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NCCN

Non–Small Cell Lung Cancer

Clinical Practice Guidelines in Oncology

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Overview

Lung cancer is the leading cause of cancer-related death in the United States. An estimated 219,440 new cases (116,090 men; 103,350 women) of lung and bronchus cancer were diagnosed in 2009, and 159,390 deaths (88,900 men; 70,490 women) occurred from 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).

NCCN Clinical Practice Guidelines in Oncology on Non–Small Cell Lung Cancer

Key Words

NCCN Clinical Practice Guidelines, NCCN Guidelines, non–small cell lung cancer, lung cancer, multimodality therapy, targeted therapy, chemotherapy, radiation therapy, thoracic surgery

(JNCCN 2010;8:740–801)

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.

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

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Non–Small Cell Lung Cancer

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines on Non–Small Cell Lung Cancer panel members can be found on page 801. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

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 for lung cancer increases with the number of cigarettes smoked per day and the number of years spent smoking. In addition to the hazard of first-hand smoke, exposed nonsmokers have an increased relative risk for 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 undergo hormone replacement therapy, because it increases the risk for 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 for lung cancer in people exposed to the airborne fibers, especially those who smoke. An estimated 3% to 4% of lung cancers are caused by asbestos exposure.[6] Other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens, such as bis(chloromethyl) ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds.[7,8]

Text continues on p. 771

NCCN Non-Small Cell Lung Cancer Panel Members

LUNG CANCER PREVENTION AND SCREENING

- Lung cancer is a unique disease in that the etiologic agent is an industry. More than 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, FDA oversight of tobacco products, and other tobacco control measures.

- Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/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 for 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/clinic/cpgsix.htm) to identify, counsel, and treat patients with nicotine habituation.

- Patients who are current or former smokers have a 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 International Early Lung Cancer Action Program (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;355:1763-1771.
[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;13:439-444.
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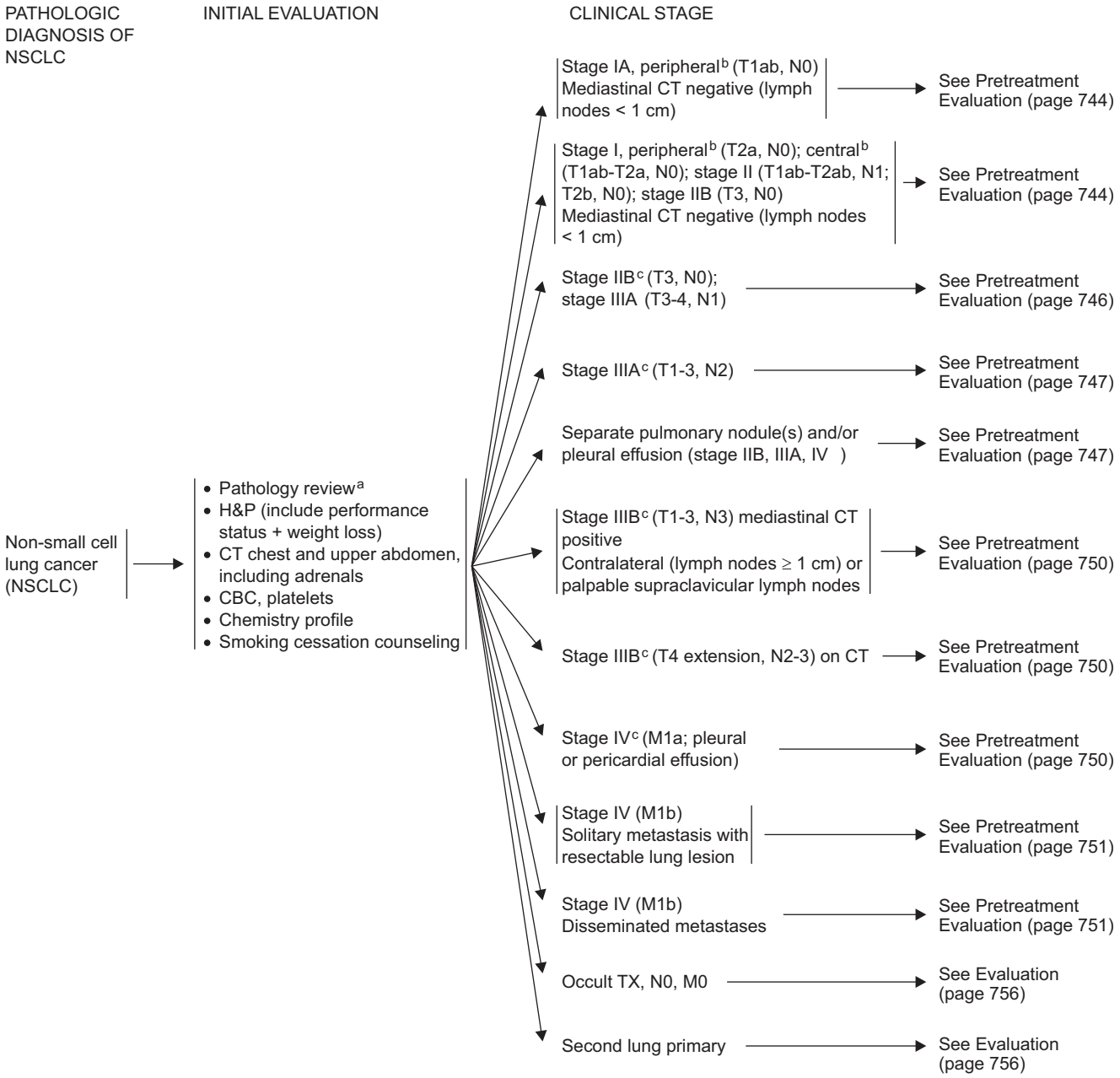
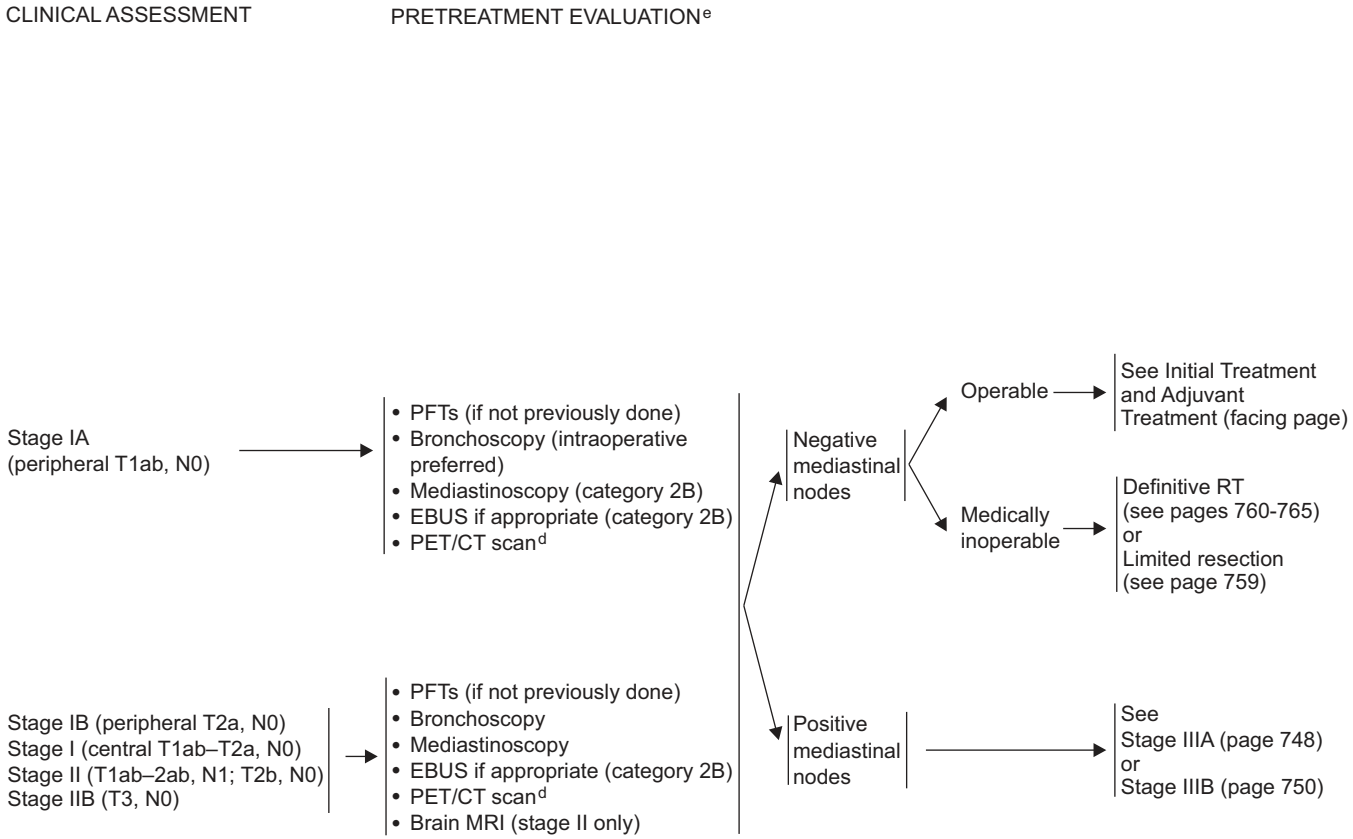
Non–Small Cell Lung Cancer Version 2:2010



[a] See Principles of Pathologic Review (pages 757 and 758).
[b] Based on CT of the chest: peripheral = outer third of lung; central = inner two thirds of lung.
[c] For patients considered to have stage IIB and III tumors, in whom more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.



[d]Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[e]See Principles of Surgical Therapy (page 759).

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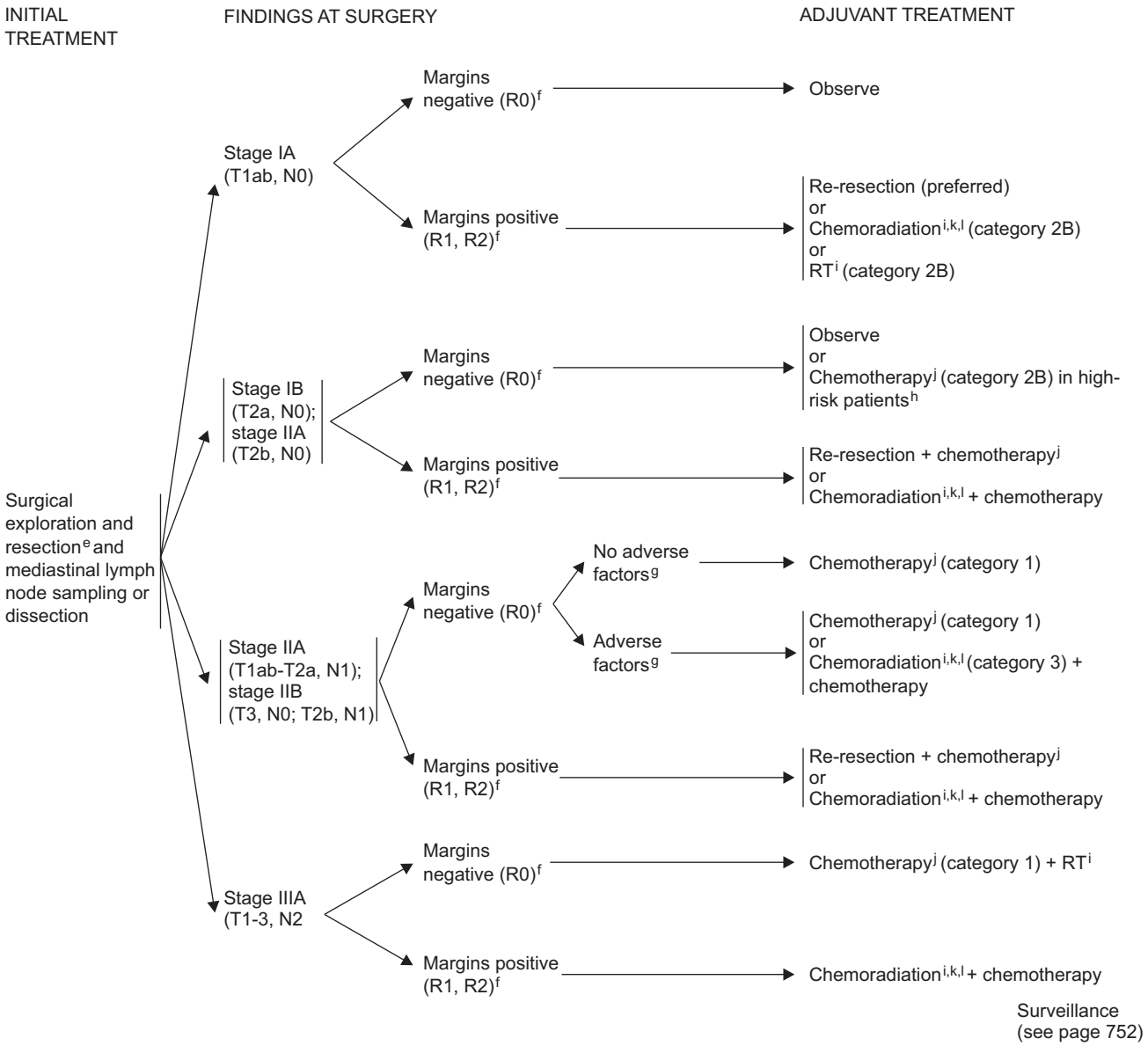
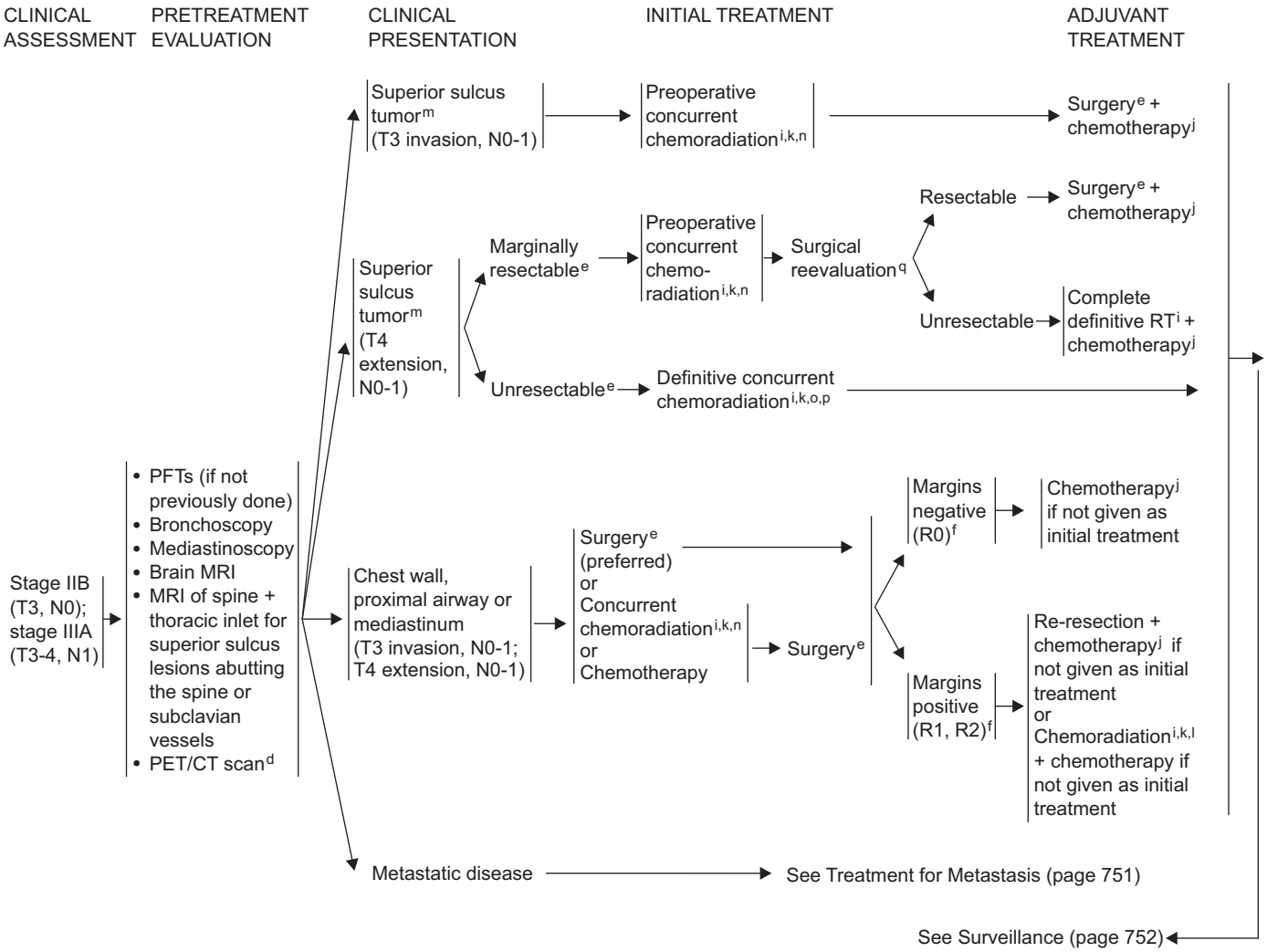


