National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Non-Small Cell Lung Cancer

V.2.2008

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

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

Click here to find a clinical trial at an NCCN Center

Print the Non-Small Cell Lung Cancer Guideline

Summary of the Guidelines updates

The 2.2008 version of the Non-small Cell Cancer Guidelines represents the addition of the updated manuscript (MS-1).

Summary of the changes in the 1.2008 version of the Non-small Cell Lung Cancer guidelines from the 1.2007 version include:

- The sixth bullet was removed from "Lung Cancer Prevention and Screening". The guidelines were clarified that the NCCN panel does not recommend "the routine use" of a screening CT. The sentence was added that if a screening CT strategy is used, the I-ELCAP screening protocol should be followed (PREV-1).
- The category of "medically inoperable" was added with a referral to page NSCL-B for treatment recommendations (NSCL-2).
- Adjuvant Treatment (NSCL-3):
  - Footnote "k" is new to the page.
  - Stage IA, margins negative - the recommendation for chemotherapy for high risk patients was changed to a category 3.
  - Stage IA, margins positive - the recommendation for chemotherapy after reresection was changed to a category 3. Chemotherapy was added as an option after chemoradiation. RT alone was added as a treatment option.
  - Stage IIIA, margins negative - the recommendation for chemoradiation followed by chemotherapy was removed. Mediastinal RT was added to chemotherapy.
- Adjuvant Treatment (NSCL-5) - footnote "m", the dose was changed from 44-45 Gy to 45-50 Gy.
- The recommendation for mediastinoscopy was changed to pathologic mediastinal lymph node evaluation with a foonote describing the types of evaluation (NSCL-6).
- Footnote "r" is new to page NSCL-7 and a category 3 designation was added to "Consider surgical resection" if the patient has an excellent response after definitive chemoradiation.
- For stage IIIB (resectable other than satellite), the recommendation for chemotherapy following chemoradiation was added for R1, R2 disease after initial treatment with surgery. (NSCL-8).
- For solitary brain metastases, "±" changed to "+" for RT and defined as whole brain or stereotactic radiosurgery (NSCL-11).
- The Surveillance recommendations are for all stages of disease. A chest CT was changed from every "6 mo" to "every 4-6 mo" for 2 y and a category 2B designation was added (NSCL-12).
- Therapy for Recurrence and Metastasis (NSCL-13):
  - The criteria was clarified for treatment with bevacizumab.
  - The Performance status 2 patients were removed from the grouping with PS 0 and 1 patients and their recommended treatment is chemotherapy.
  - Footnote "w" - a clarification was added that bevacizumab should not be used as a single agent, "unless as maintenance when used with chemotherapy".
- Principles of Surgical Resection (NSCL-B): bullet 7 - the end of the sentence was changed to "...patients should receive potentially curative RT as their local approach."
- Principles of Radiation Therapy (NSCL-C)- this section was revised and updated.
- Chemotherapy Regimens for Adjuvant Therapy (NSCL-D 1 of 3):
  - Two tables were added with drug and dosing regimens for "Other acceptable Cisplatin-based Regimens" and "Chemotherapy Regimens for patients with comorbidities or not able to tolerate cisplatin".
- Chemotherapy Regimens Used with Radiation (NSCL-D 3 of 3):
  - The cisplatin/etoposide and cisplatin/vinblastine regimens were listed as "preferred" and a category 2B designation was added to the paclitaxel/carboplatin regimen.
  - Concurrent chemotherapy/RT followed by chemotherapy - a category 3 designation was added to cisplatin/etoposide and a category 2B designation was added to paclitaxel/carboplatin.
- Systemic Therapy for Advanced or Metastatic Disease (NSCL-E 1 of 2):
  - A bullet was added "If patient with a known active EGFR mutation or gene amplification and a never smoker, consider use of erlotinib ± chemotherapy."
- Guidelines for the management of Thymic Malignancies were added (THYM-1).

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, Federal Drug Administration (FDA) oversight of tobacco products and other tobacco control measures.**

- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/sgr_2004/00_pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from secondhand smoke exposure associated with living with a smoker (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Every person should be informed of the health consequences, addictive nature and mortal threat posed by tobacco consumption and exposure to tobacco smoke and effective legislative, executive, administrative or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke. www.who.int/tobacco/framework/final_text/en/.**

- **Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (www.ahrq.gov/clinic/cpgsix.htm) to identify, counsel, and treat patients with nicotine habituation.**

- **Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.**

- **At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3) despite the recent data from I-ELCAP demonstrating that lung cancer screening can detect stage I lung cancer, which could translate to an increase in survival of lung cancer patients.[1] The panel recommends that high risk individuals participate in a clinical trial evaluating CT screening. If a trial is not available or the high risk individual is not eligible for participation in a trial, then the individual should go to a center of excellence with expertise (in radiology, pathology, cytology, thoracic surgery, and general expertise in lung cancer treatment) to discuss the potential risks and benefits before having a screening CT.[2] If a screening strategy is used, then the I-ELCAP screening protocol should be followed. http://www.ielcap.org/professionals/docs/ielcap.pdf**

[1] Henschke CI, Yakelevitz DF, Libby DM, et al. Survival of patients with stage I lung cancer detected on CT screening. N Engl J Med 2006;355:1763-71.
[2] Bach PB, Jett JR, Pastorino U, et al. Computed tomography screening and lung cancer outcomes. JAMA 2007;297:953-961.

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PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

CLINICAL STAGE

Non-Small Cell Lung Cancer (NSCLC) →

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

Clinical Stage	
Stage I, peripheral[b] T1,N0 Mediastinal CT negative (lymph nodes < 1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage I, peripheral T2, N0, central[b] T1-2, N0 and stage II, T1-2, N1 Mediastinal CT negative (lymph nodes < 1 cm)	See Pretreatment Evaluation (NSCL-2)
Stage IIB,[c] T3, N0, Stage IIIA, T3, N1 by CT or bronchoscopy	See Pretreatment Evaluation (NSCL-4)
Stage IIIA,[c] T1-3, N2, mediastinal CT positive Ipsilateral (lymph nodes ≥ 1 cm)	See Pretreatment Evaluation (NSCL-6)
Stage IIIB,[c] T4, N0-1 (possibly resectable)	See Pretreatment Evaluation (NSCL-6)
Stage IIIB,[c] T1-3, N3, mediastinal CT positive Contralateral (lymph nodes ≥ 1 cm) or palpable supraclavicular lymph nodes	See Pretreatment Evaluation (NSCL-9)
Stage IIIB,[c] T4, N2-3 on CT	See Pretreatment Evaluation (NSCL-10)
Stage IIIB,[c] T4 (pleural or pericardial effusion)	See Pretreatment Evaluation (NSCL-10)
Stage IV, M1 Solitary metastasis with resectable lung lesion	See Pretreatment Evaluation (NSCL-11)
Stage IV, M1 Disseminated metastases	See Pretreatment Evaluation (NSCL-11)
Occult TX, N0, M0	See Evaluation (NSCL-15)
Second lung primary	See Evaluation (NSCL-15)

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

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

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

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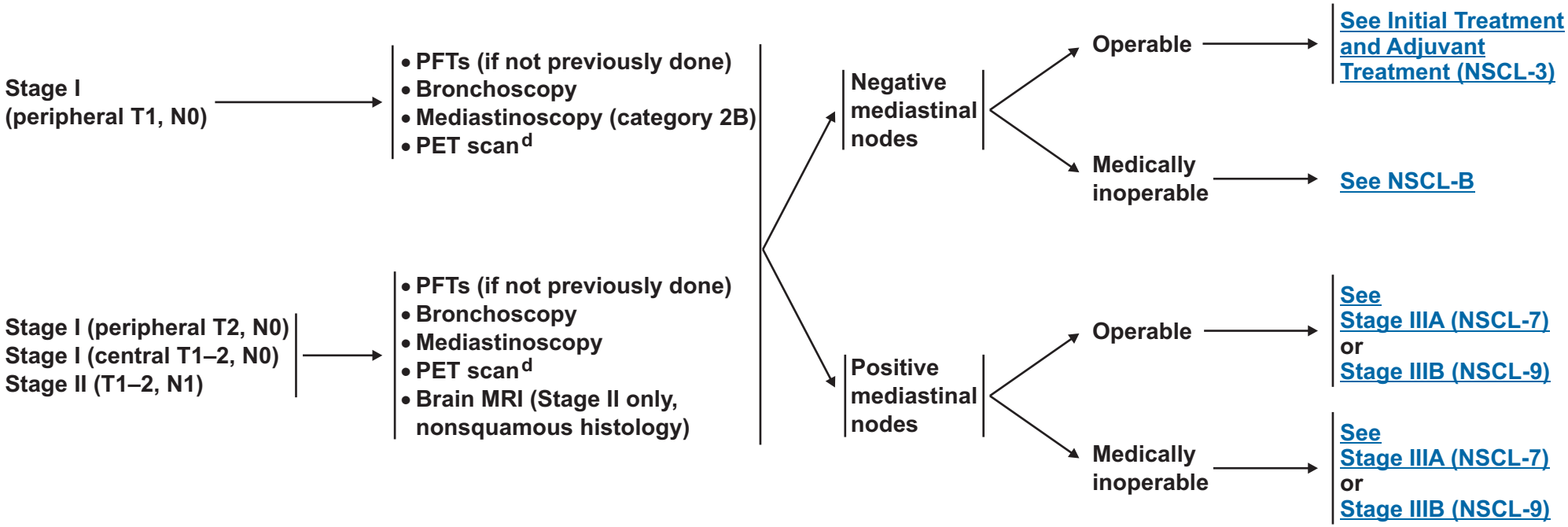
CLINICAL ASSESSMENT | **PRETREATMENT EVALUATION**



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

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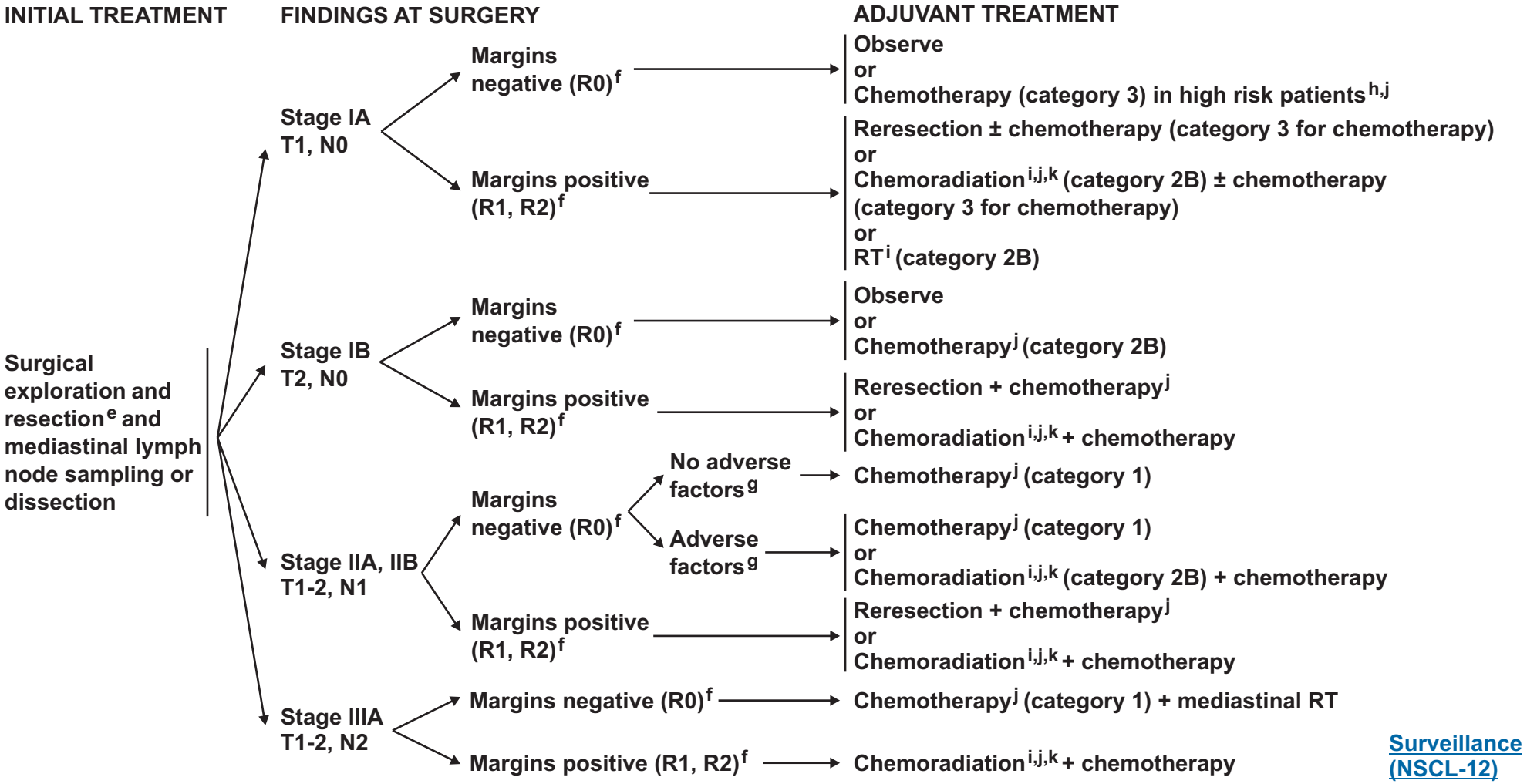

Surveillance (NSCL-12)

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

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

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

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

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

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

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

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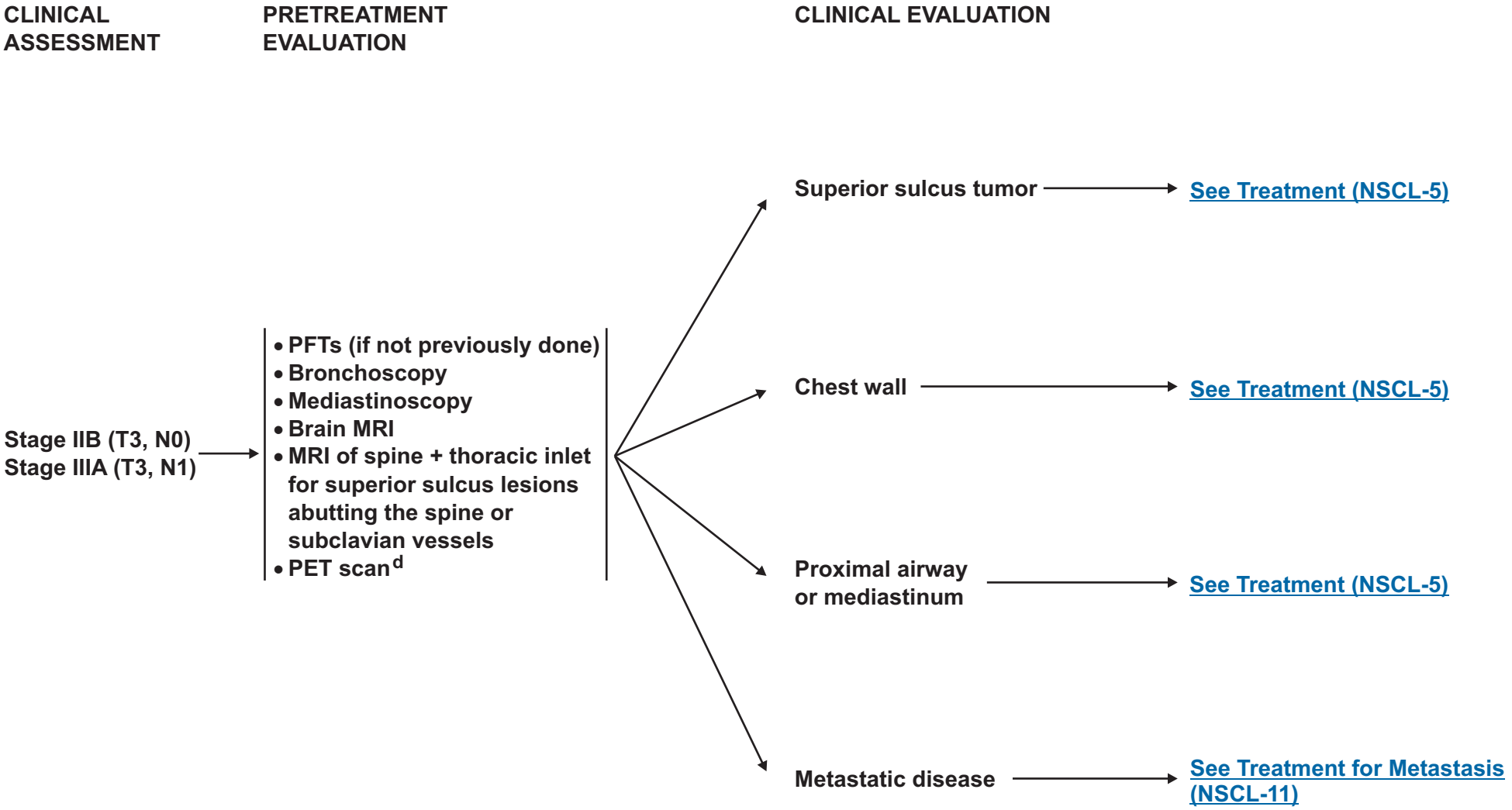

