National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology™

Non-Small Cell Lung Cancer

V.2.2010

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NCCN Non-Small Cell Lung Cancer Panel Members

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

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

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

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

Andrew Chang, MD ¶
University of Michigan Comprehensive Cancer Center

Richard T. Cheney, MD ≠
Roswell Park Cancer Institute

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

Thomas A. D'Amico, MD ¶
Duke Comprehensive Cancer Center

Todd L. Demmy, MD ¶
Roswell Park Cancer Institute

Apar Kishor P. Ganti, MD †
UNMC Eppley Cancer Center at The Nebraska Medical Center

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

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

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

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

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

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

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

Feng-Ming Kong, MD, PhD §
University of Michigan Comprehensive Cancer Center

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

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

Quynh-Thu Le, MD §
Stanford Comprehensive Cancer Center

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

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

Janis O'Malley, MD ф
University of Alabama at Birmingham Comprehensive Cancer Center

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

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

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

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

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

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

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

George R. Simon, MD †
Fox Chase Cancer Center

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

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

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

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† Medical Oncology
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Staging

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

LUNG CANCER PREVENTION AND SCREENING

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

- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from second-hand smoke exposure associated with living with a smoker (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Every person should be informed of the health consequences, addictive nature and mortal threat posed by tobacco consumption and exposure to tobacco smoke and effective legislative, executive, administrative or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke. www.who.int/tobacco/framework/final_text/en/.**

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

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

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

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

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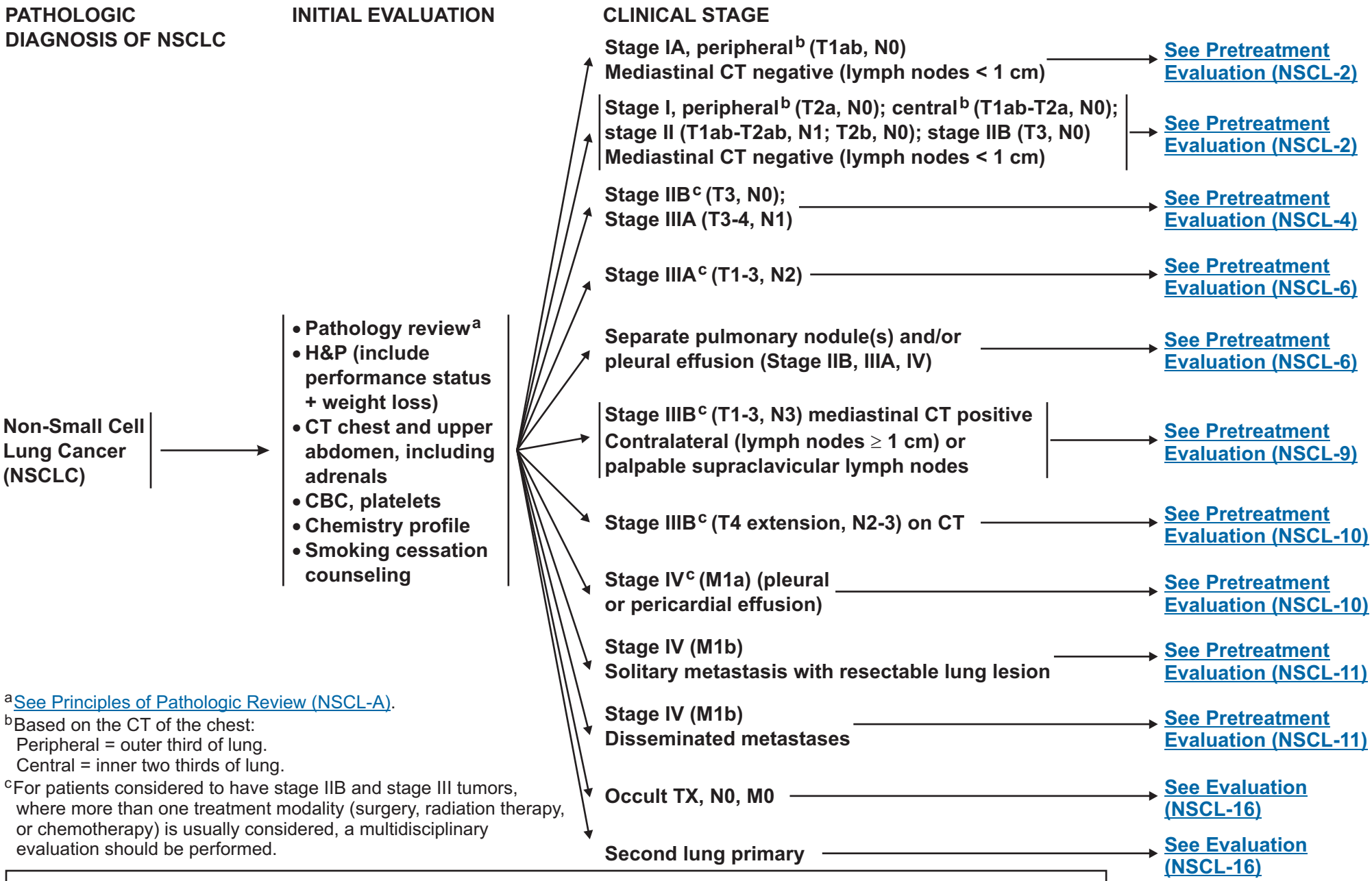