[e] See Principles of Surgical Therapy (page 759).
[f] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[g] Adverse factors include: inadequate mediastinal lymph node dissection, extracapsular spread, multiple positive hilar nodes, and close margins.
[h] High-risk patients are defined by poorly differentiated tumors, vascular invasion, wedge resection, minimal margins, tumors > 4 cm, visceral pleural involvement, Nx.
[i] See Principles of Radiation Therapy (pages 760-765).
[j] See Chemotherapy Regimens for Adjuvant Therapy (page 766).
[k] See Chemotherapy Regimens used with Radiation Therapy (page 767).
[l] For patients with negative margins, most NCCN Member Institutions give sequential chemotherapy/RT; for patients with positive margins, most give concurrent chemo/RT ± chemotherapy.



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[e] See Principles of Surgical Therapy (page 759).
[f] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[i] See Principles of Radiation Therapy (pages 760-765).
[j] See Chemotherapy Regimens for Adjuvant Therapy (page 766).
[k] See Chemotherapy Regimens used with Radiation Therapy (page 767).
[l] For patients with negative margins, most NCCN Member Institutions give sequential chemotherapy/RT; for patients with positive margins, most give concurrent chemo/RT ± chemotherapy.
[m] It is sometimes difficult to distinguish between T3 and T4 superior sulcus tumors.
[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 postoperative 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;121:472-483.

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

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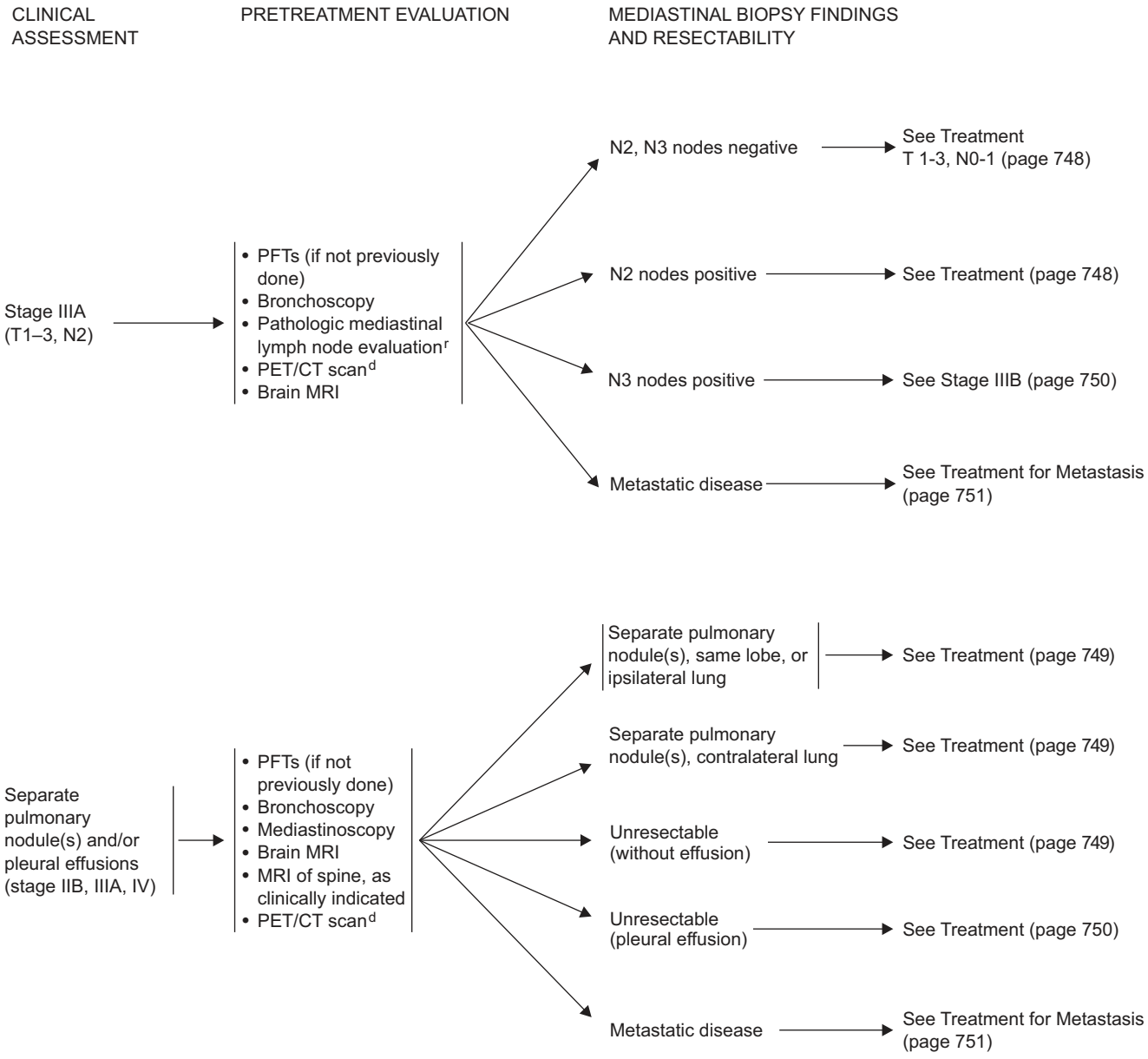
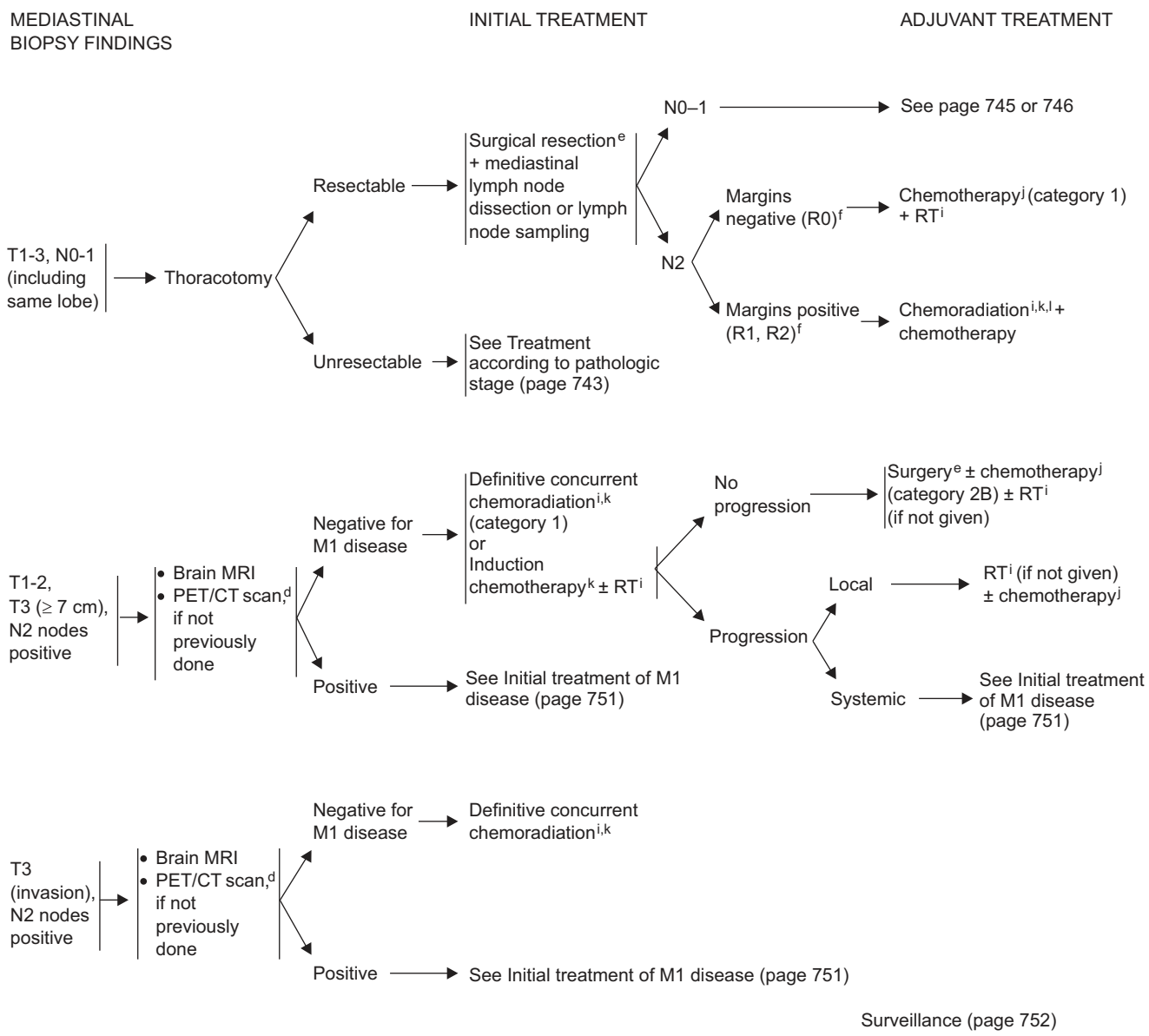


[d]Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[r]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS-FNA, EUS-FNA, and CT-guided FNA biopsy.