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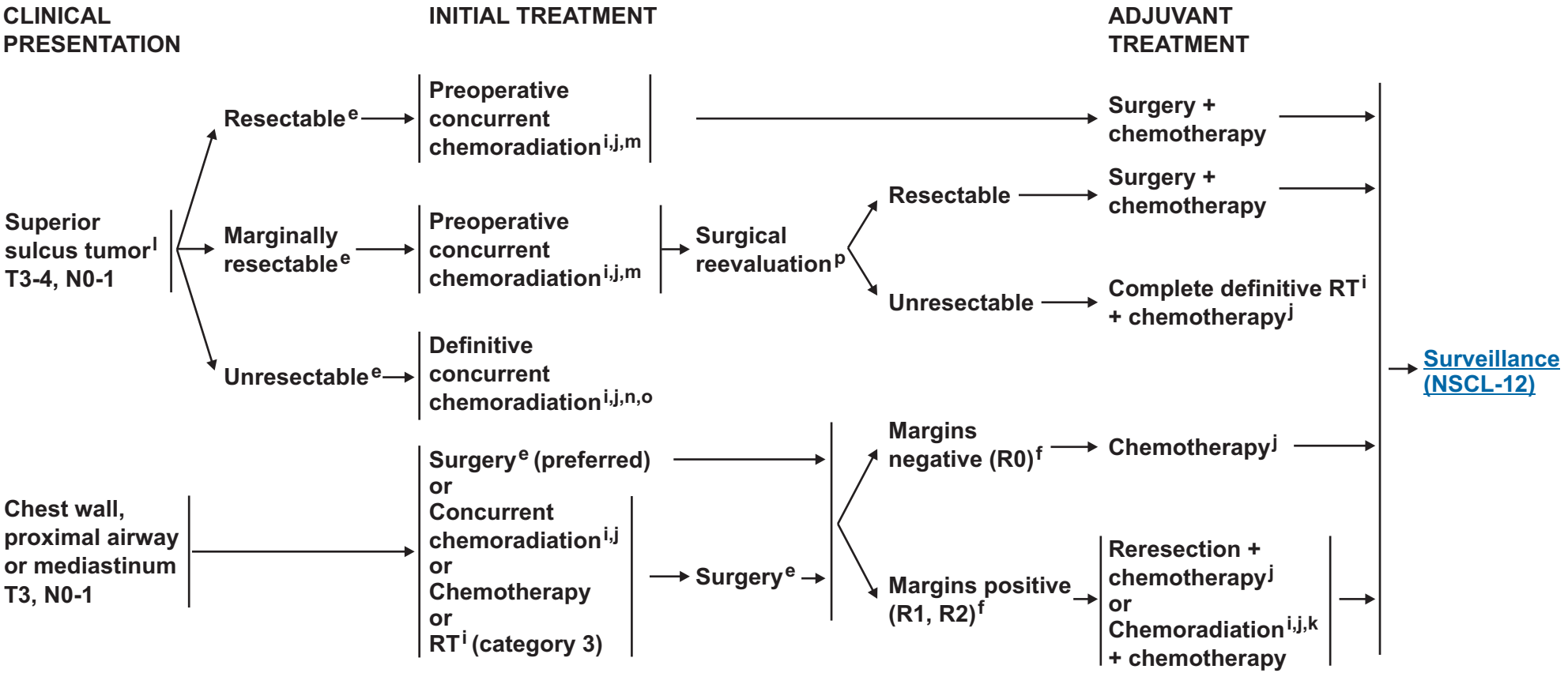

[e] See Principles of Surgical Resection (NSCL-B).

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

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

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

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

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

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

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

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

[p] Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of the Southwest Oncology Group trial 9416 (Intergroup trial 0160). J Thorac Cardiovasc Surg 2001;121(3):472-483.

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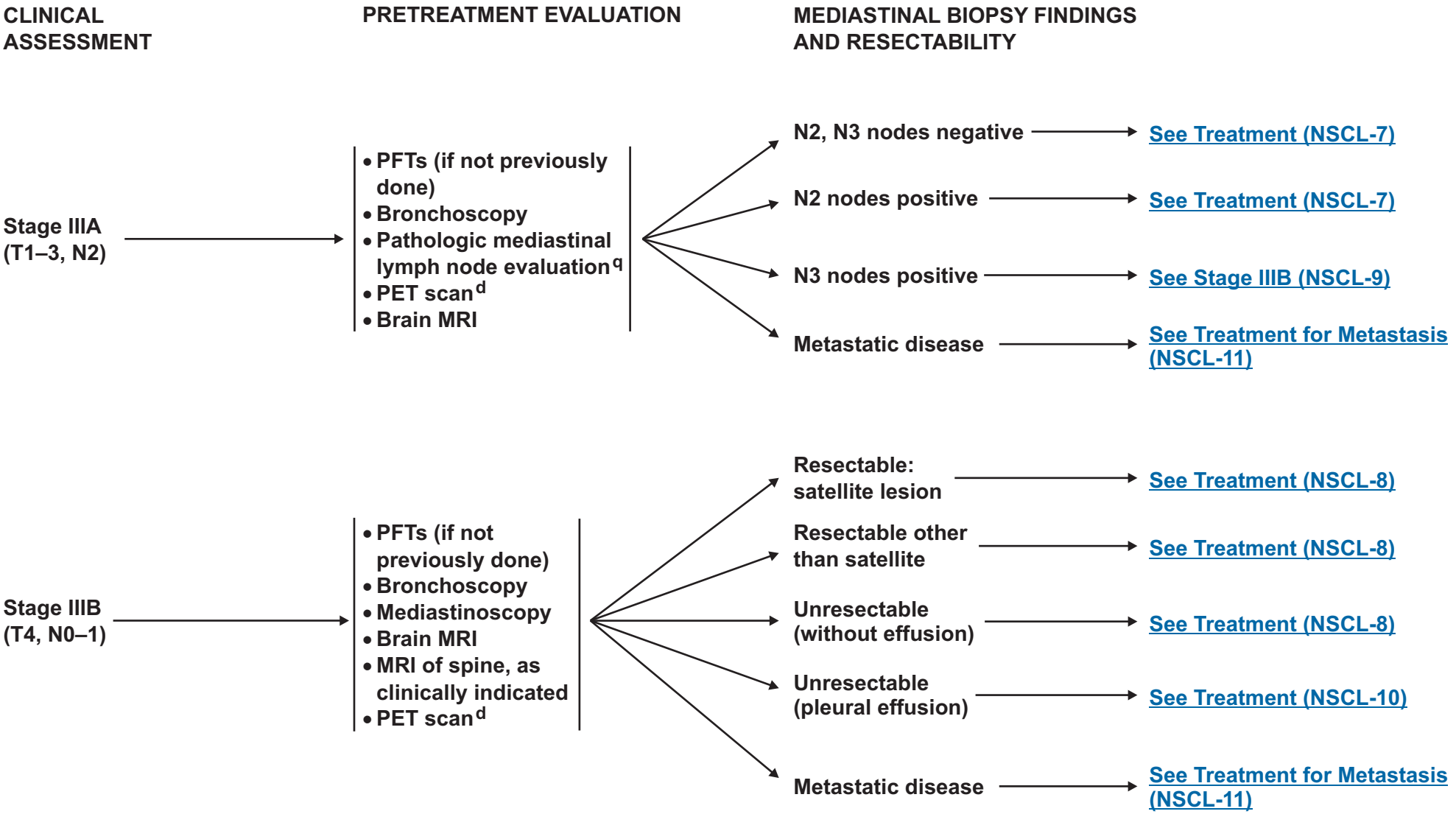

[d] Positive PET scan findings need pathologic or other radiologic confirmation. If PET scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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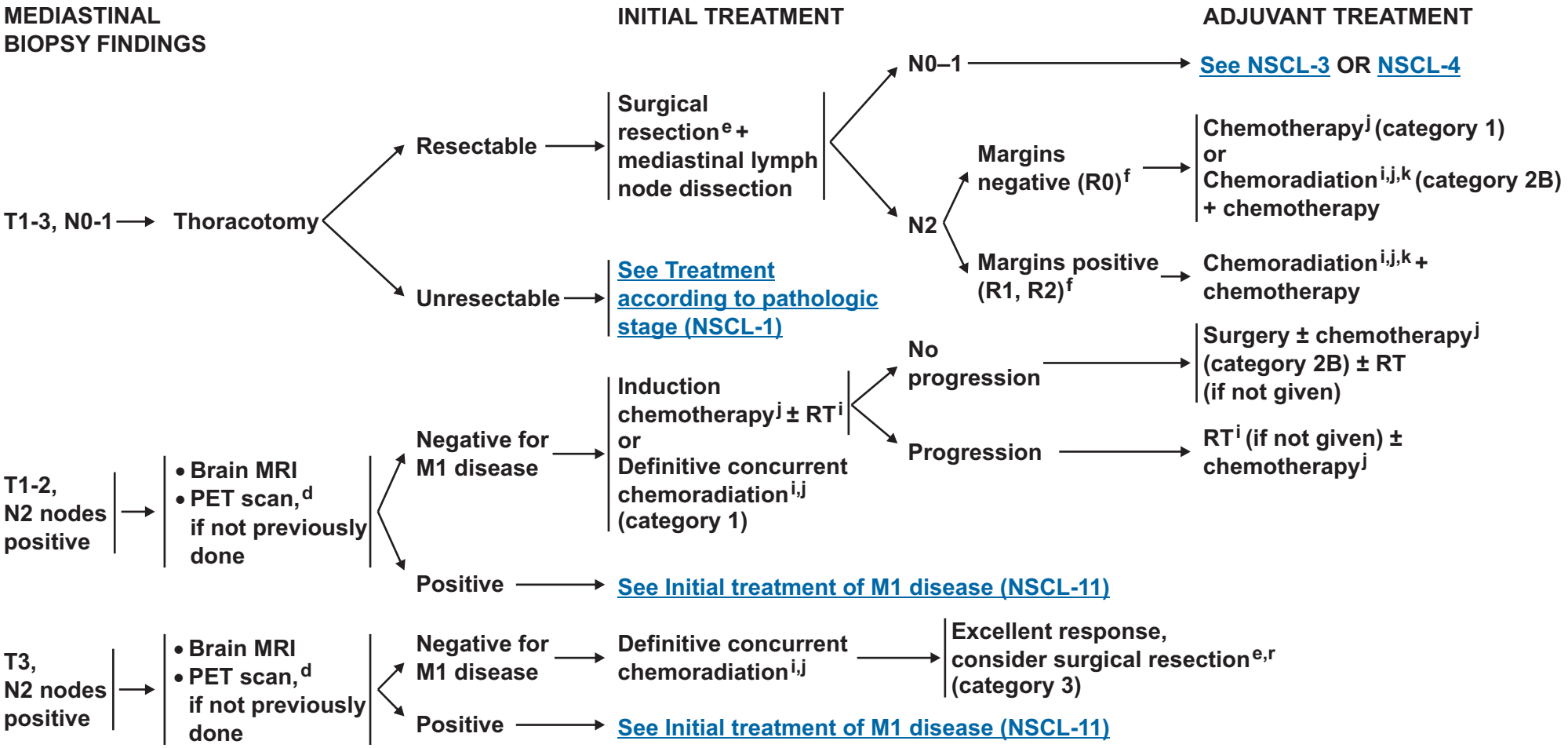

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[j] See Chemotherapy Regimens for Primary and Adjuvant Therapy (NSCL-D).

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

[r] It is preferred the surgical decision is made a priori.

Surveillance (NSCL-12)

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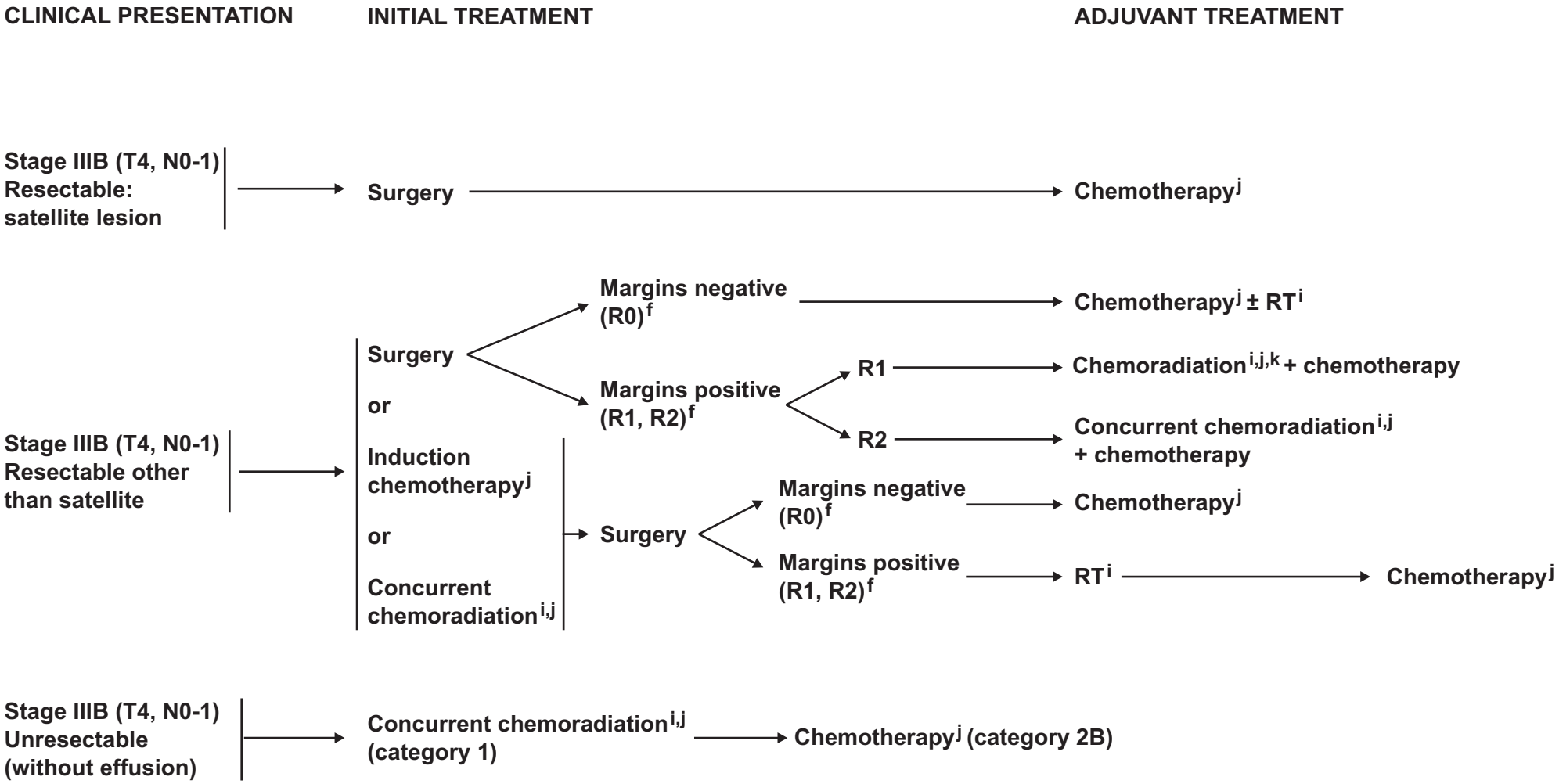

