National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Non-Small Cell Lung Cancer

Version 2.2011

NCCN.org

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National Comprehensive Cancer Network®

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Non-Small Cell Lung Cancer

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus

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NCCN Guidelines™ Version 2.2011 Updates Non-Small Cell Lung Cancer

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Summary of the changes in the 2.2011 version of the Non-Small Cell Lung Cancer guidelines from the 1.2011 version include:

NSCL-12
- Denosumab was added as a treatment option for patients with bone metastases.

Summary of the changes in the 1.2011 version of the Non-Small Cell Lung Cancer guidelines from the 2.2010 version include:

PREV-1
- Bullet 1 - Percentage of cases changed from 90% to 85-90%.
- Bullet 2 added - Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life and reduced survival.

NSCL-1
- Initial evaluation - "Smoking cessation counseling" changed to "Smoking cessation *advice*, counseling, *and pharmacotherapy*." (also applies to the follow-up on NSCL-11)
- Footnote "c" is new to the page: "T3, N0 related to size or satellite nodules." (also applies to NSCL-2)
- Footnote "e" is new to the page describing cytopathologic examinations of pleural and pericardial fluid.

NSCL-2
- Brain MRI added as a workup recommendation for Stage IB tumors with a category 2B designation.

NSCL-3:
- Lymph node sampling clarified as "systematic."
- Stage IA, margins positive - chemoradiation removed as an option for adjuvant treatment.
- Stage IB, IIA, margins positive - reresection listed as "preferred." Chemoradiation + chemotherapy changed to RT + chemotherapy.
- Stage IIA, IIB, margins negative - adverse risk factors removed as a determinant for adjuvant therapy.
  Chemoradiation followed by chemotherapy removed as an option for adjuvant treatment.
  "± RT" added with a category 3 designation.
- Footnote "i" - "lung neuroendocrine tumors" added to the high risk criteria and "minimal margins" removed.
- Footnote "l" is new to the page - "Increasing size is an important variable when evaluating the need for adjuvant chemotherapy."

NSCL-4
- EBUS added as a workup recommendation.

NSCL-5
- Superior sulcus tumor (T4 extension, N0-1), unresectable - chemotherapy added as adjuvant therapy after Definitive chemoradiation.
- Footnote "r" is new to the page: "If full-dose chemotherapy not given concurrently with RT as initial treatment." (also applies to NSCL-8, 9, 10)
- The footnote "It is sometimes difficult to distinguish between T3 and T4 superior sulcus tumors" was deleted.

NSCL-6 and NSCL-8
- Separate pulmonary nodule, same lobe or ipsilateral lung - the T and N status added for clarification.
- Separate pulmonary nodules, contralateral lung changed to Stage IV (N0, M1a): Contralateral lung (solitary nodule).
- Reference to pleural effusions deleted from this page, as this is addressed on NSCL-10.

NSCL-7
- T1-3, N0-1: Thoracotomy changed to "Surgery." Lymph node sampling clarified as "systematic."

NSCL-8
- Stage IIIA (T4, N0-1), unresectable - chemotherapy listing after chemoradiation changed from a category 3 to a category 2A designation.

NSCL-9
- The term "consolidation" deleted and the category designation changed from 2B to category 2A.

NSCL-10
- T and N status added for clarification.
- The term "consolidation" deleted and the category designation changed from 2B to category 2A.

NSCL-11
- Brain presentation - "Resect brain lesion ± WBRT (category 1) ± SRS (category 2B)" changed to "Surgical resection, followed by WBRT (category 1) or stereotactic radiosurgery (SRS)".
- Adrenal presentation - Category designation for local therapy changed from category 3 to category 2B.

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Summary of the changes in the 1.2011 version of the Non-Small Cell Lung Cancer guidelines from the 2.2010 version include:

NSCL-12
- Locoregional recurrence, SVC - Concurrent chemoradiation added as a treatment option, if not previously given.

NSCL-13
- The evaluation process for systemic therapy for patients with recurrent or metastatic disease has changed to first address histologic subtype and than recommend EGFR testing based on histologic subtype.
- EGFR testing is a category 1 recommendation for the following histologies: adenocarcinoma, large cell, and NSCLC NOS.
- EGFR testing is not recommended for squamous cell carcinoma.
- This page now addresses first-line systemic therapy for adenocarcinoma, large cell, NSCLC NOS, and squamous cell carcinoma with a positive EGFR mutation.
- Footnote "w" is new to the page, "The observed incidence is 2.7% with a confidence that the true incidence of mutations is less than 3.6% in patients with squamous cell carcinoma. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11."
- Footnote "y" is new to the page, clarifying that the erlotinib is for performance status 0-4.
- Footnote "z" is new to the page stating that gefitinib could be used in place of erlotinib in areas of the world where it is available. (also applies to NSCL-16)

NSCL-14
- This page now addresses first-line systemic therapy for adenocarcinoma, large cell, and NSCLC NOS with a negative or unknown EGFR mutation.
- Tumor response evaluation after the first cycle of chemotherapy was deleted.
- The category designation for pemetrexed as an option for switch maintenance was changed from a 2B to a 2A.

NSCL-15
- This page now addresses first-line systemic therapy for squamous cell carcinoma.
- Tumor response evaluation after the first cycle of chemotherapy was deleted.

NSCL-16
- Performance status 0-2 - bevacizumab was added as a treatment option to the combination of a platinum doublet for patients who received erlotinib as first-line and the histology of adenocarcinoma.

NSCL-A 2 of 3

Molecular Diagnostics:
- Sub-bullets 5 through 7 under EGFR and KRAS are new to the page.
- New section added for EML4-ALK.

NSCL-B 1 of 4
- Bullet 2: A new sentence was added: "In cases where stereotactic RT is considered for high-risk patients, a multidisciplinary evaluation including a radiation oncologist is recommended."

NSCL-B 2 of 4 through NSCL-B 4 of 4
- New pages added to discuss the controversial issue of surgery in the management of patients with Stage IIIA (N2) disease.

NSCL-C
- Revisions made throughout the Principles of Radiation Therapy section.

NSCL-C 5 of 7
- Table 2 - title changed from "Recommended Doses for Conventionally Fractionated Radiation Therapy" to "Commonly Used Doses for Conventionally Fractionated Radiation Therapy."

NSCL-C 6 of 7
- Table 4 - title changed from "SBRT Regimens and Indications for Lung Tumors" to "Commonly Used SBRT Regimens."

NSCL-E
- The consolidation regimen of docetaxel was removed as an option.
- Footnote "*" changed from "Randomized data support..." to "There are data to support..."

LUNG CANCER PREVENTION AND SCREENING

- **Lung cancer is a unique disease in that the etiologic agent is an industry. Approximately 85-90% of cases are caused by voluntary or involuntary (second hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products and other tobacco control measures.**
- **Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life and reduced survival.**
- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from second-hand smoke exposure associated with living with a smoker (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/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.**
- **Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.**
- **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.

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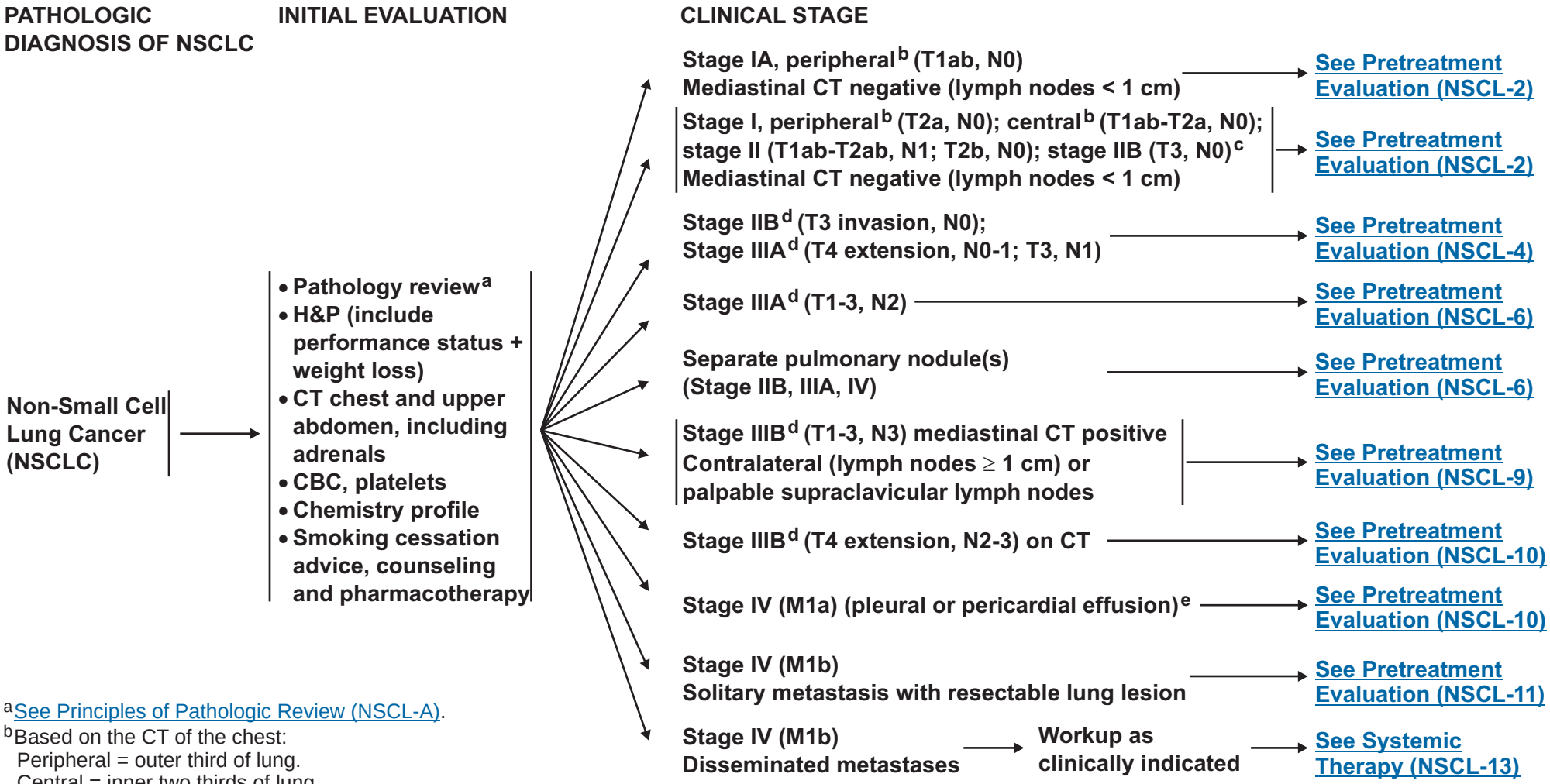

[a] See Principles of Pathologic Review (NSCL-A).

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

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

[d] 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.

[e] 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.

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CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION[g]**

Stage IA (peripheral T1ab, N0) →
- PFTs (if not previously done)
- Bronchoscopy (intraoperative preferred)
- Mediastinoscopy (category 2B)
- EBUS if appropriate (category 2B)
- PET/CT scan[f]

Stage IB (peripheral T2a, N0)
Stage I (central T1ab–T2a, N0)
Stage II (T1ab–2ab, N1; T2b, N0)
Stage IIB (T3, N0)[c] →
- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy
- EBUS if appropriate (category 2B)
- PET/CT scan[f]
- Brain MRI (Stage II, Stage IB [category 2B])

Negative mediastinal nodes
- **Operable** → **See Initial Treatment and Adjuvant Treatment (NSCL-3)**
- **Medically inoperable** → **Definitive RT (see NSCL-C)**

Positive mediastinal nodes → **See Stage IIIA (NSCL-7) or Stage IIIB (NSCL-9)**

[c] T3, N0 related to size or satellite nodules.
[f] 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.
[g] See Principles of Surgical Therapy (NSCL-B).

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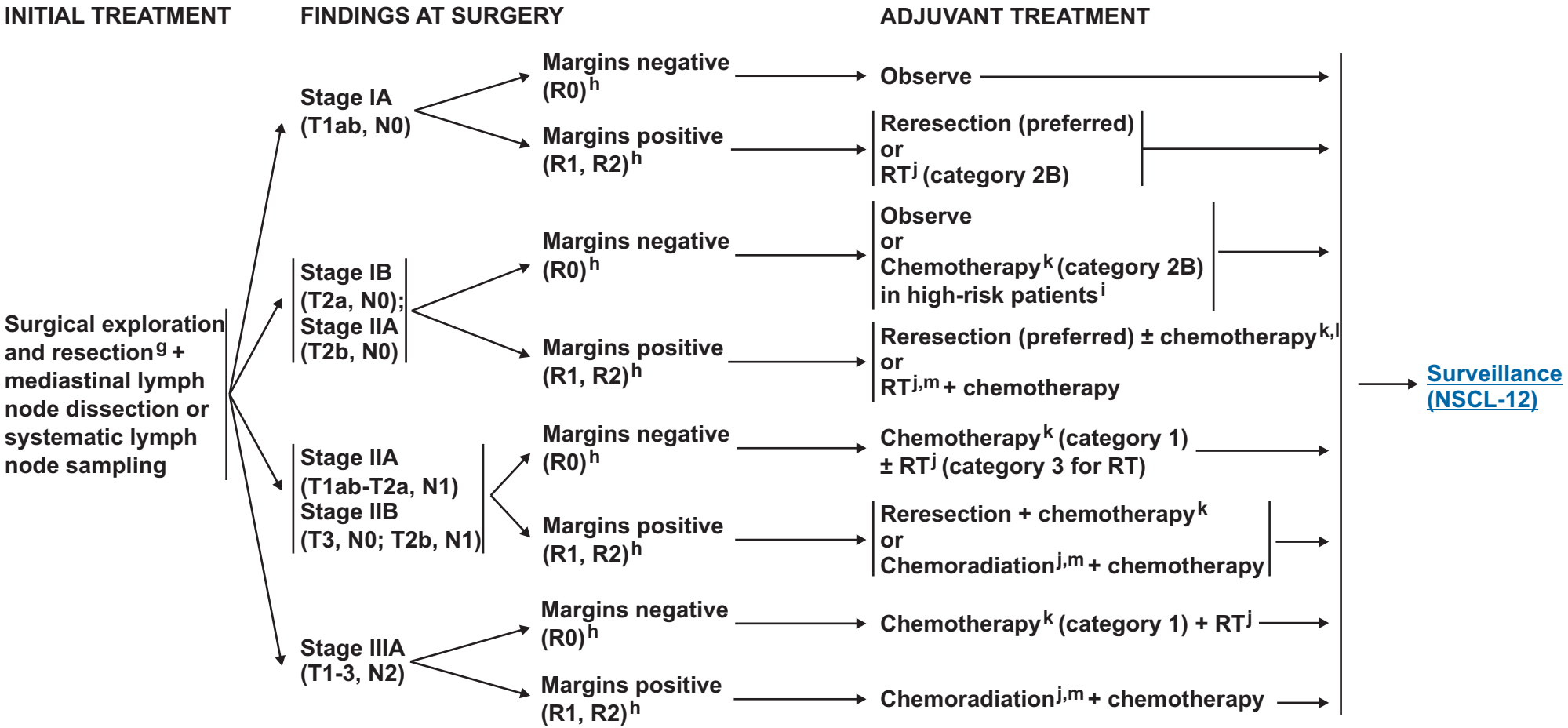

[g] See Principles of Surgical Therapy (NSCL-B).
[h] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[i] High-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors), vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, Nx.
[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).
[l] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.
[m] See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

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CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

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

- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy or EBUS
- Brain MRI
- MRI of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels
- PET/CT scan[f]

CLINICAL EVALUATION

- Superior sulcus tumor → See Treatment (NSCL-5)
- Chest wall → See Treatment (NSCL-5)
- Proximal airway or mediastinum → See Treatment (NSCL-5)
- Metastatic disease → See Treatment for Metastasis solitary site (NSCL-11) or disseminated (NSCL-13)

[f]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.

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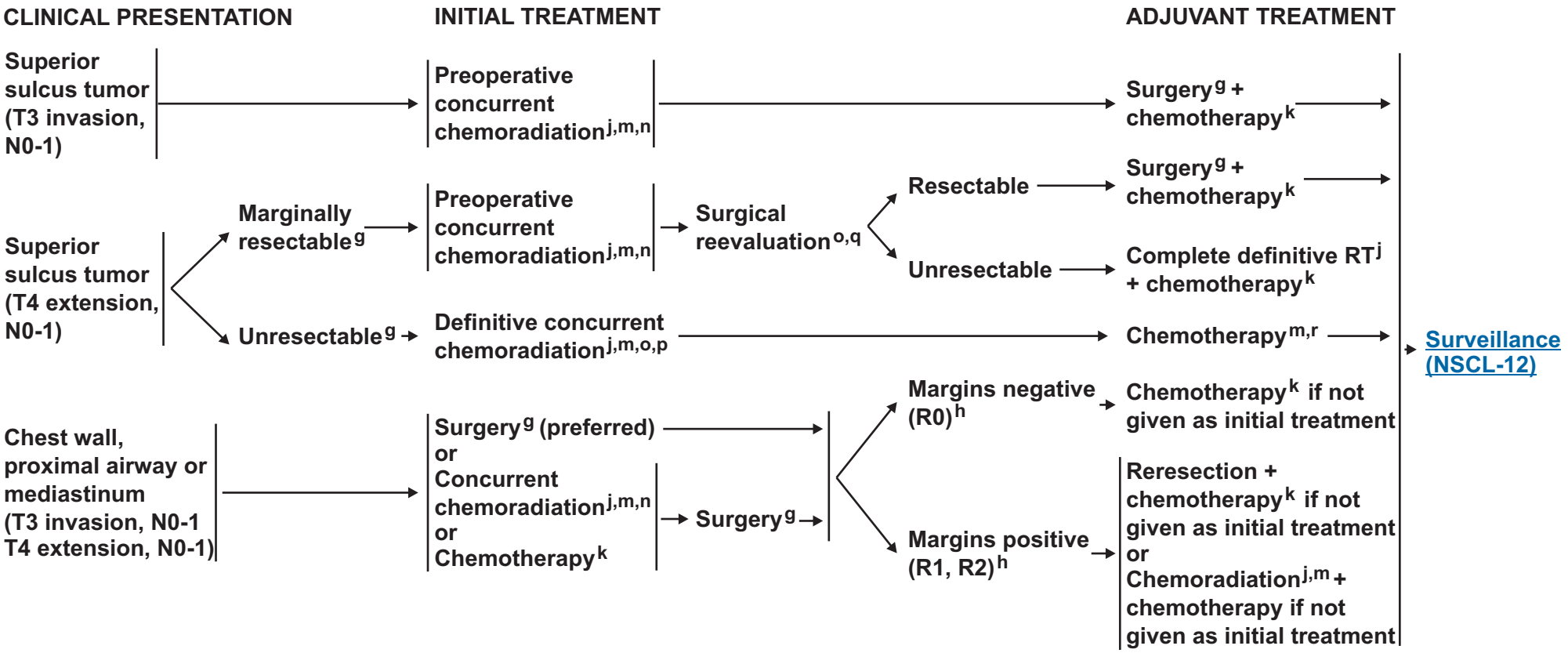

[g] See Principles of Surgical Therapy (NSCL-B).
[h] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).
[m] See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).
[n] 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.
[o] RT should continue to definitive dose without interruption if patient is not a surgical candidate.
[p] In the definitive chemoradiation setting, a total dose of 60-70 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.
[q] 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.
[r] If full-dose chemotherapy not given concurrently with RT as initial treatment.