[a] See Principles of Pathologic Review (NSCL-A).

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

[c] 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**[e]

Stage IA (peripheral T1ab, N0) →

- PFTs (if not previously done)
- Bronchoscopy (intraoperative preferred)
- Mediastinoscopy (category 2B)
- EBUS if appropriate (category 2B)
- PET/CT scan[d]

Stage IB (peripheral T2a, N0)
Stage I (central T1ab–T2a, N0)
Stage II (T1ab–2ab, N1; T2b, N0)
Stage IIB (T3, N0) →

- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy
- EBUS if appropriate (category 2B)
- PET/CT scan[d]
- Brain MRI (Stage II only)

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

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

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

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

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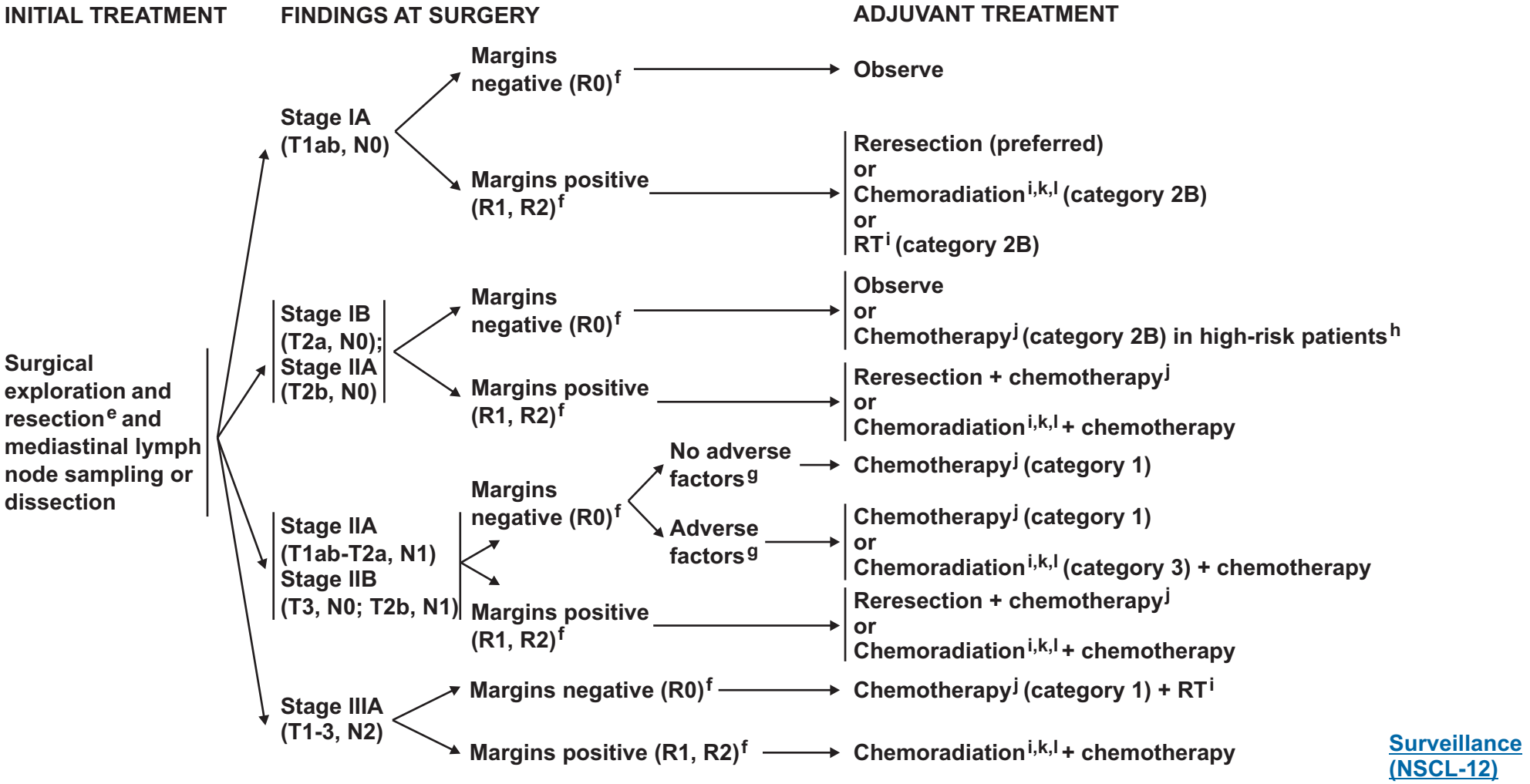