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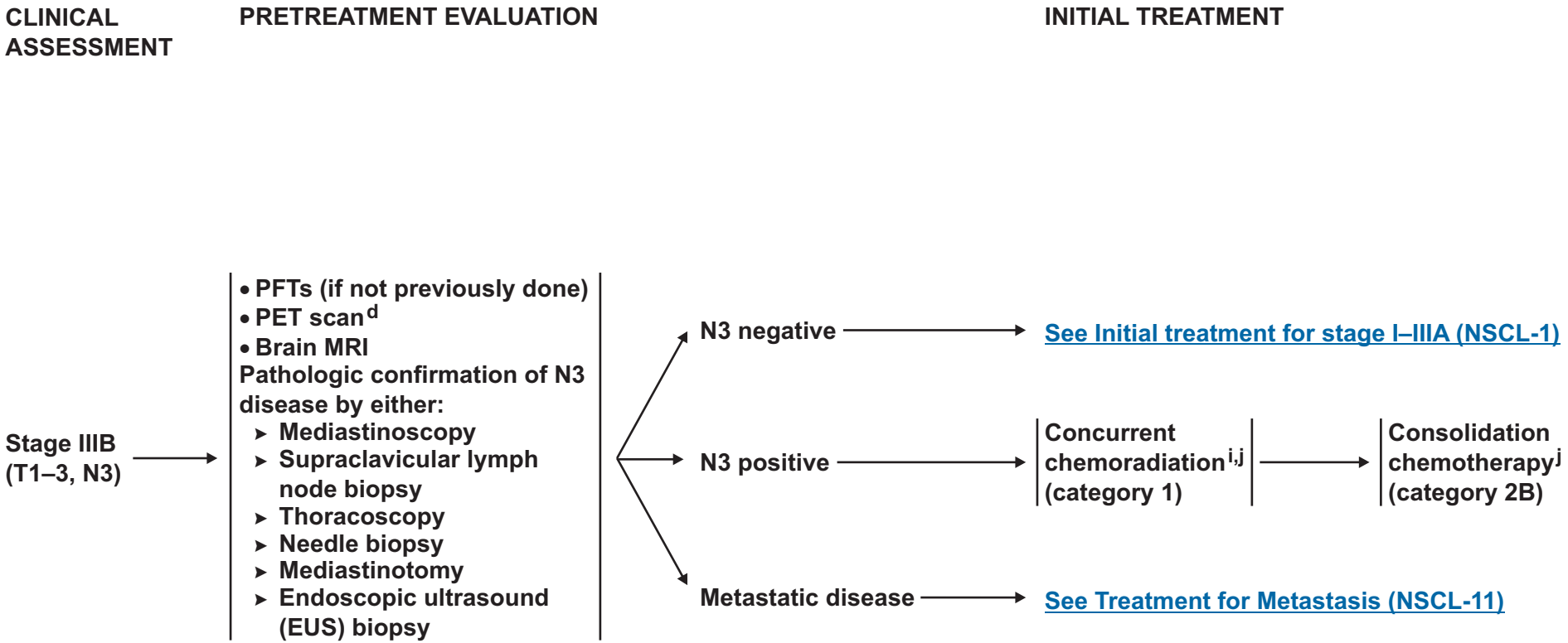

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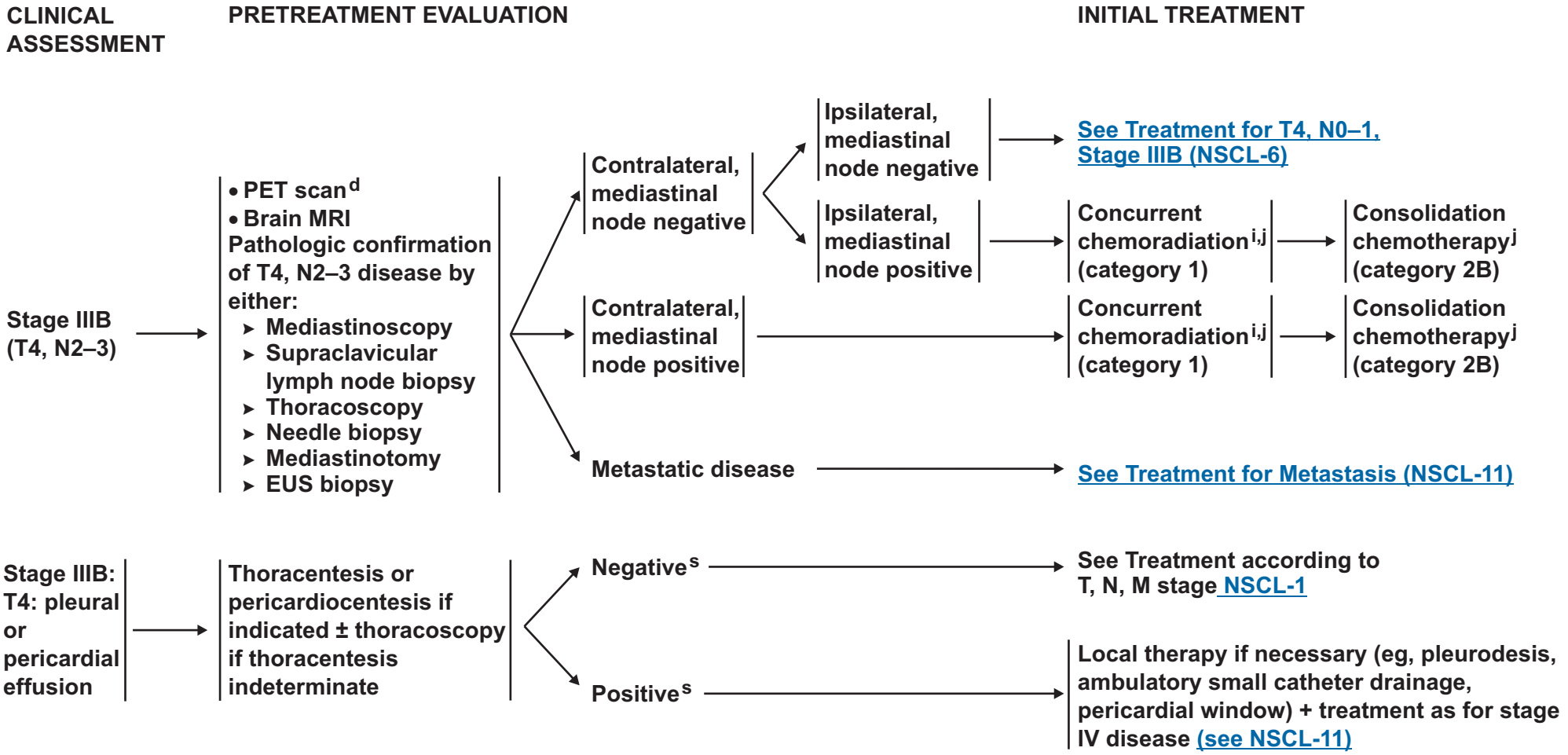

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[i] See Principles of Radiation Therapy (NSCL-C).

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

[s] 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. 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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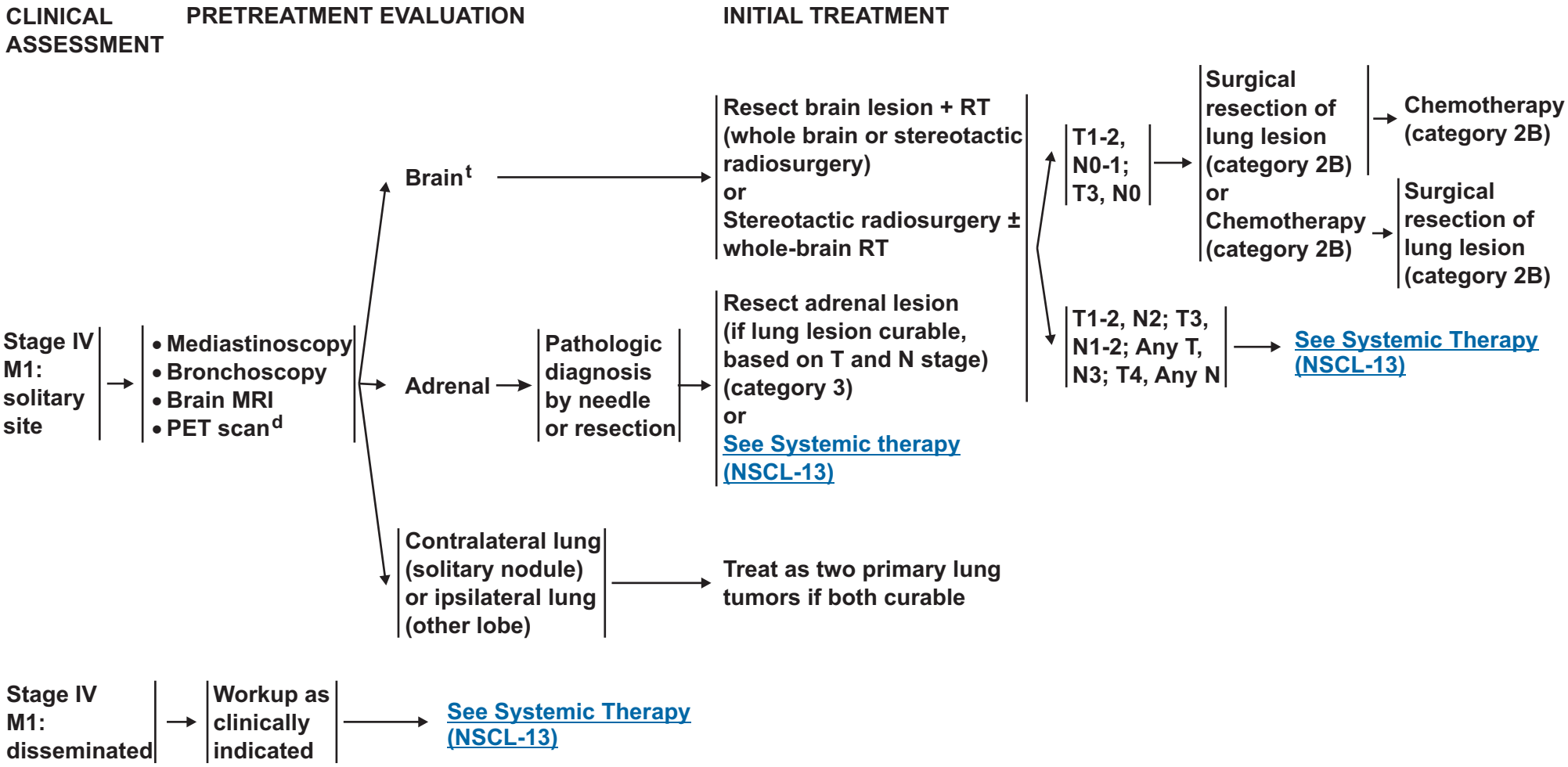

[d]Positive PET scan findings need pathologic or other radiologic confirmation. If PET scan positive in the mediastinum, lymph node status needs pathologic confirmation.

[t]See NCCN CNS Guidelines.

Surveillance (NSCL-12)

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

Non-Small Cell Lung Cancer

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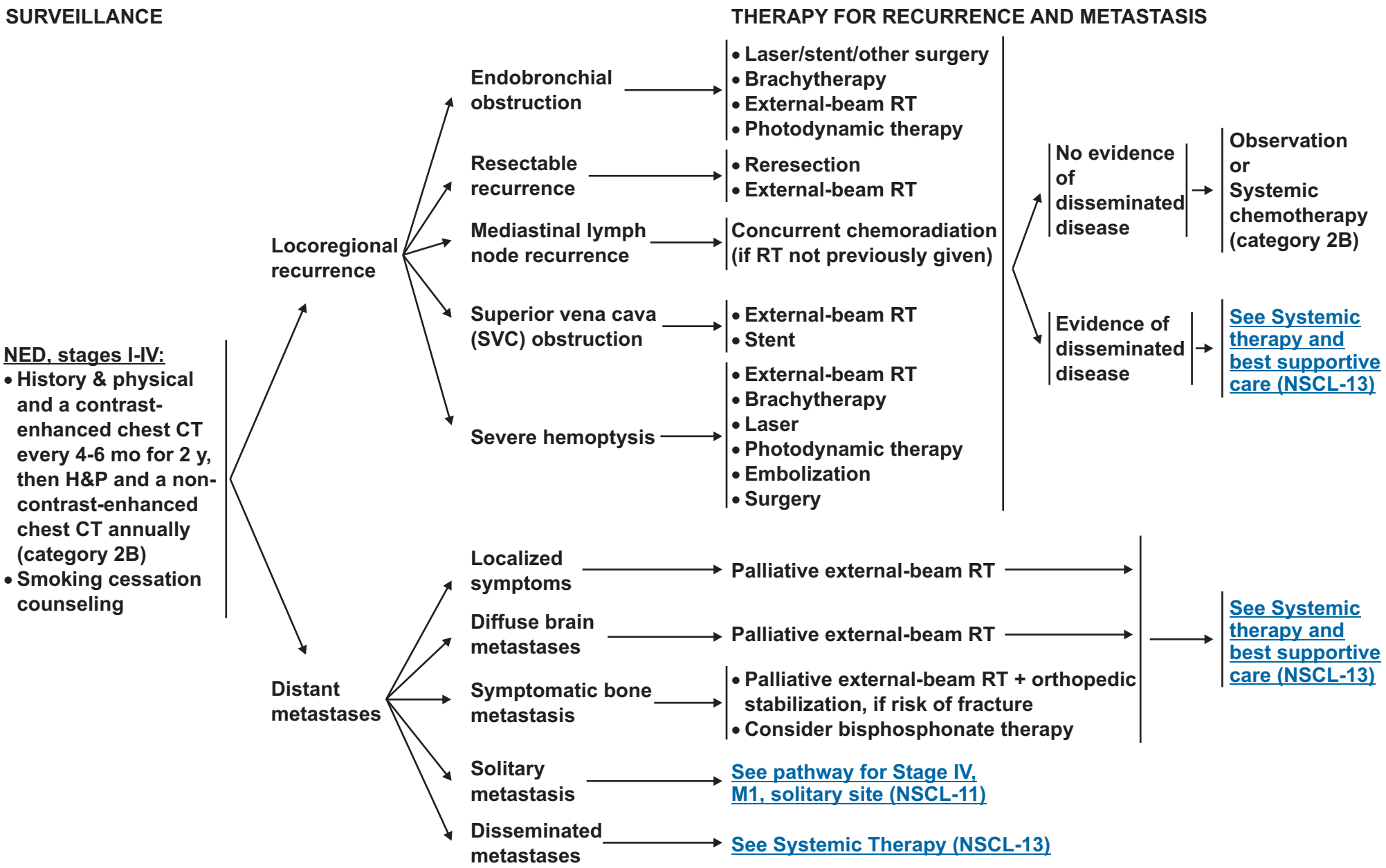
Staging, MS, References



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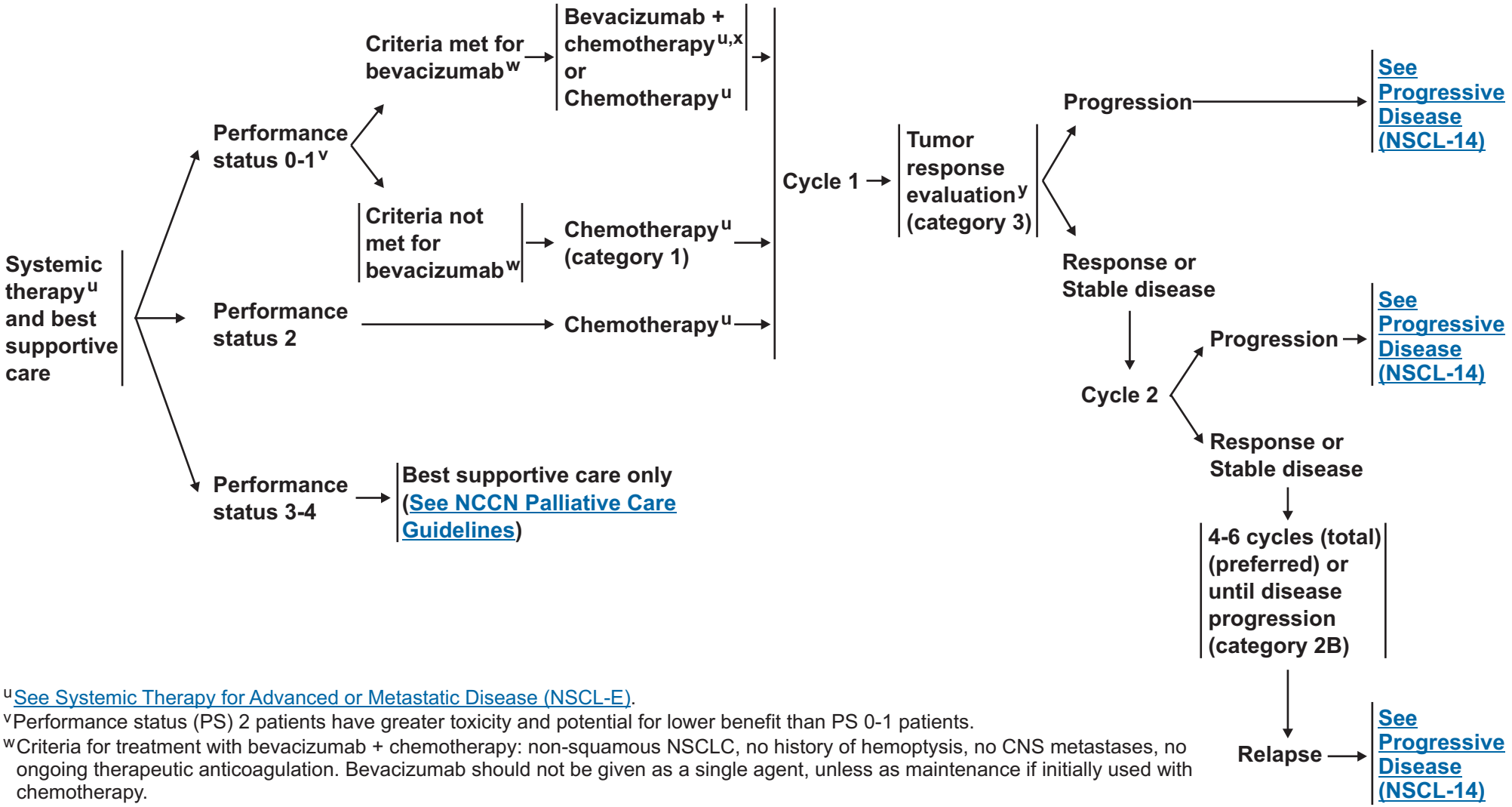
THERAPY FOR RECURRENCE AND METASTASIS