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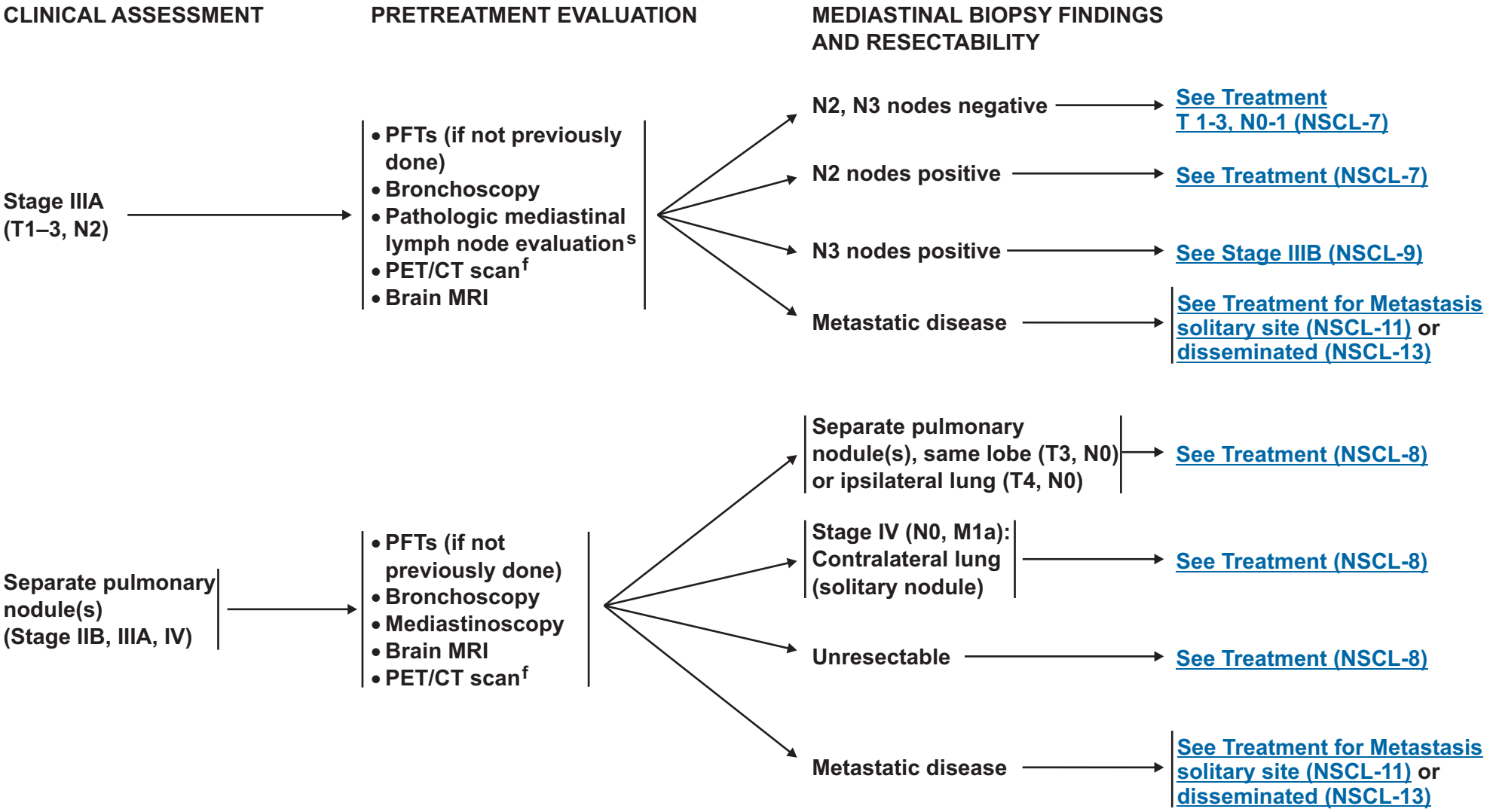

[f]Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[s]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS and CT-guided biopsy.

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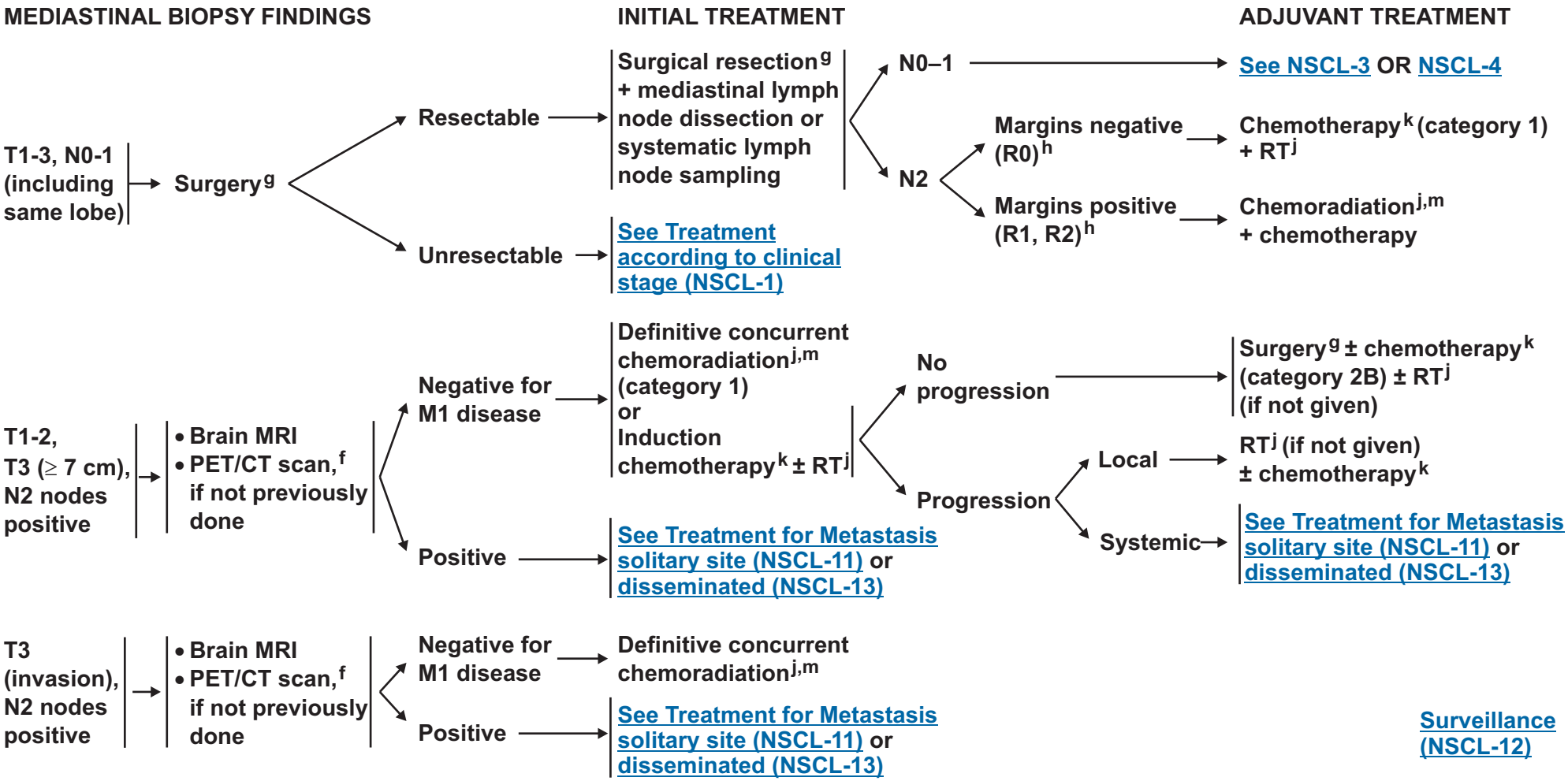

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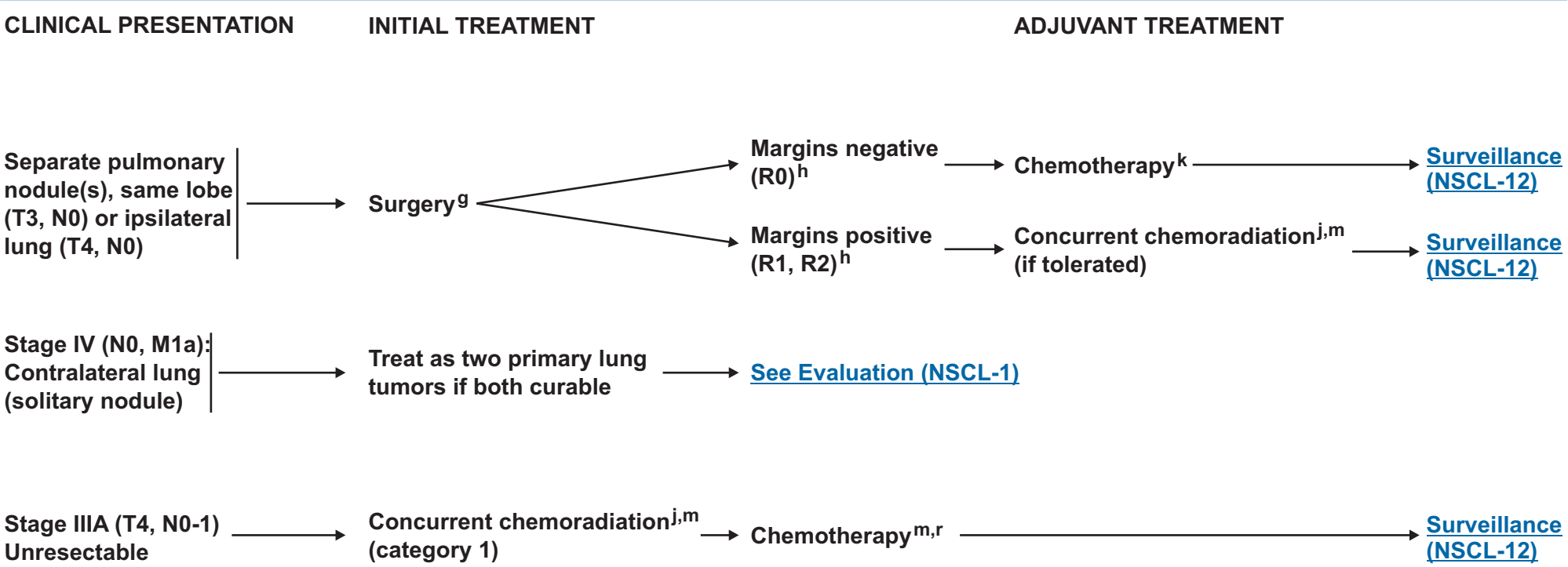

[g] See Principles of Surgical Therapy (NSCL-B).
[h] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).
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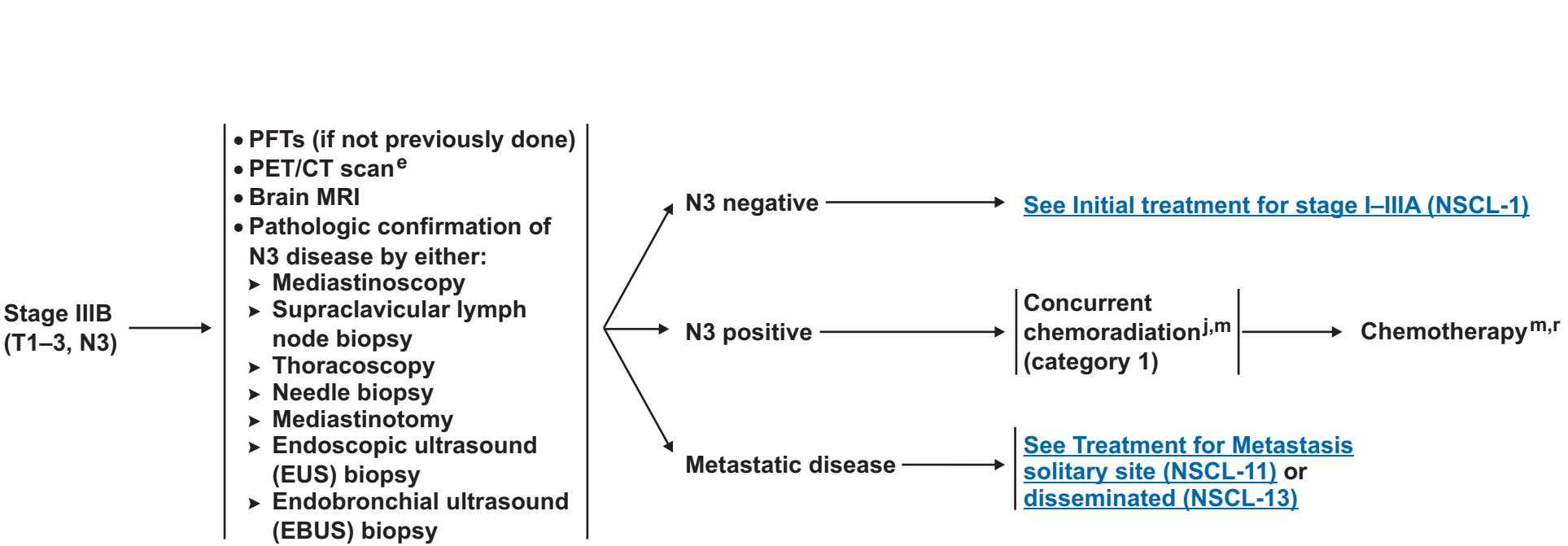

[e] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

[m] See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

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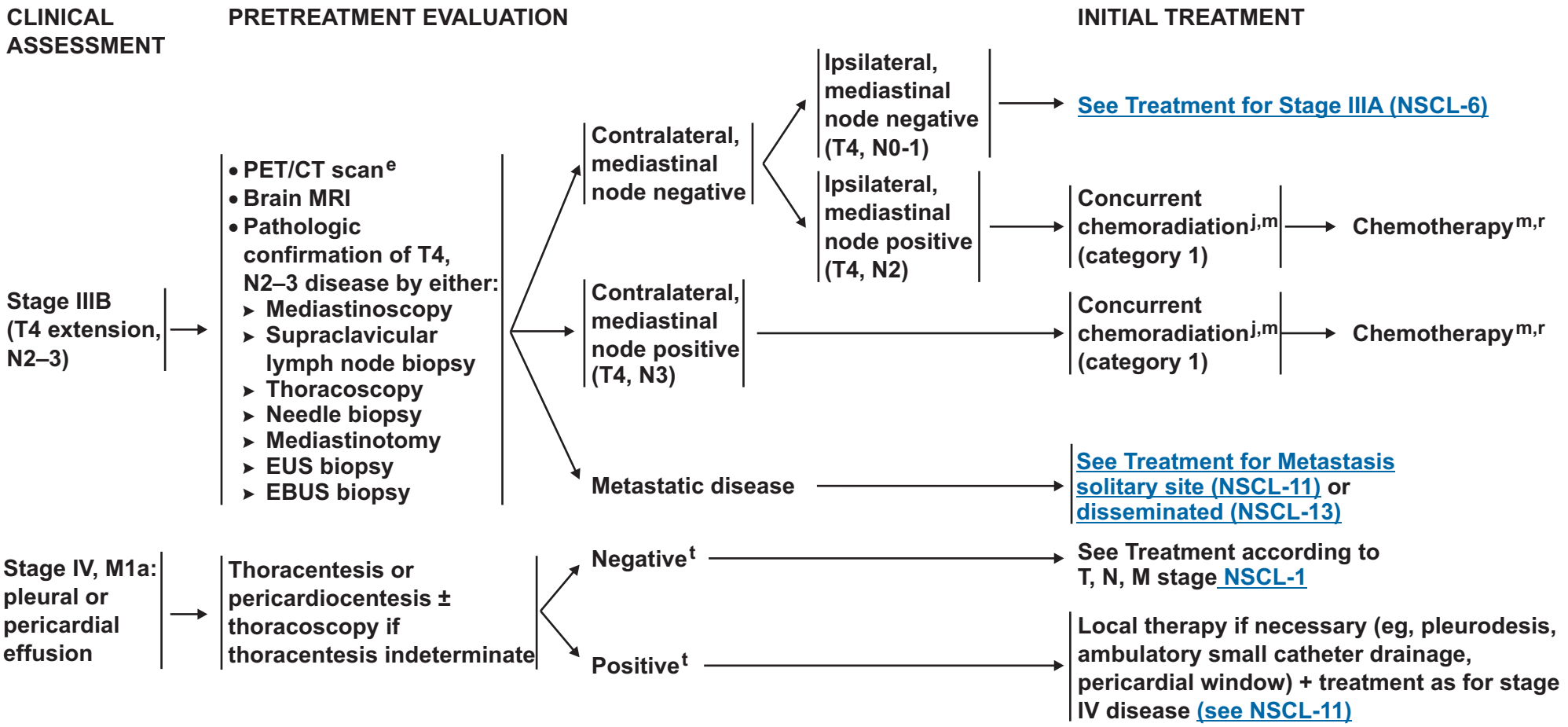

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[j] See Principles of Radiation Therapy (NSCL-C).