Surveillance (NSCL-12)

[e] See Principles of Surgical Therapy (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 tumors, vascular invasion, wedge resection, minimal margins, tumors > 4 cm, visceral pleural involvement, Nx.

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

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

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

[l] 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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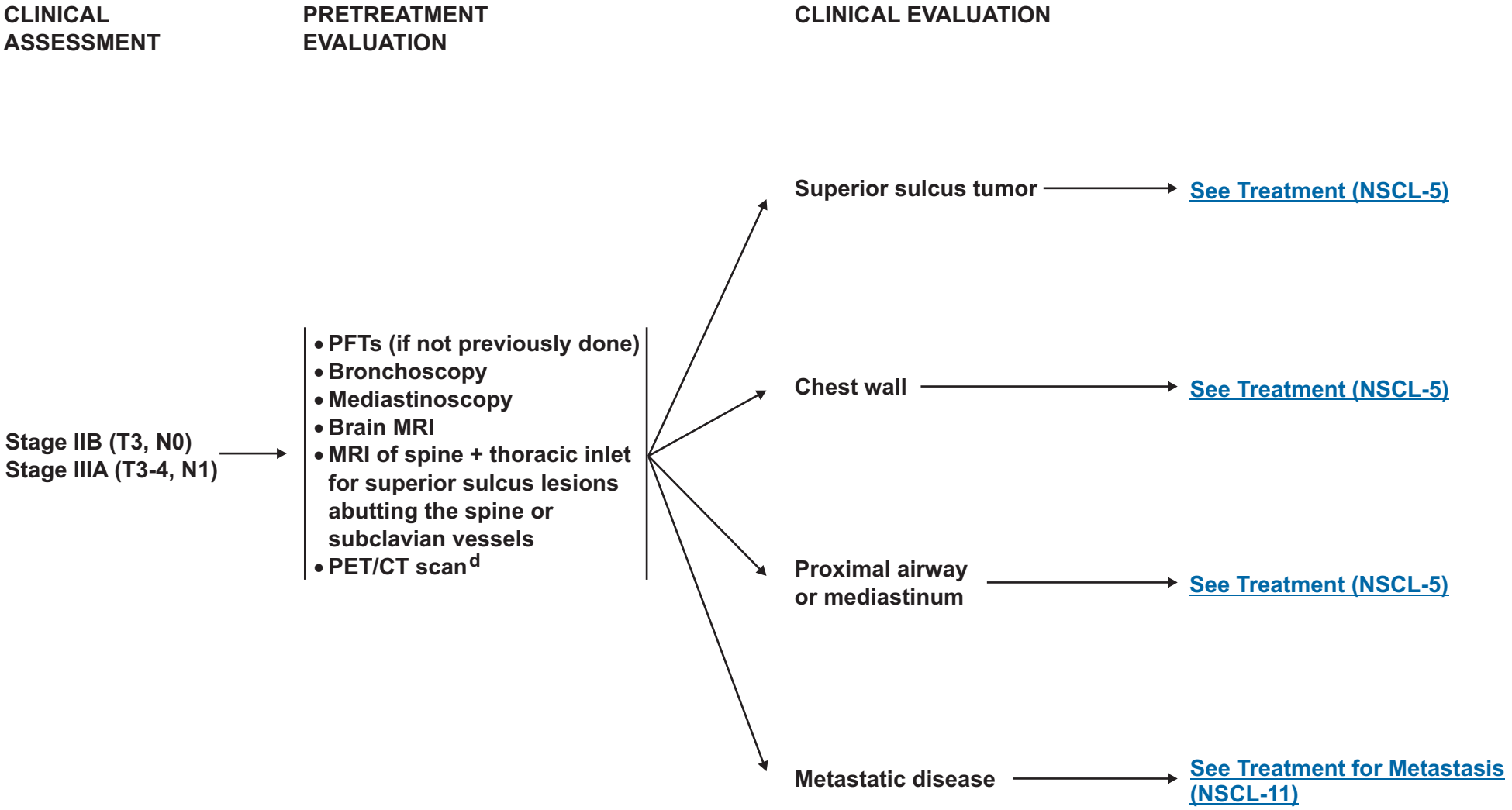