FIRST-LINE THERAPY



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

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

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

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

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

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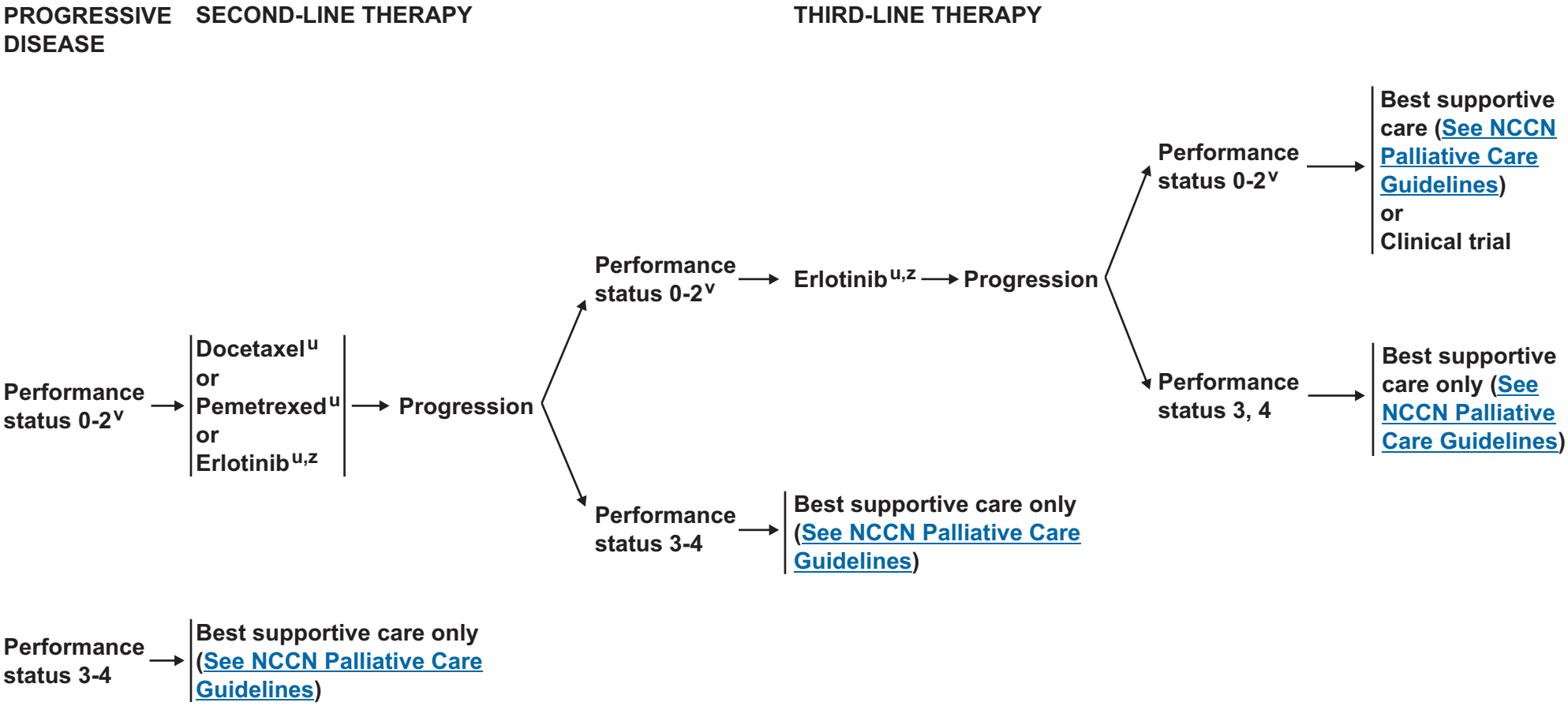

[u] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-E).
[v] Performance status (PS) 2 patients have greater toxicity and potential for lower benefit than PS 0-1 patients.
[z] Patients with a performance status of 3 were included in the National Cancer Institute of Canada-Clinical Trials Group (NCIC-CTG) trial BR.21. Erlotinib may be considered for PS 3 patients.

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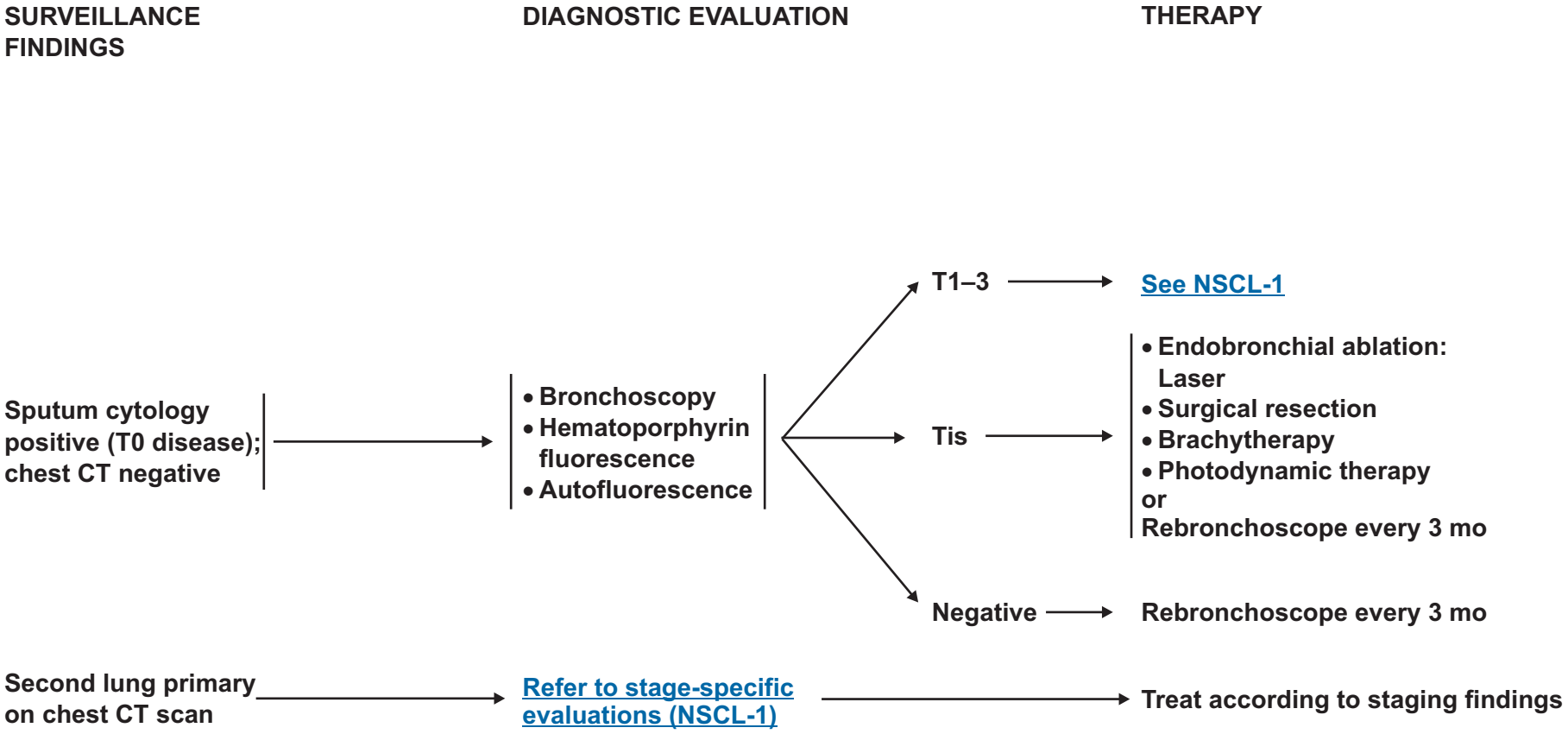
Non-Small Cell Lung Cancer

NSCL Table of Contents
Staging, MS, References



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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 2)

Pathologic Evaluation

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

Bronchioloalveolar carcinoma (BAC)

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

Immunohistochemical staining

- Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma and to determine the neuroendocrine status of tumors.
- Differentiation between primary pulmonary adenocarcinoma and metastatic adenocarcinoma
  - TTF-1 is a homeodomain-containing nuclear transcription protein of the *Nkx2* gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid.
  - TTF-1 is important in distinguishing primary from metastatic adenocarcinoma: the majority of primary lung carcinomas is positive for TTF-1 whereas metastatic adenocarcinoma to the lung is virtually always negative.
  - Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum.
  - CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies, that could help distinguish from primary lung tumors. Prostate specific antigen, prostatic acid phosphatase and gross cystic disease fluid protein 15 may identify metastatic adenocarcinoma of prostate and breast origin, respectively.
- Determining neuroendocrine status of tumors
  - Chromogranin and synaptophysin are used to diagnose neuroendocrine tumors of the lung. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin whereas small cell lung cancer is negative in 25% of cases.
- Distinguishing between malignant mesothelioma and lung adenocarcinoma
  - A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) is used routinely.
  - The stains negative in mesothelioma, but positive in adenocarcinoma are CEA, B72.3, Ber-EP4 and MOC31.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40[9,10] and cytokeratin 5/6.

Continued NSCL-A 2 of 2

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 2)

Molecular Diagnostic Studies in Lung Cancer

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

[1] Fosella FV, Putnam JB & Komaki R. Lung Cancer. New York: Springer, 2003.
[2] Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib.J Clin Oncol. 2005;23:5900-9.
[3] Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:423-9.
[4] Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.
[5] Travis WD, World Health Organization. International Agency for Research on Cancer. International Academy of Pathology & International Association for the Study of Lung Cancer. Pathology and genetics of tumours of the lung, pleura, thymus and heart. Lyon: IARC Press, 2004.
[6] Jackman DM, Chirieac LR & Janne PA. Bronchioloalveolar carcinoma: A Review of the Epidemiology, Pathology, and Treatment. Seminars in Respiratory and Critical Care Medicine 2005:342-352.
[7] Blons H, Cote JF, Le Corre D, et al. Epidermal growth factor receptor mutation in lung cancer are linked to bronchioloalveolar differentiation. Am J Surg Pathol 2006;30:1309-15.
[8] Goldstein NS & Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001;116:319-25.
[9] Chirieac LR, et al. Modern Pathology 2006;19:305A 1422.
[10] Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-80.
[11] Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
[12] Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-500.
[13] Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-8.
[14] Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-95.
[15] Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-62.
[16] Finberg KE, Sequist LV, Joshi VA, et al. Mucinous Differentiation Correlates with Absence of EGFR Mutation and Presence of KRAS Mutation in Lung Adenocarcinomas with Bronchioloalveolar Features. J Mol Diagn 2007;9:320-6.

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PRINCIPLES OF SURGICAL RESECTION

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

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

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PRINCIPLES OF RADIATION THERAPY (1 of 3)

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical, radiation, medical oncologists and pulmonologists.
- Radiation therapy ± chemotherapy should be offered as potentially curative treatment to patients with stage I and II NSCLC who are medically inoperable but of reasonable performance status and life expectancy. SBRT (stereotactic body radiation therapy) can be considered for patients with node negative peripheral lesions that are less than 5 cm in maximal dimension.
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (ie, Grade 3 esophagitis or hematologic toxicities) should be avoided. Careful patient monitoring and aggressive supportive care are preferable to treatment breaks.
- For resected tumors with pathologic mediastinal nodal involvement and negative surgical margins, adjuvant chemotherapy followed by postoperative radiotherapy is preferred. For tumors with positive resection margins, postoperative chemoradiation is recommended. Close margin and/or involved mediastinal nodes, postoperative radiotherapy followed by chemotherapy is recommended.
- Treatment planning should be on CT scans obtained in the treatment position. IV contrast should be used for better target and normal tissue delineation whenever possible. CT/PET is preferable to CT alone for the GTV delineation in cases with significant atelectasis.
- In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume and the cone-down fields should cover the post-chemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the post-chemotherapy volume should be used to avoid excessive pulmonary toxicity.
- Modern three-dimensional (3D) conformal radiation therapy techniques should be used on all patients. It is necessary to evaluate the dose volume histogram (DVH) for the lungs, esophagus, heart and spinal cord to minimize normal tissue toxicity. Whenever feasible, respiratory management techniques such as 4-dimensional (4D) CT and respiratory gating should be incorporated in the radiation set up and delivery to individualize respiratory motion and/or decrease dose to the normal tissues respectively.
- In general, photon beam energy between 4 to 10 MV is recommended. For large mediastinal tumors or for patient's separation greater than 20 cm, 15 MV or 18 MV photon energies can also be used but is discouraged due to concerns of increasing dose to the lung through lateral scatter which is not accounted for in current treatment planning algorithms as well as concerns of underdosing tumor at the air-tissue interface. If the tumor is fixed to the vertebral body, located at the superior sulcus or involving bilateral mediastinum, intensity modulated radiotherapy (IMRT) should be considered to improve tumor coverage and reduce dose to surround critical structures. In this situation, where very small margins are incorporated, more frequent imaging (< 1 week) with orthogonal radiographs or cone beam CT is encourage to reduce daily set up error.

For Recommended Radiation Doses see NSCL-C 2 of 3

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 3 of 3

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF RADIATION THERAPY 2 of 3

Recommended Radiation Doses:

Treatment type	Total dose	Fraction size
Preoperative*[1]	45-50 Gy	1.8-2 Gy
Postoperative[2,3]		
• Negative margins	50 Gy	1.8-2 Gy
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy 60-66 Gy	1.8-2 Gy
• Gross residual tumor	up to 70 Gy	1.8-2 Gy
Definitive		
• Without concurrent chemotherapy[4]	up to 83.8 Gy for volume < 25% up to 77.4 Gy for volume between 25-36%	1.8-2 Gy 2.15 Gy
• With concurrent chemotherapy[5] (mainly carboplatin + paclitaxel)[5]	up to 74 Gy	2 Gy

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

For Dose Volume Data for Radiation Pneumonitis see NSCL-C 3 of 3

[1]Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25(3):313-8.

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

[3]Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000;343(17):1217-22.

[4]Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2005;61(2):318-28.

[5]Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B non-small cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92(5):1213-23.

[6]The Lung Cancer Study Group NEJM 1986;(315):1377-1381.

[7]Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small cell lung cancer. J Clin Oncol 1999;17:2692-2699.

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PRINCIPLES OF RADIATION THERAPY 3 of 3

Dose Volume Data for Radiation Pneumonitis:

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

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

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

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

[2]Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51:650-9.

[3]Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small cell lung cancer: predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006;65(4):1075-86.

[4]Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-15.

