel Lewis D, et al. Cancer survival and incidence from the surveillance, epidemiology, and end results (SEER) program. The Oncologist 2003; 8;541-552.

[2] 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 June 5, 2008)

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.

NON-SMALL CELL LUNG CANCER SURVIVORSHIP

Cancer Screening Recommendations[3,4]

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

- **Colorectal Cancer: For men and women, Colonoscopy every 10 years (preferred) or fecal occult blood test (FOBT) annually and flexible sigmoidoscopy every 5 years, beginning at age 50**
  See NCCN Colorectal Cancer Screening Guidelines
- **Prostate Cancer: For men-annual prostate specific antigen (PSA) testing beginning at age 50; for African American males and those with family history of prostate cancer, PSA testing beginning at age 40.**
  See NCCN Prostate Cancer Early Detection Guidelines
- **Breast Cancer: For women-monthly self breast exam (SBE) beginning at age 20 (optional); annual clinical breast exam (CBE) beginning at age 25; annual mammogram beginning at age 40.**
  See NCCN Breast Cancer Screening Guidelines
- **Cervical Cancer: Annual cervical cytology testing for women up to age 30; after age 30, annual cervical cytology testing or cervical cytology testing every 2-3 years (if 3 negative/satisfactory annual cervical cytology tests) or cervical cytology and HPV-DNA testing. If both negative, testing every 3 years.**
  See NCCN Cervical Cancer Screening Guidelines

[3]Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed June 5, 2008)
[4]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 June 5, 2008)

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.

Staging

***Table 1* - Revised Stage Grouping of TNM Subsets*†**

Stage	TNM Subset	Stage	TNM Subset
0	Carcinoma in situ	IIIB	T4, N0, M0
IA	T1, N0, M0		T4, N1, M0
IB	T2, N0, M0		T4, N2, M0
IIA	T1, N1, M0		T1, N3, M0
IIB	T2, N1, M0		T2, N3, M0
	T3, N0, M0		T3, N3, M0
IIIA	T1, N2, M0		T4, N3, M0
	T2, N2, M0	IV	Any T, any N, M1
	T3, N1, M0		
	T3, N2, M0		

*Staging is not relevant for occult carcinoma designated TX, N0, M0.

†Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) 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-Verlag New York, Inc., on behalf of the AJCC.

Table 2* - Revised Definition of TNM

Primary Tumor (T)

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

T0 No evidence of primary tumor

Tis Carcinoma in situ

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

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

- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T3 Tumor of any size that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, mediastinal pleura, parietal pericardium; or tumor in the main bronchus less than 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or separate tumor nodules in the same lobe; or tumor with a malignant pleural effusion‡

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

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

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

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present§

Continued...

Table 2 Continued

Histologic Grade (G)

GX Grade cannot be assessed
G1 Well differentiated
G2 Moderately differentiated
G3 Poorly differentiated
G4 Undifferentiated

Histopathologic Type

Squamous cell carcinoma
- Variants: Papillary, clear cell, small cell, basaloid

Adenocarcinoma
- Acinar
- Papillary
- Bronchioloalveolar carcinoma
  - Non-mucinous
  - Mucinous
  - Mixed mucinous and non-mucinous or indeterminate
  - Solid adenocarcinoma with mucin formation

Adenocarcinoma with mixed subtypes
- Variants: Well differentiated fetal adenocarcinoma, mucinous ("colloid") adenocarcinoma, mucinous cystadenocarcinoma, signet ring adenocarcinoma, clear cell adenocarcinoma

Large cell carcinoma
- Variants: Large cell neuroendocrine carcinoma, combined large cell neuroendocrine carcinoma, basaloid carcinoma, lymphoepithelioma-like carcinoma, clear cell carcinoma, large cell carcinoma with rhabdoid phenotype

†The uncommon superficial tumor of any size with its invasive component limited to the bronchial wall, which may extend proximal to the main bronchus, is also classified T1.

‡Most pleural effusions associated with lung cancer are due to tumor. However, in a few patients, multiple cytopathologic examinations of pleural fluid are negative for tumor. In these cases, fluid is not bloody and is not an exudate. Such patients may be further evaluated by videothoracoscopy (VATS) and direct pleural biopsies. 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 and the patient should be staged T1, T2, or T3.

§M1 includes separate tumor nodule(s) in a different lobe (ipsilateral or contralateral).

*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, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) 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-Verlag New York, Inc., on behalf of the AJCC.

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

Lung cancer is the leading cause of cancer death in the United States. An estimated 215,020 new cases (114,690 in men and 100,330 in women) of lung and bronchus cancer will be diagnosed in 2008, and 161,840 deaths (90,810 in men, 71,030 in women) are estimated to occur due to the disease.[1] Only 15% 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.

The primary risk factor for lung cancer is smoking, which accounts for more than 85% of all lung cancer-related deaths.[2] The risk of lung cancer increases with the number of cigarettes smoked per day and with the number of years spent smoking. In addition to the hazard of first-hand smoke, exposed nonsmokers have an increased relative risk of developing lung cancer.[3] Radon gas, a radioactive gas that is produced by the decay of radium 226, is the second leading cause of lung cancer.[4] The decay of this isotope leads to the production of substances that emit alpha-particles, which may cause cell damage and, therefore, increase the potential for malignant transformation. 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.[5] In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (such as bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds).[6,7]

Prevention and Screening

Lung cancer is a unique disease, because the etiologic agent is an industry and more than 85% of cases are caused by voluntary or involuntary “second-hand” cigarette smoking. Reports from the Surgeon General on active smoking and second-hand smoke state that both cause lung cancer. There is a causal relationship between active smoking and lung cancer and with other cancers, such as esophageal, oral, laryngeal, and pharyngeal cancers (http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/00_pdfs/executivesummary.pdf). Smoking harms nearly every organ in the body. There is a 20% to 30% increased risk for lung cancer associated with living with a smoker (http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Further complicating this problem, cigarettes also contain the highly addictive substance nicotine. Oncologists should encourage smoking cessation, especially in patients with cancer

(http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf). 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/path/tobacco.htm).

Varenicline is a new class of drug for smoking cessation; other drugs include nicotine replacement (eg, gum, inhaler, nasal spray, patch) and bupropion. Studies have shown that varenicline is better than bupropion for smoking cessation.[8,9] However, almost 30% of patients had nausea while using varenicline, and most of the participants did not quit smoking even with varenicline. The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms (http://www.fda.gov/cder/drug/infopage/varenicline/default.htm).

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.[10,11] 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 computed tomography (CT) in lung cancer screening are promising with a frequency of stage I detectable lung cancer in more than 80% of newly diagnosed cases.[12-14] The National Lung Screening Trial (NLST, ACRIN Protocol A6654) is a randomized, controlled study involving 50,000 current or former smokers; this trial is assessing the risks and benefits of spiral CT scans compared with chest x-rays for detecting lung cancer. The NSLT is now closed, and data will be collected until 2009. Additional information on NLST can be found at http://www.cancer.gov/nlst.

The International Early Lung Cancer Action Program (I-ELCAP) has been assessing whether annual screening by spiral 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.[15] 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 and yields excellent survival data. However, whether mortality is decreased by screening has not yet been conclusively demonstrated and is expected to be answered by the NLST.

At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Available data[15-18] are conflicting[19,20]; thus, conclusive data from ongoing trials are necessary to define the benefits and risks associated with screening for lung cancer with low dose CT. The panel recommends that high-risk individuals participate in a clinical trial evaluating CT screening. If a trial is not available or if the high-risk individual is not eligible for a trial, then the individual should go to a center of excellence with expertise (in radiology, pathology, cytology, thoracic surgery, and general expertise in lung cancer treatment) to discuss the potential risks and benefits before having a screening CT.[21] If a screening strategy is used, then the I-ELCAP screening protocol should be followed (http://www.ielcap.org/professionals/docs/ielcap.pdf).

Classification and Prognostic Factors

The World Health Organization divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: non-small cell lung cancer (NSCLC, discussed in this guideline) and small cell lung cancer ([SCLC], see NCCN Small Cell Lung Cancer Guideline). 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. Gene expression profiling (using DNA microarrays) has identified subtypes of lung adenocarcinomas (ie, bronchioid, squamoid, magnoid), which correlate with stage-specific survival and metastatic pattern. Bronchioid tumors were associated with increased survival in early-stage disease, whereas, squamoid tumors were associated with increased survival in advanced disease.[22]

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.[23] Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (*p53*), the activation of *k-ras* oncogenes, and other biologic markers, may have significant value in predicting a poor prognosis.[24,25] Patients with stage I lung adenocarcinoma who have specific genetic abnormalities, such as *k-ras* oncogene activation, have a poor prognosis and disease-free survival.