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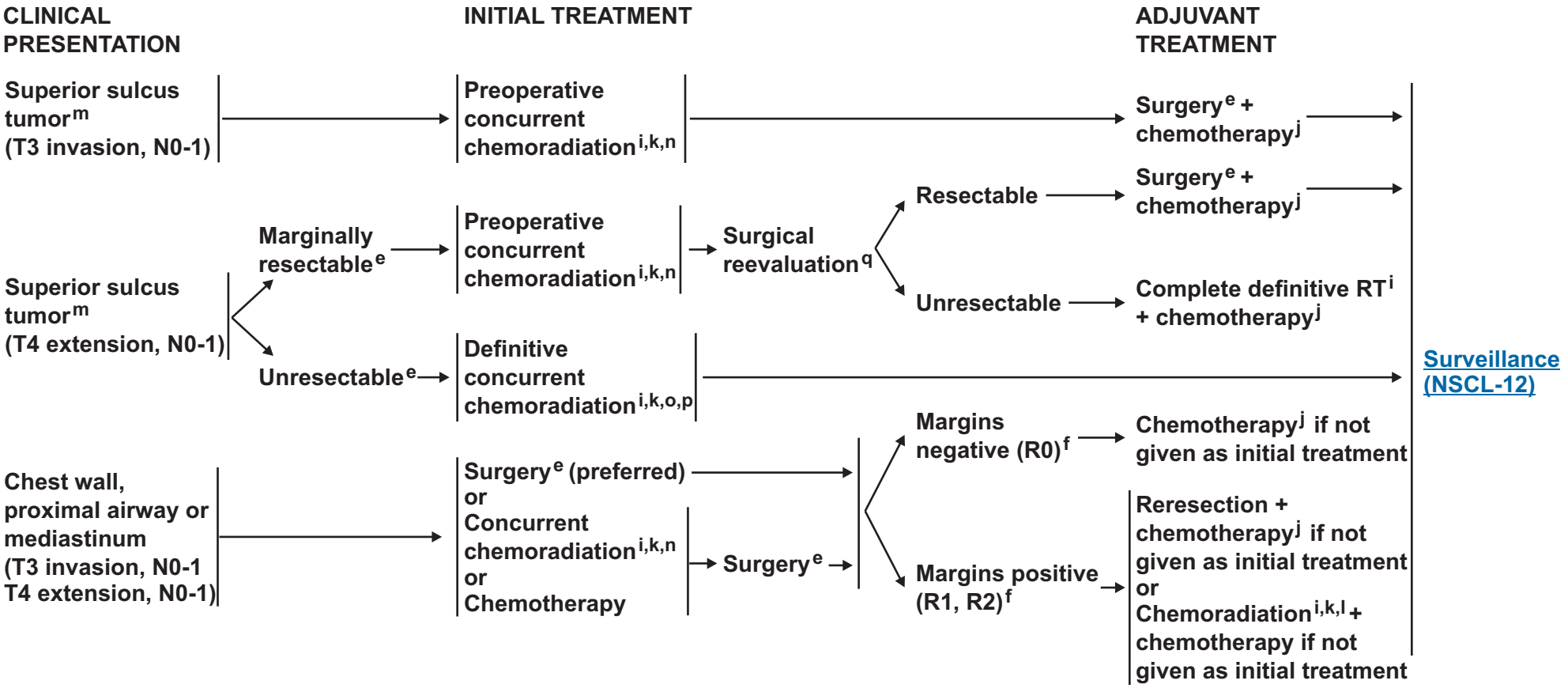