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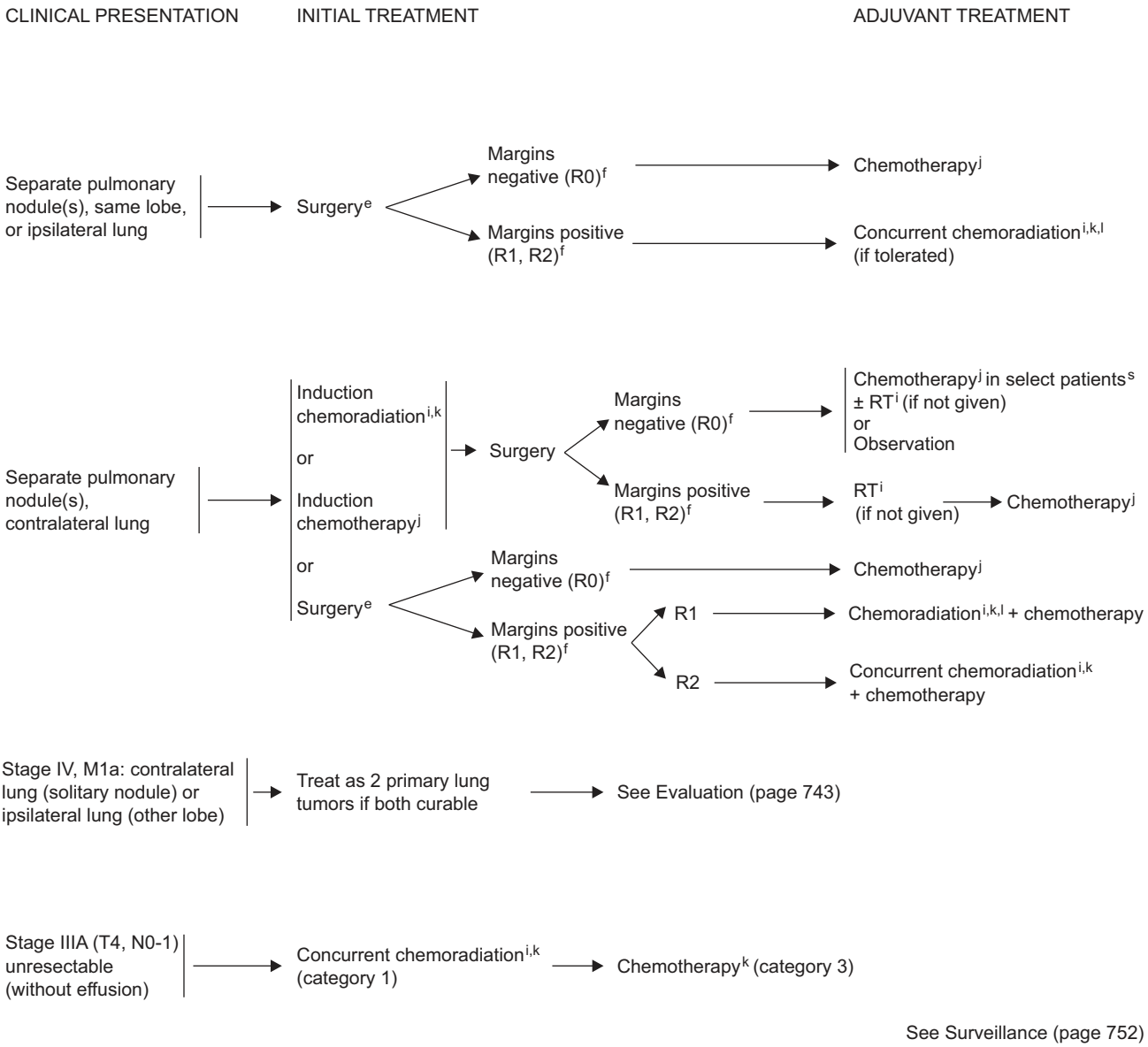
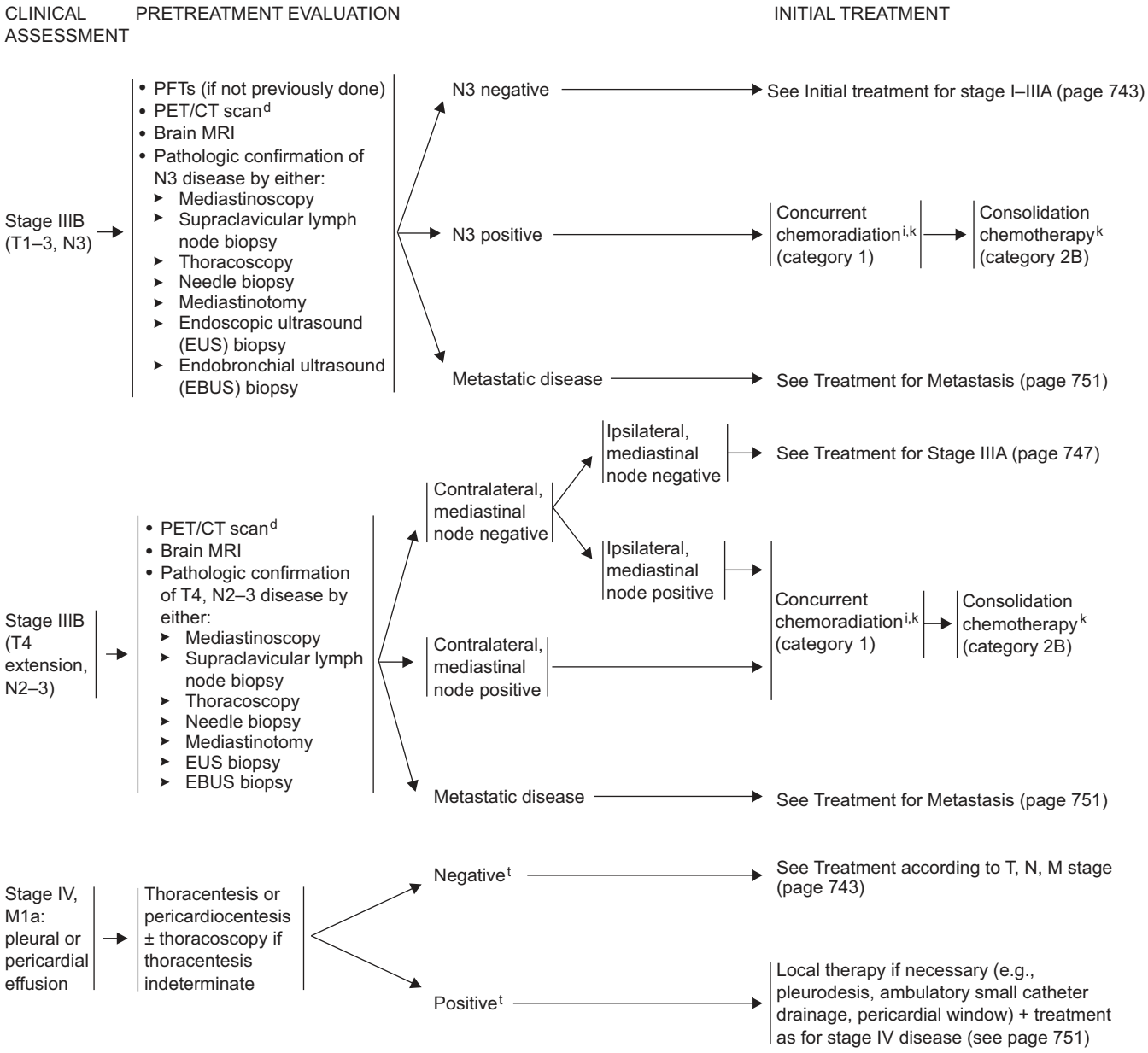


[e] See Principles of Surgical Therapy (page 759).
[f] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[i] See Principles of Radiation Therapy (pages 760-765).
[j] See Chemotherapy Regimens for Adjuvant Therapy (page 766).
[k] See Chemotherapy Regimens used with Radiation Therapy (page 767).
[l] For patients with negative margins, most NCCN Member Institutions give sequential chemotherapy/RT; for patients with positive margins, most give concurrent chemo/RT ± chemotherapy.
[s] The administration of chemotherapy in the adjuvant setting depends on the type of neoadjuvant therapy and the patient's tolerance.



[d] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[i] See Principles of Radiation Therapy (pages 760-765).
[k] See Chemotherapy Regimens used with Radiation Therapy (page 767).
[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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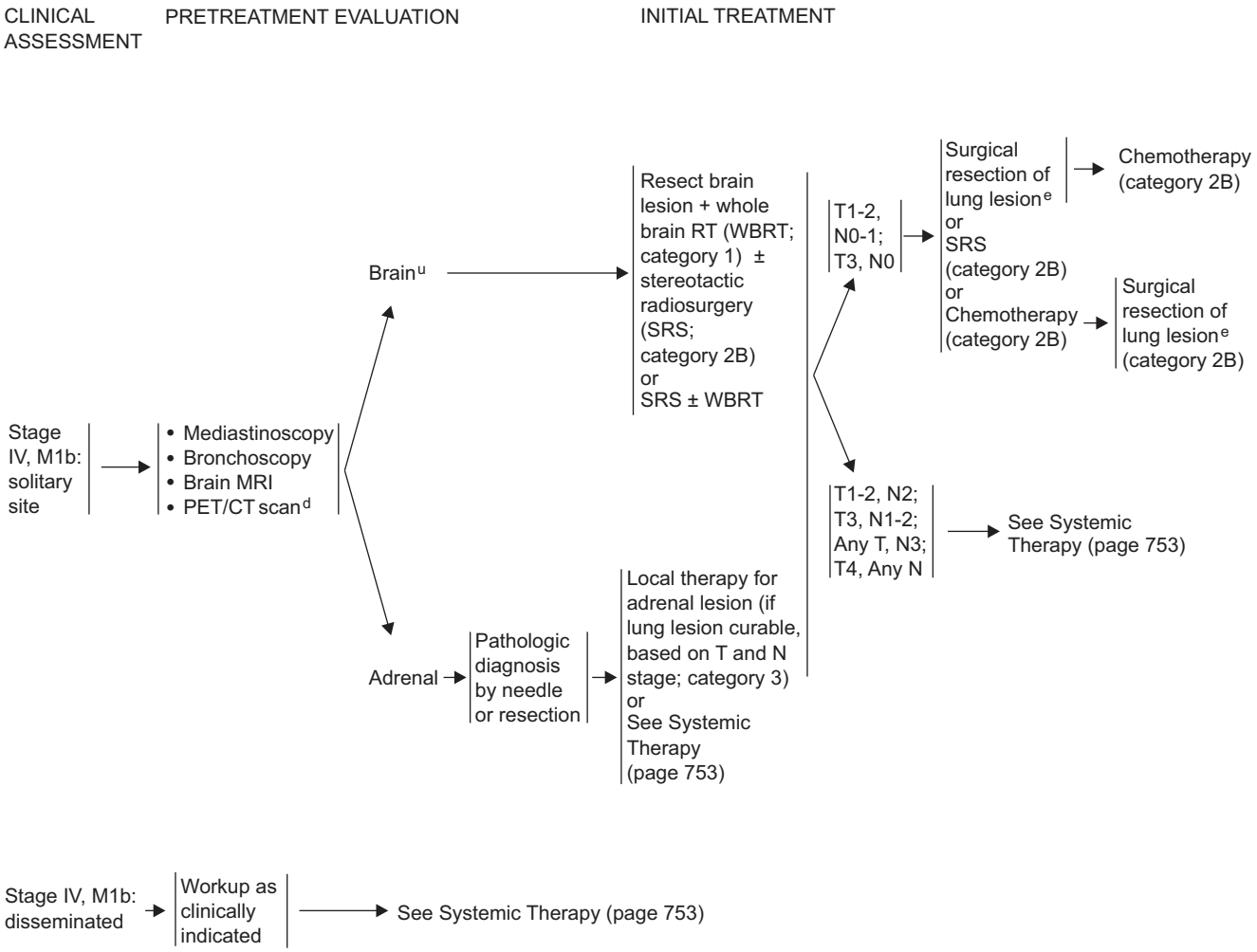
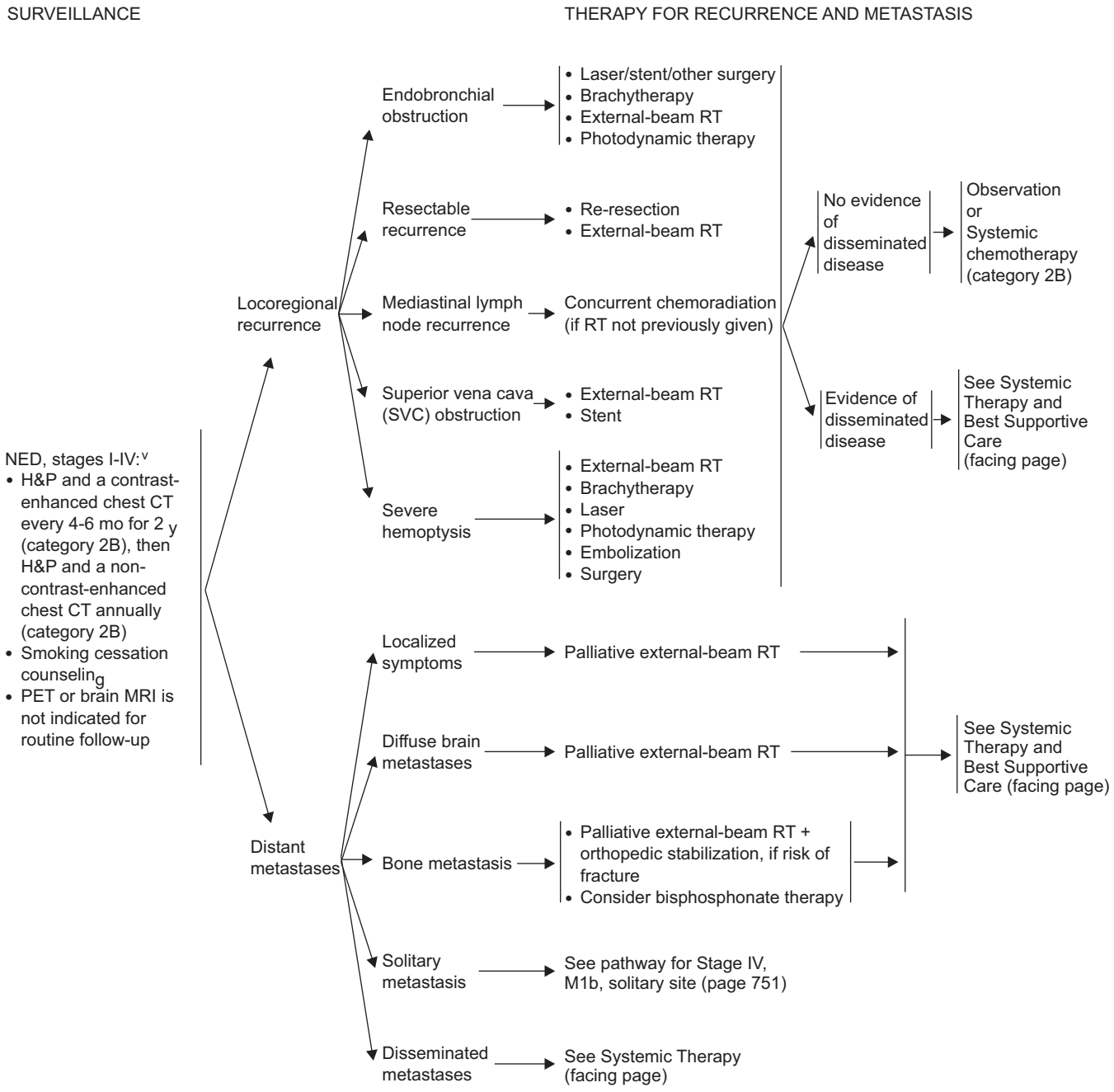