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the lung cancer, determine the extent of invasion, establish the cancer involvement status of the surgical margins, and determine the molecular abnormalities of lung cancer that may be able to predict for sensitivity and resistance to epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKI).[26-28] Preoperative evaluations include examination of one of the following specimens: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy. In addition, the mediastinal lymph nodes are 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 World Health Organization for carcinomas of the lung.[29] The principles of pathology review are listed in NSCL-A.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important subtype of pulmonary adenocarcinoma and has received increasing attention because of evidence that EGFR mutation in lung cancer is linked to bronchioloalveolar differentiation;[30-32] data suggest that gefitinib and erlotinib are useful for patients with BAC.[32,33] BAC includes only noninvasive tumors where the neoplastic cells spread out along pre-existing alveolar structures (lepidic spread). Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.[34] BAC is divided into 3 subtypes: 1) mucinous, 2) nonmucinous, and 3) a mixed mucinous and nonmucinous or indeterminate form. Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1). Mucinous BACs express CK20 and CK7, but reportedly lack TTF-1 expression.[35] BACs are usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. Mucinous BACs are often CK7+/CK20+.[36] CDX-2 is a highly sensitive and specific marker of adenocarcinomas of intestinal origin that could be used to distinguish mucinous BAC from metastatic primary gastrointestinal cancers.

Immunohistochemical Staining

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma. A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) are used routinely. The stains that are negative in mesothelioma, but positive in adenocarcinoma, are CEA (carcinoembryonic antigen), B72.3, Ber-EP4, and MOC31. Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40,[37] and cytokeratin 5/6. Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. TTF-1 is a homeodomain-containing 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, whereas metastatic adenocarcinomas to the lung are virtually always TTF-1 negative. TTF-1 is positive in patients with thyroid cancer. In addition, thyroglobulin is present in patients with thyroid cancer, while it is negative in patients with lung cancer. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies that could be used to differentiate them from primary lung tumors. Neuroendocrine tumors of the lung are diagnosed with chromogranin (reacts with cytoplasmic neuroendocrine granules) and synaptophysin (reacts with a cell membrane glycoprotein). All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin, whereas small cell lung carcinoma is negative in 25% of the cases.

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and TTF-1. 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.[38]

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.[39-42] The revised stage grouping is summarized in Table 1, and the descriptors of the TNM classification scheme are summarized in Table 2.

Although classified as M1 disease, ipsilateral metastasis presents a difficult scenario in the preoperative period. There is very little information in the medical literature on lung metastases from lung cancer. However, when a lung metastasis is present, it usually occurs in patients with other systemic metastases.

Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (such as thoracotomy, mediastinoscopy examination of resected lymph nodes).[39]

For 1996-2004, the overall 5-year relative survival rate for lung cancer was 15.2% (from 17 SEER [Surveillance, Epidemiology, and End Results] geographic areas in the United States). Of lung and bronchus cancer cases, 16% were diagnosed while the cancer was still confined to the primary site (localized stage); 25% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 51% were diagnosed after the cancer had already

metastasized (distant stage); and for the remaining 8%, the staging information was unknown. The corresponding 5-year relative survival rates were: 49.5% for localized, 20.6% for regional, 2.8% for distant, and 8.3% 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 is stage 1A or 1B and on the location of the tumor.[43] 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%.[44] Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Note that a new lung cancer staging system has been proposed by the International Association of the Study of Lung Cancer (IASLC).[45] The revised staging will be published by the AJCC (7th ed) in 2009.

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 proto-oncogene Kirsten-Rous sarcoma virus (K-ras), and the regulatory subunit of ribonucleotide reductase (RRM1). 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 or exon 21 L858R mutation does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.[46] However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR-TKI therapy.[32,47] High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.[48,49] High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy.[49,50] 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.[24] Presence of K-ras mutations is also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.[32,51] High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression, independent of therapy.[52,53] High levels of RRM1 expression are also predictive of poor response to gemcitabine-based chemotherapy.[50,54]

EGFR Mutations, Gene Copy Number, and Level of Expression

EGFR is a transmembrane receptor. When EGF binds to the extracellular domain, receptor dimers are formed with activation of the intracellular tyrosine kinase domain. This results in autophosphorylation and in phosphorylation of downstream molecules with activation of multiple cellular functions including proliferation and survival. EGFR is detectable in approximately 80%-85% of patients with NSCLC, and the levels of expression vary widely on a continual scale.

Three different methods are currently used to determine the EGFR status in tumor cells. The methods include mutation analysis, gene copy number determination, and the level of EGFR expression. The most commonly found EGFR mutations are deletions in exon 19 (E19del) and a mutation in exon 21 (L858R). 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 mutations are found in approximately 10%-15% of Caucasian patients with NSCLC and in 30%-40% of Asian patients.

The prognostic effect of EGFR mutations E19del and L858R is not clear, because most reports are limited to patients receiving active therapy. Tsao and colleagues determined mutations in 177 patients who participated in a randomized trial of second-line gefitinib versus placebo.[46] Mutations were found in 40 patients, and 20 had E19del or L858R. They did not find a correlation between mutational status and gene copy number or expression by standard immunohistochemistry. In the placebo-treated group, 19 patients had any EGFR mutation, and their overall survival was apparently not different from the 44 patients without mutations. 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).[27]

The predictive effects of EGFR mutations E19del 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.[55,56] 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.[32] A recent prospective study has demonstrated that the objective response rate in North American patients with non-squamous cell histology and EGFR mutations (53% E19del, 26% L858R, 21% other mutations) is 55% with a median progression-free survival of 9.2 months.[47] 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).[27] The response rates in the group of patients receiving only chemotherapy were 21% for those with mutations and 27% for those without mutations.

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. Patients whose tumors had high levels (N=26, relative *ERCC1* expression above the cohort median of 50) lived significantly longer than patients whose tumors had low levels (N=25, relative expression below 50).[48] These results were independently confirmed in a similar cohort of patients (N=372) using standard immunohistochemistry. Patients with high tumoral ERCC1 expression had a median overall survival of 55 months compared to 42 months for patients with low ERCC1 expression.[49]

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. Initially, studies used semiquantitative determination of *ERCC1* mRNA levels. Using prospectively collected fresh-frozen tumor samples, an association between *ERCC1* mRNA levels and response to 2 cycles of gemcitabine and carboplatin was described.[50] Tumors with low *ERCC1* expression had a better response than tumors with high *ERCC1* expression in 35 patients with inoperable, locally advanced NSCLC. In a retrospective analysis of tumor specimens from 56 patients with

advanced NSCLC who were treated with gemcitabine and cisplatin, no significant correlation between disease response and *ERCC1* mRNA levels was observed. However, overall survival was significantly longer in patients with low *ERCC1* expression (14.2 months) when compared to patients with high expression (4.7 months).[57] Olaussen and colleagues found that ERCC1 protein expression, as determined by standard immunohistochemistry, was predictive of benefit from adjuvant cisplatin-based therapy in a large group of patients with surgically resected NSCLC who participated in the International Adjuvant Lung Trial (IALT).[49] In this study, only patients with low tumoral ERCC1 protein levels benefited from adjuvant chemotherapy (adjusted hazard ratio for death, 0.65; 95% CI, 0.50 to 0.86; *P*=.002). Most recently, Bepler and colleagues reported that in situ ERCC1 protein levels in tumor specimens collected prospectively from a community-based randomized phase III clinical trial were significantly and inversely correlated with disease response to carboplatin/gemcitabine or gemcitabine alone (*P*=.003, *r*=0.39); that is, response was better in patients with low levels of ERCC1 expression.[54]

K-ras Mutations

K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, it is constitutively active, able to transform immortalized cells, and promotes cell proliferation and survival. Initially, K-ras was described as mutated in codon 12 in 5/10 adenocarcinomas and 0/15 squamous and 0/10 large cell carcinomas.[58] Current data suggest that approximately 25% of adenocarcinomas in a North American population have K-ras mutations.[27,32,51] K-ras mutation prevalence is associated with cigarette smoking.[59]

K-ras mutational status is prognostic of survival. Patients with K-ras mutations have a shorter survival then patients with wild-type K-ras. Slebos and colleagues determined K-ras codon 12 mutations in 69 patients with completely resected adenocarcinomas, who did not receive additional therapy.[24] They found that disease-free and overall survival were significantly (*P*=.038 and *P*=.002, respectively) shorter in the 19 patients with mutations compared to the 50 patients without mutations. These data were independently confirmed in a cohort of 66 patients (11 with K-ras codon 12 mutations; *P*=.03 for overall survival difference) by Mitsudomi and colleagues.[60] However, Tsao and colleagues did not find a significant difference (*P*=.40) in survival by ras mutational status on the observation arm of the Canadian adjuvant chemotherapy trial (JBR10).[51] In this report, the authors investigated codons 12, 13, and 61 of all 3 ras genes and categorized patients as ras mutated if any mutation was detected.