[m] See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

[r] If full-dose chemotherapy not given concurrently with RT as initial treatment.

[t] 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.

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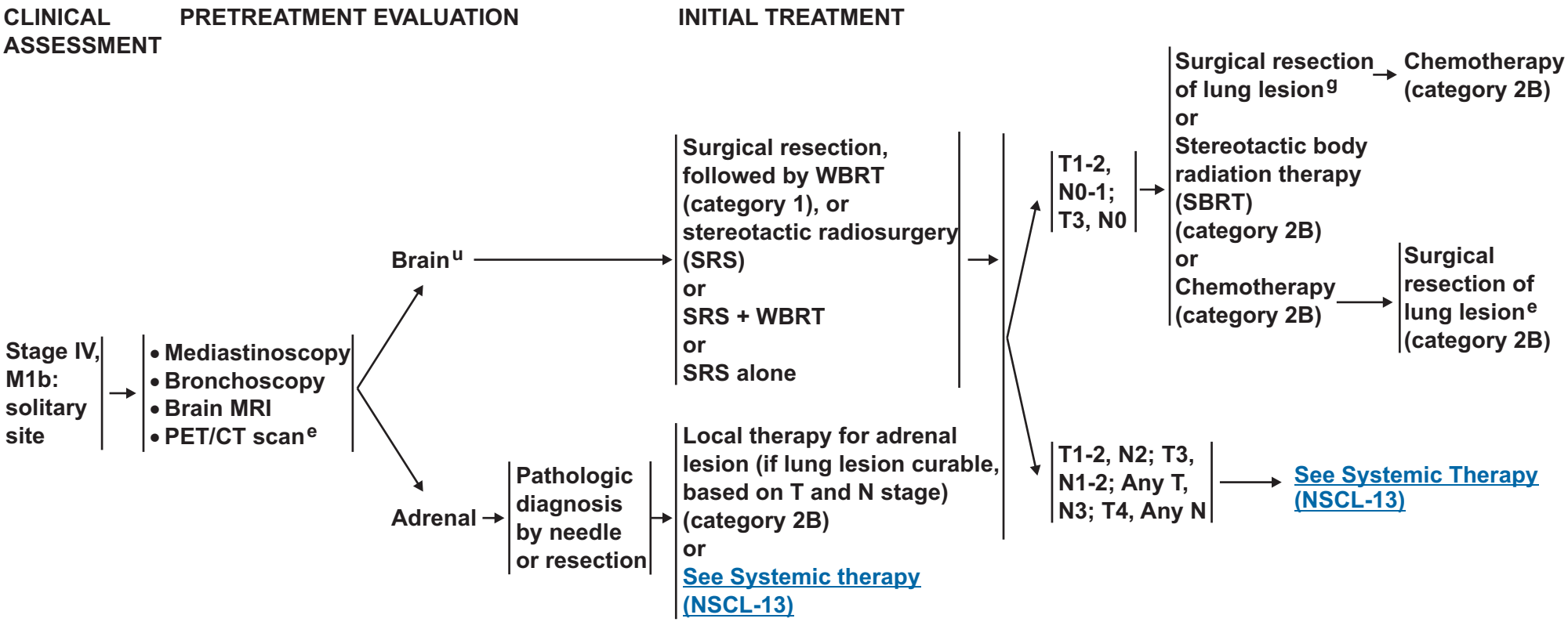

[e] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

[g] See Principles of Surgical Therapy (NSCL-B).

[u] See NCCN CNS Guidelines.

Surveillance (NSCL-12)

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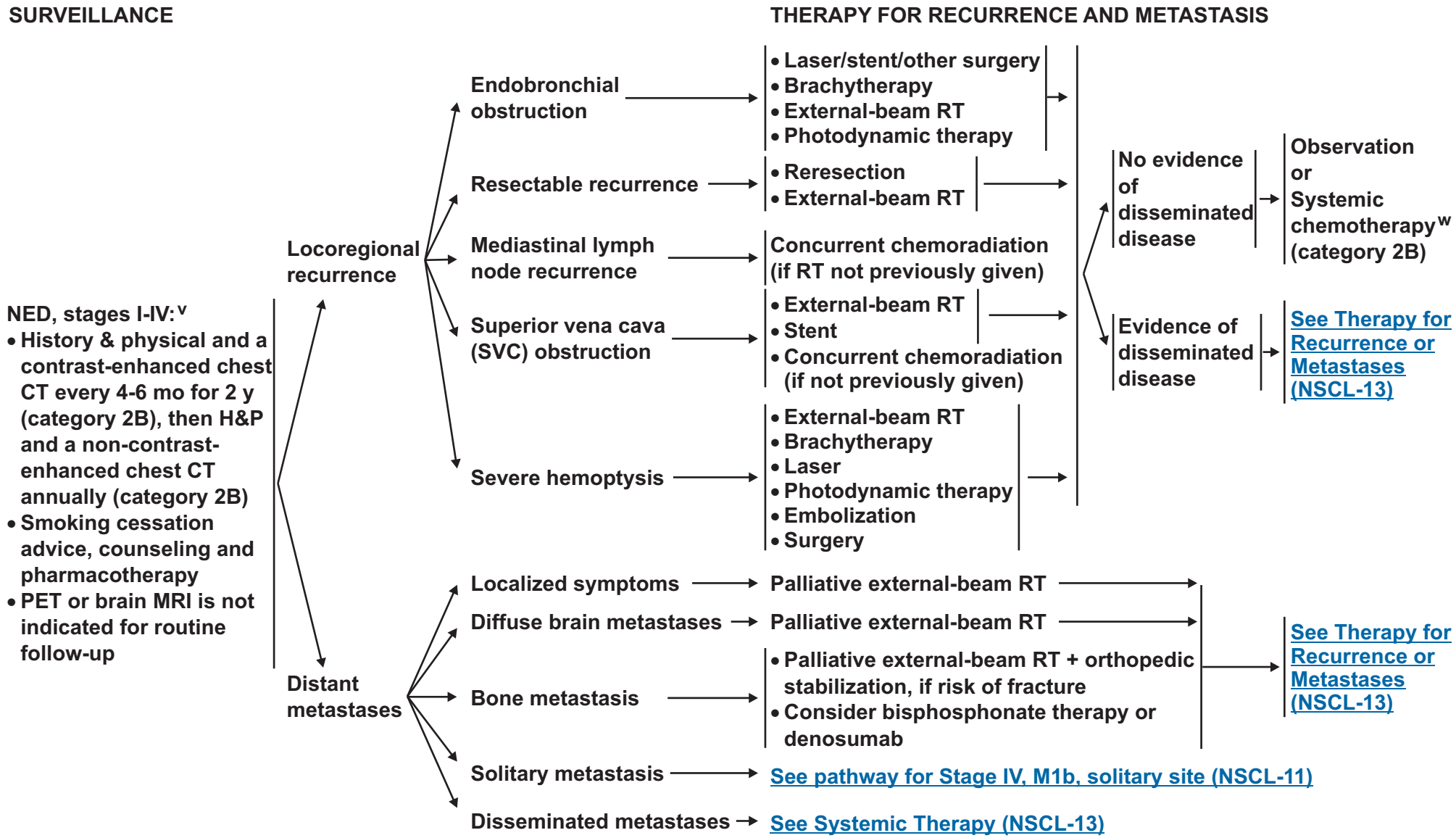

[v] See Cancer Survivorship Care (NSCL-G).
[w] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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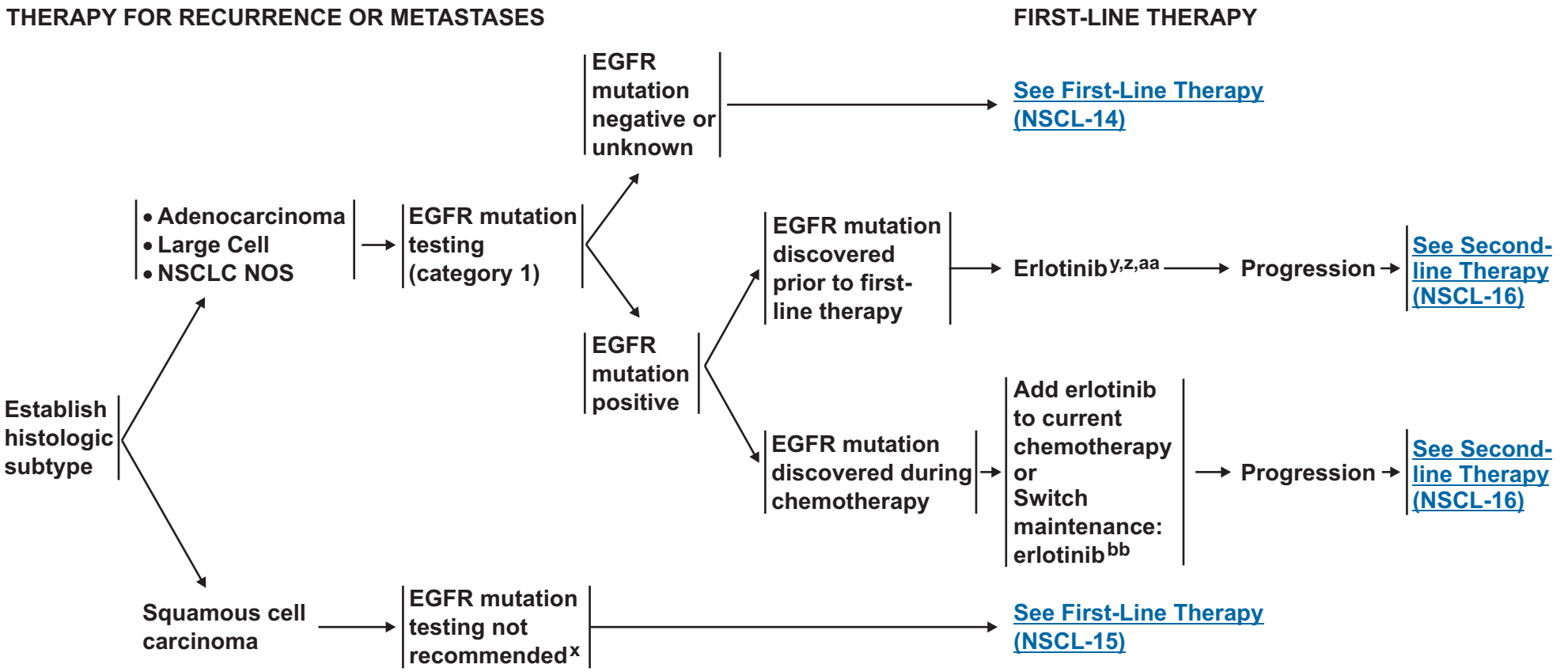


[x] The observed incidence is 2.7% with a confidence that the true incidence of mutations is less than 3.6% in patients with squamous cell carcinoma. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic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

[y] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-1400.

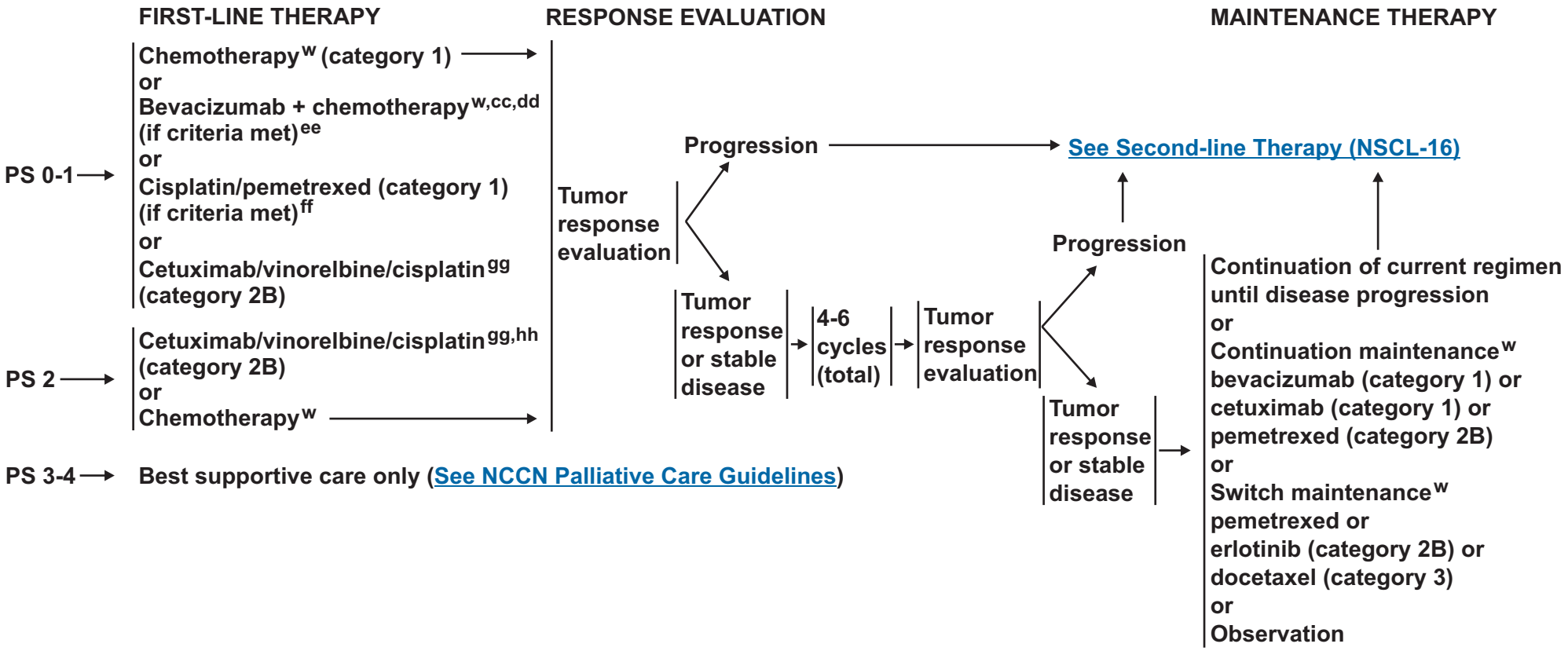
[z] For performance status 0-4.

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

[bb] Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol. 2010;11(6):521-529. Epub 2010 May 20.

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

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION NEGATIVE OR UNKNOWN



[w] See Systematic Therapy for Advanced or Metastatic Disease (NSCL-F).

[cc] Bevacizumab should be given until progression.

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

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

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

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

[hh] Full-dose cisplatin for PS 2 patients should be given selectively.

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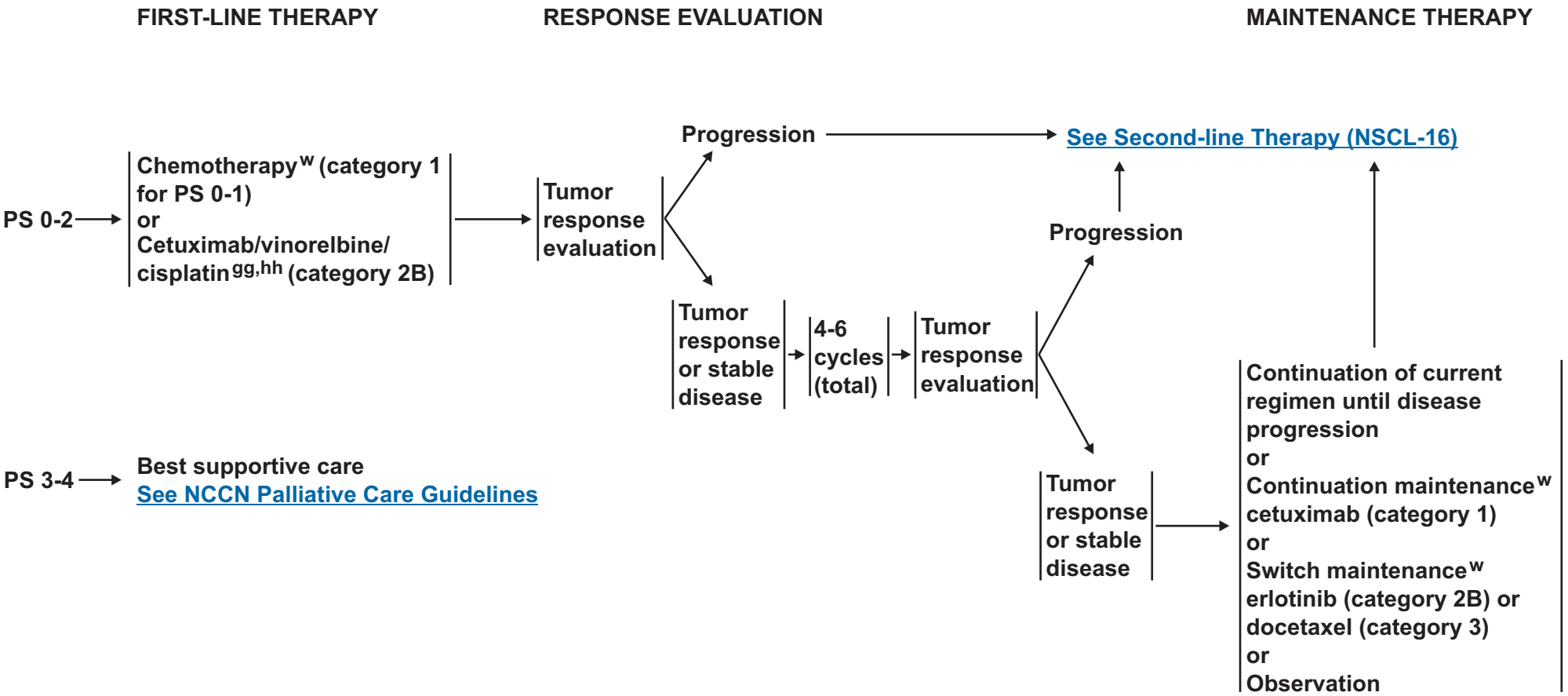
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SQUAMOUS CELL CARCINOMA



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

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

[hh] Full-dose cisplatin for PS 2 patients should be given selectively.