[d]Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
[e]See Principles of Surgical Therapy (page 759).
[u]See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) on Central Nervous System Cancers; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org



[v] See Cancer Survivorship Care (page 770).

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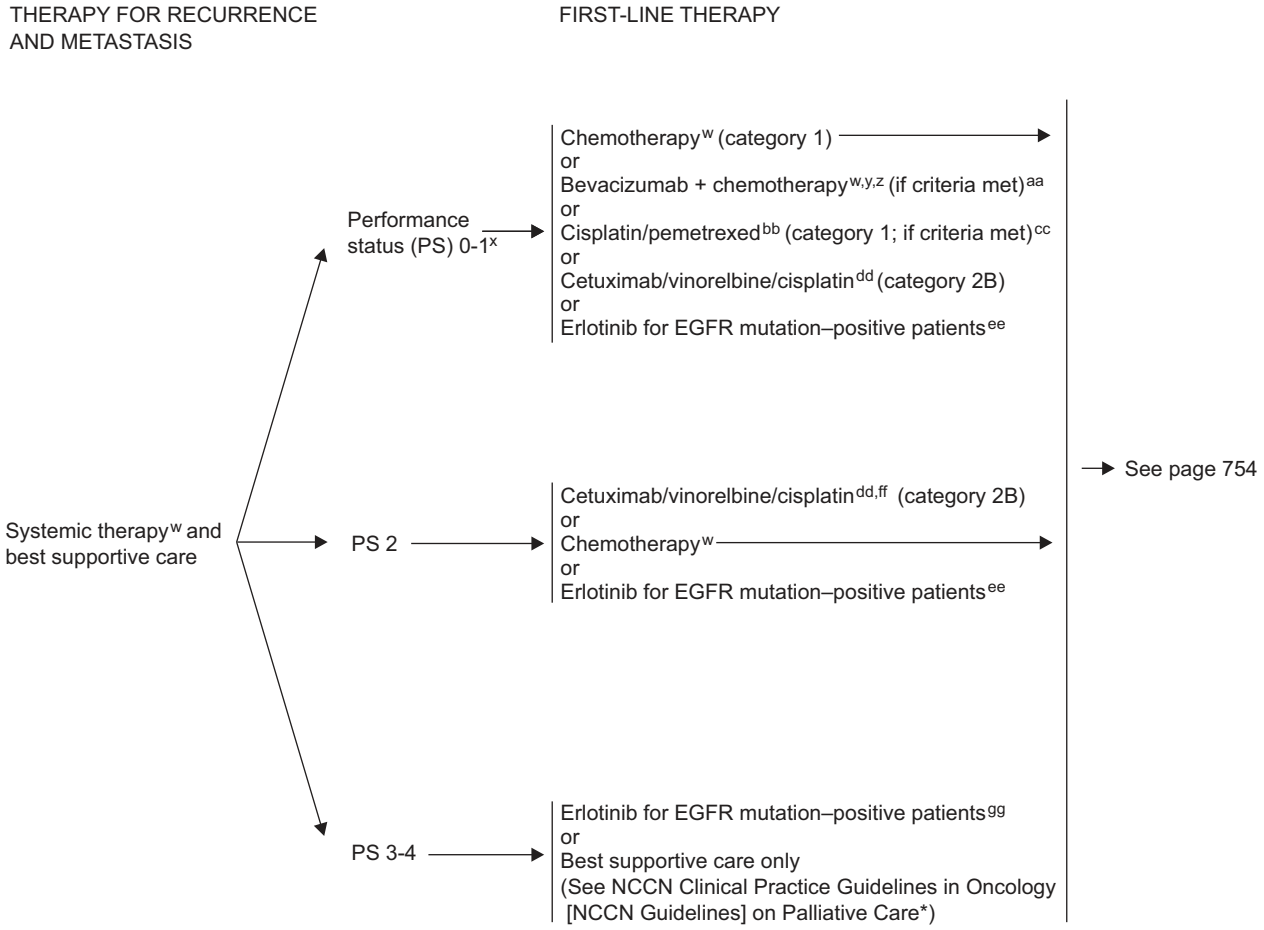
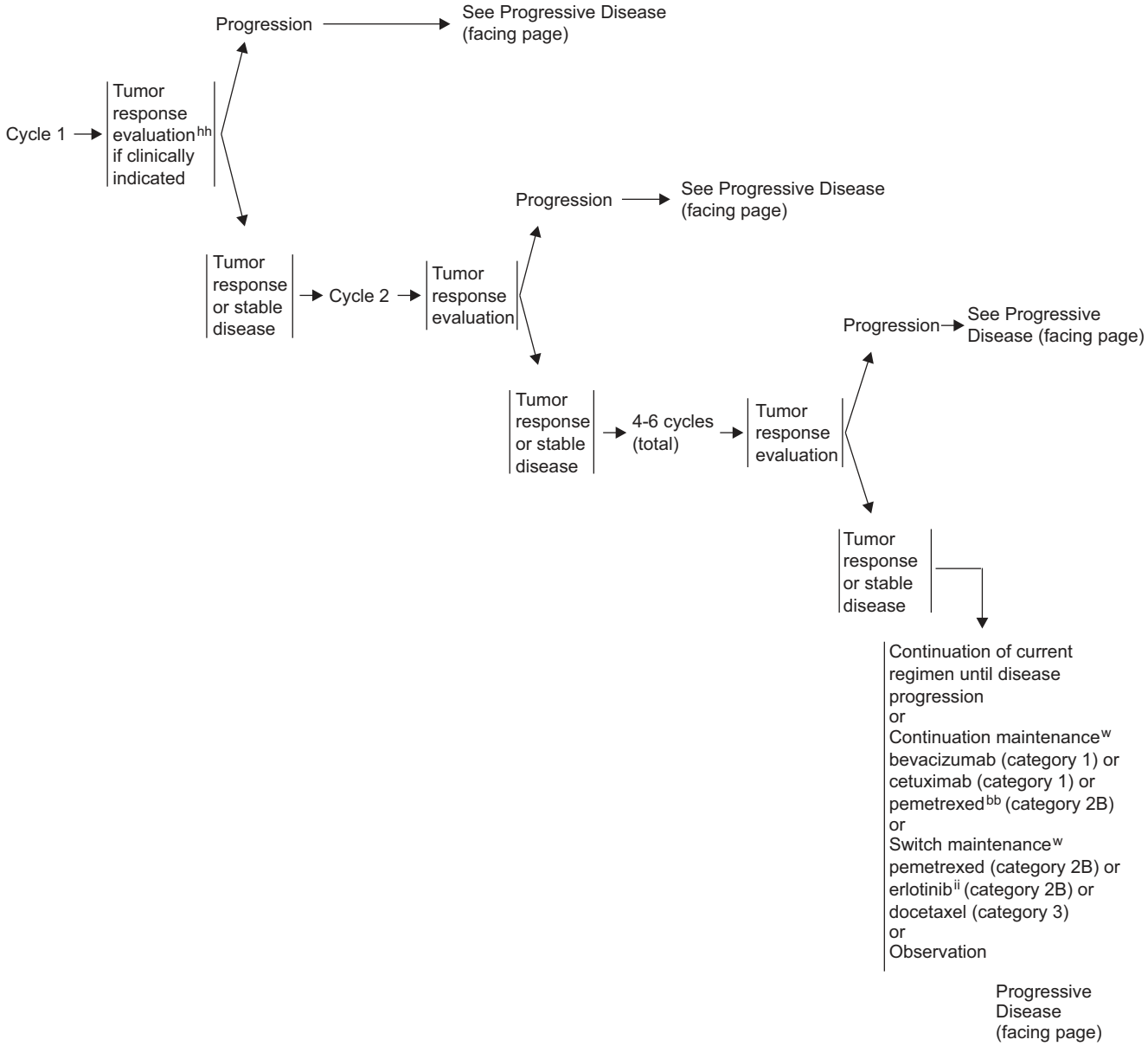


*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

[w] See Systemic Therapy for Advanced or Metastatic Disease (pages 768 and 769).
[x] PS 2 patients have greater toxicity and potential for lower benefit than PS 0-1 patients.
[y] Any regimen with a high risk of thrombocytopenia and the potential risk for bleeding should be used with caution in combination with bevacizumab.
[z] Bevacizumab should be given until progression.
[aa] 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.
[bb] Pemetrexed is not recommended for squamous histology.
[cc] There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients who do not have squamous histology compared with 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.
[dd] 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.
[ee] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-957.
[ff] Full-dose cisplatin for PS 2 patients should be given selectively.
[gg] 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.

THERAPY FOR RECURRENCE AND METASTASIS



[w] See Systemic Therapy for Advanced or Metastatic Disease (pages 768 and 769).
[bb] Pemetrexed is not recommended for squamous histology.
[hh] Some institutions advocate imaging (CT) studies to evaluate tumor progression after the first course.
[ii] Cappuzzo F, Coudert B, Wierzbicki R, et al. Efficacy and safety of erlotinib as first-line maintenance in NSCLC following non-progression with chemotherapy: results from the phase III SATURN study. Presented at 13th World Conference on Lung Cancer; August 4, 2009; San Francisco, California. Abstract A2.1

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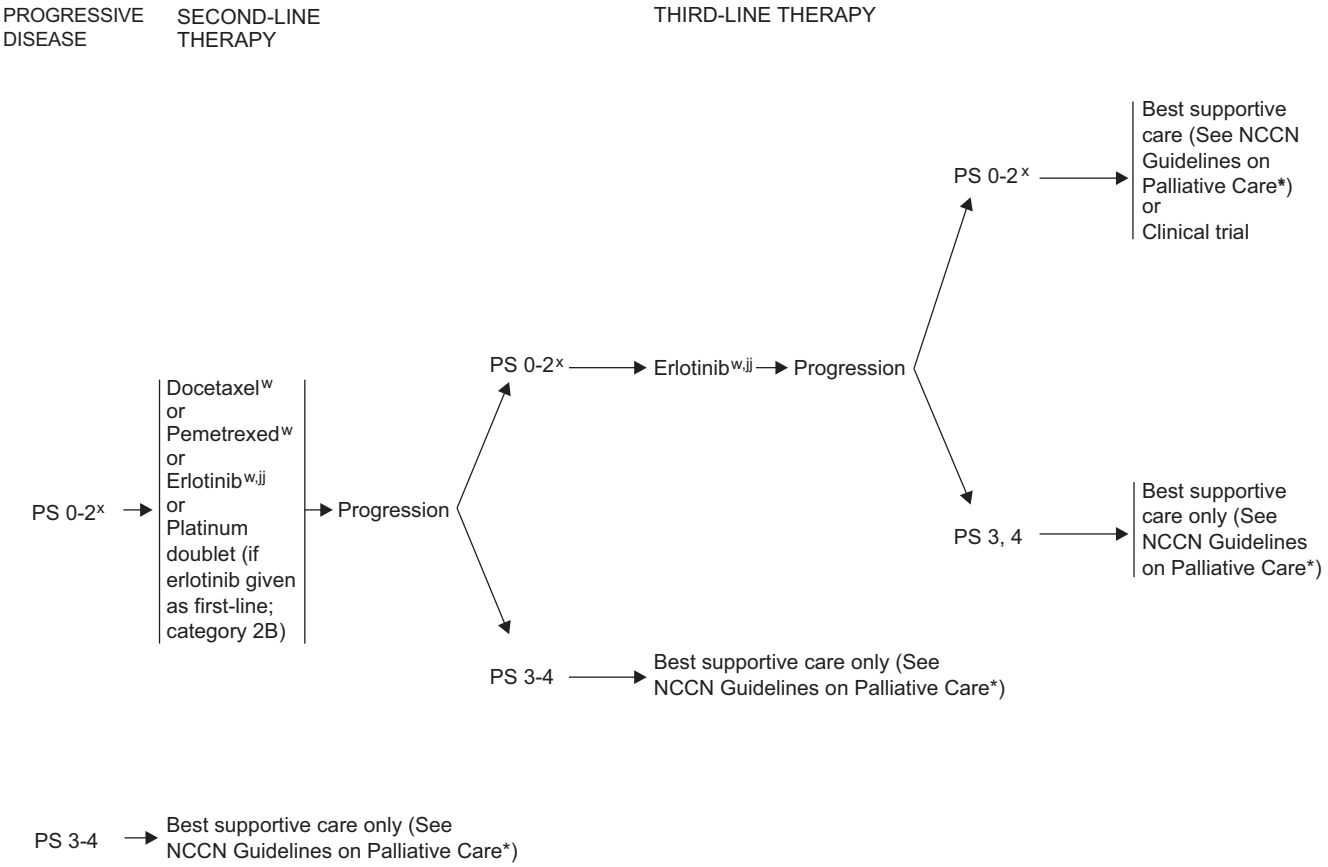