[e] See Principles of Surgical Therapy (NSCL-B).

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

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

[l] 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.

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

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

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

[p] In the definitive chemoradiation setting, a total dose of 60-70 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.

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

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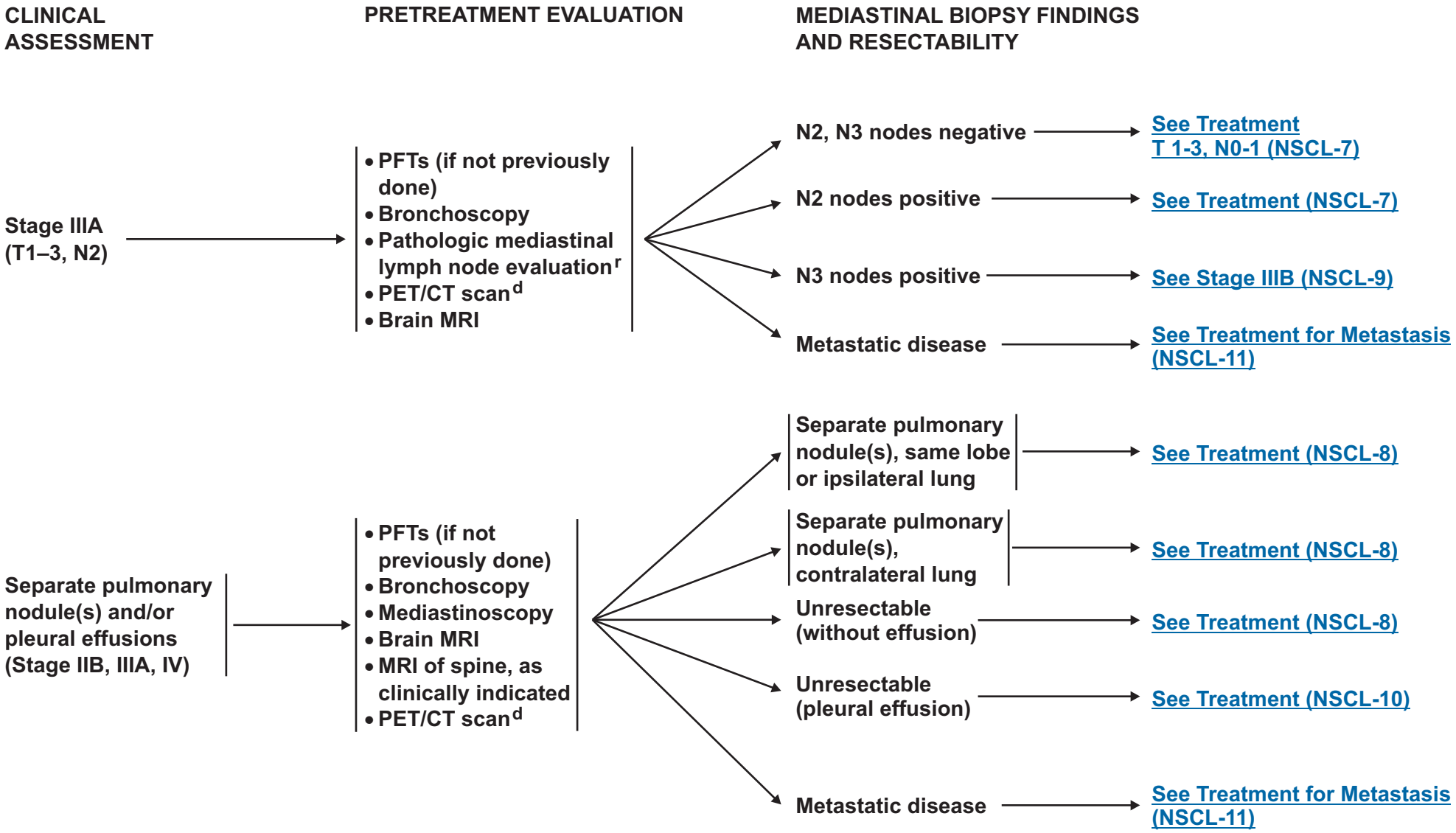