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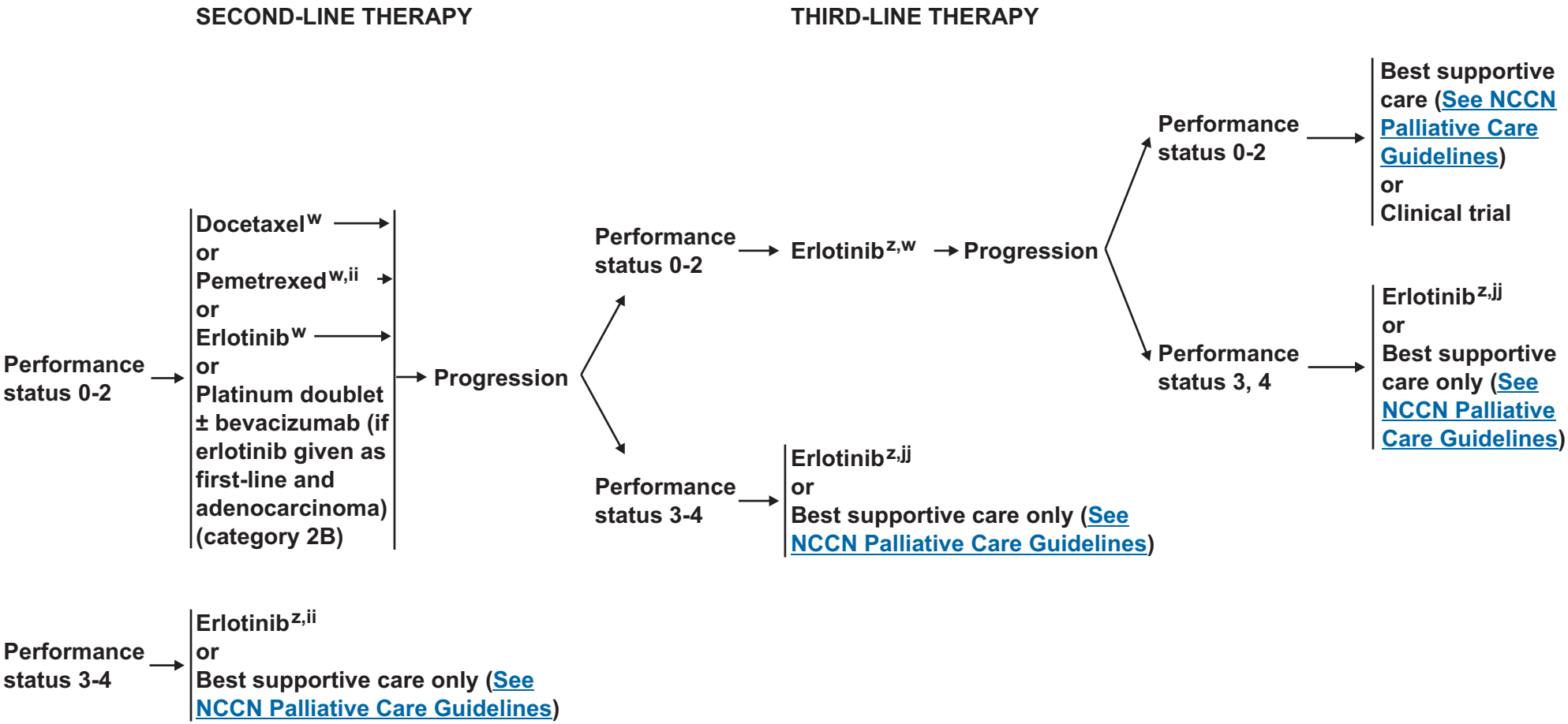

[w] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[z] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ii] Pemetrexed is not recommended for squamous histology.
[jj] Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 3)

Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the lung cancer, determine the extent of invasion, 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)

- 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.[6]

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, MOC31, and TTF-1.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40[7,8] and cytokeratin 5/6.

Continued NSCL-A 2 of 3

Note: All recommendations are category 2A unless otherwise indicated.
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References NSCL-A 3 of 3

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 3)

Molecular Diagnostic Studies in Lung Cancer

- **EGFR and KRAS**
  - EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents critical biological factors for proper patient selection.
  - There is a significant association between EGFR mutations — especially exon 19 deletion, exon 21 mutation (L861Q), and exon 18 (G719X) — and response to TKIs.[9-12]
  - EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.[13]
  - KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy.[14]
  - The prevalence of EGFR mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher EGFR mutation frequency in non-smokers, women, and non-mucinous tumors. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.[15] The most common EGFR mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations more common in non-mucinous lung adenocarcinoma with BAC features and in lung adenocarcinoma with papillary (and or micropapillary) features.
  - Resistance to TKI therapy is associated with KRAS mutation and specific acquired EGFR mutations, such as T790M.
  - Because EGFR gene mutations are the best predictor of a patient's response to EGFR TKI, various DNA mutational assays have been reported in the literature.[16]
- **EML4-ALK**
  - ALK-rearrangements in a subset of anaplastic large cell lymphomas (ALCL) have been recognized for over 15 years.[17] The fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) has recently been identified in a subset of non-small cell lung cancers (NSCLCs). EML4-ALK NSCLC represents a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.[18]
  - EML4-ALK NSCLC occurs most commonly in a unique clinical subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor EGFR mutations.[19,20] However, for the most part, EML4-ALK and EGFR mutations are mutually exclusive.[19,21-23] EML4-ALK translocations tend to occur in younger patients and those with more advanced NSCLC while this relationship has not been reported for EGFR mutant NSCLC.[21,24]
  - There is currently no standard method for detecting EML4-ALK NSCLC. Several methods are currently being evaluated, including polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH) . A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged ALCLs, is applicable for the diagnosis of ALK-rearranged lung adenocarcinomas. The IHC tests used to diagnose ALK-rearranged ALCLs in clinical laboratories worldwide are inadequate for the detection of the majority of ALK-rearranged lung adenocarcinomas.[25,26] This is due to the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs.

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References NSCL-A 3 of 3

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 3) - References

[1]Fossella 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]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.
[7]Chirieac LR, et al. Modern Pathology 2006;19:305A 1422.
[8]Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-80.
[9]Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
[10]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.
[11]Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98.
[12]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.
[13]Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res 2006;12:7232-7241.
[14]Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-62.
[15]Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. J Mol Diagn 2007;9:320-326.
[16]Pao W, Ladanyi M . Epidermal growth factor receptor mutation testing in lung cancer: searching for the ideal method. Clin Cancer Res 2007;13:4954-4955.
[17]Cataldo KA, Jalal SM, Law ME, et al. Detection of t(2;5) in anaplastic large cell lymphoma: comparison of immunohistochemical studies, FISH, and RT-PCR in paraffin-embedded tissue. Am J Surg Pathol 1999;23:1386-1392.
[18]Kwak EL, Camidge DR, Clark J, et al. Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066. Journal of Clinical Oncology 2009;27:15s:abstract 3509.
[19]Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-4253.
[20]Koivunen JP, Kim J, Lee J, et al. Mutations in the LKB1 tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. Br J Cancer 2008;99:245-252.
[21]Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol 2009;22:508-515.
[22]Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008;14:4275-4283.
[23]Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-19897.
[24]Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. Cancer 2009;115:1723-1733.
[25]Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. Clin Cancer Res 2009;15:5216-5223.
[26]Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. Clin Cancer Res 2010;16:1561-1571.

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PRINCIPLES OF SURGICAL THERAPY (1 of 4)

- **Determination of resectability should be performed by Board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
- **Resection, including wedge resection, is a preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, stereotactic radiation). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where stereotactic RT is considered for high-risk patients, a multidisciplinary evaluation including a radiation oncologist is recommended.**
- **Surgical staging and pulmonary resection should be performed by Board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
- **The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.**
- **Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (e.g. multidisciplinary clinic and/or Tumor Board).**
- **Anatomic pulmonary resection is preferred for the majority of patients with non-small cell lung cancer.**
- **Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥ 2 cm or ≥ the size of the nodule. Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk. Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:**
  - **Poor pulmonary reserve or other major co-morbidity that contraindicates lobectomy**
  - **Peripheral nodule[1] ≤ 2 cm with at least one of the following:**
    - **Pure bronchioloalveolar carcinoma (BAC) histology (category 2B)**
    - **Nodule has ≥ 50% ground glass appearance on CT (category 2B)**
    - **Radiologic surveillance confirms a long doubling time (≥ 400 days) (category 2B)**
- **Video-assisted thoracic surgery (VATS) is a reasonable and acceptable approach for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.**
- **Lung-sparing anatomic resection (sleeve lobectomy) preferred over pneumonectomy, if anatomically appropriate and margin-negative resection achieved.**
- **N1 and N2 node resection and mapping (ATS map) (minimum of three N2 stations sampled or complete lymph node dissection).**
- **Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease.**
- **Patients with pathologic stage II or greater should be referred to medical oncology for evaluation.**
- **Consider referral to medical oncologist for stage IB, and consider referral to radiation oncologist for stage IIIA.**

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

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

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF SURGICAL THERAPY (2 of 4)

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

The role of surgery in patients with pathologically documented N2 disease remains controversial. This population is heterogeneous. On one side of the spectrum we have a patient with negative pre-operative evaluation of the mediastinum, found to have involvement of a single station at the time of thoracotomy.[1] On the other side we have patients with multiple pathologically proven malignant lymph node (LNs) greater than 3 cm. Most would consider the first patient a candidate for resection, while the majority would recommend definitive chemoradiotherapy, without surgery for the second. The goal of this text is to review concepts in the therapy of patients with stage IIIA (N2) NSCLC, based on the review of available evidence by the panel members of the NCCN guidelines committee. The panel recognizes that there are two randomized trials that evaluated the role of surgery in this population and that both did not show an overall survival benefit with the use of surgery.[2,3] However, we believe that these trials do not sufficiently evaluate the nuances present with the heterogeneity of N2 disease, and the likely oncologic benefit of surgery in specific clinical situations.

- **The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. (NSCL-1, NSCL-2, and NSCL-6)**
- **Patients with occult positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal LN dissection.**
- **The determination of the role of surgery in a patient with N2 positive LNs should be made prior to the initiation of any therapy, by a multidisciplinary team, including a board-certified thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.[4]**
- **The presence of N2 positive LNs substantially increases the likelihood of positive N3 LNs. Pathological evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS have provided additional techniques for pathologic mediastinal staging that are complementary, but do not replace mediastinoscopy. Even when these modalities are employed it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral LN involvement prior to a final treatment decision.**
- **Patients with a single LN smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,5,6]**
- **Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[6,7]**
- **Radiographic methods have poor positive and negative predictive values in the evaluation of the mediastinum after neoadjuvant therapy.[8] Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (+/- EUS) in the initial pre-treatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.[9]**

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PRINCIPLES OF SURGICAL THERAPY (3 of 4)

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

- **Neoadjuvant chemoradiotherapy is used in 50% of the NCCN institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[9,10] Neoadjuvant chemoradiotherapy is associated with higher rates of pathological complete response and negative mediastinal lymph nodes.[11] However, that is achieved at the expense of higher rates of acute toxicity and increased cost.**
- **When neoadjuvant chemoradiotherapy is used with doses lower than the ones considered standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Breaks of more than 1 week are considered unacceptable. When timely surgical evaluation is not available, the strategy of neoadjuvant chemoradiotherapy should not be used. Another option in individual cases, and with the agreement with the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.[12,13]**
- **Data from a large multi-institutional trial indicates that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality.[2] However, it is not clear if this is also true with neoadjuvant chemotherapy alone. Further, many groups have challenged that cooperative group finding with single institution experiences demonstrating safety of pneumonectomy after induction therapy.[14-17]**

We have submitted a questionnaire to the NCCN institutions regarding their approach to patients with N2 disease. Their responses are reported to give an idea to the readers of the patterns of practice when approaching this difficult clinical problem.

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

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PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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

[1]Cerfolio RJ, Bryant AS. Survival of Patients With Unsuspected N2 (Stage IIIA) Nonsmall-Cell Lung Cancer. Ann Thorac Surg 2008;86:362-367.

[2]Albain K, Swann RS, Rusch et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. Lancet 2009;374:376-86.

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

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

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

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

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

[8]Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non–small cell lung cancer after neoadjuvant chemoradiotherapy: A prospective study. J Thorac Cardiovasc Surg 2006;131:1229-1235.

[9]Thomas M, Rübe C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol. 2008;9(7):607-608.

[10]Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;75(5):1462-1467.

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

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

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

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

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

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

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

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PRINCIPLES OF RADIATION THERAPY (1 of 7)

General Principles

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical oncologists, radiation oncologists, medical oncologists, pulmonologists, pathologists, and diagnostic radiologists.
- Radiation therapy can be offered as an adjunct for operable patients with resectable diseases, as the primary local treatment for patients with medically inoperable or unresectable diseases, and as an important palliative modality for patients with incurable diseases. The terminology and abbreviations for radiation therapy are summarized in Table 1. Commonly Used RT Abbreviations NSCL-C 5 of 7.
- For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy followed by postoperative radiotherapy is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established[1-3]
- For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiotherapy is recommended if the patient is medically fit.[4,5] Radiation therapy should start earlier as local recurrence is the most common failure in this group of patients.[6]
- Conformal radiation therapy with concurrent chemotherapy should be offered to patients with stage II and III NSCLC who are medically inoperable but of reasonable performance status and life expectancy. Modern technology is indicated when there is a need to deliver adequate dose to tumor without compromising normal tissue tolerance.
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (i.e. Grade 3 esophagitis or hematologic toxicities) should be minimized by conformal treatment planning and aggressive supportive care.
- Radiation therapy can be offered to primary or distant sites as palliative care for stage IV patients with extensive metastasis as indicated.

See Dose, Volume and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy (NSCL-C 2 of 7)

See Radiation Simulation, Planning and Delivery (NSCL-C 3 of 7)

See Stereotactic Body Radiation Therapy (NSCL-C 4 of 7)

See Prophylactic Cranial Irradiation (NSCL-C 4 of 7)

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PRINCIPLES OF RADIATION THERAPY (2 of 7)

Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy

- Commonly used dose regimens for definitive and palliative radiation are summarized in Table 2. Commonly Used Doses for Conventionally Fractionated Radiation Therapy NSCL-C 5 of 7. Tissue heterogeneity correction is recommended in radiation treatment planning for all patients. When CT with IV contrast is used for planning, the area with a large amount of contrast may be treated as water density so that the impact of IV contrast is minimized.
- Preoperatively, a dose of 45-50 Gy in 1.8 to 2 Gy fraction size is recommended.[7] Although it has been reported to be safe and achieved favorable survival outcome,[8-10] doses > 50 Gy are not recommended unless with an experienced team.
- Postoperative radiation dose should be based on margin status.[2,4] Lung tolerance to radiation after surgery seems to be remarkably smaller than those with the presence of both lungs. Every effort should be made to minimize the dose of radiation therapy. More conservative consideration is recommended for the dose constraints of normal lungs in the postoperative setting.
- For definitive radiation therapy, the commonly prescribed dose is 60-70 Gy.[11,12] A retrospective study revealed that dose ≥ 74 Gy was significantly associated with better survival in patients treated with radiation alone or sequential chemoradiation.[13] Radiation dose was also reported to be a significant factor for overall survival in stage I-II after radiation alone[14] or stage III disease treated with concurrent chemoradiation.[15] When radiation is given concurrently with chemotherapy, a dose up to 74 Gy may be delivered safely,[16-18] if the doses to normal structures are strictly limited to their tolerance (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7). The role of high dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).
- For treatment volume consideration, PTV should be defined per ICRU-62 guidelines, based on GTV, plus CTV margin for microscopic diseases, ITV margins for target motion, and margins for daily set-up errors. GTV should be confined to visible tumors (include both primary and nodal diseases) on CT and/or PET-CT.
- Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial[19] and ENI should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. Involved field radiation without ENI is a common practice as it has been shown to allow higher dose radiation to tumor with acceptable toxicity and a low risk of isolated nodal relapse.[11,13,20-23]
- In patients who receive postoperative radiotherapy, CTV may consist of the bronchial stump and high-risk draining lymph node stations.[24]
- It is essential to evaluate the DVH of GTV, CTV, and PTV for target coverage and DVHs of critical structures and to limit the doses to the lungs, heart, esophagus, brachial plexus, and spinal cord (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7) to minimize normal tissue toxicity. These limits are largely empirical.[25-32]
- For patients receiving postoperative radiation therapy, more strict DVH parameters should be considered for the lung. The exact limit is unknown for lobectomy cases. Based on data from pneumonectomy of mesothelioma cases, mean lung dose should be limited to ≤ 8.5 Gy in pneumonectomy patients.[33,34]

See Radiation Simulation, Planning and Delivery (NSCL-C 3 of 7)
See Stereotactic Body Radiation Therapy (NSCL-C 4 of 7)
See Prophylactic Cranial Irradiation (NSCL-C 4 of 7)

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 7)

Radiation Simulation, Planning and Delivery

- Treatment planning should be performed by CT scans obtained in the treatment position. IV contrast is recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal disease. PET-CT is highly recommended for the treatment plan especially in cases with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improve the target accuracy.[35] Since IV contrast interferes with dose heterogeneity correction, a separate scan without contrast can be used for planning.
- 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 cover the post-chemotherapy tumor volume. However, in patients with compromised lung or cardiac function, large initial tumor or any other predicted high normal tissue toxicity, the post-chemotherapy volume can be used to avoid excessive normal tissue toxicity.
- Photon beam energy is to be individualized based on the anatomic location of the tumors and beam path. In general, photon beam energy between 4 to 10 MV is recommended for beams passing through low density lung tissue before entering the tumor. For large mediastinal tumors or tumors attached to chest wall, when there is no air gap before the beam entering the tumor, 15 MV or 18 MV energies can be considered for more optimal dose arrangement.
- In certain situations where there is a large volume of normal lung being irradiated or where tumors are located close to critical structures (i.e. spinal cord), intensity modulated radiotherapy (IMRT) can be considered for high-dose radiation to avoid overdose to normal tissues. Significantly lower risk of radiation pneumonitis and improved overall survival have been observed with IMRT compared to 3-D conformal radiation therapy for lung cancer.[36] When IMRT is used, the NCI IMRT guideline (http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf) should be followed. Under strictly defined protocols, proton therapy may be allowed.[37-41] When IMRT and proton therapy are used, daily image guidance at delivery is recommended for quality assurance. The modality of IGRT should be based on the institutional experience and the required treatment accuracy.
- The respiratory motion management needs to be considered for all patients with NSCLC when they receive radiation to the thorax for definitive purpose. Acceptable methods of accounting for tumor motion, per *AAPM Task Group 76* guideline, include: 1) Motion-encompassing methods such as slow CT scanning, inhale and exhale breath-hold CT, four-dimensional (4-D) respiration-correlated CT, 2) Respiratory gating methods using an external respiration signal or using internal fiducial markers, 3) Breath-hold methods by deep-inspiration breath-hold, active-breathing control (ABC) device, self breath-hold without respiratory monitoring, 4) Forced shallow breathing with abdominal compression, and 5) Real-time tumor-tracking methods.