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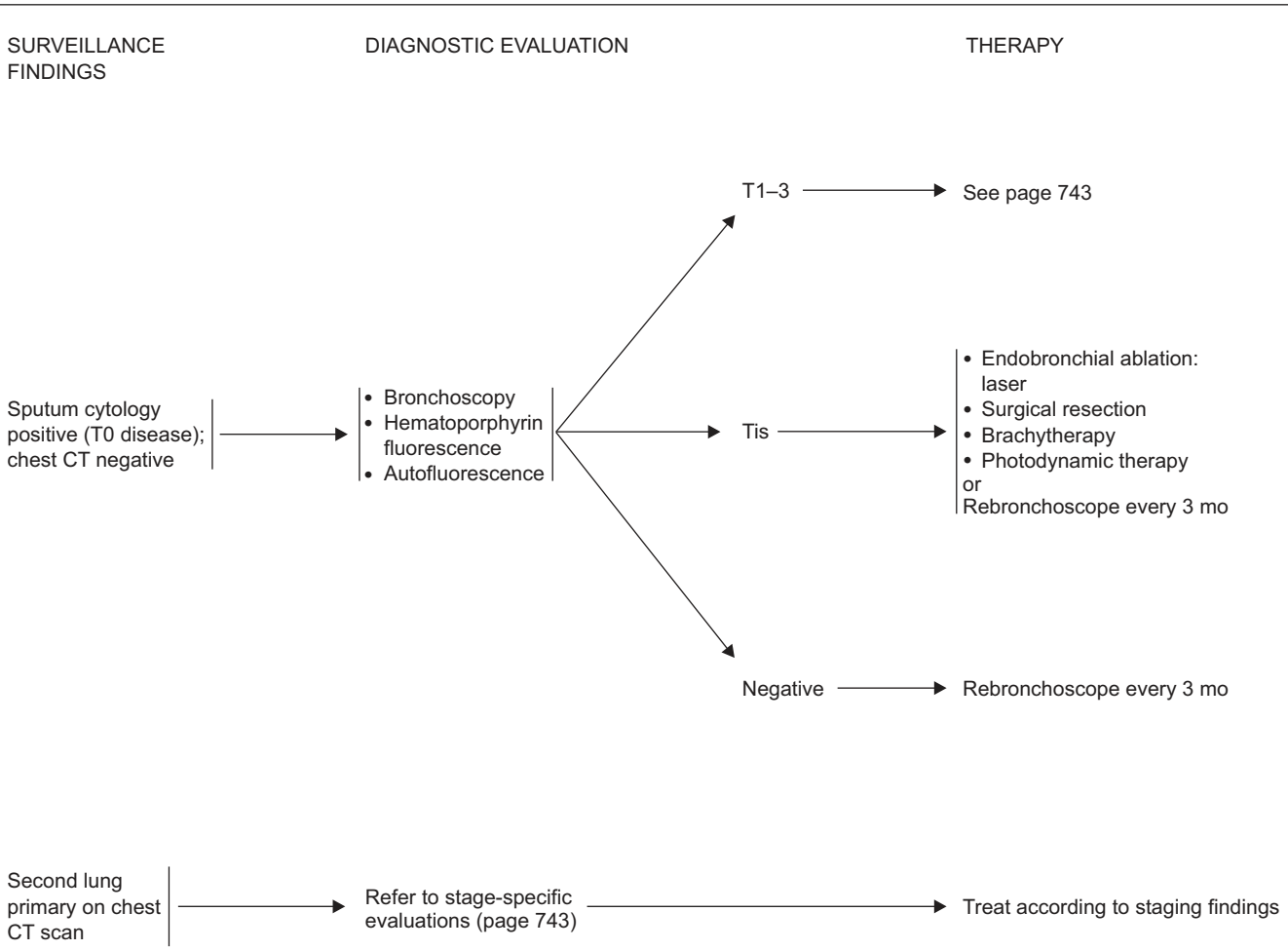
[w] See Systemic Therapy for Advanced or Metastatic Disease (pages 768 and 769).
[x] PS 2 patients have greater toxicity and potential for lower benefit than PS 0-1 patients.
[jj] Patients with a PS of 3 were included in the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) trial BR.21. Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.


SURVEILLANCE FINDINGS
DIAGNOSTIC EVALUATION
THERAPY
Sputum cytology positive (T0 disease); chest CT negative
• Bronchoscopy
• Hematoporphyrin fluorescence
• Autofluorescence
T1–3
See page 743
Tis
• Endobronchial ablation: laser
• Surgical resection
• Brachytherapy
• Photodynamic therapy
or
Rebronchoscope every 3 mo
Negative
Rebronchoscope every 3 mo
Second lung primary on chest CT scan
Refer to stage-specific evaluations (page 743)
Treat according to staging findings

PRINCIPLES OF PATHOLOGIC REVIEW

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 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 in which neoplastic cells spread along preexisting alveolar structures (lepidic spread).[5]
- Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.[4]
- BAC is divided into 3 subtypes: mucinous, non-mucinous, and a mixed mucinous and nonmucinous or indeterminate form. Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1) and 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: most primary lung carcinomas are positive for TTF-1, whereas metastatic adenocarcinoma to the lung is virtually always negative.
  - Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum.
  - CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies, that could help distinguish from primary lung tumors. Prostate specific antigen, prostatic acid phosphatase, and gross cystic disease fluid protein 15 may identify metastatic adenocarcinoma of prostate and breast origin, respectively.
- Determining neuroendocrine status of tumors
  - Chromogranin and synaptophysin are used to diagnose neuroendocrine tumors of the lung. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin, whereas small cell lung cancer is negative in 25% of cases.
- Distinguishing between malignant mesothelioma and lung adenocarcinoma
  - A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma), is used routinely.
  - The stains negative in mesothelioma, but positive in adenocarcinoma are CEA, B72.3, Ber-EP4, and MOC31.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40,[7,8] and cytokeratin 5/6.

Molecular Diagnostic Studies in Lung Cancer

- EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents critical biologic factors for proper patient selection.
- There is a significant association between EGFR mutations, especially exon 19 deletion and exon 21 mutation, and response to TKIs.[9-12]
- EGFR and k-ras mutations are mutually exclusive in patients with lung cancer.[13]
- K-ras mutations are associated with intrinsic TKI resistance, and k-ras gene sequencing could be useful for the selection of patients as candidates for TKI therapy.[14]

See references on page 758

PRINCIPLES OF PATHOLOGIC REVIEW
(References)

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PRINCIPLES OF SURGICAL THERAPY

- 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 preferred over ablation (radiofrequency ablation, cryotherapy, stereotactic radiation). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy.
- 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 and needed imaging studies should be determined before any nonemergency 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 most 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 comorbidity that contraindicates lobectomy
  - Peripheral nodule[1] ≤ 2 cm with at least one of the following:
    - Pure BAC histology (category 2B)
    - Nodule has ≥ 50% ground glass appearance on CT (category 2B)
    - Radiologic surveillance confirms a long doubling time (≥ 400 d; 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) is preferred over pneumonectomy if anatomically appropriate and margin negative resection achieved.
- N1 and N2 node resection and mapping (ATS map; minimum of 3 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.

PRINCIPLES OF RADIATION THERAPY

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 Radiation Therapy Abbreviations, page 762).
- 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, because local recurrence is the most common failure in this group of patients.[6]
- Conformal radiation therapy ± chemotherapy should be offered to patients with stage I, II, and III NSCLC who are medically inoperable but have reasonable performance status and life expectancy. Modern technology can be applied as indicated. Both treatment outcome and cost should be considered.
- 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 patients with stage IV NSCLC and extensive metastasis.

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

- The dose recommendations for definitive and palliative radiation are summarized in Table 2 (Recommended Doses for Conventionally Fractionated Radiation Therapy, page 762). Tissue heterogeneity correction should be used in radiation treatment planning for all patients.
- Preoperatively, a dose of 45-50 Gy in 1.8- to 2-Gy fraction size is recommended.[7] Doses > 50 Gy in the preoperative setting have been reported to be safe and achieved favorable survival outcome.[8-10] However, this should only be performed with an experienced team.
- Postoperative radiation dose should be based on margin status.[2,4] Lung tolerance to radiation after surgery is 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 should be applied for the dose constraints of normal lungs.
- For definitive radiation therapy, the commonly prescribed dose is 60-70 Gy.[11,12] Limited evidence suggested that a dose ≥ 74 Gy is significantly associated with better survival in patients treated with radiation alone or sequential chemoradiation.[13] Radiation dose may be one 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 ≤ 74 Gy may be delivered safely,[16-18] if the dose to normal structures are strictly limited (see Table 3, Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT, page 762). 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 setup errors. GTV should be confined to visible tumors (include both primary and nodal diseases) on CT or PET/CT.
- Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial[19] 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.[11,13,20-23]
- In patients who receive postoperative radiotherapy, CTV should consist of the bronchial stump and high-risk draining lymph node stations.[24]
- It is essential to evaluate the dose–volume histogram (DVH) 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, page 762) 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; mean lung dose should be limited to < 8.5 Gy in pneumonectomy patients.

PRINCIPLES OF RADIATION THERAPY (Cont.)

Radiation Simulation, Planning, and Delivery

- Treatment planning should be performed by 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 disease. PET/CT is preferable in cases with significant atelectasis and when IV contrast is contraindicated. PET/CT scan significantly improve the target accuracy.[33]
- In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume, and the cone-down fields should cover the post-chemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the post-chemotherapy volume 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 and 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 or 18 MV energies can be considered for more optimal dose arrangement.
- When there is a large volume of normal lung being irradiated or tumors that are located close to critical structures (i.e., spinal cord), IMRT may be considered for high-dose radiation to avoid overdose to normal tissues. A significantly lower risk for radiation pneumonitis and improved overall survival have been observed with IMRT compared with 3DCRT for lung cancer.[34] 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.[35-39] When IMRT and proton therapy are used, daily image guidance at delivery should be used for quality assurance. The modality of IGRT should be based on the institutional experience and the treatment accuracy.
- Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per AAPM Task Group 76 guideline, include: 1) motion-encompassing methods, such as slow CTscanning, inhale and exhale breath-hold CT, and 4-dimensional 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, and self breath-hold without respiratory monitoring; 4) forced shallow breathing with abdominal compression; and 5) real-time tumor-tracking methods.

Stereotactic Body Radiation Therapy (SBRT)

- SBRT provides statistically significantly higher 5-year survival than 3DCRT in stage I NSCLC.[40] SBRT can be considered for patients with inoperable stage I NSCLC with node-negative peripheral lesions (see Figure 1, Schema of Central and Peripheral Locations [page 763]) that are < 5 cm in maximal dimension[41,42] or limited lung metastasis[43]
- SBRT fractionation regimens range from one single fraction[44] to 3 fractions,[45,46] 4 fractions,[47] and 5 fractions[48,49] (see Table 4, SBRT Regimens and Indications for Lung Tumors, page 763). Although the optimal number of fractionation may be estimated based on the tumor size and total dose,[50] an accumulative BED of ≥ 100 Gy is associated with better survival.[51] RTOG 0915 is ongoing to compare the outcomes between one single fraction and 4 fractions.
- SBRT normal tissue dose constraints should be strictly followed (see Table 5, Normal Tissue Dose Volume Constraints for SBRT, page 763).

Prophylactic Cranial Irradiation (PCI)

- The role of prophylactic brain irradiation is controversial. The recommendation of whole brain irradiation should be a decision after multidisciplinary discussion, weighing the potential benefit against the risk for each individual patient. Dose and fractionation of PCI can be the same as for small cell lung cancer (25 Gy in 10 fractions over 2 wk).[52]

Continued on page 762

PRINCIPLES OF RADIATION THERAPY

Table 1. Commonly Used Radiation Therapy Abbreviations

3DCRT	3-dimensional conformal radiation therapy
GTV	Gross tumor volume
CTV	Clinical target volume
PTV	Planning target volume
ITV	Internal target volume
BED	Biological equivalent dose
OAR	Organ at risk
V20	% volume an OAR receiving ≥ 20 Gy
MLD	Mean lung dose
ABC	Active breathing control
IMRT	Intensity-modulated radiation therapy
OBI	On board image
IGRT	Image-guided radiation therapy
SBRT	Stereotactic body radiation therapy
4DCT	4-dimensional computerized tomography
CBCT	Cone beam computerized tomography

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

Table 2. Recommended Doses for Conventionally Fractionated Radiation Therapy

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

Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT†

Structures	Limits
Spinal cord	50 Gy in 1.8-to 2-Gy fractions
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-to 2-Gy fractions

†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.
Abbreviation: MLD, mean total lung dose.