[5]Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis in patients with non-small cell lung cancer treated with concurrent chemotherapy and three-dimensional conformal radiotherapy. Int J Radiat Oncol Biol Phys 2006;67(5):1399-1407

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CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY (1 OF 3)

Published Chemotherapy Regimens	Schedule
Cisplatin 50 mg/m^2 days 1 and 8 Vinorelbine 25 mg/m^2 days 1, 8, 15, 22	Every 28 days for 4 cycles[a]
Cisplatin 100 mg/m^2 on day 1 Vinorelbine 30 mg/m^2 days 1, 8, 15, 22	Every 28 days for 4 cycles[b,c]
Cisplatin 75-80 mg/m^2 day 1; Vinorelbine 25-30 mg/m^2 days 1 + 8	Every 21 days for 4 cycles[a]
Cisplatin 100 mg/m^2 on day 1 Etoposide 100 mg/m^2 days 1-3	Every 28 days for 4 cycles[b]
Cisplatin 80 mg/m^2 on day 1, 22, 43, 64 Vinblastine 4 mg/m^2 days 1, 8, 15, 22 then every 2 wks after day 43	Every 21 days for 4 cycles[b]

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

Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin	Schedule
Gemcitabine 1000 mg/m^2 on days 1, 8, 15 Carboplatin AUC 5 on day 1	Every 28 days for 4 cycles[f]
Paclitaxel 200 mg/m^2 on day 1 Carboplatin AUC 6 on day 1	Every 21 days[d]
Docetaxel 75 mg/m^2 Carboplatin AUC 6	Every 21 days[e]
Gemcitabine 1000 mg/m^2 days 1, 8 Docetaxel 85 mg/m^2 day 8	Every 21 days for 8 cycles[g]

See Chemoradiation on page NSCL-D (3 of 3)

See References on page NSCL-D (2 of 3)

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

CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY (2 OF 3)
REFERENCES

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

[b] Arriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-60.

[c] Douillard JY, Rosell R, De Lena M, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7(9):719-727.

[d] Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323. Epub 2006 Nov 1.

[e] Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol 2003;21(16):3016-24. Epub 2003 Jul 1.

[f] Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003;98(3):542-553.

[g] Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610. Epub 2005 Mar 1.

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CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY (3 OF 3)

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

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

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

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

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

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

[c] Belani CP, Choy H, Bonomi P, et al. Combined chemoradiotherapy regimens of paclitaxel and carboplatin for locally advanced non-small-cell lung cancer: a randomized phase II locally advanced multi-modality protocol. J Clin Oncol 2005;23(25):5883-5891.

[d] Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. J Clin Oncol 2003;21(10):2004-2010.

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

ADVANCED DISEASE:

- Baseline prognostic variables (stage, weight loss, PS, gender) predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control and yields superior quality of life compared to best supportive care.
- New agent platinum combinations have generated a plateau in overall response rate (≥ 25-35%), time to progression (4-6 mo), median survival (8-10 mo), 1 y survival rate (30-40%) and 2 y survival rate (10-15%) in fit patients.
- No specific platinum-based cytotoxic combination is clearly superior.
- Fit elderly merit appropriate treatment.
- Unfit of any age (performance status 3-4) do not benefit from cytotoxic treatment.

First-line therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC.
- Two drug regimens are preferred; three drug regimens do not add a benefit, with the exception of bevacizumab in treatment-naïve PS 0-1 NSCLC, in the absence of antecedent hemoptysis, squamous histology, brain metastases, or ongoing anti-coagulation or clotting diathesis.
- Single agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Systemic chemotherapy is not indicated in PS 3 or 4 patients.
- In locally advanced NSCLC, chemoradiation is superior to radiation alone: concurrent chemoradiation appears to be better than sequential chemoradiation.
- Cisplatin-based combinations have been proven superior to best supportive care in advanced, incurable disease, with improvement in median survival of 6-12 wks, and a doubling of one-year survival rates (absolute 10-15% improvement).
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine.
- New agent/non-platinum combinations are reasonable alternatives if available phase I/II data show activity and tolerable toxicity.
- If patient with known active EGFR mutation or gene amplification and a never smoker, consider use of erlotinib ± chemotherapy.

Second-line therapy

- In patients who have experienced disease progression either during or after first-line therapy, single agent docetaxel or pemetrexed, or tyrosine kinase inhibitor, erlotinib are established second-line agents.
  - ► Docetaxel has been proven superior to BSC, vinorelbine, or ifosfamide with improved survival/QOL.
  - ► Pemetrexed has been shown to be equivalent to docetaxel with less toxicity.
  - ► Erlotinib has proven superior to BSC with significantly improved survival and delayed time to symptom deterioration.

Third-line therapy

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

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

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

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

- Cisplatin [1-9]
- Carboplatin [4,6-11]
- Paclitaxel [1,4,6,8-11]
- Docetaxel [5,7,8,12]
- Vinorelbine [6-8]
- Gemcitabine [3,5,6,8,9]
- Etoposide [4]
- Irinotecan [9]
- Vinblastine
- Mitomycin
- Ifosfamide
- Pemetrexed [13]
- Erlotinib [14]
- Bevacizumab [15]

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

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

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

[4] Bellani CP, Lee JS, Socinski MA, et al. Randomized phase III trial comparing cisplatin-etoposide to carboplatin-paclitaxel in advanced or metastatic non-small cell lung cancer. Ann Oncol 2005;16(7):1069-1075

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

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

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

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

[9] Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2006 Nov 1;[Epub ahead of print].

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

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

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

[13] 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.

[14] Shepard FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353(2):123-32.

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

Note: All recommendations are category 2A unless otherwise indicated.
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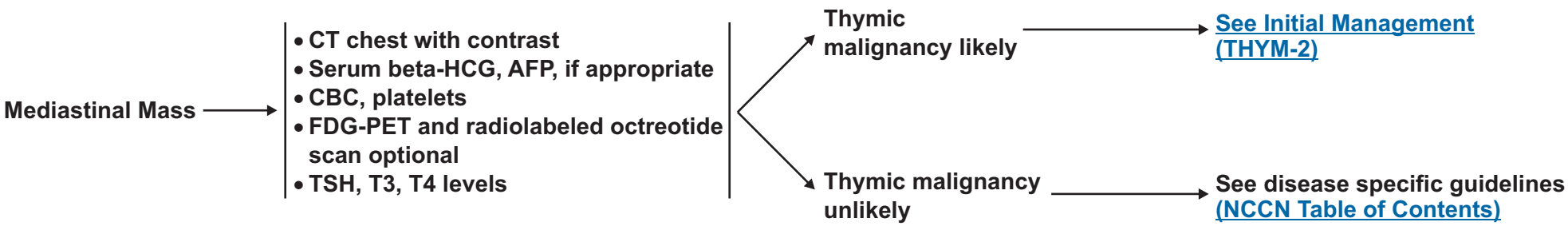
Thymic Malignancies

INITIAL EVALUATION



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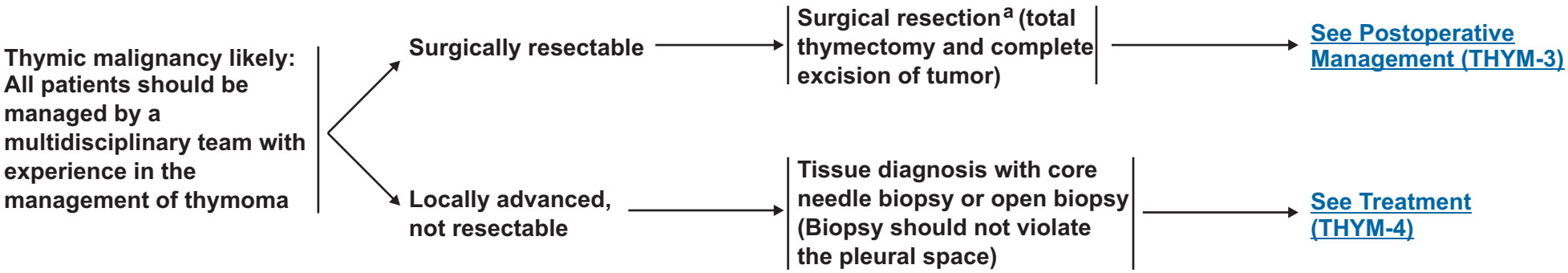
Thymic Malignancies

INITIAL MANAGEMENT



[a] See Principles of Surgical Resection for Thymic Malignancies (THYM-A).

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Thymic Malignancies

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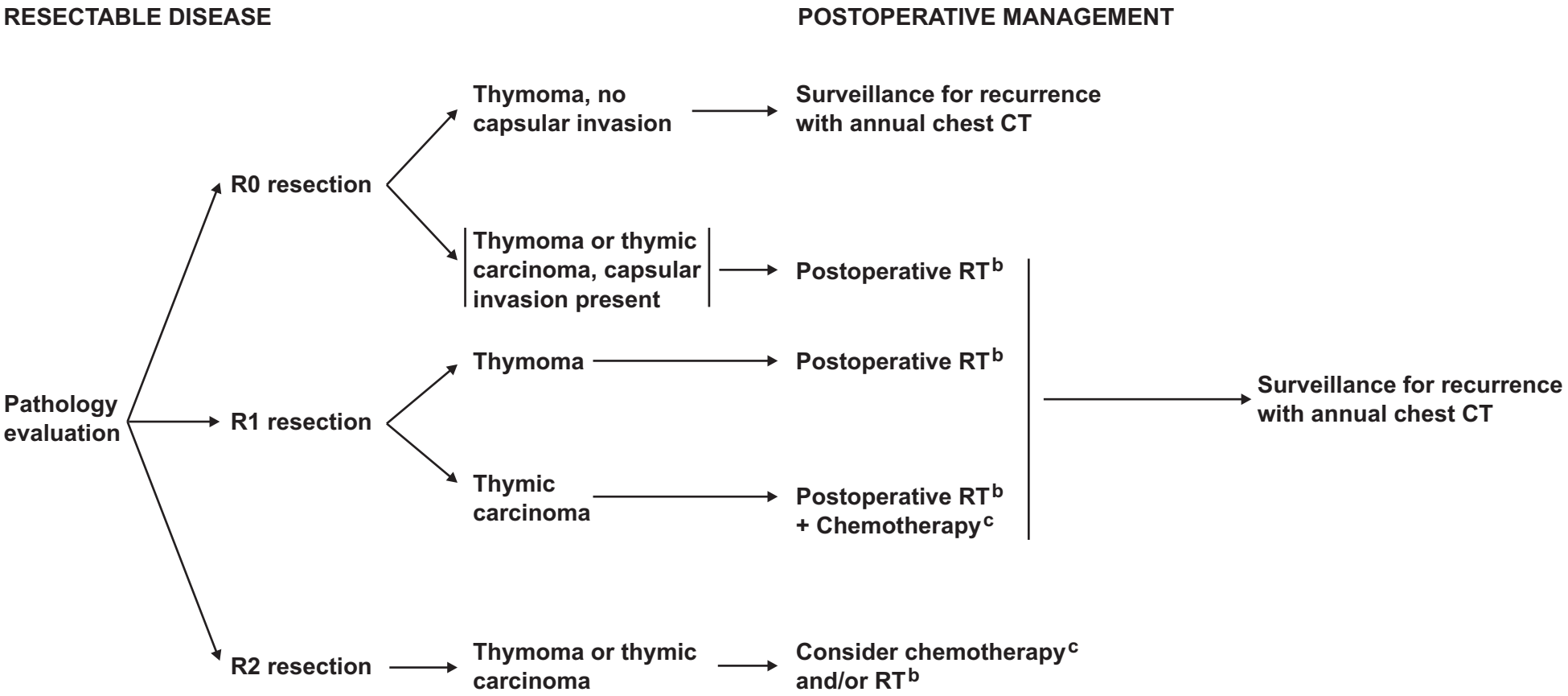

[b] See Principles of Radiation Therapy for Thymic Malignancies (THYM-B).
[c] See Principles of Chemotherapy for Thymic Malignancies (THYM-C).

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Thymic Malignancies

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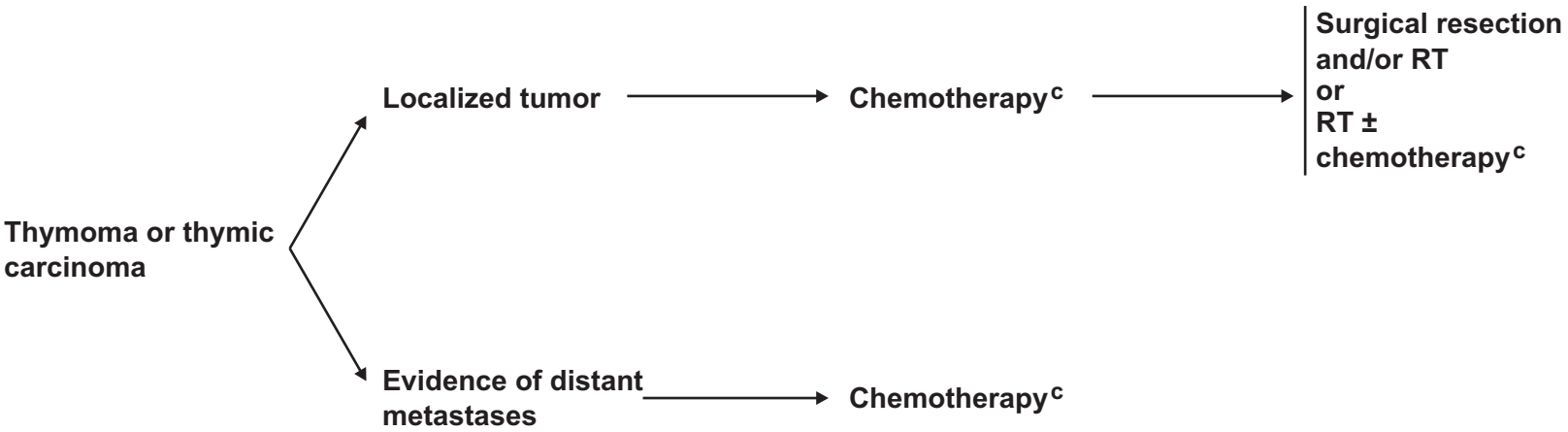
UNRESECTABLE DISEASE **TREATMENT**



[c] See Principles of Chemotherapy for Thymic Malignancies (THYM-C).

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Thymic Malignancies

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PRINCIPLES OF SURGICAL RESECTION FOR THYMIC MALIGNANCIES

- Prior to surgery, all patients should have clinical evaluation for signs and symptoms of myasthenia gravis
- Goal of surgery is complete excision of the lesion
- Procedure of choice is total thymectomy and complete resection of contiguous and noncontiguous disease
- Complete resection may require the resection of adjacent structures including pericardium, pleura, lung, and even major vascular structures.
- VATS or VATS-assisted techniques may be appropriate for encapsulated thymomas

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PRINCIPLES OF RADIATION THERAPY FOR THYMIC MALIGNANCIES

- Prior to surgery, all patients should be evaluated by radiation oncologists, surgeons, medical oncologists, diagnostic Imaging specialists and pulmonologists for evaluation resectability of the tumor and operability of the patients.
- Goal of radiation therapy is to reduce local recurrence.
- Radiation therapy needs to be given for patients with unresectable, incompletely resected and invasive thymoma or thymic carcinoma.
- Radiation therapy should be given by 3 dimensional radiotherapy or intensity modulated radiotherapy to reduce surrounding normal tissue damage, e.g. heart, lungs, esophagus and spinal cord.
- Prior radiation therapy, any cardiac, pulmonary and or neurological toxicities related to the paraneoplastic syndrome,surgery or the induction chemotherapy need to be documented as baseline
- Radiation oncologists need to communicate with the surgeons to investigate the operative findings and the pathologists regarding the detailed pathology report regarding extra-capsular extension and histology.