[d]Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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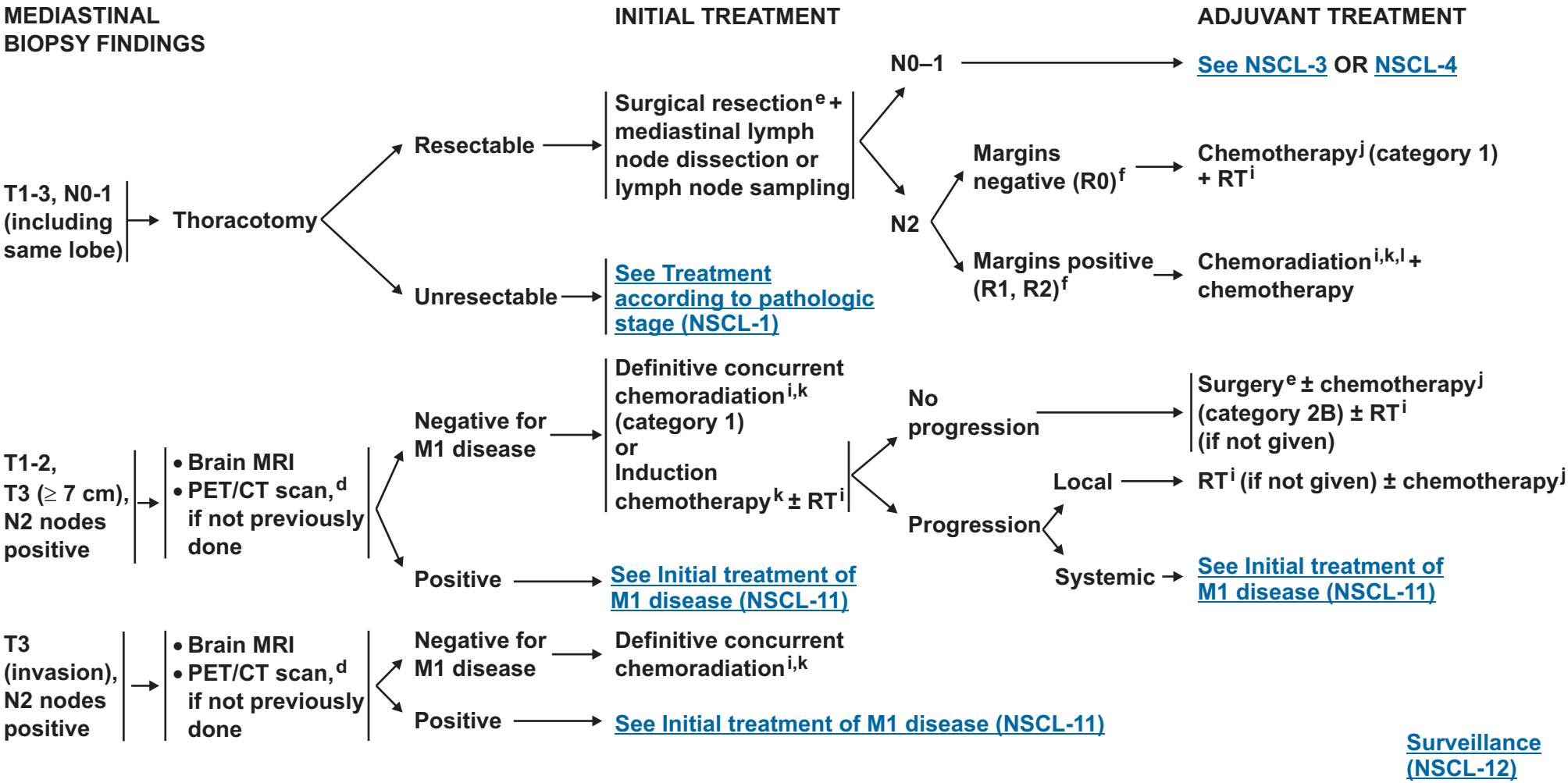