PRINCIPLES OF RADIATION THERAPY

Table 4. SBRT Regimens and Indications for Lung Tumors

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

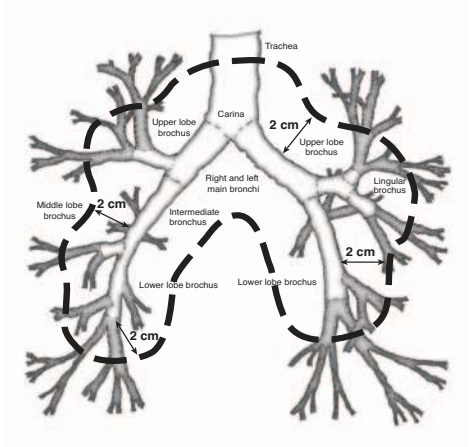
Table 5. Normal Tissue Dose Volume Constraints for SBRT*

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)	32 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 the maximum point doses, based on a combined consideration of recommendations from ongoing multicenter trials (RTOG 0618 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

Reprinted with permission © 2008 American Society of Clinical Oncology. All rights reserved. Timmerman R, McGarry R, Yainnoutsos 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;24:4837.

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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 d for 4 cycles[a]
Cisplatin, 100 mg/m^2, on day 1 Vinorelbine, 30 mg/m^2, days 1, 8, 15, 22	Every 28 d for 4 cycles[b,c]
Cisplatin, 75-80 mg/m^2, on day 1 Vinorelbine, 25-30 mg/m^2, days 1 + 8	Every 21 d for 4 cycles[a]
Cisplatin, 100 mg/m^2, on day 1 Etoposide, 100 mg/m^2, days 1-3	Every 28 d 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 wk after day 43	Every 21 d 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 d
Cisplatin, 75 mg/m^2 Docetaxel, 75 mg/m^2	Every 21 d[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 d 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 d[d]

See Chemotherapy Regimens Used With Radiation Therapy on facing page

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

Sequential Chemotherapy/RT Regimens
Cisplatin, 100 mg/m^2, on day 1, 29 Vinblastine, 5 mg/m^2, weekly on days 1, 8, 15, 22, 29 followed by RT with 60 Gy in 30 fractions beginning on day 50[b]
Paclitaxel, 200 mg/m^2, every 3 wk over 3 h, 2 cycles Carboplatin, AUC 6, 2 cycles followed by thoracic RT 63 Gy[c] beginning on day 42

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

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

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

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 with 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 (PS 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 patients with 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 wk, and a doubling of 1-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 (e.g., gemcitabine/docetaxel).
- If patient has a known *KRAS* mutation, therapy other than erlotinib should be considered first.

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 (category 2B).
  - 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.

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

SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE

Agents listed below are used in the treatment of patients with NSCLC. Most are used in combination, whereas others are used as monotherapy (e.g., 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[6-8]
- 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] Bellani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005;16:1069-1075.

[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.

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

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[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.

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

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

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[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.

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*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.

CANCER SURVIVORSHIP CARE

Cancer Survivorship[1]

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

NSCLC Long-Term Follow-Up Care

- Cancer surveillance
  - H&P and a contrast-enhanced chest CT scan every 4-6 mo for 2 y (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 min of moderate-intensity physical activity on most days of the week)
- Consume a healthy diet with emphasis on plant sources
- Limit consumption of alcohol if you consume alcoholic beverages

Additional Health Monitoring

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

Resources

- National Cancer Institute Facing Forward: Life After Cancer Treatment (http://wwwcancer.gov/cancertopics/life-after-treatment/allpages)

NON-SMALL CELL LUNG CANCER SURVIVORSHIP

Cancer Screening Recommendations[3,4]

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

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

*To view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org.

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Prevention and Screening

Lung cancer is a unique disease in that 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, following 2 links). A causal relationship exists 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) can be very useful (see *Treating Tobacco Use and Dependence: 2008 Update*, available at 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. Although studies show that varenicline is better than bupropion for smoking cessation,[9,10] its use caused nausea in almost 30% of patients[11] and its effectiveness 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-related death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.[13,14] Because localized cancer can be managed curatively and survival in other solid tumors (e.g., breast, cervix, colon, prostate) seems 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 CT in lung cancer screening are promising, detecting stage I lung cancer in more than 80% of newly diagnosed cases.[15–17] The National Lung Screening Trial (NLST; American College of Radiology Imaging Network [ACRIN] Protocol A6654) is a randomized, controlled study involving 50,000 current or former smokers comparing the risks and benefits of spiral CT scans with those of chest radiographs for detecting lung cancer. The NSLT is now closed, with results 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 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. For patients with stage I disease, the 10-year survival rate was 92% when the cancers were promptly removed; however, those 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 provides excellent survival data. However, whether screening decreases mortality has not yet been shown conclusively and is expected to be answered by the NLST.

Currently, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Because available data[18–21] are conflicting,[22,23] conclusive data from ongoing trials are necessary to define the benefits and risks associated with screening for lung cancer with low-dose CT. For high-risk individuals, the panel recommends participation in a clinical trial evaluating CT screening. Individuals for whom a trial is not available or who are not eligible should go to a center of excellence with expertise in radiology, pathology, cytology, thoracic surgery, and general lung cancer treatment to discuss the potential risks and benefits before undergoing 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 from a CT screening clinic show that a malignant tumor was detected in 3% of patients; many patients (45%) did not complete follow-up.[25]

Classification and Prognostic Factors

The WHO divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: NSCLC and small cell lung cancer (SCLC; see the NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] on Small Cell Lung Cancer; for the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org). NSCLC accounts for more than 85% of all lung cancer cases and includes 2 major types: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types) and 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; ECOG 0, 1, or 2), no significant weight loss (≤ 5%), and female gender.[27] Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (*p53*), 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-TKIs).[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. The mediastinal lymph nodes are also 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 surgery, or evaluate the regional lymph nodes. Postoperative evaluation provides the pathology characteristics necessary for classifying tumor type, staging, and prognostic factors. The surgical pathology report should include the histologic classification published by the WHO for carcinomas of the lung.[33] The principles of pathology review are listed on page 757.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important subtype of pulmonary adenocarcinoma,[34] and data suggest that gefitinib and erlotinib are useful treatments.[35–37] BAC includes only noninvasive tumors with neoplastic cells that spread out along preexisting 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 BAC expresses CK20 and CK7, but reportedly lacks TTF-1 expression.[39] BACs are usually CK7+ and CK20–, and are 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 are used routinely, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma). Stains that are negative in mesothelioma but positive in adenocarcinoma are carcinoembryonic antigen (CEA), 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, distinguish adenocarcinoma from malignant mesothelioma, and 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 thyroid cancer tumors, whereas 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 SCLC 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, 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 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.[48,49] These guidelines were updated based on the revised AJCC (7th edition) staging system.[50] Tables summarizing the revised stage grouping and describing the TNM classification scheme are available online, in these guidelines, at www.NCCN.org (ST-1 and ST-2).

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 and advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging: for example, T2bN0M0 is upstaged from stage IB to IIA; T2aN1M0 is downstaged from stage IIB to IIA; T4N0-N1M0 is downstaged from stage IIIB to IIIA; and wet stage 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 through 2004, the overall 5-year relative survival rate for lung cancer was 15.2% (from 17 SEER 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 the staging information was unknown for the remaining 8%. 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 SCLC, 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 IA or IB and on the tumor location.[52] Another study in patients with stage I disease (n = 19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; however, for untreated stage I NSCLC, 5-year overall survival was only 6%.[53] Of patients with stage I disease 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, evidence is strongest for EGFR, the 5′ endonuclease of the nucleotide excision repair complex (ERCC1), K-*ras* oncogene, and the regulatory subunit of ribonucleotide reductase (RRM1). A *prognostic* biomarker is a biomolecule that indicates patient survival independent of the treatment received; it is an indicator of the innate tumor aggressiveness. A *predictive* biomarker is a biomolecule that indicates therapeutic efficacy; that is, an interaction exists between the biomolecule and therapy that impacts patient outcome.

The presence of the EGFR exon 19 deletion or exon 21 L858R mutation does not seem 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 with 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 with the absence of these 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 with 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 phosphorylation of downstream molecules with activation of multiple cellular functions, including proliferation and survival. EGFR is detectable in approximately 80% to 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 result in activation of the tyrosine kinase domain and are associated with sensitivity to the small-molecule TKIs, erlotinib and gefitinib. These mutations are found in approximately 10% to 15% of Caucasian and 30% to 40% of Asian patients with NSCLC.

The prognostic effect of EGFR mutations E19del and L858R is not clear, because most reports are limited to patients undergoing active therapy. In 177 patients who participated in a randomized trial of second-line gefitinib versus placebo, Tsao et al.[54] found mutations in 40, and 20 patients had E19del or L858R. The investigators did not find a correlation between mutational status and gene copy number or expression through 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 the 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.[64,65] In patients with a bronchioloalveolar variant of adenocarcinoma and an EGFR mutation, subsequent retrospective studies have shown an objective response rate to single-agent therapy of approximately 80%, with a median progression-free survival of 13 months.[36] A recent prospective study shows that the objective response rate in North American patients with nonsquamous 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% with mutations vs. 18% without).[31] The response rates in the group of patients undergoing only chemotherapy were 21% for those with mutations and 27% for those without.

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 undergo 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 with 42 months for those 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, whereas 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 those 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) than in those with high expression (4.7 months).[66]

Olaussen et al.[57] found that ERCC1 protein expression, as determined through 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). In this study, only patients with low tumoral ERCC1 protein levels benefited from adjuvant chemotherapy (adjusted hazard ratio [HR] for death, 0.65; 95% CI, 0.50–0.86; P = .002). Most recently, Bepler et al.[62] 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). Thus, response was better in patients with low levels of ERCC1 expression.[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, the K-*ras* gene was described as mutated in codon 12 in 5 of 10 adenocarcinomas, 0 of 15 squamous, and 0 of 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 those with wild-type K-*ras*. Slebos et al.[28] determined K-*ras* codon 12 mutations in 69 patients with completely resected adenocarcinomas who did not undergo additional therapy. They found that disease-free and overall survival were significantly shorter (P = .038 and P = .002, respectively) in the 19 patients with mutations than in the 50 without. Mitsudomi et al.[69] independently confirmed these data in a cohort of 66 patients (11 with K-*ras* codon 12 mutations; P = .03 for overall survival difference). However, Tsao et al.[59] did not find a significant difference (P = .40) in survival according to *ras* mutational status among patients in the observation arm of the Canadian adjuvant chemotherapy trial (JBR.10).[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 seem 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 experienced response (0/18), compared with 20 without K-*ras* mutations who did (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 and 4 of 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 undergoing chemotherapy plus erlotinib, suggesting that the addition of erlotinib to chemotherapy in patients with K-*ras* mutations may adversely interfere with chemotherapeutic efficacy.

Tsao et al.[59] 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 (JBR.10). They found that patients with *ras* mutations did not derive benefit from adjuvant cisplatin/vinorelbine (HR for death with chemotherapy vs. observation, 0.95; CI, 0.53–1.71; $P = .87$), whereas those without mutations (N = 333) benefited significantly (HR for death with chemotherapy vs. 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 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 with 60.2 months for patients with low *RRM1* expression.[61]

In fresh frozen tumor specimens that had been prospectively collected from 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 those 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, whereas those 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, suggesting that a substantial interaction exists between the biomarker and treatment regimen that impacts on patient outcome.

Most recently, Bepler et al.[62] 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 ($P = .001$; $r = 0.41$). Thus, response was better in patients with low levels of *RRM1* expression.[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. The following sections describe the clinical trials that have led to the standard treatments.

Surgery

In general, for patients with stage I or 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 conducted 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 patients with lung cancer (e.g., multidisciplinary clinic and/or tumor board). Patients with pathologic stage II or greater disease should be referred to medical oncology for evaluation. Referral to a medical oncologist should also be considered for patients with stage IB disease, and to a radiation oncologist for those with stage IIIA disease. Treatment delays because of poor coordination among specialists should be avoided.

The surgical procedure used depends on the extent of disease and the cardiopulmonary reserve of the patient. If anatomically appropriate and margin-negative resection can be achieved, lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy; otherwise, lobectomy or pneumonectomy should be performed if physiologically feasible.[73,74] Resection (including wedge resection) is preferred over ablation (i.e., radiofrequency ablation [RFA], cryotherapy, stereotactic radiation).[74] However, 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 is controversial.[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 than mediastinal lymph node sampling in patients undergoing resection for N0 or nonhilar 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. The IASCL (International Association for the Study of Lung Cancer) 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 this is not technically feasible because it would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in selected patients: those who are not eligible for lobectomy because of poor pulmonary reserve or other major comorbidity and 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 either 2 cm or more, or the size of the nodule or more.[80,81]

Video-assisted thoracic surgery (VATS) is a relatively new minimally invasive surgical treatment that is being investigated in all aspects of lung cancer.[82,83] Published studies suggest that VATS has several advantages over 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 for intraoperative bleeding, and minimal locoregional recurrence.[90–94]

In patients with stage I NSCLC who undergo VATS with lymph node dissection, the 5-year survival, long-term survival, and local recurrence rates were comparable to those achieved with routine open lung resection.[95–97] VATS has also been shown to improve discharge independence in older populations and high-risk patients.[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 (see page 759) 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: RT 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 on page 762). Treatment recommendations should be made after joint consultation and/or discussion among 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 RT is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established (see pages 745 and 748).[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 for patients who are medically fit.[105,106] RT 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 stages I through III NSCLC who are medically inoperable but have reasonable PS and life expectancy.[108] Modern 3-dimensional conformal RT techniques with CT or CT/PET-based treatment planning should be used on all patients. Both treatment outcome and cost should be considered. In patients undergoing RT or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (e.g., grade 3 esophagitis, hematologic toxicities) should be minimized through conformal treatment planning and aggressive supportive care. RT can be offered to primary or distant sites as palliative care for patients with stage IV disease 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 received 60 Gy is difficult, because the landmarks disappear with high doses of radiation. Thus, surgeons are often wary of resection in areas that previously received RT doses of more than 45 Gy, especially in patients who received RT doses of more than 60 Gy (i.e., those who received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. RT should continue to definitive dose without interruption for patients who are not surgical candidates.