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Thymic Malignancies

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PRINCIPLES OF CHEMOTHERAPY FOR THYMIC MALIGNANCIES

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

CAP[1]
Cisplatin 50 mg/m^2 IV d1
Doxorubicin 50 mg/m^2 IV d1
Cyclophosphamide 500 mg/m2 IV d1
Administered every 3 weeks

CAP with Prednisone[2]
Cisplatin 30 mg/m^2 d1-3
Doxorubicin, 20 mg/m^2/d IV continuous infusion on d 1 to 3
Cyclophosphamide 500 mg/m^2 IV on d 1
Prednisone 100 mg/day d1-5
Administered every 3 weeks

ADOC[3]
Cisplatin 50 mg/m^2 IV d1
Doxorubicin 40 mg/m^2 IV d1
Vincristine 0.6 mg/m^2 IV d3
Cyclophosphamide 700 mg/m^2 IV d4
Administered every 4 weeks

PE[4]
Cisplatin 60 mg/m^2 IV d1
Etoposide 120 mg/m^2/d IV d1-3
Administered every 3 weeks

VIP[5]
Etoposide 75 mg/m^2 on d 1-4
Ifosfamide 1.2 g/m^2 on d 1-4
Cisplatin 20 mg/m^2 on d 1-4
Administered every 3 weeks

Carboplatin/Paclitaxel
Carboplatin AUC 6
Paclitaxel 200 mg/m^2
administered every 3 weeks

SECOND-LINE CHEMOTHERAPY

Etoposide
Ifosfamide
Pemetrexed
Octreotide +/- Prednisone
5-Fluorouracil and Leucovorin
Gemcitabine
Paclitaxel

[1]Loehrer, PJ et al. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an Intergroup trial. J Clin Oncol 1994; 12:1164,
[2]Shin DM, et al. A multidisciplinary approach to therapy for unresectable malignant thymoma. Ann Intern Med 1998; 129: 100–4.
[3]Fornasiero, A et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991; 68:30
[4]Giaccone, G et al. Cisplatin and etoposide combination chemotherapy for locally advanced or metastatic thymoma. A phase II study of the European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group. Journal of Clinical Oncology 1996; 14:814
[5]Loehrer PJ Sr, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. Cancer 2001; 91: 2010–5.

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

Staging

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

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

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

†Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

Table 2 **- Revised Definition of TNM***

Primary Tumor (T)

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

T0 No evidence of primary tumor

Tis Carcinoma in situ

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

T2 Tumor with any of the following features of size or extent:
- More than 3 cm in greatest dimension
- Involves main bronchus, 2 cm or more distal to the carina
- Invades the visceral pleura
- Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

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

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

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

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

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

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

Distant Metastasis (M)

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis present§

Continued...

Table 2 Continued

Histologic Grade (G)

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

Histopathologic Type

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

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

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

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

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

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

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

*Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York. (For more information, visit www.cancerstaging.net.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer-Verlag New York, Inc., on behalf of the AJCC.

Manuscript

NCCN Categories of Evidence and Consensus

Category 1: There is uniform NCCN consensus, based on high-level evidence, that the recommendation is appropriate.

Category 2A: There is uniform NCCN consensus, based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 2B: There is nonuniform NCCN consensus (but no major disagreement), based on lower-level evidence including clinical experience, that the recommendation is appropriate.

Category 3: There is major NCCN disagreement that the recommendation is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Lung cancer is the leading cause of cancer death in both men and women in the United States. An estimated 213,380 new cases (114,760 in men and 98,620 in women) of lung and bronchus cancer will be diagnosed in 2007 and 160,390 deaths (89,510 in men, 70,880 in women) are estimated to occur due to the disease.[1] Only 15% of all lung cancer patients are alive 5 years or more after diagnosis. Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.

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

Prevention and Screening

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

Smoking cessation should be encouraged, especially in patients with cancer (http://www.surgeongeneral.gov/tobacco/tobaqrg.pdf). Programs using behavioral counseling combined with stop-smoking medications (approved by the FDA [Food and Drug Administration]) are useful for smoking cessation as described in *Treating Tobacco Use and Dependence—Clinical Practice* Guideline, which is published by the Agency for Healthcare Research and Quality (AHRQ) (http://www.surgeongeneral.gov/tobacco/smokesum.htm#Findings). Varenicline is a new class of drug for smoking cessation; other drugs include nicotine replacement (eg, gum, inhaler, nasal spray, patch) and bupropion. Recent studies have shown that varenicline is better than bupropion for smoking cessation.[8,9] The FDA recently approved varenicline for smoking cessation. However, almost 30% of patients had nausea while using varenicline, and most of the participants in the recent studies did not quit smoking even with varenicline.

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.[10,11] Because localized cancer can be managed curatively and because survival in other solid tumors (eg, breast, cervix, colon, and prostate) appears to be increased by screening and early detection, lung cancer would be an appropriate candidate for a population-based screening approach. Pilot trials of spiral computed tomography (CT) in lung cancer screening are promising with a frequency of stage I detectable lung cancer in more than 80% of newly diagnosed cases.[12-14] The National Lung Screening Trial (NLST, ACRIN Protocol A6654) is a randomized, controlled study involving 50,000 current or former smokers; this trial is assessing the risks and benefits of spiral CT scans compared with chest x-rays for detecting lung cancer. The NSLT is now closed, and data will be collected until 2009. Additional information on NLST can be found at http://www.cancer.gov/nlst.

The International Early Lung Cancer Action Program (I-ELCAP) has been assessing whether annual screening by spiral CT scan increases the detection of early-stage lung cancer in patients at risk for cancer. Recently, data from I-ELCAP showed that stage I lung cancer can be detected using annual low-dose CT screening. The 10-year survival rate was 92% for stage I patients whose cancers were promptly removed; however, all stage I patients who chose not to be treated died within 5 years.[15] Additional information on I-ELCAP can be found at http://www.ielcap.org/index.htm. Screening can increase the diagnosis of early-stage lung cancers and yields excellent survival data. However, whether mortality is decreased by screening has not yet been conclusively demonstrated and is expected to be answered by the NLST.

At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3) despite the recent data from I-ELCAP demonstrating that lung cancer screening can detect stage I lung cancer, which could translate to an increase in survival of lung cancer patients.[15,16] 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 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.[17] If a screening strategy is used, then the I-ELCAP screening protocol should be followed (http://www.ielcap.org/professionals/docs/ielcap.pdf).

Classification and Prognostic Factors

The World Health Organization divides lung cancer into 2 major classes based on its biology, therapy, and prognosis: non-small cell lung cancer (NSCLC, discussed in this guideline) and small cell lung cancer ([SCLC], see NCCN Small Cell Lung Cancer Guideline). NSCLC

accounts for 80% to 85% of all lung cancer cases, and it includes 3 major types: (1) adenocarcinoma; (2) squamous cell (epidermoid) carcinoma; and (3) large-cell 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. Recently, gene expression profiling (using DNA microarrays) has identified subtypes of lung adenocarcinomas (ie, bronchioid, squamoid, magnoid), which correlate with stage-specific survival and metastatic pattern. Bronchioid tumors were associated with increased survival in early-stage disease, whereas, squamoid tumors were associated with increased survival in advanced disease.[18]

Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early stage disease at diagnosis, good performance status (Eastern Cooperative Oncology Group 0, 1, or 2), no significant weight loss (not more than 5%), and female gender.[19] Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (*p53*), the activation of *k-ras* oncogenes, and other biologic markers, may have significant value in predicting a poor prognosis.[20,21] 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.

Thymic Malignancies

Masses in the anterior mediastinum can be either neoplasms (such as, thymomas, lymphomas, thymic carcinomas) or non-neoplastic conditions (such as, goiter, thymic cysts).[22] Many mediastinal masses are benign, especially those occurring in asymptomatic patients; however, symptomatic patients often have malignant mediastinal lesions. Thymomas are the most common tumor in the anterior mediastinum. The NCCN panel has added a new guideline for Thymic Malignancies (see THYM-1) outlining the evaluation, treatment, and management of thymomas and thymic carcinomas (see “Thymic Masses”).

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the lung cancer, determine the extent of invasion, establish the cancer involvement status of the surgical margins, and determine the molecular abnormalities of lung cancer that may be able to predict for sensitivity and resistance to epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKI).[23-25] Preoperative evaluations include examination of one of the following specimens: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy. In addition, the mediastinal lymph nodes are sampled to assess the staging and therapeutic options. Lobectomy or pneumonectomy specimens are evaluated intraoperatively to determine the surgical resection margin status, to diagnose incidental nodules discovered at the time of surgery, or to evaluate the regional lymph nodes. Postoperative evaluation provides the pathology characteristics necessary for the classification of tumor type, staging, and prognostic factors. The surgical pathology report should include the histologic classification published by the World Health Organization for carcinomas of the lung.[26] The principles of pathology review are listed in NSCL-A.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important subtype of pulmonary adenocarcinoma and has received increasing attention in recent years because of evidence that EGFR mutation in lung cancer is linked to bronchioloalveolar differentiation.[27,28] BAC includes only noninvasive tumors where the neoplastic cells spread out along pre-existing alveolar structures (lepidic spread). Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.[29] BAC is divided into 3 subtypes: mucinous, nonmucinous, as well as a mixed

mucinous and nonmucinous or indeterminate form. Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1). Mucinous BACs express CK20 and CK7, but reportedly lack TTF-1 expression.[30] BACs are usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. Mucinous BACs are often CK7+/CK20+.[31] CDX-2 is a highly sensitive and specific marker of adenocarcinomas of intestinal origin that could be used to distinguish mucinous BAC from metastatic primary gastrointestinal cancers.

Immunohistochemical Staining

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma. A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) are used routinely. The stains that are negative in mesothelioma, but positive in adenocarcinoma, are CEA (carcinoembryonic antigen), B72.3, Ber-EP4, and MOC31. WT-1, calretinin, D2-40,[32] and cytokeratin 5/6 stains are sensitive and specific for mesothelioma. Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. TTF-1 is a homeodomain-containing transcription factor that regulates tissue-specific expression of surfactant apoprotein A (SPA), surfactant apoprotein B (SPB), surfactant apoprotein C (SPC), Clara cell antigen, and T1α. Thyroid transcription factor 1 (TTF-1) is very important in distinguishing primary from metastatic adenocarcinoma, because most primary carcinomas are TTF-1 positive, whereas metastatic adenocarcinomas to the lung are virtually always TTF-1 negative. TTF-1 is positive in patients with thyroid cancer. In addition, thyroglobulin is present in patients with thyroid cancer, while it is negative in patients with lung cancer. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies that could be used to differentiate them from primary lung tumors. Neuroendocrine tumors of the lung are diagnosed with chromogranin (reacts with cytoplasmic neuroendocrine granules) and synaptophysin (reacts with a cell membrane glycoprotein). All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin, whereas small cell lung carcinoma is negative in 25% of the cases.

Nearly all SCLCs are immunoreactive for keratin, epithelial membrane antigen, and TTF-1. Many SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM), and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs are immunoreactive for at least one of these neuroendocrine markers.[33]

Molecular Diagnostic Studies

Epidermal growth factor receptor (EGFR) is normally found on the surface of epithelial cells and is often overexpressed in various human malignancies. There is a significant association between EGFR mutations, especially exon 19 deletion, and the response of patients to TKIs, such as gefitinib.[34-37] Thus, the presence of EGFR-activating mutations can be used to select the best treatment for these patients.

K-ras is a critical downstream effector of the EGFR pathway that has been found to be mutated in approximately 15% to 30% of lung adenocarcinomas and to be associated with tobacco smoke exposure. EGFR and K-ras mutations are mutually exclusive in patients with lung cancer.[38] 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.[39]

Staging

Since the initial publication of the NCCN NSCLC guidelines in March 1996, the international staging system for lung cancer has been revised and adopted by the American Joint Committee on Cancer (AJCC) and by the Union Internationale Contre le Cancer.[40,41-43] The purpose of the revisions was to refine the placement of patients with lung cancer into strategies with similar survival rates and therapeutic options. The revised stage grouping is summarized in Table 1, and the descriptors of the TNM classification scheme are summarized in Table 2. In the revised staging system, the following changes have been made:

- Stage I disease has been divided into stage IA (T1, N0, M0) and stage IB (T2, N0, M0), because the survival rate is higher for patients with T1, N0 than that for patients with T2, N0.
- Stage II disease was similarly divided into stage IIA (T1, N1, M0) and stage IIB (T2, N1, M0 and T3, N0, M0) for the same reason.
- Stage IIIA disease remains the same except for tumors designated as T3, N0, M0, because the survival of patients with these tumors is similar to that of patients with T2, N1, M0 disease; consequently, both of these categories are now grouped together as stage IIB disease.
- Stage IIIB and stage IV disease remain unchanged except for the changes made to the T4 and M1 descriptors shown in Table 2. Malignant pericardial or pleural effusion has been added to the T4 descriptor, and the presence of satellite tumor nodule(s) within the ipsilateral primary-tumor lobe of the lung is classified as T4. Separate metastatic tumor nodule(s) in the ipsilateral or contralateral lobe of the lung are also classified as M1.

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

Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (such as thoracotomy, mediastinoscopy examination of resected lymph nodes).[40]

For patients who are staged, 25% will have stage I disease; 7%, stage II; 32%, stage III; and 36%, stage IV. This data was determined using pathologic stage group when available, otherwise clinical stage group was used.[40]

The 5-year survival rates[40] for those patients are:

- Stage I: 47%
- Stage II: 26%
- Stage III: 8.4%
- Stage IV: 1.6%

Note that a new lung cancer staging system has been proposed by the International Association of the Study of Lung Cancer (IASLC).[44] The revised staging will be published by the AJCC (7th ed) in 2009.

Treatment Approaches

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

Surgery

In general, for patients with stage I or stage II disease, surgery provides the best chance for cure. The surgical procedure used depends on the extent of disease, as well as the cardiopulmonary reserve of the patient. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; otherwise, lobectomy or pneumonectomy should be done if physiologically feasible. It is controversial whether lung-sparing surgeries, such as segmentectomy and wedge resection, are useful in patients with severely reduced pulmonary function who are otherwise not candidates for surgery.[45,46] If clinical stage I and II patients are deemed medically inoperable by a thoracic surgeon, then these patients should receive potentially curative RT (see NSCL-B).

At the time of surgical staging, the role of a complete mediastinal lymphadenectomy versus lymph node sampling remains controversial.[47,48] To address this issue, the American College of Surgeons Oncology Group is conducting a randomized trial (ACOSOG Z0030) of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with N0 (no demonstrable metastasis to regional lymph nodes) or N1 (metastasis to lymph nodes in the ipsilateral peribronchial and/or hilar region, including direct extension) NSCLC disease. The primary objective of this study is to evaluate whether complete mediastinal lymph node dissection results in better overall survival when compared to mediastinal lymph node sampling in the patient undergoing resection for N0 or non-hilar N1 NSCLC.[49]

Video-assisted thoracic surgery (VATS) is a relatively new minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.[50] Published studies suggest that VATS has several advantages over the standard thoracotomy (or pleuracotomy). Acute and chronic pain associated with VATS is minimal; thus, this procedure requires shorter length of hospitalization. VATS is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[51-53] In stage I NSCLC patients who have VATS with lymph node dissection, the 5-year survival rate, long-term survival, and local recurrence were comparable to those achieved by routine open lung resection.[54-56] VATS has also been shown to improve discharge independence in older populations and in high-risk patients as well.[57,58] Based on its favorable effects on postoperative recovery and morbidity, VATS is included in the guidelines (see NSCL-B) as a feasible option for patients who are surgically resectable as long as standard oncologic and dissection principles of thoracic surgery are not compromised.

Radiation Therapy

Modern 3-dimensional conformal RT techniques with CT or CT/positron emission tomography (PET)-based treatment planning should be used on all patients. It is necessary to evaluate the dose volume histogram (DVH) for the lungs, esophagus, heart, and spinal cord to minimize normal tissue toxicity (see NSCL-C).[59-63] Whenever feasible, respiratory management techniques (such as 4-dimensional CT and respiratory gating) should be incorporated in the radiation set up and delivery to individualize respiratory motion and/or decrease dose to the normal tissues, respectively. Treatment planning should be on CT scans obtained in the treatment position; IV contrast should be used for better target and normal tissue delineation whenever possible. Computed tomography/PET is preferable for treatment plans rather than CT alone for the gross tumor volume (GTV) delineation in cases with substantial atelectasis. The selection of optimal beam energy for the treatment of lung cancer is complex. ^{60}Cobalt and orthovoltage beams are not appropriate for curative treatment. In general, photon beam energy between 4-10 MV is recommended for most patients. If a large tumor is involving the mediastinum or the primary tumor is a large and proximal

lesion with patient's separation more than 20 cm, 15 MV or 18 MV photon energy can also be used but is discouraged because of concerns of increasing dose to the lung through lung scatter, which is not accounted for in current treatment planning algorithms as well as concerns of under-dosing the tumor at the air-tissue interface. If the tumor is fixed to the vertebral body, located at the superior sulcus, or involves the bilateral mediastinum, then intensity-modulated radiotherapy (IMRT) or proton therapy should be considered to improve tumor coverage and reduce dose to surrounding critical structures. In this situation, where very small margins are incorporated, more frequent imaging (less than 1 week) with orthogonal radiographs or cone beam CT is encouraged to reduce daily set up error.