K-ras mutational status is also predictive of therapeutic efficacy from EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy. In a retrospective study of 101 patients with a bronchioloalveolar variant of adenocarcinoma, K-ras codon 12 and 13 mutations were found in 23% (18/80) of patients.[32] All patients had been treated with first-line single-agent erlotinib. None of the patients with K-ras mutations responded (0/18), while 20 without K-ras mutations responded (20/62, 32%). This difference was statistically significant (*P*<.01). In patients treated with first-line chemotherapy plus erlotinib or chemotherapy plus placebo (the TRIBUTE trial), K-ras codon 12 and 13 mutations were present in 51/264 and 4/264 patients respectively.[27] Patients with K-ras mutations had a response rate of 8% in the chemotherapy plus erlotinib arm (2/25) and 23% in the chemotherapy only arm (7/30). Patients without K-ras mutations had a response rate of 26% in the chemotherapy plus erlotinib arm (27/104) and 26% in the chemotherapy only arm (27/103). In this report, time-to-progression and overall survival were also shortest in the group of patients with K-ras mutations receiving chemotherapy plus erlotinib, which suggests that the addition of erlotinib to chemotherapy in patients with K-ras mutations may adversely interfere with chemotherapeutic

efficacy. Tsao and colleagues identified 88 patients with and 333 without any ras mutation (codons 12, 13, and 61 of K-ras, N-ras, H-ras) in the Canadian adjuvant chemotherapy trial (JBR10).[51] They found that patients with ras mutations did not derive benefit from adjuvant cisplatin/vinorelbine (hazard ratio of death for chemotherapy versus observation 0.95, CI, 0.53-1.71; *P*=.87), while those without ras mutations (N=333) benefited significantly (hazard ratio of death for chemotherapy versus observation 0.69, CI, 0.49-0.97; *P*=.03) from adjuvant therapy. However, when taking both the treatment arm and the ras mutational status into account (that is, when testing for interaction), the *P*-value did not reach statistical significance (*P*=.29).

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.[61,62] 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).[52] These results were independently confirmed in a cohort of 187 patients with stage I disease. 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.[53]

In fresh frozen tumor specimens that had been prospectively collected on patients treated with gemcitabine and carboplatin, *RRM1* expression levels were predictive of tumor response. Tumors with low *RRM1* expression responded significantly better to treatment than tumors with high levels of expression.[50] In addition, *RRM1* mRNA levels were significantly associated with overall survival in patients with advanced stage NSCLC who were treated with gemcitabine and cisplatin.[63] In this analysis, patients with low *RRM1* levels had a median overall survival of 13.7 months while patients with high levels had a median overall survival of 3.6 months. The addition of a vinca alkaloid to a gemcitabine regimen abolished the effect of *RRM1* expression on overall survival, which suggests that a substantial interaction exists between the biomarker and treatment regimen on patient outcome.

Most recently, Bepler and colleagues reported that in situ RRM1 protein levels in tumor specimens collected prospectively from a community-based randomized phase III clinical trial were significantly and inversely correlated with disease response to gemcitabine or carboplatin/gemcitabine (*P*=0.001, *r*=0.41); that is, response was better in patients with low levels of RRM1 expression.[54]

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. The surgical procedure used depends on the extent of disease and 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; otherwise, lobectomy or pneumonectomy should be done if physiologically feasible.[64,65] 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.[65-67] If clinical stage I and II patients are deemed medically inoperable by a thoracic surgeon, then these patients should receive potentially curative RT (see NSCL-B).[65]

At the time of surgical staging, the role of a complete mediastinal lymphadenectomy versus lymph node sampling remains controversial.[68,69] To address this issue, the American College of Surgeons Oncology Group is conducting a randomized trial (ACOSOG Z0030) of 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. The primary objective of this study is to evaluate whether complete mediastinal lymph node dissection results in better overall survival when compared to mediastinal lymph node sampling in the patient undergoing resection for N0 or non-hilar N1 NSCLC.[70, 71]

Video-assisted thoracic surgery (VATS) is a relatively new minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.[72,73] Published studies suggest that VATS has several advantages over the standard thoracotomy (or pleurotomy).[74-77] Acute and chronic pain associated with VATS is minimal; thus, this procedure requires shorter length of hospitalization.[78] VATS is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[79-83] In stage I NSCLC patients who have VATS 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.[84-86] VATS has also been shown to improve discharge independence in older populations and in high-risk patients as well.[87,88] Recent data show that VATs improves the ability of patients to complete postoperative chemotherapy regimens.[89,90] Based on its favorable effects on postoperative recovery and morbidity, VATS is included in the guidelines (see NSCL-B) as a feasible option for patients who are surgically resectable as long as standard oncologic and dissection principles of thoracic surgery are not compromised.

Radiation Therapy

Modern 3-dimensional conformal RT techniques with CT or CT/positron emission tomography (PET)--based treatment planning should be used on all patients. The dose volume histogram (DVH) for the lungs, esophagus, heart, liver, kidney, and spinal cord should be used to minimize normal tissue toxicity (see NSCL-C).[91-95] Whenever feasible, respiratory management techniques (such as 4-dimensional CT and respiratory gating) should be incorporated in the radiation set up and delivery. Treatment planning should be on CT scans obtained in the treatment position. IV contrast for diagnostic or simulation CT should be used for better target and normal tissue delineation whenever possible. PET/CT is preferable for treatment plans rather than CT alone for the gross tumor volume (GTV) delineation in cases with substantial atelectasis.

In general, photon beam energy between 4-10 MV is recommended for most patients. If a large tumor is involving the mediastinum or the primary tumor is a large and proximal lesion with patient's separation more than 20 cm, 15 MV or 18 MV photon energy can also be used. If the tumor is fixed to the vertebral body, located at the superior sulcus, or involves the bilateral mediastinum, intensity-modulated radiotherapy (IMRT) should be considered to avoid overdose to normal tissues. Involved field radiation to high dose without elective nodal treatment has been shown to have less toxicity, superior survival, and low risk of isolated nodal relapse.[96,97] In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (that is, grade 3 esophagitis,

pneumonitis, hematologic toxicities) should be avoided by following the recommended dose-volume constraints (see NSCL-C).[98-100] In the preoperative chemoradiation setting, a total dose of 45-50 Gy in 1.8-2 Gy fractions should be used to treat all volumes of gross disease (see NSCL-5 and NSCL-C).[101] Doses greater than 50 Gy in the preoperative setting have been reported to be safe at select institutions; however, this is still considered experimental.[102-104] To avoid postoperative pulmonary toxicity, preoperative chemoradiotherapy should be avoided if pneumonectomy is required.[105,106] 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. Postoperative radiation should include the bronchial stump and mediastinum. A total dose of 50 Gy should be delivered in 1.8 to 2 Gy fractions for negative margins. For extranodal extension or microscopic positive margins, a total dose of 54-60 Gy (in 1.8 to 2 Gy fractions) should be used (see NSCL-C). For gross residual tumor, a total dose up to 70 Gy should be used. Because of the higher risk of local failure, concurrent adjuvant chemoradiation can be used if recommended in the guidelines and if the patient can tolerate it.[107]

In the definitive concurrent chemoradiation setting, a total radiation dose up to 74 Gy in 2 Gy fractions should be used to treat all volumes of gross disease.[107-109] Three-dimensional treatment planning is imperative with dose volume histogram assessments of lung function to estimate the risk of pneumonitis (see NSCL-C).[110,111] Elective nodal radiation is not mandated.[112]

Studies suggest that stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) may be options 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. When stereotactic radiosurgery was used in 245 patients (T1-2), local control was 85% at 2 years and 5 years.[113,114] The Radiation Therapy Oncology Group (RTOG) 0236 trial is currently assessing SBRT.[115,116] Optimal candidates for SBRT include patients with node negative peripheral tumors less than 5 cm.[113,117,118] 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.[119] A recent 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. Patients with stage I NSCLC (n=13) had a 2-year overall survival of 75% (45–92%).[120] RT with (or without) chemotherapy should be offered as potentially curative treatment to patients with stage I and II NSCLC who are medically inoperable but of reasonable PS and life expectancy (see NSCL-B and NSCL-C). However, a study in 4,357 patients with stage I or II NSCLC who did not have surgical resection found that median survival was improved (by 5-7 months) in patients treated with RT, although 5-year survival was not significantly different when compared with patients not receiving RT.[121]

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease. In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.[122-124] Currently, concurrent chemoradiation appears superior to sequential therapy for patients with unresectable stage III disease.[108,125] Surgery is rarely done for patients with stage IV disease. For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.[126,127]

Surgery Followed by Chemotherapy

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.[122] 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 (44.5% versus 40.4% 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 (39.4% versus 34.3% 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. Recent data from the IALT found that after 7.5 years of followup, there were more deaths in the chemotherapy group.[128]

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 (242 patients) or to observation (240 patients).[123] The median age was 61 years in both groups. Chemotherapy was not excessively toxic. 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 46.7 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).