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 on page 762). Tissue heterogeneity correction should be used in RT treatment planning for all patients. Preoperatively, a dose of 45 to 50 Gy in 1.8- to 2-Gy fractions is often recommended.[111] Doses greater than 50 Gy in the preoperative setting have been reported to be safe and associated with a favorable survival outcome;[112–114] however, this should only be performed by an experienced team.

The postoperative RT dose should be based on margin status. After surgery, lung tolerance to RT is remarkably less 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 on page 762). For definitive RT, the commonly prescribed dose is 60 to 70 Gy.[115] A retrospective study showed that a dose of 74 Gy or more was associated with better survival in patients treated with radiation alone or sequential chemotherapy followed by radiation.[116] The radiation dose is one significant factor affecting overall survival in patients with either stage I or II disease 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 on page 762). The role of high-dose radiation with concurrent chemotherapy is being tested in a phase III randomized trial (RTOG 0617).

For treatment volume consideration, planning target volume should be defined according to the International Commission on Radiation Units and Measurements Report 62 (ICRU-62) guidelines,

based on gross tumor volume, plus clinical target volume margins for microscopic diseases, internal target volume margins for target motion, and margins for daily set-up errors.[122] Gross tumor volume should be confined to visible tumors (including both primary and nodal diseases) on CT or PET/CT.

In patients undergoing postoperative radiotherapy, clinical target volume should consist of the bronchial stump and high-risk draining lymph node stations.[123] Regarding the clinical target volume of nodal regions, elective nodal irradiation 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 elective nodal irradiation has been shown to allow a higher dose of radiation with acceptable toxicity and low risk for isolated nodal relapse.[115,116,125–128]

It is essential to evaluate the dose–volume histogram 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 on page 762). These limits are largely empiric.[129–136] For patients undergoing postoperative RT, more strict dose–volume histogram parameters should be considered for the lung. The exact limit is unknown for lobectomy cases; mean lung dose should be limited to less than 8.5 Gy in patients undergoing pneumonectomy.

Radiation Simulation, Planning, and Delivery: Treatment planning should be based on CT scans obtained in the treatment position. Intravenous contrast should be used for better target delineation whenever possible, especially in patients with central tumors or nodal diseases. PET/CT is preferable when significant atelectasis is present and intravenous 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 prechemotherapy tumor volume and the cone-down fields should cover the postchemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the postchemotherapy 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 and 10 MV is recommended for beams passing through low-density lung tissue before entering the tumor. For large mediastinal tumors or tumors attached to the chest wall, 15 or 18 MV energies can be considered for more optimal dose arrangement.

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

When IMRT is used, the 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 image-guided RT (IGRT) should be based on institutional experience and treatment accuracy.

Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the American Association of Physicists in Medicine (AAPM) Task Group 76 guideline, include: 1) motion-encompassing methods, such as slow CT scanning, inhale and exhale breath-hold CT, and 4-dimensional respiration-correlated CT; 2) respiratory gating methods using an external respiration signal or internal fiducial markers; 3) breath-hold methods, such as deep-inspiration breath-hold, an 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: In patients with stage I NSCLC, stereotactic body RT (SBRT) provides a statistically significantly higher 5-year survival than 3-dimensional conformal RT.[145] SBRT can be considered for patients with inoperable stage I NSCLC with node-negative peripheral lesions (see Figure 1 on page 763) 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 page 751 and "Whole-Brain RT

and SBRT," below).[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 on page 763). Although the optimal number of fractions may be estimated based on the tumor size and total dose,[162] an accumulated biologic 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 on page 763).

RFA: Studies suggest that RFA may be an option for patients with node-negative NSCLC who either refuse surgery or cannot tolerate it 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 of RFA in 33 patients with NSCLC yielded an overall survival rate 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 rate 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 regarding whether to recommend surgery, whole-brain irradiation, SBRT, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing potential benefit against 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 those who experienced response (with tumor shrinkage) after whole-brain RT had improved neurocognitive function, and that tumor progression affects neurocognition more than whole-brain RT.[169] Survival was similar among 132 patients with 1 to 4 brain metastases who underwent SBRT either with or without whole-brain RT.[155] In a subset of 92 of these patients, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function.[170] However, a study of 58 patients found that those who received SBRT plus whole-brain RT had fewer central nervous system recurrences but experienced worse neurocognition compared with patients who underwent 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) involving patients with stage III NSCLC showed that the incidence of brain metastases was decreased in patients who received PCI (18% vs. 7.7%), although overall survival was not improved.[171] The dose and fractionation of PCI is the same as that used for SCLC (25 Gy in 10 fractions over 2 weeks; see NCCN Guidelines on Small Cell Lung Cancer).[172]

Combined Modality Therapy

Surgery provides the best chance for cure for patients with stage I or 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 those with early-stage disease.[173–175] Currently, concurrent chemoradiation seems superior to sequential therapy for patients with unresectable stage III disease.[119,176] Surgery is rarely performed 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 IALT trial 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 to undergo either cisplatin-based adjuvant chemotherapy or observation, with a median follow-up of 56 months. Patients in the chemotherapy arm had significantly higher survival (44.5% vs. 40.4% at 5 years; HR for death, 0.86; 95% CI, 0.76–0.98; $P < .03$) and disease-free survival rates (39.4% vs. 34.3% at 5 years; HR, 0.83; 95% CI, 0.74–0.94; $P < .003$) than those who underwent 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 follow-up, more deaths had occurred among the chemotherapy group and that the benefit of chemotherapy decreased over time.[181,182] However, data show that adjuvant chemotherapy prevents recurrences.

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) JBR.10 trial and the Adjuvant Navelbine International Trialist Association (ANITA) 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 to undergo either vinorelbine plus cisplatin (n = 242) or observation (n = 240).[174] The median age was 61 years in both groups. Chemotherapy was not excessively toxic, and adjuvant chemotherapy significantly prolonged overall survival (94 vs. 73 months; HR for death, 0.69; $P = .04$) and relapse-free survival (not reached vs. 46.7 months; HR for recurrence, 0.60; $P < .001$) 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 follow-up show that when compared with observation alone, adjuvant chemotherapy is beneficial for patients with stage II NSCLC but not those with stage IB.[183] In patients with stage II NSCLC undergoing adjuvant chemotherapy, median survival is 6.8 versus 3.6 years in those who only underwent observation. Notably, patients undergoing chemotherapy did not have an increased death rate. These guidelines have been revised to delete certain chemotherapy options for early-stage disease (see Summary of the Guidelines Updates for Non–Small Cell Lung Cancer in this issue).

The ANITA trial randomly assigned 840 patients (median age, 59 years) with stage IB (T2, N0), II, or IIIA NSCLC to either adjuvant vinorelbine plus cisplatin or 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 those with 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 4584 patients (the Lung Adjuvant Cisplatin Evaluation) found that postoperative cisplatin-based chemotherapy increased survival over 5 years (absolute benefit, 5.4%); no difference was seen among the chemotherapy regimens (e.g., vinorelbine, etoposide).[184] The benefit was greater in patients with stage II and III disease and good PS.

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 (aged 34–81 years) were randomly assigned to either carboplatin/paclitaxel or observation within 4 to 8 weeks of resection, with a median follow-up 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 (79% vs. 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 > 4 cm). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin (see page 766).[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 to treat 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 IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[189,190,192,193] However, concurrent chemoradiation seems 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 give concurrent chemotherapy/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 ini-

tial treatment include cisplatin/etoposide (preferred), cisplatin/vinblastine (preferred), and carboplatin/paclitaxel (category 2B; see page 767).[119,194,195] Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.[196]

A phase II trial, SWOG 9504, assessed concurrent chemoradiation (using cisplatin/etoposide) followed by consolidation docetaxel in 83 patients with unresectable stage IIIB NSCLC.[197] Results 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 but did show increased toxicity.[199,200] A randomized controlled trial in 203 unresectable patients with either stage IIIA or IIIB NSCLC assessing induction chemotherapy followed by either radiotherapy alone or chemoradiation using paclitaxel showed median survivals of 14.1 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 (see pages 768 and 769). 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 have similar objective response rates and survival.[207,208] The platinum-doublet regimens differ slightly in toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. Despite the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor. Other carboplatin-based regimens include gemcitabine/carboplatin and docetaxel/carboplatin;[203,209,210] gemcitabine/docetaxel is another option.[211]

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel either for patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or those in whom the standard premedications (i.e., dexamethasone, H2 blockers, H1 blockers) are contraindicated.[212,213]

Specific targeted therapies have been developed for treating 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. ECOG recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase II and III clinical trials (ECOG 4599).[216] To undergo 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 the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib can also be given as first-line therapy in patients with advanced or metastatic NSCLC who have a known active EGFR mutation or gene amplification (see page 753).[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 vs. 10.1 months; P = .04).

Maintenance Therapy: Maintenance therapy may be given after 4 to 6 cycles of chemotherapy for patients with tumor response or stable disease who have not experienced progression. *Continuation maintenance* refers to the use of at least one of the agents given in first-line chemotherapy. *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 to 6 cycles of initial therapy (e.g., platinum-doublet chemotherapy given with bevacizumab).[216,221] Likewise, cetuximab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (e.g., cisplatin, vinorelbine, and cetuximab therapy).[220] Pemetrexed (category 2B) may also be given as continuation maintenance therapy.[221] No randomized trials support the continuation maintenance of conventional cytotoxic agents beyond 4 to 6 cycles of therapy.

For switch maintenance therapy, 2 recent studies have shown a benefit in progression-free 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 to 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 to 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 (see page 743). The clinical stage is initially determined from disease history (e.g., cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests, including a pathology review (see page 757), chest CT (including the upper abdomen and adrenals), CBC and platelet count, and chemistry profile. The panel also recommends that smoking cessation counseling be made available (http://www.smokefree.gov/expert.aspx). Based on initial evaluation, the clinical stage is determined and assigned to one of the pathways that is defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy: Evaluation of the mediastinal nodes is a key step in further staging the patient. Although PET/CT scans can be used in 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 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 and 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,[227] some NCCN institutions do not use routine mediastinoscopy in patients with peripheral T1ab, N0 lesions (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 (see page 744).

Dillemans et al.[228] reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT. This strategy resulted in a 16% incidence of positive N2 nodes discovered only at 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% vs. 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 et al.[229] specifically examined lung cancer metastases to normal-sized 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.

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I,

II, and IIIA tumors. However, in patients who present with a solitary pulmonary nodule that is highly suspected to be malignant, surgical resection without prior invasive testing may be reasonable.

Other Imaging Studies: 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 provide more accurate staging. The NCCN Guidelines panel reviewed the diagnostic performance of CT and PET scans and assessed studies examining 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 et al.[231] reported on the number of metastatic lymph nodes discovered on routine mediastinoscopy and chest CT in patients with the most favorable tumors (e.g., T1 cancer). This study showed 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; 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, little correlation exists between the size of the mediastinal lymph nodes and tumor involvement.[232] Chin et al.[233] found that when used to stage the mediastinal nodes, PET was 78% sensitive and 81% specific, with a negative predictive value of 89%. Kernstine et al.[234,235] compared PET with CT scan for identifying N2 and N3 disease in NSCLC. PET scan was found to be more sensitive in identifying mediastinal node disease (70% vs. 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, such as in identifying stage I (peripheral and central T1–2, N0), II, III, and 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 scan 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 in staging patients or diagnosing 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 MRI to rule out asymptomatic brain metastases, and bone scans to exclude bone metastases, is not recommended. Brain MRI is recommended for patients with stage II, III, and IV diseases to rule out metastatic disease if aggressive combined-modality therapy is being considered.[245]

Initial Therapy

Stage I, IIA, and 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 on page 759.

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) modified accordingly. Therefore, the algorithms include 2 different tracks for T1–3, N2 disease: T1–3, N2 disease discovered unexpectedly at surgical exploration (see page 745); and T1–3, N2 disease confirmed before thoracotomy (see page 747). In the second case, an initial brain MRI and PET/CT scan (if not previously performed) are recommended to rule out metastatic disease.

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

For patients with clinical stage IIB (T3, N0) and stage IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidis-

ciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0) and IIIA (T3–4, N1) tumors, treatment options are organized according to tumor location (e.g., 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 (see page 746). The principles of RT and chemotherapy are listed on pages 760–765 and 766, respectively. For patients with negative margins, most NCCN Member Institutions give sequential chemotherapy and radiation (i.e., chemotherapy followed by RT); for patients with positive margins, most NCCN Member Institutions give concurrent chemoradiation with (or without) chemotherapy. Patients with marginally resectable superior sulcus tumors should undergo concurrent chemoradiation before surgical reevaluation. For patients with unresectable tumors (T4 extension, N0–1) in the superior sulcus, definitive RT with chemotherapy (i.e., definitive concurrent chemoradiation) is recommended.