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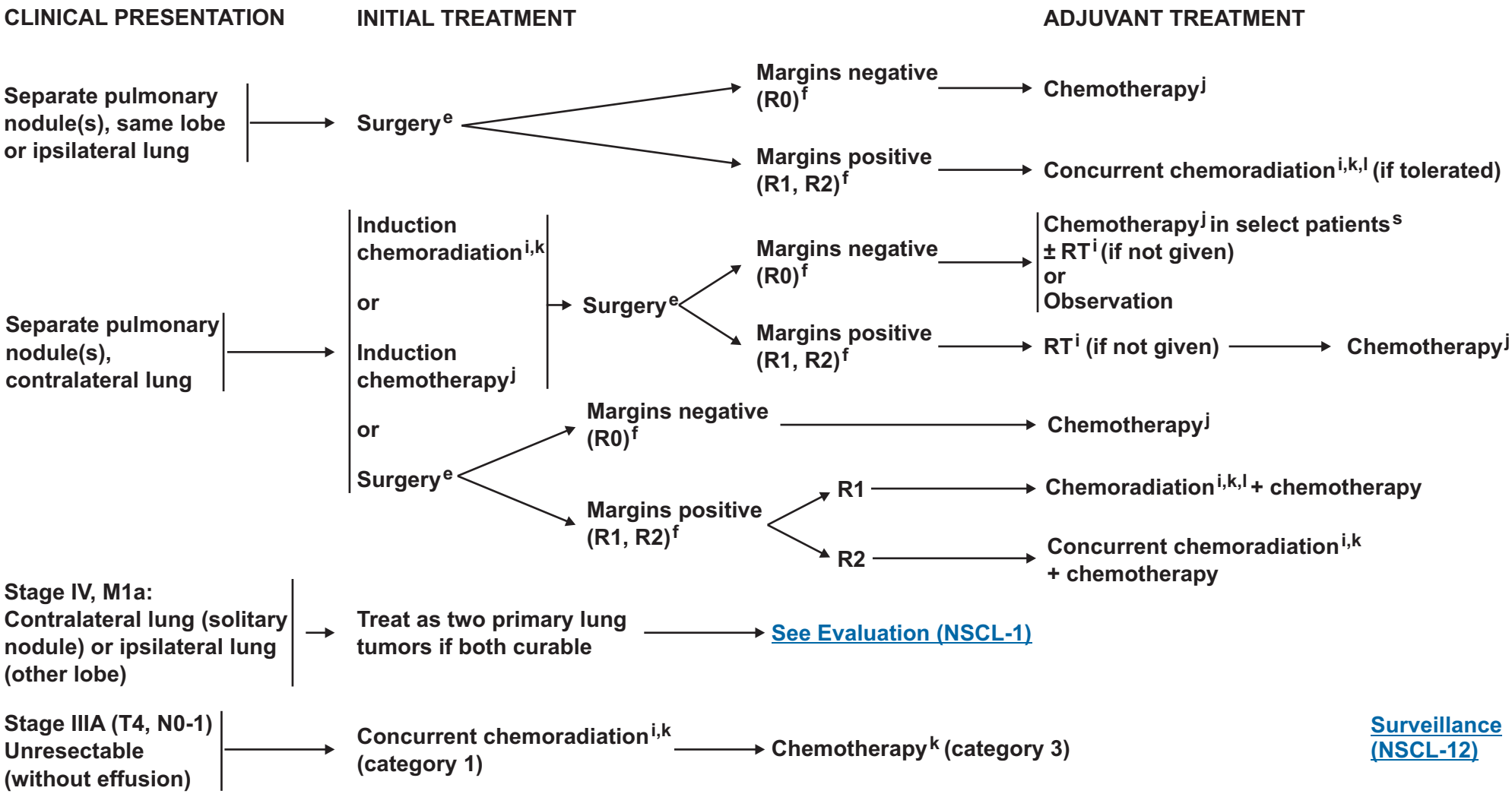