In the ANITA trial, 840 patients (median age, 59 years) with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned either to adjuvant vinorelbine plus cisplatin or to observation.[124] 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 65.7 months in the chemotherapy group and 43.7 months in the observation group.[124] Adjuvant chemotherapy significantly improved 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.

A recent 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).[129] The benefit was greater in patients with stage II and III disease and good performance status.

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;[130] updated results have been reported.[131] In this trial, 344 patients (34-81 years) 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).[131] 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

greater than 4 cm). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin (see NSCL-D).[132]

Chemoradiation

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.[133-137] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[133,134,136,137] However, concurrent chemoradiation appears to be superior to sequential therapy.[108,125] Concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. For patients with negative margins, most NCCN institutions give sequential chemotherapy followed by RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT with (or without) chemotherapy). 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) (see NSCL-D).[107,108,138] Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.[139]

A phase II trial from SWOG (9504) assessed concurrent chemoradiation (using cisplatin/etoposide) followed by consolidation docetaxel in 83 patients with unresectable stage IIIB NSCLC.[140] Results from SWOG 9504 have shown a median survival of 26 months and a 5-year survival rate of 29%.[141] However, results from a phase III trial in patients with unresectable stage III NSCLC assessing consolidation docetaxel after cisplatin/etoposide with concurrent chemoradiation did not show improved survival with docetaxel and did show increased toxicity.[142,143] 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.[144]

Chemotherapy

For disseminated disease (stage IV) in selected patients with a solitary metastasis, especially a brain metastasis, surgical resection of the metastasis may improve survival.[145] Surgical resection of a solitary metastasis located in sites other than the brain remains controversial.

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.[126] Many drugs are active against stage IV NSCLC. These drugs include the taxanes (paclitaxel, docetaxel), vinorelbine, the camptothecin analogs (irinotecan, topotecan), and gemcitabine (see NSCL-E). 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, and docetaxel/cisplatin.[107,132,146-148] Phase III randomized trials have shown that many of the platinum-doublet combinations are similar for objective response rates and survival.[149,150] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin;[146,151,152] gemcitabine/docetaxel is another option.[153]

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel 1) for patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication,

or 2) for patients in whom the standard premedications (that is, dexamethasone, H2 blockers, H1 blockers) are contraindicated.[154,155]

Specific targeted therapies have been developed for the treatment of advanced lung cancer.[156,157] Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor to the EGFR. 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).[158] To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC, no history of hemoptysis, and no untreated central nervous system metastases. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab.

Erlotinib was approved by 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 (with or without chemotherapy) can also be given as first-line therapy in patients with advanced or metastatic NSCLC who have known active EGFR mutation or gene amplification and who never smoked.[27,159]

A large phase III randomized trial (FLEX) recently assessed cisplatin/vinorelbine with or without cetuximab for patients with advanced NSCLC (most patients had stage IV disease).[160] Adding cetuximab slightly increased overall survival (11.3 versus 10.1 months, P = .04). Criteria for treatment with cetuximab include stage IIIB (pleural effusion)/IV NSCLC, EGFR expression by immunohistochemistry (greater than 1 positive tumor cell), age 18 years or older, and ECOG PS 0-2 (see NSCL-13). In addition, patients should not have prior chemotherapy, anti-EGFR therapy, or brain metastases.

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC (see NSCL-1). The clinical stage is initially determined from disease history (ie, cough, dyspnea, weight loss, chest pain) and physical examination together with a limited battery of tests, including a pathology review, chest CT (including the upper abdomen and adrenals), a complete blood cell (CBC) and platelet count, and chemistry profile. The panel also recommends that smoking cessation counseling be made available to patients (http://www.smokefree.gov/expert.html). Based on the initial evaluation, the clinical stage is determined and assigned to 1 of 10 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.[161-163] 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 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 T1 lesions,[164] some NCCN institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2, central T1 or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy is recommended.

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.[165] 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% false-negative chest CT scans with histologic identification of occult N2 or N3 disease.[166]

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, stage IIIA, and stage IIIB (T4, N0-1) 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.[161] 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.[167] 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).[168] 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.[169] 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%.[170] Kerstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[171,172] 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.[173,174]

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.[175,176] However, PET/CT is even more sensitive and is now recommended by NCCN. When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.[177] However, positive PET/CT scans findings need pathologic or other radiologic confirmation (for example, 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 endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) have proven useful to stage patients or to diagnose mediastinal lesions; these techniques can be used instead of invasive staging procedures.[178] 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.[179]

The routine use of magnetic resonance imaging (MRI) to rule out asymptomatic brain metastases and of bone scans to exclude bone metastases are not recommended. Brain MRI is recommended for patients with stage II, stage III, and stage IV diseases to rule out metastatic disease if aggressive combined-modality therapy is being considered.[180]

Initial Therapy

Stage I, Stage IIA, and Stage IIB (T1-2, N1) Disease

It is strongly recommended that determination of tumor resectability be made by a surgical thoracic oncologist who performs lung cancer surgery as a prominent part of his or her practice. The principles of surgical resection are listed on NSCL-B.

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 node mapping. 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 (such as inclusion of mediastinal lymph node dissection) must be modified accordingly. Therefore, the algorithms include 2 different tracks for T1–2, N2 disease: 1) T1–2, N2 disease discovered unexpectedly at surgical exploration (see NSCL-3); and 2) T1–2, N2 disease confirmed before thoracotomy (see NSCL-7). In the second case, an initial brain MRI and PET/CT scan (if not previously done) are recommended to rule out metastatic disease.

Stage IIB (T3, N0), Stage IIIA, and Stage IIIB Disease

For patients with clinical stage IIB (T3, N0) and stage III tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0) and stage IIIA-B (T3-4, N1) 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 determination is made regarding the surgical resectability.

For patients with resectable tumors (T3-4, N0-1) in the superior sulcus, the panel suggests concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see NSCL-5). The principles of RT and chemotherapy are listed on NSCL-C and NSCL-D, respectively. For patients with negative margins, most NCCN institutions give sequential chemotherapy and radiation (that is, chemotherapy followed by RT); for patients with positive margins, most NCCN institutions give concurrent chemoradiation with (or without) chemotherapy. Patients with marginally resectable superior sulcus tumors should undergo

concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T3-4, N0-1) in the superior sulcus, definitive RT with chemotherapy (that is, definitive concurrent chemoradiation) is recommended.

In superior sulcus tumors, among the patients treated by surgery and postoperative radiotherapy with or without concurrent chemotherapy, the overall 5-year survival rate has been approximately 40%.[181] Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.[182-185]

Surgical resection is the preferred treatment option for patients with invasion of the chest wall, proximal airway, or mediastinum (T3-4, N0-1). Other treatment options include chemotherapy, concurrent chemoradiation, or radiotherapy (category 3 for RT only) 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 (including mediastinoscopy, mediastinotomy, EBUS-FNA, EUS-FNA, and CT-guided FNA), bronchoscopy, brain MRI, MRI of spine (as clinically indicated), and PET/CT scan; PFTs should be ordered if not previously done. 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 should be performed during the surgery. Those individuals found to have unresectable lesions should be treated according to pathologic stage, as defined on NSCL-1. 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 (see NSCL-7); for patients with T3, N2 nodes who have an excellent response, reassess for surgical resection (category 3), although the panel disagreed about whether resection is appropriate. Although definitive concurrent chemoradiation is recommended (category 1), induction chemotherapy with (or without) RT is another option for patients with T1-2, N2 disease.[186] Recommended therapy for metastatic disease is detailed on NSCL-11 for stage IV diseases.