See Stereotactic Body Radiation Therapy (NSCL-C 4 of 7)

See Prophylactic Cranial Irradiation (NSCL-C 4 of 7)

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PRINCIPLES OF RADIATION THERAPY (4 of 7)

Stereotactic Body Radiation Therapy (SBRT)

- Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Radiotherapy (SABR) results in higher local control and possibly better long-term survival than 3DCRT in stage I NSCLC.[42] SBRT is one of the well established treatments for inoperable stage I NSCLC patients with node negative peripheral lesions, although optimal dose fractionation needs to be determined (See Figure 1. Schema of Central and Peripheral Locations NSCL-C 6 of 7)
- SBRT fractionation regimens vary widely in current practice, ranging from one single fraction[43] to 3 fractions,[44,45] 4 fractions,[46] and 5 fractions[47,48] (See Table 4. Commonly Used SBRT Regimens NSCL-C 6 of 7). While the optimal number of fractionation may be estimated based on the tumor size and total dose,[49] an accumulative BED of ≥100 Gy is associated with better survival.[50] Optimal dose and fractionation regimens for SBRT have not been fully characterized. RTOG 0915 is ongoing to compare the outcomes between one single fraction and 4 fractions.
- While evidence is limited, conservative normal tissue constraints are recommended (See Table 5. Normal Tissue Dose Volume Constraints for SBRT NSCL-C 6 of 7).

Prophylactic Cranial Irradiation (PCI)

- The benefit for the overall survival of prophylactic brain irradiation has not been proven for NSCLC. The recommendation of whole brain irradiation should be a decision after physician-patient discussion, weighing the potential benefit over the risk for each individual patient.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIATION THERAPY (5 of 7)

Table 1. Commonly Used RT Abbreviations

3DCRT	3-D Conformal Radiation Therapy
DVH	Dose Volume Histogram
GTV[1]	Gross Tumor Volume
CTV[1]	Clinical Target Volume
PTV[1]	Planning Target Volume
ITV[1]	Internal Target Volume
BED	Biologically Effective Dose
OAR	Organ At Risk
V20	% Volume of an OAR Receiving ≥ 20 Gy
MLD	Mean Lung Dose
ABC	Active Breathing Control
IMRT	Intensity Modulated Radiation Therapy
OBI	On-Board Imaging
IGRT	Image Guided Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
SABR	Stereotactic Ablative Radiotherapy, aka SBRT
4DCT[2]	Four Dimensional Computerized Tomography
CBCT	Cone Beam Computerized Tomography

[1]Please use ICRU62 for detailed target definitions.
[2]4DCT to assess respiratory motion.

Table 2. Commonly Used Doses for Conventionally Fractionated Radiation Therapy

Treatment Type	Total Dose	Fraction Size	Treatment Duration
Preoperative	45-50 Gy	1.8-2 Gy	4-5 weeks
Postoperative			
• Negative margins	50-54 Gy	1.8-2 Gy	4-5 weeks
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy	5-6 weeks
• Gross residual tumors	60 to 70 Gy	1.8-2 Gy	6-7 weeks
Definitive			
• Radiation alone or sequential chemoradiation	60-74 Gy	2 Gy	6-7.5 weeks
• Concurrent chemotherapy	60 to 70 Gy	2 Gy	6-7 weeks
Palliative			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30-45 Gy	3 Gy	2-3 weeks
• Bone metastases with soft tissue mass	30 Gy	3 Gy	2 weeks
• Bone metastases without soft tissue mass	8 Gy	8 Gy	1 day
• Brain metastasis	See CNS Guidelines	See CNS Guidelines	See CNS Guidelines

Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT[3,4]

Structures	Limits
Spinal Cord	50 Gy in 1.8-2 Gy
Lung	V20 < 37% MLD < 20 Gy
Heart	V40 < 100% V45 < 67% V60 < 33%
Esophagus	Mean dose < 34 Gy
Brachial Plexus	66 Gy in 1.8-2/Gy

[3]The limits are consistent with those of the ongoing phase III trial RTOG 0617. Vxx refers to the percentage of whole organ receiving more or equal to xx Gy. Lung V20 refers to the percentage of both lungs with subtraction of overlapping CTV receiving ≥ 20 Gy, MLD=mean total lung dose.
[4]Please also consider dose limit recommendations from Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-19.

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PRINCIPLES OF RADIATION THERAPY (6 of 7)

Table 4. Commonly Used SBRT Regimens

Regimen	Indications
30-34 Gy x 1	Peripheral small (< 2 cm) tumors, > 1 cm from chest wall
15-20 Gy x 3	Peripheral < 5 cm tumors, > 1 cm from chest wall
12-12.5 Gy x 4	Peripheral tumors, particularly those < 1 cm from chest wall
10-11 Gy x 5	Peripheral tumors, particularly those < 1 cm from chest wall

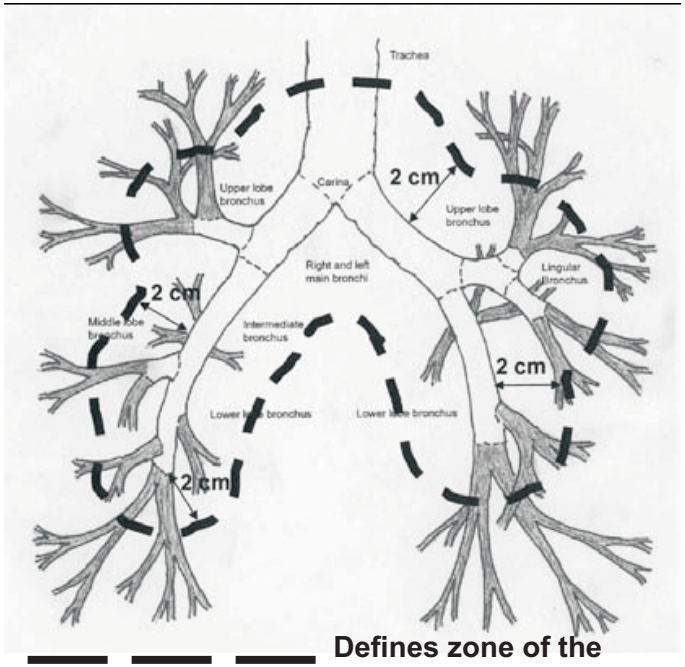
Table 5. Normal Tissue Dose Volume Constraints for SBRT*

OAR	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great vessels	37 Gy	39 Gy 13 Gy/fx	49 Gy 12.25 Gy/fx	55 Gy 11 Gy/fx
Trachea/ Large Bronchus	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	40 Gy (8 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	31.2 Gy (7.8 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy 10 Gy/fx	36 Gy (9 Gy/fx)	40 Gy 8 Gy/fx
Stomach	12.4 Gy	27 Gy 9 Gy/fx	30 Gy (7.5 Gy/fx)	35 Gy 7 Gy/fx

*The limits are based on a combined consideration of recommendations from ongoing multicenter trials (RTOG 0617, RTOG 0618, RTOG 0813 and RTOG 0915).

Figure 1. Schema of Central and Peripheral Locations

Peripheral tumors are those located ≥ 2 cm in all directions around the proximal bronchial tree.



Defines zone of the proximal bronchial tree

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

PRINCIPLES OF RADIATION THERAPY - References (7 of 7)

1 The Lung Cancer Study Group. Effects of postoperative mediastinal radiation therapy on completely resected stage II and stage III epidermoid cancer of the lung. N Engl J Med 1986;315:1377-1381.

2 Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med. 2000;343:1217-1222.

3 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, and IIIA non-small cell lung cancer treated with adjuvant therapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701.

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

5 Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol 2007;2:287-292.

6 Jaklitsch MT, Herndon JE 2nd, DeCamp MM Jr, et al. Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancerin CALGB protocol #8935. J Surg Oncol 2006;94:599-606.

7 Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-8.

8 Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. Eur J Cardiothorac Surg 2009 Apr;35(4):718-23; discussion 723.

9 Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. J Thorac Cardiovasc Surg 2005;129:1250-7.

10 Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. Ann Thorac Surg 2004;78:1200-5.

11 Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. Int J Radiat Oncol Biol Phys 2005;61:318-28

12 Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-91.

13 Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. Int J Radiat Oncol Biol Phys 2005;63:324-33.

14 Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2007;68:103-10.

15 Wang L, Correa CR, Zhao L, et al. The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;73:1383-90.

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

17 Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:1106-11.

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

19 Belderbos JS, Kepka L, Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2008;72:335-42.

20 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;30:239-44.

21 Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007;25:5557-61.

22 Sanuki-Fujimoto N, Sumi M, Ito Y, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. Radiother Oncol 2009;91:433-7.

23 Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. Radiat Oncol 2009;4:5.

24 Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006;65:1097-105.

25 Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol. 2007;17:108-20.

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

27 Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006;65:1075-86.

28 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.

29 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.

30 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;66:1399-407.

31 Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 2009;91:282-7.

32 Hall WH, Guiou M, Lee NY, et al. Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2008;72:1362-7.

33 Rice DC, Smyth RW, Liao Z, et al. Pulmonary toxicity following postoperative intensity modulated radiation therapy for malignant pleural mesothelioma. Int J Radiat Oncol Biol Phys 2007;69:350-357.

34 Komaki R, Liao Z, Liu H, et al. Fatal pneumonitis associated with intensity-modulated radiation therapy for mesothelioma: In regard to Allen et al. Int J Radiat Oncol Biol Phys 2006;65:640-645.

35 MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiother Oncol 2009;91:85-94.

36 Liao ZX, Komaki RR, Thames HD Jr, et al. Influence of technologic advances on outcomes in patients With unresectable, locally advanced non-small-cell lung cancer receiving concomitant chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009 Jun 8. [Epub ahead of print]

37 Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional conformal or intensity-modulated radiation therapy in stage I or stage III non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:1087-96.

38 Cox JD, Sejpal S, Komaki R, et al. Proton therapy with concurrent chemotherapy can reduce toxicity and allow higher radiation doses in advanced non-small cell lung cancer. J Thorac Oncol 2008;3:S303-S304.

39 Komaki R, et al. Rad Oncol 2009;90(suppl 4):61.

40 Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. Chest 2004;126:1198-1203

41 Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for stage I non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2006;65:107-111.

42 Gruters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons, and carbon-ions for non-small cell lung cancer: A meta-analysis. Radiother Oncol 2009;Sept 3 [Epub ahead of print].

43 Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. Cancer 2006;106:1347-52.

44 Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. J Clin Oncol 2009;27:3290-6.

45 Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.

46 Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-71.

47 Takeda A, Sanuki N, Kunieda E, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. Int J Radiat Oncol Biol Phys 2009;73:442-8.

48 Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. J Thorac Oncol 2009;4:976-82.

49 Jin JY, Kong FM, Chetty IJ, et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. Int J Radiat Oncol Biol Phys 2009;Jul 3. [Epub ahead of print]

50 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.

CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY

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
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 75 mg/m^2 on day 1 Gemcitabine 1250 mg/m^2 on days 1, 8	Every 21 days
Cisplatin 75 mg/m^2 Docetaxel 75 mg/m^2	Every 21 days [e]
Pemetrexed 500 mg/m^2 on day 1 Cisplatin 75 mg/m^2 on day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype)	Every 21 days for 4 cycles

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

See Chemoradiation on page NSCL-E

[a] Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. N Engl J Med 2005;352:2589-2597.
[b] Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-60.
[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] Strauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-5051.
[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.
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CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

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[a] (preferred)
Cisplatin 100 mg/m^2 day 1, 29 Vinblastine 5 mg/m^2/weekly x 5 Concurrent thoracic RT[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[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[b]
Paclitaxel 200 mg/m^2 every 3 weeks over 3 hours, 2 cycles Carboplatin AUC 6, 2 cycles followed by thoracic RT[c]

*There are data that support 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 followed by cisplatin 50 mg/m^2 and etoposide 50 mg/m^2 x 2 additional cycles (category 2B)[a]
Paclitaxel 45-50 mg/m^2 weekly Carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m^2 and carboplatin AUC 6[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.

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

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.**
- **Histology of NSCLC is important in the selection of systemic therapy.**
- **New agent platinum combinations have generated a plateau in overall response rate (≈ 25-35%), time to progression (4-6 mo), median survival (8-10 mo), 1 y survival rate (30-40%) and 2 y survival rate (10-15%) in fit patients.**
- **No specific platinum-based cytotoxic combination is clearly superior.**
- **Unfit of any age (performance status 3-4) do not benefit from cytotoxic treatment, except erlotinib for EGFR mutation positive patients.**

First-line therapy

- **Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.**
- **Cetuximab + vinorelbine/cisplatin is indicated in PS 0-2 patients with advanced or recurrent NSCLC.**
- **Erlotinib is indicated for EGFR mutation positive patients.**
- **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.**
- **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 has a known KRAS mutation, therapy other than erlotinib should be considered first.**

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

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

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

Maintenance Therapy

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

- **Continuation Maintenance: Biologic agents given in combination with conventional chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. There are no randomized data supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.**
  - **Continuation of bevacizumab after 4-6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).**
  - **Continuation of cetuximab after 4-6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).**
  - **Continuation of pemetrexed after 4-6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 2B).**
- **Switch Maintenance: Two recent studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4-6 cycles of therapy.**
  - **Initiation of pemetrexed after 4-6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma.**
  - **Initiation of erlotinib after 4-6 cycles of first-line platinum-doublet chemotherapy (category 2B).**
  - **Initiation of docetaxel after 4-6 cycles of first-line platinum-doublet chemotherapy (category 3).**
  - **Close follow-up of patients without therapy is a reasonable alternative to switch maintenance.**

Second-line therapy

- **In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, or erlotinib are established second-line agents.**
  - **Docetaxel has been proven superior to BSC, vinorelbine, or ifosfamide with improved survival/QOL.**
  - **Pemetrexed has been shown to be superior to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.**
  - **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.**

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

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

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

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

- Cisplatin[1-9]
- Carboplatin[4,6-11]
- Paclitaxel[1,4,6,8-11]
- Docetaxel[5,7,8,12,13]
- Vinorelbine[7,9,10]
- Gemcitabine[3,5,6,8,9,13]
- Etoposide[4]
- Irinotecan[9]
- Vinblastine
- Mitomycin
- Ifosfamide[12]
- Pemetrexed[14,15]
- Erlotinib[16]
- Bevacizumab[17]
- Cetuximab[18]
- Albumin-bound paclitaxel[19,20 †]

[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] Belani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005;16(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, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21(16):3016-3024.

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

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

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

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

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

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 one consumes alcoholic beverages

Additional Health Monitoring

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

Resources

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

Cancer Screening Recommendations[2,3]

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

- Colorectal Cancer: 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

[1] ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED (Accessed November 18, 2009)

[2] Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed November 24, 2009)

[3] American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 24, 2009)

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

Table 6. Definitions for T, N, M*

T	Primary Tumor
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤ 3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)[a]
T1a	Tumor ≤ 2 cm in greatest dimension
T1b	Tumor > 2 cm but ≤ 3 cm in greatest dimension
T2	Tumor > 3 cm but ≤ 7 cm or tumor with any of the following features:[b] Involves main bronchus, ≥ 2 cm distal to the carina Invades visceral pleura Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension
T3	Tumor > 7 cm or one that directly invades any of the following: chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus < 2 cm distal to the carina[a] but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina; separate tumor nodule(s) in a different ipsilateral lobe

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

M	Distant Metastasis
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion[c]
M1b	Distant metastasis

[a] The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1.