Among the patients with superior sulcus tumors treated with 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 resulted in 2-year survival rates ranging from 50% to 70%.[11,113,247–249]

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 should be ordered if not performed previously. Patients with negative mediastinal biopsy findings are candidates for surgery, with additional assessment of resectability at thoracotomy. For patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during surgery. Individuals found to have unresectable lesions should be treated according to pathologic stage, as defined on page 743. For patients with node-positive disease (T1–2 or T3), an additional brain MRI and PET/CT scan (if not performed previously) are recommended to search for distant metastases. When distant metastases are not present, the panel recommends patients be treated with definitive concurrent chemoradiation therapy (see page 748). 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 on page 751.

When a lung metastasis is present, it usually occurs in patients with other systemic metastases. Because the prognosis is poor, 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 nodules in the same lobe or ipsilateral lung without other systemic metastases are potentially curable by surgery; 5-year survival rates are approximately 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 (see page 749).

The recommended initial treatment options for patients with separate pulmonary nodules in the contralateral lung include surgery, induction chemotherapy before surgery, or induction chemoradiation before surgery (see page 749). For unresectable T4, N0–1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy (category 3; see page 766).[198–200] When synchronous nodules are present (either in the contralateral or ipsilateral lung), the NCCN Guidelines suggest treating them as 2 primary lung tumors if both are curable, even if their histologies are similar (see page 743).

Stage IIIB tumors comprise 2 groups, including tumors with contralateral mediastinal nodes (T1–3, N3), and tumors with T4 extension and N2–3 disease, which are unresectable. Surgical re-

section 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 through either mediastinoscopy, supraclavicular lymph node biopsy, thoracoscopy, needle biopsy, mediastinotomy, EUS biopsy, or EBUS (see page 750).[254,255] In addition, pulmonary function tests (if not performed previously), PET/CT scans, and brain MRI should also be included in the pretreatment evaluation. If these tests are negative, then treatment options for the appropriate nodal status should be followed (see page 743). If these tests are positive, concurrent chemoradiation (category 1) followed by consolidation chemotherapy (category 2B) is recommended.[198,200] Treatment for metastatic diseases confirmed with PET/CT scan and brain MRI is detailed on page 751.

For patients with T4 extension, N2–3 disease (stage IIIB), surgical resection is not generally recommended. The initial workup 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 (see page 749). If either the contralateral or ipsilateral mediastinal node is positive, the patient must be treated with concurrent chemoradiation therapy (category 1), although panel members did not all agree that consolidation chemotherapy (category 2B) should be given after chemoradiation (see page 750).[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 through thoracentesis or pericardiocentesis is recommended. When 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 regardless of the results of cytologic examination. If the pleural effusion is considered negative, the algorithm tracks back to the confirmed T and N stage (see page 743). However, all pleural effusions, despite whether they are malignant, 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 (e.g., ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see page 751).

The algorithm for patients with distant metastases (i.e., stage IV, M1b) depends on the location of the metastases (e.g., 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 (see page 751).[166] The 5-year survival rates associated with this approach range from 10% to 20%;[214,257] median survival is approximately 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] This therapy can be effective in patients who have surgically inaccessible brain metastases and those with multiple lesions.[258] After the brain lesions are treated, further treatment options for patients with T1–2, N0–1 or T3, N0 NSCLC then include either surgical resection of the lung lesion followed by chemotherapy (category 2B), stereotactic radiosurgery (category 2B), or 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 (see page 751).

Adrenal metastases from lung cancer are common, found in approximately 33% of patients 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 the lung lesion is curable, resection has produced some long-term survivors (category 3).[259,260] However, resection generated major disagreement among the panel members

(category 3), with some believing 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 (see page 753) is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Treatment options for patients with stage IA disease (T1ab, N0) and positive surgical margins (R1, R2) include re-resection (preferred), chemoradiation (category 2B), or RT (category 2B). Patients with T1ab, N0 tumors and negative surgical margins (R0) undergo observation. Patients with T2ab, N0 tumors with negative surgical margins are usually observed, although chemotherapy (category 2B) is recommended as adjuvant treatment for those 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 (see page 745). If the surgical margins are positive in patients with T2ab, N0 tumors, they should have undergo re-resection with chemotherapy or chemoradiation and chemotherapy.

For patients with T1ab or 2ab, N1 or T3, N0 disease and negative surgical margins, the panel recommends chemotherapy (category 1) or chemoradiation (category 3) and chemotherapy for patients with adverse factors (e.g., 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 re-resection and chemotherapy, or chemoradiation and chemotherapy.

Patients with T1 through T3, N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy (see page 745). 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 patients with stage II and IIIA disease who had a surgical resection and underwent 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 panel members believe that survival rates may increase with newer chemotherapeutic agents and 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 a 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 II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in patients with stage III NSCLC who have undergone surgery (see page 766).

If marginally resectable superior sulcus tumors (T4 extension, N0–1) convert to a resectable status after initial treatment, resection is performed and chemotherapy is given (see page 746). 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. Patients with chest wall lesions with T3 invasion to T4 extension, N0–1 disease who are initially treated with surgery (preferred) may undergo chemotherapy alone if the surgical margins are negative; when surgical margins are positive, they may undergo 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).

Patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2) should be treated with surgery with (or without) chemotherapy if no disease progression occurs after initial treatment (category 2B; see page 748). In addition, postoperative RT should be given if not used preoperatively. Alternatively, patients experiencing disease progression may be treated with either local therapy using RT (if not given previously) with (or without) chemotherapy, or systemic treatment (see page 751).

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 chemoradiation therapy (see page 749). If the margins are negative, observation is usually recommended, although 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 experience both local and distant failures, the use of chemotherapy theoretically may eradicate micrometastatic disease that is obviously present but undetectable at diagnosis. The timing of this chemotherapy varies, with no clear preference; it may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given pre- or postoperatively in appropriate patients.

Based on the results of clinical studies on adjuvant chemotherapy for NSCLC,[173–175] the panel included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the NCCN Guidelines; other options include cisplatin combined with gemcitabine, pemetrexed, or docetaxel (see page 766).[188,203,206] For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used.[188]

Several 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.[264–267] The SWOG S9900 trial, 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 and overall survival favored the preoperative chemotherapy arm.[266,267] All 3 studies showed a survival advantage for patients who underwent neoadjuvant chemotherapy. The 2 earlier phase III studies included a small number of patients, whereas the SWOG study was stopped early because of the positive results of the IALT study. The induction chemotherapy/surgery approach must be compared with induction chemotherapy/RT in large, randomized clinical trials.

Radiation Therapy

Based on a 1998 published report (PORT Meta-analysis Trialists Group), panel members disagreed (category 2B) on the use of RT alone as adjuvant treatment for T1ab, N0 tumors.[268] This study showed that postoperative radiotherapy is detrimental and should not be given routinely to patients with early-stage, completely resected NSCLC. However, the panel members found several flaws in the meta-analysis, including:

- Many patients were treated with ^{60}cobalt equipment, which delivers an inhomogeneous dose distribution;
- The meta-analysis included studies from the 1960s, when no adequate staging system was available;
- The data analysis lacked detailed timing for postoperative RT;
- Patients with node-negative NSCLC were included (who do not routinely undergo postoperative RT); and
- The meta-analysis included unpublished data.

An assessment of postoperative radiation in 7465 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 underwent adjuvant chemotherapy.[104] Adjuvant chemotherapy (category 1) with RT is recommended for patients with T1 through T3, N2 NSCLC with negative margins (see page 745).

Surveillance and Treatment of Recurrences and Metastases

Surveillance

The guidelines suggest routine history and physical examinations every 4 to 6 months in the first 2 years and then annually for patients with stages I to IV disease (see page 752). Spiral contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years (category 2B), and then a non–contrast-enhanced chest CT annually thereafter (category 2B), although the panel disagreed about this recommendation.[15] PET or brain MRI is not indicated for routine follow-up. Smoking cessation counseling should be provided to help treat the cancer and improve the patients' quality-of-life (http://www.smokefree.gov/).

These guidelines include an algorithm for long-term follow-up care of NSCLC survivors (see page 770), including 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 (see page 752). Symptoms can be palliated through reducing tumor size with external-beam RT. Various regional therapy options are also listed for locoregional recurrences. Resectable local recurrence may be managed with re-resection or external-beam RT. For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in those who are severely compromised, 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. Photodynamic therapy (PDT) is also a simple and effective alternative to conventional techniques for palliative debridement of endobronchial obstructions in patients with lung cancer.

Mediastinal lymph node recurrence should be treated with concurrent chemoradiation (if RT has not been given previously). External-beam RT or stent placement is indicated for superior venal cava obstruction. For severe hemoptysis, several treatment options are recommended, such as external-beam RT, brachytherapy, laser therapy, PDT, surgery, or embolization. Ultimately, surgery may be performed to remove the bleeding site. If no further disseminated disease is seen after the locoregional recurrence is treated, observation or systemic chemotherapy (category 2B) is recommended. However, systemic chemotherapy and best supportive care should be applied immediately if disseminated disease is observed, depending on the PS (see page 753).

For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT (see page 752).[271] Orthopedic stabilization also should be performed in patients who are at risk of fracture, and bisphosphonate therapy should be considered for 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 (see page 751).

In a small subset of patients, recurrence will be suspected based only on positive sputum cytology (see page 756). 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, PDT, and surgical resection. Alternatively, the patient may be re-bronchoscoped every 3 months. If T1 through T3 tumors are discovered, the algorithms track back to the appropriate clinical stage (see page 743). Surveillance may also detect a new lung primary, and these patients should be treated according to the staging findings.

For recurrent and metastatic disease in patients with a PS of 0 to 1, first-line therapy includes several options (see page 753): 1) chemotherapy (category 1; see pages 768 and 769); 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. Options for patients with a PS of 2 include: 1) cetuximab in combination with vinorelbine and cisplatin (category 2B) for patients who meet the eligibility criteria; 2) chemotherapy; or 3) erlotinib for patients with an EGFR mutation (see page 767).

Eligibility criteria for bevacizumab include a PS of 0 to 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 associated with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Although patients with brain metastases were previously excluded from bevacizumab treatment because of concerns about central nervous system hemorrhage, recent data suggest that bevacizumab can be used in those who have undergone treatment for brain metastases.[273]

Eligibility criteria for cisplatin and pemetrexed include a PS of 0 or 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 vs. 10.1 months; $P = .04$).[220] Note that full-dose cisplatin for patients with a PS of 2 should be given selectively.

Trial Data: In a phase II/III trial (ECOG 4599),

842 patients were randomly assigned to either bevacizumab in combination with paclitaxel and carboplatin, or paclitaxel and carboplatin alone.[216,274] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin showed an improved response rate (27% vs. 10%; $P < .0001$), progression-free survival (6.4 vs. 4.5 months; $P < .0001$), and median survival (12.5 vs. 10.2 months; $P = .0075$) compared with those receiving paclitaxel and carboplatin alone. The overall 1- and 2-year survival rates were 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 than with paclitaxel and carboplatin (grade 4 neutropenia: 24% vs. 16.4%; grade 3/4 hemorrhage: 4.5% vs. 0.7%; hemoptysis: 1.9% vs. 0.2%; and hypertension: 6.0% vs. 0.7%, respectively). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (9 patients) than with paclitaxel and carboplatin (2 patients). 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 vs. 10.9 months, respectively). Patients with squamous cell histology had improved survival with the cisplatin/gemcitabine regimen (10.8 vs. 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 cetuximab in combination with vinorelbine and cisplatin, or vinorelbine and cisplatin alone.[220] The response rate was increased with cetuximab (36% vs. 29%, $P = .012$), and no difference was seen in progression-free survival. Overall survival was significantly better in patients receiving cetuximab (11.3 vs. 10.1 months, $P = .04$). However, patients receiving cetuximab experienced increased grade 3 or 4 febrile neutropenia (22% vs. 15%; $P < .05$), and also experienced grade 2 acne-like rash. Treatment-related deaths were similar in both groups (3% vs. 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 showed an improved median survival of 6 to 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/nonplatinum regimens are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel).[211] No evidence yet shows the superiority of one particular platinum-based regimen.[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 show 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 (see page 754). 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 undergone platinum-based chemotherapy but had not progressed.[222] Tumor response ($P = .001$) and progression-free survival (4.3 vs. 2.6 months; $P < .0001$) were increased in patients who received pemetrexed, especially in those with adenocarcinoma or large cell histology (i.e., nonsquamous). In patients with nonsquamous histology,

preliminary results showed increased overall survival with pemetrexed (15.5 vs. 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; their discontinuation leads to more rapid disease progression (symptoms, tumor size, and fluorodeoxyglucose 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 experience disease progression on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy was 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.

Data are accumulating on 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 insulin-like growth factor-1 receptor (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-1R activation, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely et al.[278] show 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. 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 a PS of 0 to 2 who experienced disease progression during or after first-line therapy (see page 755).[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 a PS of 0 to 2; erlotinib may be considered for a PS of 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 after 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 (HR, 0.70; $P < .001$). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (HR, 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 a PS of 0 to 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 a PS of 3 to 4 and progressive disease during any stage of the treatment (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] on Palliative Care; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

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