Stage IIIB tumors comprise a heterogeneous set of presentations, each requiring a different approach. These 4 groups include: 1) T4 tumors with N0-N1 nodal status, a group potentially curable with surgery (this group includes tumors upstaged to T4 because of satellite lesions); 2) tumors with contralateral mediastinal nodes (T1-3, N3); 3) T4 tumors with N2-3 disease, which are unresectable; and 4) tumors that are stage IIIB because of pleural or pericardial effusion. For resectable T4, N0-1 tumors with satellite lesions, initial surgical resection is recommended followed by chemotherapy. The recommended initial treatment options for resectable tumors (other than satellite) are similar to stage IIIA disease: surgery, induction chemotherapy before surgery, or concurrent chemoradiation before surgery (see NSCL-8). In support of this option, Naruke and colleagues reported a 5-year survival rate of 8% in patients with resected T4 disease.[187] For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by consolidation chemotherapy (category 2B) (see NSCL-D).[141-143]

Surgical resection is not recommended in patients with T1-3, N3 disease (ie, metastases to contralateral nodes). However, in patients with suspected N3 disease, the guidelines recommend pathologic confirmation of nodal status by either mediastinoscopy, supraclavicular lymph node biopsy, thoracoscopy, needle biopsy, mediastinotomy, EUS biopsy, or EBUS) (see NSCL-9).[188,189] In addition, PFTs (if not previously done), 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 (see NSCL-1). If these tests are positive, concurrent chemoradiation (category 1) followed by consolidation chemotherapy (category 2B) is recommended.[141,143] For metastatic diseases that are confirmed by PET/CT scan and brain MRI, treatment is detailed on NSCL-11.

For patients with T4, 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 IIIB (T4, N0-1) disease (see NSCL-6). If either the contralateral or ipsilateral mediastinal node is positive, the patient needs to be treated with concurrent chemoradiation therapy (category 1), although panel members did not all agree that consolidation chemotherapy (category 2B) should be given after chemoradiation (see NSCL-10).[141-143] Pleural or pericardial effusion is another criterion for T4 disease. 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 algorithm tracks back to the confirmed T and N stage (see NSCL-1). However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.[190] In patients with positive effusion, the tumor is treated as M1 with local therapy (such as pleural catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see NSCL-11).

Stage IV

The algorithm for patients with distant metastases (ie, stage IV) depends on the location of the metastases—a solitary nodule in the brain, adrenal, or lung (ie, a satellite lesion)—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. 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. The 5-year survival rates with such an approach range from 10% to 20%.[156,191] Follow-up whole brain RT or stereotactic radiosurgery may be used, because the combined therapy is superior to RT alone in prolonging life and preventing local recurrence.[192] Stereotactic radiosurgery alone or followed by whole brain radiation is an additional treatment option. Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.[193] Additional chemotherapy or surgical resection of the lung lesion in this setting can also be used, but this is a category 2B recommendation. Controversy exists because all these patients have M1 (stage IV) disease that has been resected, but the recommendation is to treat the primary lung tumor according to the T and N status (see NSCL-1).

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 has produced some long-term survivors (category 3).[194,195] However, resection generated major disagreement among the panel members (category 3). Some panel members feel that resection of adrenal glands only makes sense if the synchronous lung disease is stage I or maybe stage II (ie, resectable). Systemic therapy (see NSCL-13) is another treatment option for adrenal metastasis.

In patients with synchronous nodules (either in contralateral lung or ipsilateral 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 (see NSCL-1).

Adjuvant Treatment

Chemotherapy or Chemoradiation

Patients with T1, N0 tumors and with negative surgical margins (R0) are either observed or chemotherapy (category 3) is recommended as adjuvant treatment for patients with high-risk features, such as poorly differentiated tumor, vascular invasion, wedge resection, and minimal margins (see NSLC-3). Treatment options for patients with T1, N0 disease and with positive surgical margins (R1, R2) include 1) re-resection; 2) chemoradiation (category 2B); or 3) RT (category 2B). Although chemotherapy can be added to either option 1 or 2, there was widespread disagreement because of a lack of data to support this recommendation (category 3).[196] Patients with T2, N0 tumors should either be observed or receive adjuvant chemotherapy (category 2B) when the surgical margins are negative; if the surgical margins are positive, these patient should have re-resection with chemotherapy or chemoradiation and chemotherapy.

For patients with T1-2, N1 disease and negative surgical margins, the panel recommends chemotherapy (category 1) or chemoradiation (category 2B) and chemotherapy for patients with adverse factors (such as, inadequate mediastinal lymph node dissections, extracapsular spread, multiple positive hilar nodes, and close margins). If surgical margins are positive (T1-2, N1), options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy (see NSCL-3). Patients with negative margins may be treated with chemotherapy (category 1) and mediastinal RT. Panel members disagreed about the use of chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.[197] 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 is less than 90%, 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.[198] A recent phase II trial in 42 patients had similar results (5-year survival, 68%) except those with adenocarcinoma had poorer survival (only 28%).[199] 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 (see NSCL-D).

In the case of marginally resectable superior sulcus tumors (T3-4, N0-1), if the lesion converts to a resectable status following initial treatment, resection is performed and chemotherapy is given (see NSCL-5). If the lesion does not convert (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 T3-4, 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 (T1-2, N2), if there is no disease progression after initial treatment, patients should be treated with surgery with (or without) chemotherapy (category 2B) (see NSCL-7). 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 (see NSCL-11).

In patients with clinical stage IIIB (T4, N0-1) disease, the option for adjuvant therapy includes surgery, if initial therapy consisted of induction chemotherapy or concurrent chemoradiation therapy (see NSCL-8). If the margins are negative, adjuvant chemotherapy is recommended. If the resection margin is positive, RT is given (if not given previously) followed by chemotherapy.

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,[122-124] the panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with either gemcitabine or docetaxel (see NSCL-D).[132,146] For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used.[132]

A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery.[200-202] Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[203-205] 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.[205] 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. 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 T1-2, N0-2 tumors based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).[206] 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.[207]

Surveillance and Treatment of Recurrences and Metastases

Surveillance

The guidelines suggest routine history and physical examinations every 4 to 6 months in the first 2 years and then annually for patients with stages I to IV disease (see NSCL-12). Spiral contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years (category 2B) and then a non-contrast-enhanced chest CT annually thereafter, (category 2B), although the panel disagreed about this recommendation.[12] Smoking cessation counseling should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients.

The NCCN guidelines have a new algorithm for long-term followup care of NSCLC survivors (see NSCL-F). These new recommendations include guidelines for routine cancer surveillance, immunizations, counseling for wellness and health promotion, and cancer screening.

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases (see NSCL-12). Palliation of symptoms can be achieved with external-beam RT by reducing tumor size. In addition, various regional therapy options are listed for locoregional recurrences. Resectable local recurrence may be managed by re-resection. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life.[208] Obstructed airways can be treated with brachytherapy (endobronchial RT), laser treatment, or endobronchial stent placement; these modalities can be used individually or in combination. In addition, photodynamic therapy (PDT) offers a simple and effective alternative to conventional techniques for palliative debridement of endobronchial obstructions in lung cancer patients. Mediastinal lymph node recurrence should be treated with concurrent chemoradiation (if RT has not been given previously). For superior venal cava (SVC) obstruction, RT or stent placement is indicated. For severe hemoptysis, several treatment options are recommended (such as brachytherapy, laser therapy, PDT, or embolization). Ultimately, surgery may be done to remove the bleeding site. After the treatment for the locoregional recurrence, if no further disseminated disease is evidenced, observation or systemic chemotherapy (category 2B) is recommended. However, for observed disseminated disease, systemic chemotherapy and best supportive care should be applied right away (see NSCL-13).

For distant metastases with localized symptoms, diffuse brain metastases, or symptomatic bony metastasis, palliation of symptoms can be achieved with external-beam RT. In addition, orthopedic stabilization should be performed if patients are at risk of fracture, and bisphosphonate therapy should be considered in patients with bone metastasis. For other solitary metastasis, the treatment guidelines

follow the same pathway as that for stage IV, M1 (solitary site) tumors (see NSCL-11).

In a small subset of patients, recurrence will be suspected only on the basis of positive sputum cytology (see NSCL-16). In this situation, the guidelines recommend further evaluation with bronchoscopy, hematoporphyrin fluorescence, or autofluorescence. If tumor in situ (Tis) is detected, treatment options include endobronchial laser ablation, brachytherapy, photodynamic therapy, and surgical resection. Alternatively, the patient may be re-bronchoscoped every 3 months. If T1-3 tumors are discovered, the algorithms track back to the appropriate clinical stage (see NSCL-1). Surveillance may also detect a new lung primary, and these patients should be treated according to the staging findings.