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

[c] Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as T1, T2, T3, or T4.

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

Table 7. Descriptors, T and M Categories, and Stage Grouping*

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

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

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

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 03/05/10

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 219,440 new cases (116,090 in men and 103,350 in women) of lung and bronchus cancer will be diagnosed in 2009, and 159,390 deaths (88,900 in men, 70,490 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. Data suggest that postmenopausal women who smoke or are former smokers should not receive hormone replacement therapy, because it increases the risk of death from non-small cell lung cancer (NSCLC).[5]

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.[6] In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (i.e., bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds).[7, 8]

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. Active smoking and second-hand smoke both cause lung cancer (see Reports from the Surgeon General, which are the next 2 links). There is a causal relationship between active smoking and lung cancer and also with other cancers, such as esophageal, oral, laryngeal, pharyngeal, and

cervical cancers (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf). Smoking harms nearly every organ in the body. Those who live with someone who smokes have a 20% to 30% increased risk for lung cancer (http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf).

Further complicating this problem, cigarettes also contain the highly addictive substance nicotine. Oncologists should encourage smoking cessation, especially in patients with cancer (http://www.smokefree.gov/). 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.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf).

Varenicline is a new class of drug for smoking cessation; other drugs include nicotine replacement (e.g., gum, inhaler, nasal spray, patch) and bupropion. Studies have shown that varenicline is better than bupropion for smoking cessation.[9, 10] However, almost 30% of patients had nausea while using varenicline.[11] The effectiveness of varenicline for preventing relapse has not been clearly established.[12] The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm).

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.[13, 14] Because localized cancer can be managed curatively and because survival in other solid tumors (e.g., 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.[15-17] 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; results are expected by 2011. 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.[18] 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[18-21] are conflicting;[22, 23] 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.[24] If a screening strategy is used, then the I-ELCAP screening protocol should be followed (http://www.ielcap.org/professionals/docs/ielcap.pdf). Data show that a CT screening clinic detected a malignant tumor in 3% of patients; many patients (45%) did not complete followup.[25]

Classification and Prognostic Factors

The World Health Organization divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC (discussed in this guideline) and small cell lung cancer ([SCLC], 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 (i.e., 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.[26]

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.[27] Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (*p53*), the activation of proto-oncogene Kirsten-Rous sarcoma virus (K-ras), and other biologic markers, may have significant value in predicting a poor prognosis.[28, 29] 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).[30-32] 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.[33] The principles of pathology review are listed in the algorithm.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important subtype of pulmonary adenocarcinoma;[34] data suggest that gefitinib and erlotinib are useful for patients with BAC.[35-37] 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.[38] 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.[39] BACs are usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. Mucinous BACs are often CK7+/CK20+.[40] 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,[41] 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 (e.g., from breast cancer) are usually TTF-1 negative. However, TTF-1 is positive in tumors from patients with thyroid cancer.[42] In addition, thyroglobulin is present in tumors from patients with thyroid cancer, while it is negative in lung cancer tumors. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- 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.[43]

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.[44-47] A new lung cancer staging system has been proposed by the International Association of the Study of Lung Cancer (IASLC).[48, 49] The revised staging is available from the AJCC (7th edition).[50] These NCCN guidelines have been updated with the new AJCC (7th edition) staging revisions. The revised stage grouping is summarized in Table 6 of the staging tables. The descriptors of the TNM classification scheme are summarized in Table 7 (note that the cells in bold indicate a change from the 6th edition for a particular TNM category).

The new TNM staging revisions take effect for all new cases diagnosed after January 1, 2010.[50] With the new staging, locally advanced disease is now stage III; advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging: for example,1) T2bN0M0 is upstaged from stage IB to stage IIA; 2) T2aN1M0 is downstaged from stage IIB to stage IIA; 3) T4N0-N1M0 is downstaged from stage IIIB to stage IIIA; and 4) wet IIIB (i.e., malignant pleural effusions) is upstaged to stage IV.[51] These new changes reflect the prognosis of patients with these different tumors.

Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (i.e., thoracotomy, mediastinoscopy examination of resected lymph nodes).[44]

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.[52] 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%.[53] Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Prognostic and Predictive Biomarkers

Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, the evidence is strongest for epidermal growth factor receptor (EGFR), the 5' endonuclease of the nucleotide excision repair complex (ERCC1), the k-ras oncogene, 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.[54] However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR-TKI therapy.[36, 55] High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.[56, 57] High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy.[57, 58] 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.[28] Presence of K-ras mutations is also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.[36, 59] High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression, independent of therapy.[60,61] High levels of RRM1 expression are also predictive of poor response to gemcitabine-based chemotherapy.[58, 62, 63]

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.[54] 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).[31]

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.[64, 65] 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.[36] 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.[55] 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).[31] 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).[56] 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.[57]

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.[58] 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).[66]

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).[57] 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.[62,63]

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.[67] Current data suggest that approximately 25% of adenocarcinomas in a North American population have K-ras mutations.[31, 36, 59] K-ras mutation prevalence is associated with cigarette smoking.[68]

K-ras mutational status is prognostic of survival. Patients with K-ras mutations have a shorter survival than 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.[28] 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.[69] 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).[59] 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.[36] 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.[31] 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).[59] 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 (i.e., 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.[70, 71] 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).[60] 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.[61]

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.[58] In addition, *RRM1* mRNA levels were significantly associated with overall survival in patients with advanced stage NSCLC who were treated with gemcitabine and cisplatin.[72] 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.[62, 63]

Treatment Approaches

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

Surgery

In general, for patients with stage I or stage II disease, surgery provides the best chance for cure. However, thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy.

The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated. Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice. Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (e.g., multidisciplinary clinic and/or Tumor Board). Patients with pathologic stage II or greater should be referred to medical oncology for evaluation. Consider referral to medical oncologist for patients with stage IB and consider referral to radiation oncologist for stage IIIA. Treatment delays because of poor coordination among specialists should be avoided.

The surgical procedure used depends on the extent of disease and on the cardiopulmonary reserve of the patient. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; otherwise, lobectomy or pneumonectomy should be done if physiologically feasible.[73, 74] Resection (including wedge resection) is preferred over ablation (i.e., radiofrequency ablation, cryotherapy, stereotactic radiation).[74] However, it is controversial whether lung-sparing surgeries (i.e., sublobular resection), such as segmentectomy and wedge resection, are useful in patients with severely reduced pulmonary function who are otherwise not candidates for surgery.[74-76]

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. This study is evaluating 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. Initial results indicate that morbidity is not increased with complete lymphadenectomy.[77, 78]

Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection. Note that the IASCL (International Association for the Study of Lung Cancer) has recently proposed a new lymph node map.[79] Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because it would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in selected patients:1) those who are not eligible for lobectomy because of poor pulmonary reserve or other major co-morbidity; and 2) those with a peripheral nodule 2 cm or less with at least one of the following (pure BAC histology [category 2B], nodule has 50% or more ground glass appearance on CT [category 2B], and/or radiologic surveillance confirms a doubling time of 400 days or more [category 2B]). Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins 1) 2 cm or more, or 2) the size of the nodule or more.[80, 81]

Video-assisted thoracic surgery (VATS) is a relatively new minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.[82, 83] Published studies suggest that VATS has several advantages over the standard thoracotomy (or pleurotomy).[84-88] Acute and chronic pain associated with VATS is minimal; thus, this procedure requires shorter length of hospitalization.[89] VATS is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[90-94]

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.[95-97] VATS has also been shown to improve discharge independence in older populations and in high-risk patients as well.[98, 99] Recent data show that VATs improves the ability of patients to complete postoperative chemotherapy regimens.[100, 101] Based on its favorable effects on postoperative recovery and morbidity, VATS is included in the guidelines as a reasonable and acceptable approach for patients who are surgically resectable with no anatomic or surgical contraindications as long as standard oncologic and dissection principles of thoracic surgery are not compromised.

Radiation Therapy

General Principles

Radiation therapy can be used as 1) an adjunct for patients with resectable NSCLC who have no contraindications for surgery; 2) the primary local treatment (i.e., definitive RT) for patients with medically inoperable or unresectable NSCLC; and/or 3) an important palliative modality for patients with incurable NSCLC. The terminology and

abbreviations for RT are described in the algorithm (see Table 1). Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical oncologists, radiation oncologists, medical oncologists, pulmonologists, pathologists, and diagnostic radiologists.

For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy (category 1) followed by postoperative radiotherapy is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established.[102-104] For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT. For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiation is recommended if the patient is medically fit.[105, 106] Radiation therapy should start earlier, because local recurrence is the most common failure in this group of patients.[107]

Conformal RT with or without chemotherapy should be offered to patients with curable stage I-III NSCLC who are medically inoperable but have reasonable performance status and life expectancy.[108] Modern 3-dimensional conformal RT techniques with CT or CT/positron emission tomography (PET)--based treatment planning should be used on all patients. Both treatment outcome and cost should be considered. In patients receiving RT or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (i.e., grade 3 esophagitis, hematologic toxicities) should be minimized by conformal treatment planning and aggressive supportive care. RT can be offered to primary or distant sites as palliative care for stage IV patients with extensive metastases.

To avoid postoperative pulmonary toxicity, preoperative chemoradiotherapy should be avoided if at all possible, if pneumonectomy is required.[109, 110] 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 (i.e., 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.

Dose, Volume and Normal Tissue Constraints for Conventionally Fractionated RT

The dose recommendations for definitive and palliative RT are summarized in the algorithm (see Table 2). Tissue heterogeneity correction should be used in RT treatment planning for all patients. Preoperatively, a dose of 45-50 Gy in 1.8 to 2 Gy fraction size is often recommended.[111] Doses greater than 50 Gy in the preoperative setting have been reported to be safe and achieved favorable survival outcome;[112-114] however, this should only be performed with an experienced team.

The postoperative RT dose should be based on margin status. After surgery, lung tolerance to RT is remarkably smaller than for patients with intact lungs. Every effort should be made to minimize the [postoperative] dose of RT. Although the dose volume constraints for normal lungs are a useful guide, more conservative constraints should be used for postoperative RT (see Table 3).For definitive RT, the commonly prescribed dose is 60-70 Gy.[115] A dose of 74 Gy or more was associated with better survival in patients treated with radiation alone or with sequential chemotherapy followed by radiation in a retrospective study.[116] The radiation dose is one significant factor for

overall survival in patients with stage I-II after radiation alone[117] or stage III disease treated with concurrent chemoradiation.[118] When radiation is given concurrently with chemotherapy, a dose up to 74 Gy may be delivered safely,[119-121] if the dose to normal structures is strictly limited (see Table 3). The role of high-dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).

For treatment volume consideration, planning target volume (PTV) should be defined per the ICRU-62 (International Commission on Radiation Units and Measurements Report 62) guidelines, based on gross tumor volume (GTV), plus clinical target volume (CTV) margins for microscopic diseases, internal target volume (ITV) margins for target motion, and margins for daily set-up errors.[122] GTV should be confined to visible tumors (include both primary and nodal diseases) on CT or PET-CT.

In patients who receive postoperative radiotherapy, CTV should consist of the bronchial stump and high-risk draining lymph node stations.[123] Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial[124] and should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. Involved field radiation to high dose without ENI has been shown to allow higher dose radiation with acceptable toxicity and low risk of isolated nodal relapse.[115, 116, 125-128]

It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the spinal cord, lungs, heart, esophagus, and brachial plexus to minimize normal tissue toxicity (see Table 3). These limits are largely empirical.[129-136] For patients receiving postoperative RT, more strict DVH parameters should be considered for lung. The exact limit is unknown for lobectomy cases; mean lung dose should be limited to less than 8.5 Gy in pneumonectomy patients.

Radiation Simulation, Planning and Delivery

Treatment planning should be based on CT scans obtained in the treatment position. IV contrast should be used for better target delineation whenever possible, especially in patients with central tumors or with nodal diseases. PET/CT is preferable in cases with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improve the target accuracy.[137]

In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT before 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 can be used to avoid excessive pulmonary toxicity. Photon beam energy should be individualized based on the anatomic location of the tumors and beam angles. In general, photon beam energy between 4 to 10 MV is recommended for beams passing through low-density lung tissue before entering the tumor. For large mediastinal tumors or tumors attached to chest wall, 15 MV or 18 MV energies can be considered for more optimal dose arrangement.

In certain situations when a large volume of normal lung is being irradiated or when tumors are located close to critical structures (i.e., spinal cord), intensity modulated radiotherapy (IMRT) may be considered for high-dose radiation to avoid overdose to normal tissues. A significantly lower risk of radiation pneumonitis and improved overall survival have been observed when using IMRT compared to 3-D conformal RT for lung cancer.[138]

When IMRT is used, the National Cancer Institute (NCI) IMRT guideline should be followed (http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf). Under strictly defined protocols, proton therapy may be allowed.[139-143] When IMRT and proton therapy are used, daily image guidance at delivery should be used for quality assurance. Use of the modality of image-guided RT (IGRT) should be based on institutional experience and on the treatment accuracy.

Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the AAPM Task Group 76 guideline, include: 1) motion-encompassing methods such as slow CT scanning, inhale and exhale breath-hold CT, four-dimensional (4-D) respiration-correlated CT; 2) respiratory gating methods using an external respiration signal or using internal fiducial markers; 3) breath-hold methods by deep-inspiration breath-hold, active-breathing control (ABC) device, self-held breath-hold without respiratory monitoring; 4) forced shallow breathing with abdominal compression; and 5) real-time tumor-tracking methods.[144]

Stereotactic Body Radiation Therapy (SBRT)

In patients with stage I NSCLC, SBRT provides a statistically significantly higher 5-year survival than 3-D conformal RT.[145] SBRT can be considered for inoperable stage I patients with node negative peripheral lesions (see Figure 1) that are less than 5 cm in maximal dimension[146-150] or for limited lung metastasis.[151, 152] SBRT can also be used for brain metastases (see section on "Whole Brain Irradiation and SBRT").[153-157] Decisions about whether to recommend SBRT should be based on multidisciplinary discussion.

SBRT fractionation regimens for lung tumors range from one single fraction[158] to 3 fractions,[149, 150] 4 fractions,[159] and 5 fractions[160, 161] (see Table 4). Although the optimal number of fractions may be estimated based on the tumor size and total dose,[162] an accumulated biological equivalent dose (BED) of 100 Gy or more is associated with better survival.[163] The RTOG 0915 trial is currently comparing the outcomes between one single fraction and 4 fractions. SBRT normal tissue dose volume constraints should be strictly followed (see Table 5).

Radiofrequency Ablation

Studies suggest that radiofrequency ablation (RFA) may be an option for node-negative patients who either refuse surgery or cannot tolerate surgery because of poor PS, significant cardiovascular risk, poor pulmonary function, and/or comorbidities. Optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm; RFA can be used for previously irradiated tissue and for palliation.[164] 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%).[165]

Whole Brain RT and SBRT

Many patients with NSCLC have brain metastases (30%-50%), which substantially affect their quality of life.[166] Surgery followed by whole brain RT with or without SBRT is a reasonable option for select patients with a single brain metastasis.[167, 168] Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with whole brain RT and/or SBRT.[166] Decisions about whether to recommend surgery, whole brain irradiation, SBRT, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.

There have been concerns that whole brain RT adversely affects neurocognition. However, a study in 208 patients with brain metastases found that patients who responded (with tumor shrinkage) after whole brain radiation had improved neurocognitive function and that tumor progression affects neurocognition more than whole brain radiation.[169] In 132 patients with 1-4 brain metastases who received SBRT with or without whole brain RT, survival was similar in both groups.[155] In a subset of 92 of these patients who received SBRT with or without whole brain RT, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function.[170] However, a study in 58 patients found that patients who received SBRT plus whole brain radiation had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SBRT alone.[153]

The role of prophylactic cranial irradiation (PCI) is controversial. Although it closed early because of poor accrual, a recent trial (RTOG 0214) of PCI for patients with stage III NSCLC showed that the incidence of brain metastases was decreased in patients who received PCI (18% versus 7.7%) although overall survival was not improved.[171] The dose and fractionation of PCI is the same as used for small cell lung cancer (25 Gy in 10 fractions over 2 weeks) (see Small Cell Lung Cancer Guidelines).[172]

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease who are medically fit and can tolerate surgery. In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.[173-175] Currently, concurrent chemoradiation appears superior to sequential therapy for patients with unresectable stage III disease.[119, 176] 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.[177-180]

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.[173] 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 and that the benefit of chemotherapy decreased over time.[181, 182] However, data show that adjuvant chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA (Adjuvant Navelbine International Trialist Association) trial compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in early-stage NSCLC. In the JBR.10 trial, 482 patients (ECOG PS of 0-1) with completely resected stage IB (T2, N0) or stage II (T1, N1, or T2, N1) NSCLC were randomly assigned either to vinorelbine plus cisplatin (242 patients) or to observation (240 patients).[174] 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).

However, recent updated data from JBR.10 after 9 years of followup show that when compared with observation alone, adjuvant chemotherapy is beneficial for stage II but not for stage IB patients.[183] In stage II patients receiving adjuvant chemotherapy, median survival is 6.8 versus 3.6 years in those who were only observed. Of note, patients receiving chemotherapy did not have an increased death rate. The NCCN guidelines have been revised by deleting certain chemotherapy options for early-stage disease.