In the preoperative chemoradiation setting, a total dose of 45-50 Gy in 1.8-2 Gy fractions should be used to treat all volumes of gross disease (see NSCL-5 and NSCL-C).[64] Doses greater than 50 Gy in the preoperative setting have been reported to be safe at select institutions; however, this is still considered experimental.[65-67] Preoperative chemoradiotherapy should be avoided if pneumonectomy is required to avoid postoperative pulmonary toxicity.[68,69] Surgery in a field that has had 60 Gy is difficult, because the landmarks disappear with high doses of radiation. Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 Gy, especially patients who have received RT doses of more than 60 Gy (ie, patients who have received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. Radiation therapy should continue to definitive dose without interruption if the patient is not a surgical candidate. Postoperative radiation should include the bronchial stump and mediastinum. A total dose of 50 Gy should be delivered in 1.8 to 2 Gy fractions for negative margins. For extranodal extension, a total dose of 54-60 Gy (in 1.8 to 2 Gy fractions) should be used; for microscopic positive margins, a total dose of 60 to 66 Gy should be used (see NSCL-C). For gross residual tumor, a total dose up to 70 Gy should be used. Concurrent adjuvant chemoradiation can be used if recommended in the guidelines and if the patient can tolerate it because of the higher risk of local failure.[70]

In the definitive concurrent chemoradiation setting, a total radiation dose up to 74 Gy in 2 Gy fractions should be used to treat all volumes of gross disease.[70-72] Three-dimensional treatment planning is imperative with dose volume histogram assessments of lung function to estimate the risk of pneumonitis.[73] Elective nodal radiation is not mandated.[74]

Recent studies suggest that stereotactic body radiotherapy (SBRT) and radiofrequency ablation (RFA) may be options for node-negative patients who either refuse surgery or cannot tolerate surgery because of poor performance status, significant cardiovascular risk, poor pulmonary function, and/or comorbidities. When stereotactic radiosurgery was used in 245 patients (T1-2), local control was 85% at 2 years.[75] The Radiation Therapy Oncology Group (RTOG) 0236 trial is currently assessing SBRT.[76] Optimal candidates for SBRT include patients with tumors 5 cm or less that are not near a primary or secondary bronchus. 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.[77] RT with (or without) chemotherapy should be offered as potentially curative treatment to patients with stage I and II NSCLC who are medically inoperable but of reasonable performance status and life expectancy (see NSCL-B and NSCL-C). However, a recent study in 4,357 patients with stage I or II NSCLC who did not have surgical resection found that median survival was improved (by 5-7 months) in patients treated with RT, although 5-year survival was not significantly different when compared with patients not receiving RT.[78]

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease. In patients with completely resected NSCLC, adjuvant chemotherapy has been evaluated in several clinical trials and has been shown to improve survival in patients with early-stage disease.[79-81] Currently, concurrent chemoradiation appear superior to sequential therapy for patients with unresectable stage III disease.[71,82] Surgery is rarely done for patients with stage IV disease. For patients with stage IV disease who have a good performance status, platinum-based chemotherapy is beneficial.[83,84]

Surgery Followed by Chemotherapy

The International Adjuvant Lung Cancer Trial (IALT) reported a statistically significant survival benefit with cisplatin-based adjuvant therapy in patients with completely resected stage I, II, or III NSCLC.[79] The study included 1867 patients with surgically resected lung cancer who were randomly assigned either to cisplatin-based adjuvant chemotherapy or to observation, with a median follow-up duration of 56 months. A significantly higher survival rate (44.5% versus 40.4% at 5 years; hazard ratio for death, 0.86; 95% confidence interval, 0.76 to 0.98; *P*<.03) and disease-free survival rate (39.4% versus 34.3% at 5 years; hazard ratio, 0.83; 95% confidence interval, 0.74 to 0.94; *P*<.003), were observed for patients assigned to chemotherapy when compared with observation. IALT data suggest that cisplatin-based adjuvant chemotherapy improves survival in patients with completely resected NSCLC.

The NCIC CTG JBR.10 trial and the ANITA (Adjuvant Navelbine International Trialist Association) trial compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in early stage NSCLC. In the NCIC CTG JBR.10 trial, 482 patients (ECOG performance status [PS] of 0-1) with completely resected stage IB (T2, N0) or stage II (T1, N1, or T2, N1) were randomly assigned either to vinorelbine plus cisplatin (242 patients) or to observation (240 patients).[80] The median age was 61 years in both groups. Chemotherapy was not excessively toxic. Adjuvant chemotherapy significantly prolonged overall survival (94 versus 73 months, hazard ratio for death, 0.69, *P*=.04) as well as relapse-free survival (not reached versus 46.7 months, hazard ratio for recurrence, 0.60; *P*<.001) compared with observation alone. The 5-year survival rates were 69% and 54%, respectively (*P*=.03).

In the ANITA trial, 840 patients (median age, 59 years) with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned to adjuvant vinorelbine plus cisplatin or to observation.[81] 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.[81] Adjuvant chemotherapy significantly improved the 5-year overall survival in patients with completely resected stage II and IIIA disease, although no benefit was observed in stage I. Some clinicians consider vinorelbine/cisplatin to be the preferred regimen for completely resected early stage NSCLC based on the number of trials and the amount of use.

The CALGB 9633 trial was designed to test the effectiveness of paclitaxel and carboplatin as adjuvant chemotherapy in patients with T2, N0, M0, stage IB lung cancer;[85] updated results from this trial have recently been reported.[86] In this trial, 344 patients (34-81 years) were randomly assigned to paclitaxel and carboplatin or to observation within 4-8 weeks of resection with a median follow-up duration of 54 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 4 years was not significant, although 3-year survival was significant (79% versus 70%, *P*=.045).[86] The original results from CALBG suggested that the paclitaxel and

carboplatin regimen improved survival in patients with stage I disease; however, the updated results do not show improved survival (although a subset analysis of CALBG showed a benefit for tumors greater than 4 cm). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin (see NSCL-D).[87] Other carboplatin-based regimens for patients with comorbidities or who cannot tolerate cisplatin include gemcitabine/carboplatin[88] and docetaxel/carboplatin;[89,90] gemcitabine/docetaxel is another option.[91]

For patients with stage II disease, the Bimodality Lung Oncology Trial (BLOT) phase II study demonstrated the feasibility of delivering neoadjuvant chemotherapy (paclitaxel and carboplatin) in early stage disease.[92] Based on this study, a phase III intergroup trial was done in patients with stage IB, stage II, and stage IIIA (T3, N1, M0 only) disease who were randomly assigned either to immediate surgery alone or to 3 cycles of induction chemotherapy followed by surgery. However, the study was stopped early because of the results of the adjuvant chemotherapy studies.

Chemoradiation

The major controversies relate to the management of patients with stage IIIA disease. All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used in treating stage III disease. The ongoing debate centers on which modalities to use and in what sequence.[93-96] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[93-97] However, more recently, concurrent chemoradiation appears to be superior to sequential therapy.[71,82] Concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. For patients with negative margins, most NCCN institutions give sequential chemotherapy followed by RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT with (or without) chemotherapy). Patient selection affects not only the response to therapy but also how well the patient tolerates therapy.

Concurrent chemoradiation regimens used for initial treatment include cisplatin/etoposide (preferred), cisplatin/vinblastine (preferred), and carboplatin/paclitaxel (category 2B) (see NSCL-D).[70,71,98] Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.[99]

A phase II trial from SWOG (9504) assessed concurrent chemoradiation (using cisplatin/etoposide) followed by consolidation docetaxel in 83 patients with unresectable stage IIIB NSCLC.[100] Results from SWOG 9504 have shown a median survival of 26 months, and a 5-year survival rate of 29%.[101] However, recent results from a phase III trial in patients with unresectable stage III NSCLC assessing consolidation docetaxel after cisplatin/etoposide with concurrent chemoradiation did not show improved survival with docetaxel and did show increased toxicity.[102] A recent randomized controlled trial in 203 unresectable patients with either stage IIIA or IIIB NSCLC assessed induction chemotherapy followed by either radiotherapy alone or chemoradiation using paclitaxel; median survival was 14.1 months versus 18.7 months (P=.091), respectively.[103]

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.[104] Surgical resection of a solitary metastasis located in sites other than the brain remains controversial.

Patients with stage IV disease who have a good performance status benefit from chemotherapy, usually with a platinum-based regimen.[83] Many drugs are active against stage IV NSCLC. These drugs include the taxanes (paclitaxel, docetaxel), vinorelbine, the camptothecin analogs (irinotecan, topotecan), and gemcitabine (see NSCL-E).

Combinations using many of these drugs produce a 1-year survival rate of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, and docetaxel/cisplatin.[70,87,89,105,106] Phase III randomized trials have shown that many of the platinum-doublet combinations are similar for objective response rates and survival.[107,108] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor.

Specific targeted therapies have been developed in recent years for the treatment of advanced lung cancer.[109,110] Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor to the EGFR. In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. Based on the results of phase II-III clinical trials (ECOG 4599), the Eastern Cooperative Oncology Group (ECOG) recommends bevacizumab in combination with paclitaxel and carboplatin as the new standard treatment for patients with advanced nonsquamous NSCLC.[111] Any regimen with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Erlotinib was approved by FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib (with or without chemotherapy) can also be given as first-line therapy in patients with advanced or metastatic NSCLC who have known active EGFR mutation or gene amplification and who never smoked.[24,36]

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC (see NSCL-1). The clinical stage is initially determined from disease history (ie, cough, dyspnea, weight loss, chest pain) and physical examination together with a limited battery of tests, including a pathology review, chest CT (including the upper abdomen and adrenals), a complete blood cell (CBC) and platelet count, and chemistry profile. The panel also recommends that smoking cessation counseling be made available to patients. Based on the initial evaluation, the clinical stage is determined and assigned to 1 of 10 pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. Although chest CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease), CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.[112] Mediastinoscopy is the gold standard for evaluating mediastinal nodes. Thus, mediastinoscopy is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high (based on tumor size and location). Therefore, mediastinoscopy is appropriate for patients with T3 lesions even if the chest CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive CT scan. In contrast, because of the low prior probability of lymph node involvement in patients with peripheral T1 lesions,[113] some NCCN institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2, central T1 or T2 lesions with negative CT

scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy is recommended. Dillemans and colleagues have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT.[114] This strategy resulted in a 16% incidence of positive N2 nodes discovered only at the time of thoracotomy. For identifying N2 disease, chest CT scans had sensitivity and specificity rates of 69% and 71%, respectively. However, using both the chest CT scan plus mediastinoscopy was significantly more accurate (89% versus 71%) than using the chest CT scan alone for identifying N2 disease. When using CT scans, node positivity is based on the size of the lymph nodes. Therefore, the CT scan will miss small metastases that do not result in node enlargement. To address this issue, Arita and colleagues specifically examined lung cancer metastases to normal size mediastinal lymph nodes in 90 patients and found an incidence of 16% false-negative chest CT scans with histologic identification of occult N2 or N3 disease.[115]

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I, stage II, stage IIIA, and stage IIIB (T4, N0-1) tumors. However, in patients who present with a solitary pulmonary nodule where the suspicion of malignancy is high, surgical resection without prior invasive testing may be reasonable.

Other Imaging Studies

As previously mentioned, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.[112] Recently, PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN guideline panel reviewed the diagnostic performance of CT scans and PET scans. Panel members assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.[116] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported. Seely and coworkers reported on the number of metastatic lymph nodes discovered on routine mediastinoscopy and chest CT scan in patients with the most favorable tumors (ie, T1 cancer).[117] This study revealed a 21% incidence of identifying N2 or N3 nodes in patients who clinically appeared to have stage IA tumors. The positive predictive value of chest CT scan was only 43% per patient, and the negative predictive value was 92%.

Because they detect tumor physiology, as opposed to anatomy, PET scans may be more sensitive than CT scans. Moreover, if postobstructive pneumonitis is present, there is little correlation between the size of the mediastinal lymph nodes and tumor involvement.[118] Chin and colleagues found that PET, when used to stage the mediastinal nodes, was 78% sensitive and 81% specific with a negative predictive value of 89%.[119] Kerstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[120] The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (81% versus 76%). Recently, PET/CT has been shown to be useful in restaging patients after adjuvant therapy.[121,122]

Based on these considerations, the NCCN panel now believes that PET scan can play a role in the evaluation and more accurate staging of NSCLC, for example, in identifying stage I (peripheral and central T1-2, N0), stage II, stage III, and stage IV diseases.[123] However, positive PET scan findings need pathologic or other radiologic confirmation. If the PET scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Precisely how PET scans will fit into the overall staging and surveillance of NSCLC will become clearer as newer studies mature.

Recently, transesophageal endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound–guided

transbronchial needle aspiration (EBUS-TBNA) have proven useful to stage patients or to diagnose mediastinal lesions; these techniques can be used instead of invasive staging procedures.[124] 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.[125]

The routine use of magnetic resonance imaging (MRI) to rule out asymptomatic brain metastases and of bone scans to exclude bone metastases are not recommended. Brain MRI is recommended for patients with stage II (only nonsquamous histology for T1-2, N1), stage III, and stage IV diseases to rule out more advanced disease if aggressive combined-modality therapy is being considered.[126]

Initial Therapy

Stage I, Stage IIA, and Stage IIB (T2, N1) Disease

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

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2, N1) tumors are generally candidates for surgical resection and mediastinal node mapping. In some instances, positive mediastinal nodes (N2) are discovered at surgery; in this setting, an additional assessment of staging and tumor resectability must be made, and the treatment (such as inclusion of mediastinal lymph node dissection) must be modified accordingly. Therefore, the algorithms include 2 different tracks for T1–2, N2 disease: 1) T1–2, N2 disease discovered unexpectedly at surgical exploration (see NSCL-3); and 2) T1–2, N2 disease confirmed before thoracotomy (see NSCL-7). In the second case, an initial brain MRI and PET scan (if not previously done) are recommended to rule out metastatic disease.

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

For patients with clinical stage IIB (T3, N0) and stage III tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0) and stage IIIA (T3, N1) tumors, treatment options are organized according to the location of the tumor (ie, the superior sulcus, chest wall, and proximal airway or mediastinum). For each location, a determination is made regarding the surgical resectability.

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

In superior sulcus tumors, among the patients treated by surgery and postoperative radiotherapy with or without concurrent chemotherapy, the overall 5-year survival rate has been approximately 40%.[127] Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.[128-131]

Surgical resection is the preferred treatment option for patients with invasion of the chest wall, proximal airway, or mediastinum (T3, N0-1). Other treatment options include chemotherapy, concurrent chemoradiation, or radiotherapy (category 3) 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 EBUS-FNA, and EUS-FNA), bronchoscopy, brain MRI, and PET scan; PFTs should be ordered if not previously done. Patients with negative mediastinal biopsy findings are candidates for surgery, with additional assessment of resectability at the time of thoracotomy. For those patients with resectable lesions, mediastinal lymph node dissection should be performed during the surgery. Those individuals found to have unresectable lesions should be treated according to pathologic stage, as defined on NSCL-1. For patients with (T1-2, T3) node-positive disease, an additional brain MRI and PET scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see NSCL-7); for patients with T3, N2 nodes who have an excellent response, consider surgical resection (category 3), although the panel disagreed about whether resection is appropriate. Although definitive concurrent chemoradiation is recommended (category 1), induction chemotherapy with (or without) RT is another option for patients with T1-2, N2 disease. Recommended therapy for metastatic disease is detailed on NSCL-11 for stage IV diseases.

Stage IIIB tumors comprise a heterogeneous set of presentations, each requiring a different approach. These 4 groups include: 1) T4 tumors with N0-N1 nodal status, a group potentially curable with surgery (this group includes tumors upstaged to T4 because of satellite lesions); 2) tumors with contralateral mediastinal nodes (T1-3, N3); 3) T4 tumors with N2-3 disease, which are unresectable; and 4) tumors that are stage IIIB because of pleural or pericardial effusion. For resectable T4, N0-1 tumors with satellite lesions, initial surgical resection is recommended followed by chemotherapy. The recommended initial treatment options for resectable tumors (other than satellite) are similar to stage IIIA disease: surgery, induction chemotherapy before surgery, or concurrent chemoradiation before surgery (see NSCL-8). In support of this option, Naruke and colleagues reported a 5-year survival rate of 8% in patients with resected T4 disease.[132] For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by consolidation chemotherapy (category 2B) (see NSCL-D).[101]

Surgical resection is not recommended in patients with T1-3, N3 disease (ie, metastases to contralateral nodes). However, in patients with suspected N3 disease, the guidelines recommend pathologic confirmation of nodal status by either mediastinoscopy supraclavicular lymph node biopsy, thoracoscopy, needle biopsy, mediastinotomy, or EUS biopsy) (see NSCL-9).[133,134] In addition, PFTs (if not previously done), PET scans, and brain MRI should also be included in the pretreatment evaluation. If the results of these tests are negative, then treatment options for the appropriate nodal status should be followed (see NSCL-1). If the results of these tests are positive, concurrent chemoradiation (category 1) followed by consolidation chemotherapy (category 2B) is recommended.[101] For metastatic diseases that are confirmed by PET scan and brain MRI, treatment is detailed on NSCL-11.