For recurrent and metastatic disease, first-line therapy includes several options (see NSCL-13) for patients with PS of 0-1: 1) chemotherapy (category 1) (see NSCL-E); 2) bevacizumab in combination with chemotherapy for patients who meet the eligibility criteria; 3) cisplatin and pemetrexed (category 1) for patients who meet the eligibility criteria; and 4) cetuximab in combination with vinorelbine and cisplatin for patients who meet the eligibility criteria. Patients with PS of 2 can receive either 1) cetuximab in combination with vinorelbine and cisplatin for patients who meet the eligibility criteria; or 2) chemotherapy (see NSCL-E).

Eligibility criteria for bevacizumab include PS of 0-1, nonsquamous cell histology, no history of hemoptysis, and no untreated central nervous system metastases. Note that bevacizumab should not be given as a single agent unless as maintenance if initially used with chemotherapy. Any regimen with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Eligibility criteria for cisplatin and pemetrexed include PS 0-1, nonsquamous histology, and no prior chemotherapy. Eligibility criteria for cetuximab include stage IIIB (pleural effusion)/IV, EGFR expression (determined by immunohistochemistry), age 18 years or older, ECOG PS 0-2, no prior chemotherapy, no anti-EGFR therapy, and no brain metastases (see NSCL-13).[160]

In a phase II/III trial (ECOG 4599), 842 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.[158,209] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin demonstrated an improved response rate (27% versus 10%, $P<.0001$), progression-free survival (6.4 versus 4.5 months, $P<.0001$), and median survival (12.5 versus 10.2 months, $P=.0075$) when compared to patients receiving paclitaxel and carboplatin alone. The overall 1-year and 2-year survival was 51.9% versus 43.7% and 22.1% versus 16.9%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.[158] However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 24% versus 16.4%, grade 3/4 hemorrhage: 4.5% versus 0.7%, hemoptysis: 1.9% versus 0.2%, and hypertension: 6.0% versus 0.7%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (9 patients) than with paclitaxel and carboplatin (2 patients).

A recent noninferiority trial in 1745 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine compared with cisplatin plus pemetrexed.[210] Patients with nonsquamous cell histology (either adenocarcinoma or large cell) 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%]).

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.[160] The response rate was increased with cetuximab (36% versus 29%, *P*=.012); there was no difference in progression-free survival. Overall survival was significantly 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%).

For patients with PS of 0-1 who are not candidates for bevacizumab or cetuximab treatment, a platinum-based chemotherapy regimen is recommended (category 1) as first-line chemotherapy for the treatment of advanced disease. As yet, there is no evidence that one platinum-based regimen is better than any other. There was widespread disagreement (category 3) among panel members about when the patient should be reevaluated for tumor progression with a follow-up CT scan (ie, after the first or second cycle). 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 (preferred) of chemotherapy[211] or until the disease progresses (category 2B). Although many patients are treated until disease progression, there is no evidence that this approach improves survival.

A recent 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.[212] Tumor response (*P*=.001) and progression-free survival (4.3 versus 2.6 months, *P*=.00002) were increased in patients who received pemetrexed, especially in patients with nonsquamous histology. In patients with nonsquamous histology, preliminary results showed increased overall survival with pemetrexed (14.4 versus 9.4 months, *P*=.005).

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, and erlotinib are recommended as single agent second-line chemotherapy regimens for patients with PS of 0-2 and who have experienced disease progression during or after first-line therapy (see NSCL-15).[213-216] 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.[216] Median age was 61.4 years. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (*P*<.001). 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.[217]

Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with PS of 0-2; erlotinib may be considered for PS 3 patients. Patients receiving erlotinib who have hepatic impairment should be closely monitored during therapy.

Erlotinib should be interrupted or discontinued if changes in liver function are severe, such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside the normal range (http://www.fda.gov/medwatch/safety/2008/tarceva_dhcp_letter.pdf). If disease progression occurs after second- or third-line chemotherapy, patients with PS of 0-2 may be treated with best supportive care or be enrolled in a clinical trial. Best supportive care only should be provided to patients with PS of 3-4 and progressive disease during any stage of the treatment (see NCCN Palliative Care Guidelines).

References

1. Jemal A, Siegel R, Ward E, et al. Cancer statistics, 2008. CA Cancer J Clin 2008;58(2):71-96. Epub 2008 Feb 20.

2. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. BMJ 1976;2:1525-1536.

3. Wald NJ, Nanchahal K, Thompson SG, et al. Does breathing other people's tobacco smoke cause lung cancer? Br Med J (Clin Res Ed) 1986;293(6556):1217-1222.

4. Ginsberg RJ, Vokes EE, Rosenzweig K. Non-small cell lung cancer. In: DeVita VT Jr, Hellman S, Rosenberg SA, eds. Cancer principles and practice of oncology. 6th ed. Philadelphia: Lippincott Williams & Wilkins. 2001:925-983.

5. Omenn GS, Merchant J, Boatmann E, et al. Contribution of environmental fibers to respiratory cancer. Environ Health Perspect 1986;70:51-56.

6. Fraumeni JF Jr. Respiratory carcinogenesis: an epidemiologic appraisal. J Natl Cancer Inst 1975;55(5):1039-1046.

7. Janerich DT, Thompson WD, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990;323(10):632-636.

8. Jorenby DE, Hays JT, Rigotti NA, et al for the Varenicline Phase 3 Study Group. Efficacy of varenicline, an 4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: A randomized controlled trial. JAMA 2006;296:56-63.

9. Gonzales D, Rennard SI, Nides M, et al, for the Varenicline Phase 3 Study Group. Varenicline, an [alpha]4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47-55.

10. Carney DN. Lung cancer–time to move on from chemotherapy. N Engl J Med 2002;346(2):126-128.

11. 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(6):1794-1801.

12. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354(9173):99-105.

13. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screenings. Cancer 2001;92(1):153-159.

14. Kaneko M, Kusumoto M, Kobayashi T, et al. Computed tomography screening for lung carcinoma in Japan. Cancer 2000;89[Suppl 11]:2485-2488.

15. Henschke CI, Yankelevitz DF, Libby DM, et al; the International Early Lung Cancer Action Program Investigators. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-1771.

16. Bach PB, Silvestri GA, Hanger M, Jett JR. Screening for lung cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition). Chest 2007;132:69S-77.

17. McMahon PM, Kong CY, Johnson BE, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT screening study. Radiology 2008;248(1):278-287. Epub 2008 May 5.

18. van Klaveren RV, Oudkerk M, Mali W, et al. Baseline and second round results from the population based Dutch-Belgian randomized lung cancer screening trial (NELSON) [abstract]. J Clin Oncol 2008;26:1508.

19. Mulshine JL. Commentary: lung cancer screening--progress or peril. Oncologist 2008;13(4):435-438.

20. Jett JR, Midthun DE. Commentary: CT screening for lung cancer--caveat emptor. Oncologist 2008;13(4):439-444.

21. Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297(9):953-961.

22. Hayes DN, Monti S, Parmigiani G, et al. Gene expression profiling reveals reproducible human lung adenocarcinoma subtypes in multiple independent patient cohorts. J Clin Oncol 2006;24(31):5079-5090.

23. Finkelstein DM, Ettinger DS, Rucksdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Group Study. J Clin Oncol 1986;4(5):702-709.

24. 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(9):561-565.

25. Horio Y, Takahashi T, Kuroishi T, et al. Prognostic significance of p53 mutations and 3p deletions in primary resected non-small cell lung cancer. Cancer Res 1993;53(1):1-4.

26. Fossella FV, Putnam JB, Komaki R. Lung cancer. Springer, New York; 2003.

27. 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(25):5900-5909. Epub 2005 Jul 25.

28. 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(5):423-429.

29. Travis WD, World Health Organization, International Agency for Research on Cancer, International Academy of Pathology & International Association for the Study of Lung Cancer. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004.

30. Jackman DM, Chirieac LR, Jänne PA. Bronchioloalveolar carcinoma: A review of the epidemiology, pathology, and treatment. Semin Respir Crit Care Med 2005;26(3):342-352.

31. Blons H, Cote JF, Le Corre D, et al. Epidermal growth factor receptor mutation in lung cancer are linked to bronchioloalveolar differentiation. Am J Surg Pathol 2006;30(10):1309-1315.