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.[175] 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.[175] 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).[184] 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;[185] updated results have been reported.[186, 187] 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).[186, 187] 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.[188]

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.[189-193] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[189, 190, 192, 193] However, concurrent chemoradiation appears to be superior to sequential therapy.[119, 176] 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).[119, 194, 195] Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.[196]

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.[197] Results from SWOG 9504 have shown a median survival of 26 months and a 5-year survival rate of 29%.[198] 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.[199, 200] 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.[201]

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.[202] 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.[177-179] Many drugs are active against stage IV NSCLC. These drugs include the taxanes (paclitaxel, docetaxel), vinorelbine, etoposide, pemetrexed, the camptothecin analogs (irinotecan), and gemcitabine. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, cisplatin/pemetrexed, and docetaxel/cisplatin.[188,203-206] Phase III randomized trials have shown that many of the platinum-doublet combinations are similar for objective response rates and survival.[207, 208] 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;[203, 209, 210] gemcitabine/docetaxel is another option.[211]

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 (i.e., dexamethasone, H2 blockers, H1 blockers) are contraindicated.[212, 213]

Specific targeted therapies have been developed for the treatment of advanced lung cancer.[214, 215] Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor of 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).[216] To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC and no history of hemoptysis. 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 can also be given as first-line therapy in patients with advanced or metastatic NSCLC who have known active EGFR mutation or gene amplification.[31, 217-219]

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).[220] Adding cetuximab slightly increased overall survival (11.3 versus 10.1 months, *P* = .04).

Maintenance Therapy

Maintenance therapy may be given after 4-6 cycles of chemotherapy for patients with tumor response or stable disease who have not progressed. *Continuation maintenance* refers to the use of at least one of the agents given in first line. *Switch maintenance* refers to the initiation of a different agent, not included as part of the first-line regimen.

For continuation maintenance therapy, biologic agents (which were initially given in combination with conventional chemotherapy) should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval.

Bevacizumab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., platinum-doublet chemotherapy given with bevacizumab).[216, 221] Likewise, cetuximab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., cisplatin, vinorelbine, and cetuximab therapy).[220] Pemetrexed (category 2B) may also be given as continuation maintenance therapy.[221] There are no randomized trials supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.

For switch maintenance therapy, 2 recent studies have shown a benefit in progression-free survival and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4-6 cycles) in patients without disease progression.[222, 223] Pemetrexed (category 2B) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy, in patients with histologies other than squamous cell carcinoma.[222] Erlotinib (category 2B) or docetaxel (category 3) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy.[223]

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC. The clinical stage is initially determined from disease history (i.e., cough, dyspnea, chest pain, weight loss) 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.aspx). Based on the initial evaluation, the clinical stage is determined and assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. Although PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (i.e., 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.[224-226]

Mediastinoscopy is the gold standard for evaluating mediastinal nodes. Thus, mediastinoscopy is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high (based on tumor size and location). Therefore, mediastinoscopy is appropriate for patients with T2-T3 lesions even if the PET/CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive PET/CT scan. In contrast, because of the low prior probability of lymph node involvement in patients with peripheral T1ab, N0 lesions,[227] some NCCN institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2a, central T1ab, or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy 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.[228] 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.[229]

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I, stage II, and stage IIIA tumors. However, in patients who present with a solitary pulmonary nodule where the suspicion of malignancy is high, surgical resection without prior invasive testing may be reasonable.

Other Imaging Studies

As previously mentioned, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.[224] 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.[230] 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 (i.e., T1 cancer).[231] 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.[232] 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%.[233] Kernstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[234, 235] 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.[236, 237]

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.[238, 239] However, PET/CT is even more sensitive and is now recommended by NCCN.[240-242] When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.[240] However, positive PET/CT scans findings need pathologic or other radiologic confirmation (e.g., 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.[243] 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.[244]

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.[245]

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 board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice. The principles of surgical therapy are listed in the algorithm.

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

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

For patients with clinical stage IIB (T3, N0) and stage IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0) and stage IIIA (T3-4, N1) tumors, treatment options are organized according to the location of the tumor (i.e., 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 invasion, N0-1) in the superior sulcus, the panel suggests concurrent chemoradiation therapy followed by surgical resection and chemotherapy. The principles of RT and chemotherapy are listed in the algorithm. For patients with negative margins, most NCCN institutions give sequential chemotherapy and radiation (i.e., 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 (T4 extension, N0-1) in the superior sulcus, definitive RT with chemotherapy (i.e., 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%.[246] Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.[111, 113, 247-249]

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

For patients with stage IIIA disease and positive mediastinal nodes (T1-3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (including mediastinoscopy, mediastinotomy, EBUS-FNA, EUS-FNA, and CT-guided FNA), bronchoscopy, brain MRI, and PET/CT scan; pulmonary function tests (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 or lymph node sampling should be performed during the surgery. Those individuals found to have unresectable lesions should be treated according to pathologic stage, as defined in the algorithm. 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. Although definitive concurrent chemoradiation is recommended (category 1), induction chemotherapy with (or without) RT is another option for patients with T1-3, N2 disease.[250] Recommended therapy for metastatic disease is detailed in the algorithm.

When a lung metastasis is present, it usually occurs in patients with other systemic metastases; the prognosis is poor; therefore, many of these patients are not candidates for surgery. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery.[251] Patients with separate pulmonary nodule(s) in the same lobe or ipsilateral lung without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.[252] Intrapulmonary metastases

have been downstaged in the recent TNM revised staging.[51, 252, 253] After surgery, concurrent chemoradiation (if tolerated) is recommended for those with positive margins and chemotherapy is recommended for those with negative margins.

The recommended initial treatment options for patients with separate pulmonary nodule(s) in the contralateral lung include surgery, induction chemotherapy before surgery, or induction chemoradiation before surgery. For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy (category 3).[198-200] 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.

Stage IIIB tumors comprise 2 groups including 1) tumors with contralateral mediastinal nodes (T1-3, N3); and 2) tumors with T4 extension and N2-3 disease, which are unresectable. Surgical resection is not recommended in patients with T1-3, N3 disease. However, in patients with suspected N3 disease, the guidelines recommend pathologic confirmation of nodal status by either mediastinoscopy, supraclavicular lymph node biopsy, thoracoscopy, needle biopsy, mediastinotomy, EUS biopsy, or EBUS).[254, 255] 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. If these tests are positive, concurrent chemoradiation (category 1) followed by consolidation chemotherapy (category 2B) is recommended.[198, 200] For metastatic diseases that are confirmed by PET/CT scan and brain MRI, treatment is detailed in the algorithm.

For patients with T4 extension, N2-3 disease (stage IIIB), surgical resection is not generally recommended. The initial work-up includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0-1) disease. If either the contralateral or ipsilateral mediastinal node is positive, 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.[198-200]

Stage IV Disease

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised staging, T4 with effusion has been reclassified as stage IV, M1a.[51] 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 (e.g., 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. However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.[256] In patients with effusions that are positive for malignancy, the tumor is treated as M1a with local therapy (i.e., ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease.

The algorithm for patients with distant metastases (i.e., stage IV, M1b) depends on the location of the metastases—a solitary nodule in the

brain or adrenal—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, PET/CT scan, and brain MRI. The increased sensitivity of PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. 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.[166] The 5-year survival rates with such an approach range from 10% to 20%;[214, 257] median survival is about 40 weeks.[168] Follow-up whole brain RT (category 1) with or without SBRT (category 2B) may be used.[156, 169] Stereotactic radiosurgery alone or followed by whole brain radiation is an additional treatment option.[155] Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.[258] After their brain lesions are treated, further treatment options for these patients with T1-2, N0-1 or for those with T3, N0 then include 1) surgical resection of the lung lesion followed by chemotherapy (category 2B); 2) SRS (category 2B); or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B). Systemic therapy is an option after surgery for patients with higher stage NSCLC.

Adrenal metastases from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. If an adrenal metastasis is found and if the lung lesion is curable, the resection of the adrenal lesion has produced some long-term survivors (category 3).[259, 260] 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 (i.e., resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Treatment options for patients with stage IA (T1ab, N0 disease) and with positive surgical margins (R1, R2) include 1) re-resection (preferred); 2) chemoradiation (category 2B); or 3) RT (category 2B). Patients with T1ab, N0 tumors and with negative surgical margins (R0) are observed. Patients with T2ab, N0 tumors with negative surgical margins are usually observed; chemotherapy (category 2B) is recommended as adjuvant treatment for patients with high-risk features, such as poorly differentiated tumor, vascular invasion, wedge resection, minimal margins, tumors greater than 4 cm, visceral pleural involvement, and Nx. If the surgical margins are positive in patients with T2ab, N0 tumors, these patient should have either re-resection with chemotherapy or chemoradiation and chemotherapy.

For patients with T1ab-2ab, N1 or T3, N0 disease and negative surgical margins, the panel recommends 1) chemotherapy (category 1); or 2) chemoradiation (category 3) and chemotherapy for patients with adverse factors (i.e., inadequate mediastinal lymph node dissection, extracapsular spread, multiple positive hilar nodes, and close margins). If surgical margins are positive (T1ab-2ab, N1 or T3, N0), options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with T1-3, N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be

treated with chemoradiation and chemotherapy. Patients with negative margins may be treated with chemotherapy (category 1) and RT.

Panel members disagreed about the use of chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.[103] 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.[105] A phase II trial in 42 patients had similar results (5-year survival, 68%) except those with adenocarcinoma had poorer survival (only 28%).[106] As with stage IB and stage II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in stage III NSCLC patients who have had surgery.

In the case of marginally resectable superior sulcus tumors (T4 extension, N0-1), if the lesion converts to a resectable status following initial treatment, resection is performed and chemotherapy is given. If the lesion does not convert (i.e., it remains unresectable), the full course of definitive RT followed by chemotherapy is administered as an adjuvant treatment. Among patients with chest wall lesions with T3 invasion-4 extension, N0-1 disease, those that are initially treated with surgery (preferred) may receive chemotherapy alone if the surgical margins are negative; when surgical margins are positive, they may receive either chemoradiation and chemotherapy or re-resection with chemotherapy. A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3-4, N0-1).

For patients with stage IIIA disease and positive mediastinal nodes (T1-3, N2), if there is no disease progression after initial treatment, patients should be treated with surgery with (or without) chemotherapy (category 2B). In addition, postoperative RT should be given if not used preoperatively. Alternatively, if the disease progresses, patients may be treated with either 1) local therapy using RT (if not given previously) with (or without) chemotherapy, or 2) systemic treatment.

In patients with separate pulmonary nodules in the contralateral lung, the option for adjuvant therapy includes surgery, if initial therapy consisted of induction chemotherapy or induction chemoradiation therapy. If the margins are negative, observation is usually recommended; another option is adjuvant chemotherapy in select patients with or without RT (if not given previously). 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,[173-175] the panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with gemcitabine,

pemetrexed, or docetaxel.[188, 203, 206] For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used.[188]

A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery.[261-263] Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[264-267] 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.[266, 267] 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 T1ab, N0 tumors based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).[268] 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.[269] The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.[104] Adjuvant chemotherapy (category 1) with RT is recommended for T1-3, N2 patients with negative margins.

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. Spiral contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years (category 2B); a non-contrast-enhanced chest CT is recommended annually thereafter (category 2B), although the panel disagreed about this recommendation.[15] PET or brain MRI is not indicated for routine follow-up. Smoking cessation counseling should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients (http://www.smokefree.gov/).

The NCCN guidelines include an algorithm for long-term followup care of NSCLC survivors. These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening.

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. 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 or external-beam RT. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life.[270] 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, external-beam RT or stent placement is indicated. For severe hemoptysis, several treatment options are recommended (i.e., external-beam RT, brachytherapy, laser therapy, PDT, surgery, 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, depending on the performance status.

For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT.[271] 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.[272] For other solitary metastasis, the treatment guidelines follow the same pathway as that for stage IV, M1b (solitary site) tumors.

In a small subset of patients, recurrence will be suspected only on the basis of positive sputum cytology. 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. 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 for patients with PS of 0-1: 1) chemotherapy (category 1); 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; 4) cetuximab in combination with vinorelbine and cisplatin(category 2B); or 5) erlotinib for EGFR mutation positive patients. Patients with PS of 2 can receive 1) cetuximab in combination with vinorelbine and cisplatin (category 2B) for patients who meet the eligibility criteria; 2) chemotherapy; or 3) erlotinib for EGFR mutation positive patients.

Eligibility criteria for bevacizumab include PS of 0-1, nonsquamous cell histology and no history of hemoptysis. Note that bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy. Bevacizumab should be given until progression. Any regimen with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Previously patients with brain metastases were excluded from receiving bevacizumab because of concerns about CNS hemorrhage; however, recent data suggest that bevacizumab can be used in patients with treated CNS metastases.[273]

Eligibility criteria for cisplatin and pemetrexed include PS 0-1, adenocarcinoma or large cell histology (i.e., nonsquamous), and no prior chemotherapy. Panel members disagreed (category 2B) about using cetuximab with cisplatin and vinorelbine, because recent data only showed a slight improvement in survival with the addition of cetuximab (11.3 versus 10.1 months, $P = .04$).[220] Note that full-dose cisplatin for PS 2 patients should be given selectively.

Trial Data

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.[216, 274] 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.[216] 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). Of interest, a recent trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab.[275, 276]

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.[206] Patients with either adenocarcinoma or large cell histology (i.e., nonsquamous) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 versus 10.9 months). Patients with squamous cell histology had improved survival with the cisplatin/gemcitabine regimen (10.8 versus 9.4 months). When compared with the cisplatin/gemcitabine regimen, the cisplatin/pemetrexed regimen had significantly lower rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$). Treatment-related deaths were similar for both regimens (cisplatin plus pemetrexed, 9 patients [1.0%); cisplatin plus gemcitabine, 6 patients [0.7%]).

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.[220] 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%).

Data show that cisplatin-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Patients receiving cisplatin-based therapy had an improvement in median survival of 6-12 weeks and a doubling of 1-year survival rates (10%-15% improvement). Cisplatin or carboplatin have been proven effective in combination with any of the following agents: docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, pemetrexed, vinblastine, and vinorelbine.[188, 203-206, 209, 210] New agent/non-platinum regimens are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel).[211] As yet, there is no evidence that one platinum-based regimen is better than any other.[207, 208]

Maintenance Therapy

Patients should be reevaluated for tumor progression with a follow-up CT scan (i.e., 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[277] or until the disease progresses. Another option for these patients is continuation maintenance therapy with bevacizumab (category 1), cetuximab (category 1), or pemetrexed (category 2B).[216, 220] Switch maintenance therapy with pemetrexed (category 2B), erlotinib (category 2B), or docetaxel (category 3) is also an option.[222, 223] Observation is another option. Note that pemetrexed is not recommended for patients with squamous histology.

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.[222] Tumor response (*P*=.001) and progression-free survival (4.3 versus 2.6 months, *P*<.0001) were increased in patients who received pemetrexed, especially in patients with adenocarcinoma or large cell histology (i.e., nonsquamous). In patients with nonsquamous histology, preliminary results showed increased overall survival with pemetrexed (15.5 versus 10.3 months, *P*=.002).

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

Patients may continue to derive benefit from erlotinib or gefitinib after disease progression; discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).[278] This strategy mirrors the experience in other oncogene-addicted cancers, particularly *HER2*-amplified breast cancer. In women with *HER2*-amplified breast cancer who have had progression of disease on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy is added to trastuzumab.[279] Data support the continued use of erlotinib or gefitinib in patients with lung adenocarcinoma with *EGFR* mutations after development of acquired resistance to erlotinib or gefitinib when conventional chemotherapy is initiated.

There is accumulating data about how cancers become resistant to EGFR inhibitors. The most common known mechanism is the acquisition of a secondary mutation in EGFR, T790M, that renders the kinase resistant to erlotinib and gefitinib.[280, 281] Amplification of the MET oncogene is another validated resistance mechanism. Activation of the IGF-1R pathway has been observed in laboratory models. To overcome all 3 types of resistance, EGFR must still be inhibited. In the case of MET amplification and IGF-IR activation, new inhibitors must be added

to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely and colleagues demonstrate that when cancers that were once sensitive to EGFR inhibitors start to progress, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.[278] In total, it is likely that continuing EGFR TKIs is beneficial in many cancers even after they develop resistance to EGFR TKIs.

Second-Line Chemotherapy

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, 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.[282-285] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[282, 283] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[284,286] Based on recent data, pemetrexed is recommended in patients with adenocarcinoma or large cell histology (i.e., nonsquamous).[222] Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.[285]

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 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/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm095059.htm).

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.[285] 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.[287]

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, 2009. CA Cancer J Clin 2009;59:225-249. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19474385

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

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

4. Schrump DS, Giaccone G, Kelsey CR and Marks LB. Non-small cell lung cancer. In: DeVita VT, Lawrence TS and Rosenberg SA, eds. DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology, Eighth Edition. Vol. 1. Philadelphia: Lippincott Williams & Wilkins 2008:896-946.

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

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

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

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

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

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

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

12. Cahill K, Stead LF and Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2008:CD006103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18646137

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

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

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

16. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early lung cancer action project: initial findings on repeat screenings. Cancer 2001;92:153-159. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11443621

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

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

19. Bach PB, Silvestri GA, Hanger M and Jett JR. Screening for lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:69S-77S. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17873161

20. McMahon PM, Kong CY, Johnson BE, et al. Estimating long-term effectiveness of lung cancer screening in the Mayo CT screening study. Radiology 2008;248:278-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18458247

21. 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 (Suppl 15):Abstract 1508. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/1508

22. Mulshine JL. Commentary: lung cancer screening--progress or peril. Oncologist 2008;13:435-438. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18448558

23. Jett JR and Midthun DE. Commentary: CT screening for lung cancer--caveat emptor. Oncologist 2008;13:439-444. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18448559

24. Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-961. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17341709

25. Veeramachaneni NK, Crabtree TD, Kreisel D, et al. A thoracic surgery clinic dedicated to indeterminate pulmonary nodules: too many scans and too little pathology? J Thorac Cardiovasc Surg 2009;137:30-35. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19154897

26. 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;24:5079-5090. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17075127

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

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

29. 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;53:1-4. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8380124

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

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

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

33. Travis WD. Pathology and genetics of tumours of the lung, pleura, thymus and heart In: Organization WH, Cancer IAfRo and Cancer IAoPIAftSoL, eds. Lyon: IARC Press; 2004.