For patients with T4, N2-3 disease, surgical resection is not generally recommended. The initial work-up includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIB (T4, N0-1) disease (see NSCL-6). If either the contralateral or ipsilateral mediastinal node is positive, the patient

needs to be treated with concurrent chemoradiation therapy (category 1), although panel members did not all agree that consolidation chemotherapy (category 2B) should be given after chemoradiation (see NSCL-10).[101] Pleural or pericardial effusion is another criterion for T4 disease. Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (eg, obstructive pneumonia), an exudate or sanguinous effusion is considered malignant no matter what the results of cytologic examination. If the pleural effusion is considered negative, the algorithm tracks back to the confirmed T and N stage. However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.[135] In patients with positive effusion, the tumor is treated as M1 with local therapy (such as pleural catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see NSCL-11).

Stage IV

The algorithm for patients with distant metastases (ie, stage IV) depends on the location of the metastases—a solitary nodule in the brain, adrenal, or lung (ie, a satellite lesion)—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, and brain MRI. PET scan is also used in the diagnostic work-up for patients with a solitary metastasis. The increased sensitivity of PET scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. Positive PET scan findings need pathologic or other radiologic confirmation. If the PET scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.

Patients with solitary brain metastases may benefit from surgical resection. The 5-year survival rates with such an approach range from 10% to 20%.[109,136] Follow-up whole brain RT or stereotactic radiosurgery may be used, because the combined therapy is superior to RT alone in prolonging life and preventing local recurrence.[137] Stereotactic radiosurgery alone or followed by whole brain radiation is an additional treatment option. Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.[138] Additional chemotherapy in this setting can also be used, but this is a category 2B recommendation. Controversy exists because all these patients have M1 (stage IV) disease that has been resected, but the recommendation is to treat the primary lung tumor according to the T and N status.

Adrenal metastases from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. If an adrenal metastasis is found and if the lung lesion is curable, the resection of the adrenal lesion has produced some long-term survivors (category 3).[139,140] Although resection is listed in the guidelines, it generated major disagreement among the panel members (category 3). Some panel members feel that resection of adrenal glands only makes sense if the synchronous lung disease is stage I or maybe stage II (ie, resectable). Systemic therapy (see NSCL-13) is another treatment option for adrenal metastasis.

In patients with synchronous nodules (either in contralateral lung or ipsilateral lung), the guidelines suggest treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Patients with T1, N0 tumors and with negative surgical margins (R0) are either observed or chemotherapy (category 3) is recommended as adjuvant treatment for patients with high-risk features, such as poorly differentiated tumor, vascular invasion, wedge resection, and minimal margins (see NSLC-3). Treatment options for patients with T1, N0 disease and with positive surgical margins (R1, R2) include 1) re-resection; 2) chemoradiation (category 2B); or 3) RT (category 2B). Although chemotherapy can be added to either option 1 or 2, there was widespread disagreement about this addition (category 3). Patients with T2, N0 tumors should either be observed or receive adjuvant chemotherapy (category 2B) when the surgical margins are negative; if the surgical margins are positive, these patient should have re-resection with chemotherapy or chemoradiation and chemotherapy. For patients with T1-2, N1 disease and negative surgical margins, the panel recommends chemotherapy (category 1) or chemoradiation (category 2B) and chemotherapy for patients with adverse factors (such as, inadequate mediastinal lymph node dissections, extracapsular spread, multiple positive hilar nodes, and close margins). If surgical margins are positive (T1-2, N1), options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy (see NSCL-3). Patients with negative margins are treated with chemotherapy (category 1) and mediastinal RT. Panel members disagreed about the use of chemoradiation based on the results of the Intergroup E3590 trial.[141] In this trial, no difference in survival rates was observed between stage II and stage IIIA patients who had a surgical resection and received either adjuvant radiotherapy alone (median survival = 39 months) or radiotherapy given with concurrent chemotherapy (median survival = 38 months). Because the 5-year survival rate is less than 90%, some NCCN panel members feel that survival rates may increase with newer chemotherapeutic agents and with higher doses of radiation. For example, a phase II trial (RTOG 9705) using concurrent paclitaxel/carboplatin yielded a median survival of 56.3 months with 3-year survival of 61% in patients with resected stage II and IIIA disease.[142] As with stage IB and stage II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in stage III NSCLC patients who had surgery (see NSCL-D).

In the case of marginally resectable superior sulcus tumors (T3-4, N0-1), if the lesion converts to a resectable status following initial treatment, resection is performed and chemotherapy is given (see NSCL-5). If the lesion does not convert (it remains unresectable), the full course of definitive RT followed by chemotherapy is administered as an adjuvant treatment. Among patients with chest wall lesions with T3, N0-1 disease, those that are initially treated with surgery (preferred) should receive chemotherapy alone if the surgical margins are negative and should receive either chemoradiation and chemotherapy or re-resection with chemotherapy when surgical margins are positive. A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3, N0-1).

For patients with stage IIIA disease and positive mediastinal nodes (T1-2, N2), if there is no disease progression after initial treatment, patients should be treated with surgery with (or without) chemotherapy (category 2B) (see NSCL-7). In addition, postoperative RT should be given if not used preoperatively. Alternatively, if the disease progresses and the bulkiness of the N2 nodes precludes resection, patients may be treated with RT (if not given previously) with (or without) chemotherapy.

In patients with clinical stage IIIB (T4, N0-1) disease, the option for adjuvant therapy includes surgery, if initial therapy consisted of induction chemotherapy or concurrent chemoradiation therapy (see

NSCL-8). If the margins are negative, adjuvant chemotherapy is recommended. If the resection margin is positive, RT is given followed by chemotherapy.

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease obviously present but undetectable at diagnosis. The timing of this chemotherapy varies, with no one clear preference. Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients. On the basis of the results of recent clinical studies on adjuvant chemotherapy for NSCLC,[79-81] the panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; cisplatin combined with either gemcitabine or docetaxel are additional options (see NSCL-D).[87,89] For patients with comorbidities or those who cannot tolerate cisplatin, other regimens include carboplatin combined with either gemcitabine, paclitaxel, or docetaxel; gemcitabine combined with docetaxel may also be used.[87-91]

A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery.[143-145] Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[146-148] The S9900 trial, a SWOG (Southwest Oncology Group) study, one of the largest randomized trials examining preoperative chemotherapy in early-stage NSCLC, assessed surgery alone compared with surgery plus preoperative paclitaxel and carboplatin in patients with stage IB/IIA and stage IIB/IIIA NSCLC (excluding superior sulcus tumors). Progression-free survival and overall survival were in favor of preoperative chemotherapy.[148] All 3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase III studies had small number of patients while the SWOG study was stopped early because of the positive results of the IALT study. Induction chemotherapy-surgery approach needs to be compared with induction chemotherapy-RT in large, randomized clinical trials.

Radiation Therapy

RT alone as adjuvant treatment for T1-2, N0-2 tumors brought about major disagreement among the panel members based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).[149] This study showed that postoperative radiotherapy is detrimental to patients with early-stage, completely resected NSCLC and should not be given routinely to such patients. However, the guideline panelists found several flaws in the meta-analysis, including:

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

A recent assessment of postoperative radiation in 7,465 patients with resected stage II or III NSCLC found that postoperative radiation increased survival in patients with N2 disease but not in those with N1 or N0 disease.[150]

Surveillance and Treatment of Recurrences and Metastases

Surveillance

The guidelines suggest routine history and physical examinations every 4 to 6 months in the first 2 years and then annually for patients with

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

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases (see NSCL-12). Palliation of symptoms can be achieved with external-beam RT by reducing tumor size. In addition, various regional therapy options are listed for locoregional recurrences. Resectable local recurrence may be managed by re-resection. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life.[151] Obstructed airways can be treated with brachytherapy (endobronchial RT), laser treatment, or endobronchial stent placement; these modalities can be used individually or in combination. In addition, photodynamic therapy (PDT) offers a simple and effective alternative to conventional techniques for palliative debridement of endobronchial obstructions in lung cancer patients. Mediastinal lymph node recurrence should be treated with concurrent chemoradiation (if RT has not been given previously). For superior venal cava (SVC) obstruction, RT or stent placement is indicated. For severe hemoptysis, several treatment options are recommended (such as brachytherapy, laser therapy, PDT, or embolization). Ultimately, surgery may be done to remove the bleeding site. After the treatment for the locoregional recurrence, if no further disseminated disease is evidenced, observation or systemic chemotherapy (category 2B) is recommended. However, for observed disseminated disease, systemic chemotherapy and best supportive care should be applied right away (see NSCL-13).

For distant metastases with localized symptoms, diffuse brain metastases, or symptomatic bony metastasis, palliation of symptoms can be achieved with external-beam RT. In addition, orthopedic stabilization should be performed if patients are at risk of fracture, and bisphosphonate therapy should be considered in patients with symptomatic bony metastasis. For other solitary metastasis, the treatment guidelines follow the same pathway as that for stage IV, M1 (solitary site) tumors as explained previously.

In a small subset of patients, recurrence will be suspected only on the basis of positive sputum cytology (see NSCL-15). In this situation, the guidelines recommend further evaluation with bronchoscopy, hematoporphyrin fluorescence, or autofluorescence. If tumor in situ (Tis) is detected, treatment options include endobronchial laser ablation, brachytherapy, photodynamic therapy, and surgical resection. Alternatively, the patient may be re-bronchoscoped every 3 months. If T1-3 tumors are discovered, the algorithms track back to the appropriate clinical stage (see NSCL-1). Surveillance may also detect a new lung primary, and these patients should be treated according to the staging findings.

For recurrent and metastatic disease, first-line therapy with bevacizumab in combination with chemotherapy is used for patients with PS of 0-1 who meet the eligibility criteria (nonsquamous cell histology, no history of hemoptysis, no CNS metastases, and no ongoing therapeutic anticoagulation). Note that bevacizumab should not be given as a single agent unless as maintenance if initially used with chemotherapy. Any regimen with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Patients who do not meet the criteria for bevacizumab or those with PS of 2 should receive chemotherapy alone.

In a phase II/III trial (ECOG 4599), 842 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and

carboplatin; or 2) paclitaxel and carboplatin alone.[111,152] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin demonstrated an improved response rate (27% versus 10%, *P*<.0001), progression-free survival (6.4 versus 4.5 months, *P*<.0001), and median survival (12.5 versus 10.2 months, *P*=.0075) when compared to patients receiving paclitaxel and carboplatin alone. The overall 1-year and 2-year survival was 51.9% versus 43.7% and 22.1% versus 16.9%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.[111] However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 24% versus 16.4%, grade 3/4 hemorrhage: 4.5% versus 0.7%, hemoptysis: 1.9% versus 0.2%, and hypertension: 6.0% versus 0.7%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (9 patients) than with paclitaxel and carboplatin (2 patients). Bevacizumab in combination with paclitaxel and carboplatin provided a significant survival benefit to patients with advanced NSCLC with nonsquamous histology.

For patients with PS of 0-1 who are not candidates for bevacizumab treatment, a platinum-based chemotherapy regimen is recommended (category 1) as first-line chemotherapy for the treatment of advanced disease. As yet, there is no evidence that one platinum-based regimen is better than any other. Studies evaluating the various chemotherapy regimens are ongoing. There was widespread disagreement (category 3) among panel members about when the patient should be reevaluated for tumor progression with a follow-up CT scan (ie, after the first or second cycle). Approximately 25% of patients demonstrate disease progression after the initial cycle of chemotherapy. Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles (total) (preferred) of chemotherapy[153] or until the disease progresses (category 2B). Although many patients are treated until disease progression, there is no evidence that this approach improves survival.

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, and erlotinib are recommended as single agent second-line chemotherapy regimens for patients with PS of 0-2 and who have experienced disease progression during or after first-line therapy (see NSCL-14).[154-157] In a randomized placebo-controlled double-blind trial (NCIC CTG trial), 731 patients (stage IIIB or IV, PS 0-3) were randomly assigned (2:1) to receive either erlotinib or placebo, following failure of first- or second-line chemotherapy.[157] Median age was 61.4 years. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group (*P*<.001). Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (hazard ratio, 0.70; *P*<.001). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (hazard ratio, 0.61, adjusted for stratification categories; *P*<.001). However, 5% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first- or second-line chemotherapy. A recent randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel;[158] however, oral topotecan is not available in the United States.

Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with PS of 0-2; erlotinib may be considered for PS 3 patients. If disease progression occurs after second- or third-line chemotherapy, patients with PS of 0-2 may be treated with best supportive care or be enrolled in a clinical trial. Best supportive care only should be provided to patients with PS of 3-4 and progressive disease during any stage of the treatment (see NCCN Palliative Care Guidelines).

Thymic Masses

Masses in the anterior mediastinum can be either neoplasms (such as, thymomas, lymphomas, thymic carcinomas, thymic carcinoids, thymolipomas, germ cell tumors, parathyroid adenomas) or non-neoplastic conditions (such as, intrathoracic goiter, thymic cysts, lymphangiomas, aortic aneurysms).[22,159] Lymphomas typically manifest as generalized disease but can also be primary anterior mediastinal lesions (such as, nodular sclerosing Hodgkin's disease, and non-Hodgkin's lymphomas [large B-cell lymphoma and lymphoblastic lymphoma]); patients typically have lymphadenopathy (see the NCCN Non-Hodgkin's Lymphomas Guidelines and the NCCN Hodgkin Disease/Lymphoma Guidelines).[159] Thymic carcinoids are rare tumors that are discussed in the NCCN Neuroendocrine Tumors Guideline. Teratomas are discussed in the NCCN Testicular Cancer Guideline.

Alpha-fetoprotein (AFP) and beta—human chorionic gonadotropin (beta-HCG) levels should be obtained to rule out germ cell tumors (see THYM-1). Thyroid-stimulating hormone (TSH), triiodothyronine (T3), and thyroxine (T4) levels should also be measured to rule out mediastinal goiter. All patients with a mediastinal mass should also have other studies to determine the type of mass and to determine the extent of disease; these tests should include chest CT with contrast, FDG-PET, radiolabeled octreotide scan (optional), complete blood counts, and platelets. On CT, thymoma can look like malignant mesothelioma; however, pleural effusion does not typically occur with thymoma.

Thymomas

Thymomas are the most common tumor in the anterior mediastinum.[22] Thymomas typically occur in adults older than 40 years and are rare in children or adolescents. Although some patients are asymptomatic, others present with chest pain, cough, or dyspnea. Thymomas are typically encapsulated. Total thymectomy and complete surgical excision are generally appropriate for most cases. Although thymomas can be locally invasive (pleura, lung), they rarely spread to regional lymph nodes or distant sites. Patients without invasive thymomas have a 5-year survival rate of about 70% versus 50% for invasive tumors.[160,161] For invasive or incompletely resected tumors, postoperative radiation therapy is recommended (see THYM-3); for unresectable or metastatic disease, chemotherapy with (or without) RT is recommended (see THYM-C).[162-169] For patients who have complete resection, surveillance should include annual chest CT.

About 30% to 50% of patients with thymomas have myasthenia gravis; therefore, patients should be evaluated for myasthenia gravis. All patients suspected of having thymomas (even those without symptoms) should have their serum antiacetylcholine receptor antibody levels measured to determine whether they have myasthenia gravis before any surgical procedure to avoid respiratory failure (see THYM-A).[170,171] Less frequently, patients may have hypogammaglobulinemia and red cell aplasia.

Thymic Carcinomas

Thymic carcinomas are rare aggressive tumors that often metastasize to regional lymph nodes and distant sites; thus, they have a worse prognosis than thymomas (5-year survival rates, 20% to 30%).[22,159,172] These tumors can be distinguished from thymomas because of their malignant features; however, thymic carcinomas should be differentiated from primary lung malignancies that metastasize to the thymus. Unlike thymomas, thymic carcinomas often cause pericardial and pleural effusions.

After resection of thymic carcinomas, postoperative management includes RT with (or without) chemotherapy, depending on the extent of resection (see THYM-3). For unresectable or metastatic thymic

carcinomas, patients should receive chemotherapy with (or without) RT.[173-175]

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