32. 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.

33. West HL, Franklin WA, McCoy J, et al. Gefitinib therapy in advanced bronchioloalveolar carcinoma: Southwest Oncology Group Study S0126. J Clin Oncol 2006;24(12):1807-1813.

34. Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-1068.

35. 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.

36. Shah RN, Badve S, Papreddy K, et al. Expression of cytokeratin 20 in mucinous bronchioloalveolar carcinoma. Hum Pathol 2002;33:915-920.

37. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36(4):372-380.

38. 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 Patho 1994;102:406-414.

39. AJCC Cancer Staging Manual, Sixth Edition. Springer-Verlag: New York. 2002.

40. Mountain CF. A new international staging system for lung cancer. Chest 1986;89:225S-233S.

41. Mountain CF. Revisions in the International Staging System for Staging Lung Cancer. Chest 1997;111(6):1710-1717.

42. Mountain CF. Staging classification of lung cancer. A critical evaluation. Clin Chest Med 2002;23(1):103-121.

43. Ignatius Ou SH, Zell JA, Ziogas A, et al. Prognostic factors for survival of stage I nonsmall cell lung cancer patients. Cancer 2007;110:1532–1541.

44. Raz DJ, Zell JA, Ignatius Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132(1):193-199.

45. Goldstraw P, Crowley J, Chansky K, et al. on behalf of the International Association for the Study of Lung Cancer International Staging Committee and Participating Institutions. 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(8):706-714.

46. 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.

47. 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.

48. 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.

49. 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.

50. 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.

51. 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.

52. 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.

53. Zheng Z, Chen T, Li X, et al. The DNA synthesis and repair genes RRM1 and ERCC1 in lung cancer. N Engl J Med 2007;356:800-808.

54. 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 versus gemcitabine alone [abstract]. J Clin Oncol 2008;26:8033.

55. 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.

56. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.

57. Lord RVN, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8:2286-2291.

58. Rodenhuis S, van de Wetering ML, Mooi WJ, et al. Mutational activation of the K-ras oncogene: a possible pathogenetic factor in adenocarcinoma of the lung. N Engl J Med 1987;317:929-935.

59. Slebos RJ, Hruban RH, Dalsio 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.

60. 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.

61. Brissenden JE, Caras I, Thelander L, et al. The structural gene for the M1 subunit of ribonucleotide reductase maps to chromosome 11, band 15, in human and to chromosome 7 in mouse. Exp Cell Res 1988;174:302-308.

62. Pitterle DM, Kim YC, Jolicoeur EMC, et al. Lung cancer and the human gene for ribonucleotide reductase subunit M1 (RRM1). Mamm Genome 1999;10:916-922.

63. Rosell R, Danenberg KD, Alberola V, et al. Ribonucleotide reductase messenger RNA expression and survival in gemcitabine/cisplatin-treated advanced non-small cell lung cancer patients. Clin Cancer Res 2004;10:1318-1325.

64. 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 Feb;135(2):247-54. Epub 2007 Dec 21.

65. 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 Sep;132(3 Suppl):234S-242S.

66. 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(3):615-622; discussion 622-623.

67. 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(4):924-928.

68. Martini N, Flehinger BJ. The role of surgery in N2 lung cancer. Surg Clin North Am 1987;67(5):1037-1049.

69. Lardinois D, Suter H, Hakki H, et al. Morbidity, survival, and site of recurrence after mediastinal lymph-node dissection versus systematic sampling after complete resection for non-small cell lung cancer. Ann Thorac Surg 2005;80(1):268-274; discussion 274-225.

70. 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(3):1013-1019; discussion 1019-1020.

71. 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;25:7555.

72. Swanson SJ BH. Video-assisted thoracic surgery (VATS) resection for lung cancer. Surg Clin North Am 2002;82(3):541-549.

73. Mahtabifard A, Fuller CB, McKenna RJ Jr. Video-assisted thoracic surgery sleeve lobectomy: a case series. Ann Thorac Surg 2008;85(2):S729-732.

74. Shaw JP, Dembitzer FR, Wisnivesky JP, et al. Video-assisted thoracoscopic lobectomy: state of the art and future directions. Ann Thorac Surg 2008;85(2):S705-709.

75. 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(6):261-292.

76. Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. JSLS 2007;11(3):368-374.

77. 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(6):1965-1970.

78. 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(4):1107-1112; discussion 1112-1113.

79. Scott J, Swanson JH, D'Amico A, et al. Results of CALGB 39802: feasibility of video-assisted thoracic surgery (VATS) lobectomy for early stage lung cancer. J Clin Oncol (Meeting Abstracts) 2002;21:1158.

80. 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(5):1742-1746.

81. McKenna RJ Jr. New approaches to the minimally invasive treatment of lung cancer. Cancer J 2005;11(1):73-76.

82. Demmy TL, Nwogu C. Is video-assisted thoracic surgery lobectomy better? Quality of life considerations. Ann Thorac Surg 2008;85(2):S719-728.

83. 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(1):231-235; discussion 235-236.

84. 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(6):1094-1099.

85. Roviaro G, Varoli F, Vergani C, et al. Long-term survival after videothoracoscopic lobectomy for stage I lung cancer. Chest 2004;126(3):725-732.

86. Solaini L, Prusciano F, Bagioni P, et al. 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(1):57-62.

87. Demmy TL, Plante AJ, Nwogu CE, et al. Discharge independence with minimally invasive lobectomy. Am J Surg 2004;188(6):698-702.

88. Demmy TL. VATS lobectomy for frail or complex patients. Chest Meeting Abstracts 2003;124(4):234S.

89. 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(3):642-647.

90. 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(4):1245-1249; discussion 1250.

91. 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(2):323-329.

92. 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(4):1075-10 86. Epub 2006 May 2.

93. 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(5):1399-1407. Epub 2006 Sep 25.

94. 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(3):650-659.

95. 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(1):208-215. Epub 2005 Feb 9.

96. 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(3):239-244.

97. Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007;25(35):5557-5561. Epub 2007 Nov 5.

98. Tucker SL, Liu HH, Wang S, et al. Dose-volume modeling of the risk of postoperative pulmonary complications among esophageal cancer patients treated with concurrent chemoradiotherapy followed by surgery. Int J Radiat Oncol Biol Phys 2006;66(3):754-761. Epub 2006 Sep 11.

99. 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(5):1399-1407. Epub 2006 Sep 25.

100. Yom SS, Liao Z, Liu HH, et al. Initial evaluation of treatment-related pneumonitis in advanced-stage non-small-cell lung cancer patients treated with concurrent chemotherapy and intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2007;68(1):94-102. Epub 2007 Feb 22.

101. 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(3):313-318.

102. Cerfolio RJ, Bryant AS, Spencer SA, Bartolucci AA. Pulmonary resection after high-dose and low-dose chest irradiation. Ann Thorac Surg 2005;80(4):1224-1230; discussion 1230.

103. 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(4):1200-1205; discussion 1206.

104. 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(6):1250-1257.

105. 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(8):1880-1892.

106. Albain KS, Swann RS, Rusch VW, 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). J Clin Oncol (Meeting Abstracts) 2005;23(16S):7014.

107. 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(25):5883-5891. Epub 2005 Aug 8.

108. 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(5):1213-1223.

109. Curran WJ, Scott CB, Langer CJ, et al. Long-term benefit is observed in a phase III comparison of sequential vs concurrent chemo-radiation for patients with unresected stage III NSCLC: RTOG 9410. J Clin Oncol (Meeting Abstracts) 2003;22:621 (abstr 2499).

110. 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(4):1075-1086. Epub 2006 May 2.

111. Tsujino K, Hirota S, Endo M, et al. Predictive value of dose-volume histogram parameters for predicting radiation pneumonitis after concurrent chemoradiation for lung cancer. Int J Radiat Oncol Biol Phys 2003;55(1):110-115.

112. Chen M, Hayman JA, Ten Haken RK, et al. Long-term results of high-dose conformal radiotherapy for patients with medically inoperable T1-3N0 non-small-cell lung cancer: is low incidence of regional failure due to incidental nodal irradiation? Int J Radiat Oncol Biol Phys 2006;64(1):120-126. Epub 2005 Sep 29.

113. Onishi H, Araki T, Shirato H, et al. Stereotactic hypofractionated high-dose irradiation for stage I nonsmall cell lung carcinoma: clinical outcomes in 245 subjects in a Japanese multiinstitutional study. Cancer 2004;101(7):1623-1631.

114. 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(7 Suppl 3):S94-100.