34. Jackman DM, Chirieac LR and Janne PA. Bronchioloalveolar carcinoma: a review of the epidemiology, pathology, and treatment. Semin Respir Crit Care Med 2005;26:342-352. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16052436

35. 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;30:1309-1315. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17001163

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

37. West HL, Franklin WA, McCoy J, et al. Gefitinib therapy in advanced bronchioloalveolar carcinoma: Southwest Oncology Group Study S0126. J Clin Oncol 2006;24:1807-1813. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16622257

38. Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-1068. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11829087

39. Goldstein NS and 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11554157

40. Shah RN, Badve S, Papreddy K, et al. Expression of cytokeratin 20 in mucinous bronchioloalveolar carcinoma. Hum Pathol 2002;33:915-920. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12378517

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

42. Ordóñez NG. Thyroid Transcription Factor-1 is a Marker of Lung and Thyroid Carcinomas. Advances in Anatomic Pathology 2000;7:123-127. Available at: http://journals.lww.com/anatomicpathology/Fulltext/2000/07020/Thyroid_Transcription_Factor_1_is_a_Marker_of_Lung.7.aspx

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

63. Reynolds C, Obasaju C, Schell MJ, et al. Randomized phase III trial of gemcitabine-based chemotherapy with in situ RRM1 and ERCC1 protein levels for response prediction in non-small-cell lung cancer. J

Clin Oncol 2009;27:5808-5815. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19884554

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

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

66. Lord RV, 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12114432

67. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3041218

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

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

70. Brissenden JE, Caras I, Thelander L and Francke U. The structural gene for the M1 subunit of ribonucleotide reductase maps to chromosome 11, band p15, in human and to chromosome 7 in mouse. Exp Cell Res 1988;174:302-308. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3275546

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

72. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14977831

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

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

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

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

77. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. Ann

Thorac Surg 2006;81:1013-1019; discussion 1019-1020. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16488712

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

79. Rusch VW, Asamura H, Watanabe H, et al. The IASLC Lung Cancer Staging Project: A Proposal for a New International Lymph Node Map in the Forthcoming Seventh Edition of the TNM Classification for Lung Cancer. Journal of Thoracic Oncology 2009;4:568-577 510.1097/JTO.1090b1013e3181a1090d1082e. Available at: http://journals.lww.com/jto/Fulltext/2009/05000/The_IASLC_Lung_Cancer_Staging_Project__A_Proposal.4.aspx

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

108. 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;128:1461-1467. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16162744

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

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

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

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

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

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

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

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

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

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

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

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

121. Bradley JD, Graham M, Suzanne S, et al. Phase I results of RTOG L-0117; a phase I/II dose intensification study using 3DCRT and concurrent chemotherapy for patients with Inoperable NSCLC [abstract]. J Clin Oncol 2005;23 (Suppl 16):Abstract 7063. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/7063

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

123. Kelsey CR, Light KL and Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. Int J Radiat Oncol Biol Phys 2006;65:1097-1105. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16682136

124. Belderbos JS, Kepka L, Spring Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small-Cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 2008;72:335-342. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18793953

125. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17551299

126. Rosenzweig KE, Sura S, Jackson A and Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. J Clin Oncol 2007;25:5557-5561. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17984185

127. Sanuki-Fujimoto N, Sumi M, Ito Y, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. Radiother Oncol 2009;91:433-437. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19167118

128. Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. Radiat Oncol 2009;4:5. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19183471

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

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

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

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

133. Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-215. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15703313

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

135. Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic radiotherapy. Radiother Oncol 2009;91:282-287. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18950881

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

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

138. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non-Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy. Int J Radiat Oncol Biol Phys 2009. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19515503

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

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

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

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

143. Hata M, Tokuuye K, Kagei K, et al. Hypofractionated high-dose proton beam therapy for stage I non-small-cell lung cancer: preliminary results of a phase I/II clinical study. Int J Radiat Oncol Biol Phys 2007;68:786-793. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17379439

144. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76.

Med Phys 2006;33:3874-3900. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17089851

145. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: A meta-analysis. Radiother Oncol 2009. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19733410

146. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15378503

147. 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. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17050868

148. 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;70:685-692. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18164849

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

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

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

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

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

154. Rades D, Kueter JD, Hornung D, et al. Comparison of stereotactic radiosurgery (SRS) alone and whole brain radiotherapy (WBRT) plus a stereotactic boost (WBRT+SRS) for one to three brain metastases. Strahlenther Onkol 2008;184:655-662. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19107346

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

156. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2005;63:37-46. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16111570

157. Li B, Yu J, Suntharalingam M, et al. Comparison of three treatment options for single brain metastasis from lung cancer. Int J Cancer

2000;90:37-45. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10725856

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

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

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

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

162. Jin JY, Kong FM, Chetty IJ, et al. Impact of Fraction Size on Lung Radiation Toxicity: Hypofractionation May Be Beneficial in Dose Escalation of Radiotherapy for Lung Cancers. Int J Radiat Oncol Biol Phys 2009. Available at: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19577855

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

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

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

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

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

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

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

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

171. Gore EM, Bae K, Wong S, et al. A phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small cell lung cancer: Initial analysis of Radiation Therapy Oncology Group 0214 [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract 7506. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/7506

172. Le Pechoux C, Dunant A, Senan S, et al. Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial. Lancet Oncol 2009;10:467-474. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19386548

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

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

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

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

177. Azzoli CG, Baker S, Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2009:JCO.2009.2023.5622. Available at: http://jco.ascopubs.org/cgi/content/abstract/JCO.2009.23.5622v2

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

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

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

181. Le Chevalier T, Dunant A, Arriagada R, et al. 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 (Suppl 15):Abstract 7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7507

182. Arriagada R, Dunant A, Pignon J-P, et al. Long-Term Results of the International Adjuvant Lung Cancer Trial Evaluating Adjuvant Cisplatin-Based Chemotherapy in Resected Lung Cancer. J Clin Oncol 2009:JCO.2009.2023.2272. Available at: http://jco.ascopubs.org/cgi/content/abstract/JCO.2009.23.2272v1

183. Butts CA, Ding K, Seymour L, et al. Randomized Phase III Trial of Vinorelbine Plus Cisplatin Compared With Observation in Completely Resected Stage IB and II Non-Small-Cell Lung Cancer: Updated Survival Analysis of JBR-10. J Clin Oncol 2009:JCO.2009.2024.0333. Available at: http://jco.ascopubs.org/cgi/content/abstract/JCO.2009.24.0333v1

184. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-3559. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506026

185. Strauss GM, Herndon J, Maddaus MA, et al. Randomized Clinical Trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in Stage IB Non-Small Cell Lung Cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633 [abstract]. J Clin Oncol 2004;22 (Suppl 14):Abstract 7019. Available at: http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/7019

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

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

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

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

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

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

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

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

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

195. Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005;23:5883-5891. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16087941

196. 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;20:4191-4198. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12377962

197. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 2003;21:2004-2010. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12743155

198. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). Clin Lung Cancer 2006;8:116-121. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17026812

199. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023 [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7512. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7512

200. Mina LA, Neubauer MA, Ansari RH, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023--Updated results [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 7519. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7519

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

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

203. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21:3016-3024. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12837811

204. Smit EF, van Meerbeeck JP, Lianes P, et al. Three-arm randomized study of two cisplatin-based regimens and paclitaxel plus gemcitabine in advanced non-small-cell lung cancer: a phase III trial of the European Organization for Research and Treatment of Cancer Lung Cancer Group--EORTC 08975. J Clin Oncol 2003;21:3909-3917. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14581415

205. Zatloukal P, Petruzelka L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. Lung Cancer 2004;46:87-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15364136

206. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26:3543-3551. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18506025

207. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non--small-cell lung cancer: a

Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-3218. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11432888

208. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11784875

209. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003;98:542-553. Available at: http://www.ncbi.nlm.nih.gov/pubmed/12879472

210. Booton R, Lorigan P, Anderson H, et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). Ann Oncol 2006;17:1111-1119. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16603599

211. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15741225

212. Rizvi NA, Riely GJ, Azzoli CG, et al. Phase I/II trial of weekly intravenous 130-nm albumin-bound paclitaxel as initial chemotherapy in patients with stage IV non-small-cell lung cancer. J Clin Oncol 2008;26:639-643. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18235124

213. Green MR, Manikhas GM, Orlov S, et al. Abraxane, a novel Cremophor-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. Ann Oncol 2006;17:1263-1268. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16740598

214. Sandler AB, Johnson DH and Herbst RS. Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer. Clin Cancer Res 2004;10:4258s-4262s. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15217970

215. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. J Clin Oncol 2005;23:3235-3242. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15886311

216. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 2006;355:2542-2550. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17167137

217. Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17285735

218. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-957. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19692680

219. Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small-cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-1400. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19224850

220. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19410716

221. Patel JD, Hensing TA, Rademaker A, et al. Phase II Study of Pemetrexed and Carboplatin Plus Bevacizumab With Maintenance Pemetrexed and Bevacizumab As First-Line Therapy for Nonsquamous

Non-Small-Cell Lung Cancer. J Clin Oncol 2009;27:3284-3289. Available at: http://jco.ascopubs.org/cgi/content/abstract/27/20/3284

222. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-1440. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19767093

223. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. SATURN: A double-blind, randomized, phase III study of maintenance erlotinib versus placebo following nonprogression with first-line platinum-based chemotherapy in patients with advanced NSCLC [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract 8001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/8001

224. Patterson GA, Ginsberg RJ, Poon PY, et al. A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assessment of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1987;94:679-684. Available at: http://www.ncbi.nlm.nih.gov/pubmed/3669696

225. Gonzalez-Stawinski GV, Lemaire A, Merchant F, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg 2003;126:1900-1905. Available at: http://www.ncbi.nlm.nih.gov/pubmed/14688703

226. Tournoy KG, Maddens S, Gosselin R, et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. Thorax 2007;62:696-701. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17687098

227. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J Thorac Cardiovasc Surg 2006;131:822-829; discussion 822-829. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16580440

228. Dillemans B, Deneffe G, Verschakelen J and Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer. A study of 569 patients. Eur J Cardiothorac Surg 1994;8:37-42. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8136168

229. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. Thorax 1995;50:1267-1269. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8553299

230. McLoud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 1992;182:319-323. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1732943

231. Seely JM, Mayo JR, Miller RR and Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. Radiology 1993;186:129-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8416552

232. Kerr KM, Lamb D, Wathen CG, et al. Pathological assessment of mediastinal lymph nodes in lung cancer: implications for non-invasive mediastinal staging. Thorax 1992;47:337-341. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1609375

233. Chin R, Jr., Ward R, Keyes JW, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. Am J Respir Crit Care Med 1995;152:2090-2096. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8520780

234. Kernstine KH, Trapp JF, Croft DR and al e. Comparison of positron emission tomography (PET) and computed tomography (CT)

to identify N2 and N3 disease in non small cell lung cancer (NSCLC). J Clin Oncol (Meeting Abstracts) 1998;17:458. Available at:

235. Kernstine KH, Stanford W, Mullan BF, et al. PET, CT, and MRI with Combidex for mediastinal staging in non-small cell lung carcinoma. Ann Thorac Surg 1999;68:1022-1028. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10510001

236. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. J Clin Oncol 2006;24:3333-3339. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16849747

237. Cerfolio RJ, Bryant AS and Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. J Thorac Cardiovasc Surg 2006;131:1229-1235. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16733150

238. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254-261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10911007

239. Manente P, Vicario G, Piazza F, et al. Does PET/CT modify the therapeutic approach in medical oncology? [abstract]. J Clin Oncol 2008;26 (Suppl 15):Abstract 17525. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/17525

240. Maziak DE, Darling GE, Inculet RI, et al. Positron emission tomography in staging early lung cancer: a randomized trial. Ann Intern Med 2009;151:221-228, W-248. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19581636

241. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32-39. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19571281

242. De Wever W, Stroobants S, Coolen J and Verschakelen JA. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J 2009;33:201-212. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19118231

243. Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. Endoscopy 2005;37:833-839. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16116534

244. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. Chest 2006;130:710-718. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16963667

245. Mayr NA, Hussey DH and Yuh WT. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. AJNR Am J Neuroradiol 1995;16:215-217. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7755752

246. Komaki R, Mountain CF, Holbert JM, et al. Superior sulcus tumors: treatment selection and results for 85 patients without metastasis (Mo) at presentation. Int J Radiat Oncol Biol Phys 1990;19:31-36. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2380092

247. Rusch VW, Kraut MJ, Crowley J and al e. Induction chemoradiotherapy and surgical resection for non-small cell lung carcinomas of the superior sulcus (pancoast tumors): Mature results of Southwest Oncology Group trial 9416 (Intergroup trial 0160) [abstract]. Proc Am Soc Clin Oncol 2003 22:Abstract 2548. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=103854

248. Barnes JB, Johnson SB, Dahiya RS, et al. Concomitant weekly cisplatin and thoracic radiotherapy for Pancoast tumors of the lung: pilot experience of the San Antonio Cancer Institute. Am J Clin Oncol 2002;25:90-92. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11823705

249. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Thorac Cardiovasc Surg 2001;121:472-483. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11241082

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

251. Nakagawa T, Okumura N, Miyoshi K, et al. Prognostic factors in patients with ipsilateral pulmonary metastasis from non-small cell lung cancer. Eur J Cardiothorac Surg 2005;28:635-639. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16126398

252. Lee JG, Lee CY, Kim DJ, et al. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging assessment. Eur J Cardiothorac Surg 2008;33:480-484. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18249000

253. Oliaro A, Filosso PL, Cavallo A, et al. The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system. Eur J Cardiothorac Surg 2008;34:438-443; discussion 443. Available at: http://www.ncbi.nlm.nih.gov/pubmed/18502660

254. Pearson FG, DeLarue NC, Ilves R, et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. J Thorac Cardiovasc Surg 1982;83:1-11. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7054602

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

256. Decker DA, Dines DE, Payne WS, et al. The significance of a cytologically negative pleural effusion in bronchogenic carcinoma. Chest 1978;74:640-642. Available at: http://www.ncbi.nlm.nih.gov/pubmed/216532

257. Burt M, Wronski M, Arbit E and Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. J Thorac Cardiovasc Surg 1992;103:399-410; discussion 410-391. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1312184

258. Alexander E, 3rd, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34-40. Available at: http://www.ncbi.nlm.nih.gov/pubmed/7666461

259. Raviv G, Klein E, Yellin A, et al. Surgical treatment of solitary adrenal metastases from lung carcinoma. J Surg Oncol 1990;43:123-124. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1689433

260. Reyes L, Parvez Z, Nemoto T, et al. Adrenalectomy for adrenal metastasis from lung carcinoma. J Surg Oncol 1990;44:32-34. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2342373

261. Burkes RL, Ginsberg RJ, Shepherd FA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II Trial. J Clin Oncol 1992;10:580-586. Available at: http://www.ncbi.nlm.nih.gov/pubmed/1312587

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

263. Rusch VW, Albain KS, Crowley JJ, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. J Thorac Cardiovasc Surg 1993;105:97-104; discussion 104-106. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8380477

264. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330:153-158. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8043059

265. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994;86:673-680. Available at: http://www.ncbi.nlm.nih.gov/pubmed/8158698

266. Pisters K, Vallieres E, Bunn P, et al. S9900: A phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results [abstract]. J Clin Oncol 2005;23 (Suppl 16):Abstract LBA7012. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA7012

267. Pisters K, Vallieres E, Bunn PA, Jr., et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7520. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7520

268. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257-263. Available at: http://www.ncbi.nlm.nih.gov/pubmed/9690404

269. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. J Clin Oncol 2006;24:2998-3006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16769986

270. Gelb AF, Tashkin DP, Epstein JD, et al. Physiologic characteristics of malignant unilateral main-stem bronchial obstruction. Diagnosis and Nd-YAG laser treatment. Am Rev Respir Dis 1988;138:1382-1385. Available at: http://www.ncbi.nlm.nih.gov/pubmed/2462389

271. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-1436. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17416863

272. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613-2621. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15197804

273. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. J Clin Oncol 2009;27:5255-5261. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19738122

274. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-2191. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15169807

275. Mezger J, von Pawel J and Reck M. Bevacizumab (Bv) single-agent maintenance following Bv-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results from an exploratory analysis of the AVAiL study [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract e19001. Available at: http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e19001

276. Reck M, von Pawel J, Zatloukal P, et al. Phase III Trial of Cisplatin Plus Gemcitabine With Either Placebo or Bevacizumab As First-Line Therapy for Nonsquamous Non-Small-Cell Lung Cancer: AVAiL. J Clin Oncol 2009;27:1227-1234. Available at: http://jco.ascopubs.org/cgi/content/abstract/27/8/1227

277. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002;20:1335-1343. Available at: http://www.ncbi.nlm.nih.gov/pubmed/11870177

278. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res 2007;13:5150-5155. Available at: http://www.ncbi.nlm.nih.gov/pubmed/17785570

279. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast international group 03-05 study. J Clin Oncol 2009;27:1999-2006. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19289619

280. Nguyen KS, Kobayashi S and Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer 2009;10:281-289. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19632948

281. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene 2009;28 Suppl 1:S24-31. Available at: http://www.ncbi.nlm.nih.gov/pubmed/19680293

282. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10856094

283. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-2103. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10811675

284. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15117980

285. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132. Available at: http://www.ncbi.nlm.nih.gov/pubmed/16014882

286. Demarinis F, Paul S, Hanna N, et al. Survival update for the phase III study of pemetrexed vs docetaxel in non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2006;24 (Suppl 18):Abstract 7133. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7133

287. Ramlau R, Gervais R, Krzakowski M, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. J Clin Oncol

2006;24:2800-2807. Available at:
http://www.ncbi.nlm.nih.gov/pubmed/16682727