115. Baisden JM, Romney DA, Reish AG, et al. Dose as a function of lung volume and planned treatment volume in helical tomotherapy intensity-modulated radiation therapy-based stereotactic body radiation therapy for small lung tumors. Int J Radiat Oncol Biol Phys 2007;68(4):1229-1237. Epub 2007 May 21.

116. Timmerman RD, Paulus R, Galvin J, et al. Toxicity Analysis of RTOG 0236 Using Stereotactic Body Radiation Therapy to Treat Medically Inoperable Early Stage Lung Cancer Patients. Volume 69: S86. Int J Radiat Oncol Biol Phys 2007;69:S86.

117. 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(30):4833-4839.

118. Lagerwaard FJ, Haasbeek CJ, 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(3):685-692. Epub 2007 Dec 31.

119. Decker RH, Tanque LT, Colasanto JM, et al. Evaluation and definitive management of medically inoperable early stage non-small-cell lung cancer. Oncology 2006;20:899-905.

120. 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(7):621-628.

121. Wisnivesky JP, Bonomi M, Henschke C, et al. Radiation therapy for the treatment of unresected stage I-II non-small cell lung cancer. Chest 2005;128(3):1461-1467.

122. 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(4):351-360.

123. 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(25):2589-2597.

124. 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(9):719-727.

125. 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.

126. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993;342(8862):19-21.

127. Anonymous. Chemotherapy in non-small cell lung cancer: A meta-analysis using updated data on individual patients from 52 randomized trials. Non-Small Cell Lung Cancer Collaborative Group. Br Med J 1995;311:899-909.

128. Le Chevalier T, Dunant A, Arriagada R, et al; IALT Collaborative Group. Long-term results of the International Adjuvant Lung Cancer

Trial (IALT) evaluating adjuvant cisplatin-based chemotherapy in resected non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2008;26:7507.

129. Pignon JP, Tribodet H, Scagliotti GV, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26(21):3552-3559. Epub 2008 May 27.

130. 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. J Clin Oncol (Meeting Abstracts) 2004;7019.

131. Strauss GM, Herndon JE II, Maddaus MA, et al, for the CALGB, Radiation Therapy Oncology Group. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633. J Clin Oncol (Meeting Abstracts) 2006;24:7007.

132. 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(2):317-323. Epub 2006 Nov 1.

133. 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(14):940-945.

134. 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(6):417-423.

135. 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(8):524-530, comment 563-565.

136. Dillman RO, Seagren SL, Herndon J, et al. 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.

137. 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(17):1210-1215.

138. 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.

139. Vokes EE, Herndon JE 2nd, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. J Clin Oncol 2002;20(20):4191-4198.

140. 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(10):2004-2010.

141. 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(2):116-121.

142. 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;25:7512.

143. 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;26:7519.

144. 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(27):4397-4404.

145. 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(4):360-364.

146. 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(16):3016-3024. Epub 2003 Jul 1.

147. 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(21):3909-3917.

148. 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(1):87-98.

149. 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(13):3210-3218.

150. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346(2):92-98.

151. 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(3):542-553.

152. 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(7):1111-1119. Epub 2006 Apr 7.

153. 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(4):602-610. Epub 2005 Mar 1.

154. 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.

155. 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(8):1263-1268. Epub 2006 Jun 1.

156. Sandler AB, Johnson DH, Herbst RS. Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer. Clin Cancer Res 2004;10(12):4258S-4262.

157. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. J Clin Oncol 2005;23(14):3235-3242.

158. 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.

159. 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(1):90-98.

160. Pirker R, Szczesna A, von Pawel J, et al. FLEX: A randomized, multicenter, phase III study of cetuximab in combination with cisplatin/vinorelbine (CV) versus CV alone in the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2008;26:3.

161. Patterson GA, Ginsberg RJ, Poon Y, 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(5):679-684.

162. 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(6):1900-1905.

163. 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(8):696-701.

164. 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(4):822-829; discussion 822-829. Epub 2006 Mar 2

165. Dillemans B, Deneffe G, Verschakelen J, et al. 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(1):37-42.

166. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. Thorax 1995;50(12):1267-1269.

167. 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(2):319-323.

168. Seely JM, Mayo JR, Miller RR, et al. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. Radiology 1993;186(1):129-132.

169. 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(5):337-341.

170. Chin R, 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.

171. Kerstine KH, Trapp JF, Croft DR, et al: 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.

172. 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(3):1022-1028.

173. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with re-mediastinoscopy 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(21):3333-3339.

174. 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(6):1229-1235. Erratum in: J Thorac Cardiovasc Surg 2006;132(3):565-567.

175. 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(4):254-261.

176. Manente P, Vicario G, Piazza F, et al. Does PET/CT modify the therapeutic approach in medical oncology [abstract]? J Clin Oncol 2008;26:17525.

177. Maziak D, Darling GE, Inculet RI, et al. A randomized controlled trial (RCT) of 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) versus conventional imaging (CI) in staging potentially resectable non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2008;26:7502.

178. 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(9):833-839.

179. 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(3):710-718.

180. Mayr NA, Hussey DH, Yuh WT. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. AJNR Am J Neuroradiol 1995;16(1):215-217.

181. Komaki R, Mountain CF, Holbert JM, et al. Superior sulcus tumors: treatment selection and results for 85 patients without metastasis (M0) at presentation. Int J Radiat Oncol Biol Phys 1990;19(1):31-36.

182. Rusch VW, Kraut MJ, Crowley J, et al. 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). J Clin Oncol (Meeting Abstracts) 2003;22:634.

183. 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(1):90-92.

184. 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(3):472-483.

185. 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(6):1250-1257.

186. van Meerbeeck JP, Kramer GW, Van Schil PE, et al; European Organisation for Research and Treatment of Cancer-Lung Cancer Group. 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(6):442-450.

187. Naruke T, Goya T, Tsuchiya R, et al. Prognosis and survival in resected lung carcinoma based on the new international staging system. J Thorac Cardiovasc Surg 1988;96(3):440-447.

188. 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 Cardiovascular Surg 1982;83(1):1-11.

189. Rice TW. Thoracoscopy in the staging of thoracic malignancies. In kaiser LR, Daniel TM eds. Thoracoscopic Surgery. Philadelphia: Lippincott Williams & Wilkins. 1993:153-162.

190. Decker DA, Dines DE, Payne WS, et al. The significance of a cytologically negative pleural effusion in bronchogenic carcinoma. Chest 1978;74(6):640-642.

191. Burt M, Wronski M, Arbit E, et al. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. J Thorac Cardiovasc Surg. 1992;103(3):399-410; discussion 410-411.

192. 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(8):494-500.

193. 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(1):34-40.

194. Raviv G, Klein E, Yellin A, et al. Surgical treatment of solitary adrenal metastases from lung carcinoma. J Surg Oncol 1990;43(2):123-124.

195. Reyes L, Parvez Z, Nemoto T, et al. Adrenalectomy for adrenal metastasis from lung carcinoma. J Surg Oncol 1990;44:32-34.

196. Pisters KM, Evans WK, Azzoli CG, et al; Cancer Care Ontario; American Society of Clinical Oncology. 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(34):5506-5518. Epub 2007 Oct 22.

197. 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(17):1217-1222.

198. 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(15):3480-3487.

199. 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(4):287-292.

200. 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(4):580-586.

201. Bonomi P, Faber L. Neoadjuvant chemoradiation therapy in non-small cell lung cancer: The Rush University experience. Lung Cancer 1993;9:383-390.

202. 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(1):97-104, discussion 104-106.

203. 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(3):153-158.

204. 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(9):673-680.

205. Pisters KEV, Bunn P, Crowley J, 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. J Clin Oncol (Meeting Abstracts) 2005;Abstract No: LBA7012.

206. Postoperative radiotherapy in non-small- cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomized controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352(9124):257-263.

207. 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(19):2998-3006. Epub 2006 Jun 12.

208. Gebl 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(6):1382-1385.

209. 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(11):2184-2191.

210. 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(21):3543-3551. Epub 2008 May 27.

211. 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(5):1335-1343.

212. Ciuleanu TE, Brodowicz T, Belani CP, et al. Maintenance pemetrexed plus best supportive care (BSC) versus placebo plus BSC: A phase III study [abstract]. J Clin Oncol 2008;26:8011.

213. 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. J Clin Oncol 2000;18(12):2354-2362.

214. 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(10):2095-2103.

215. 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(9):1589-1597.

216. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):123-132.

217. 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(18):2800-2807. Epub 2006 May 8.