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[s] The administration of chemotherapy in the adjuvant setting depends on the type of neoadjuvant therapy and the patient's tolerance.

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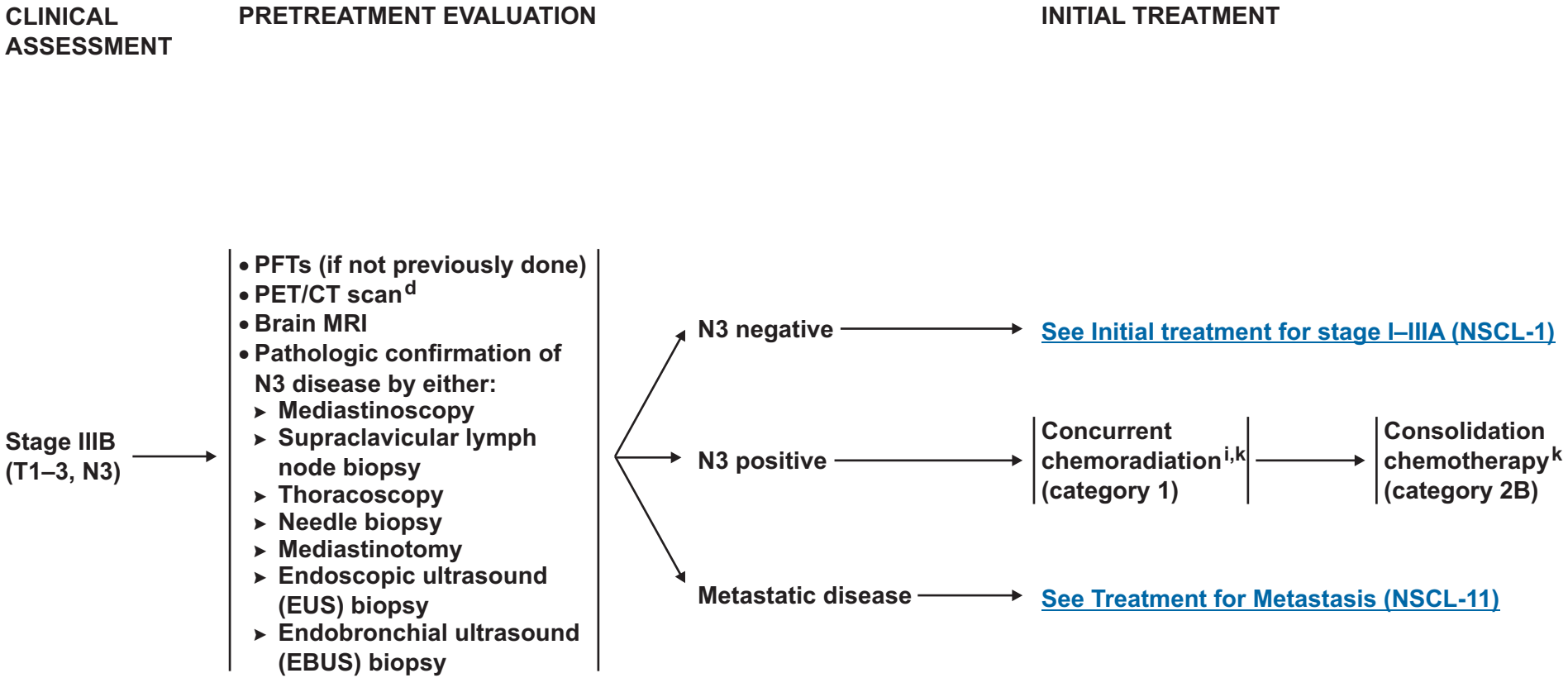

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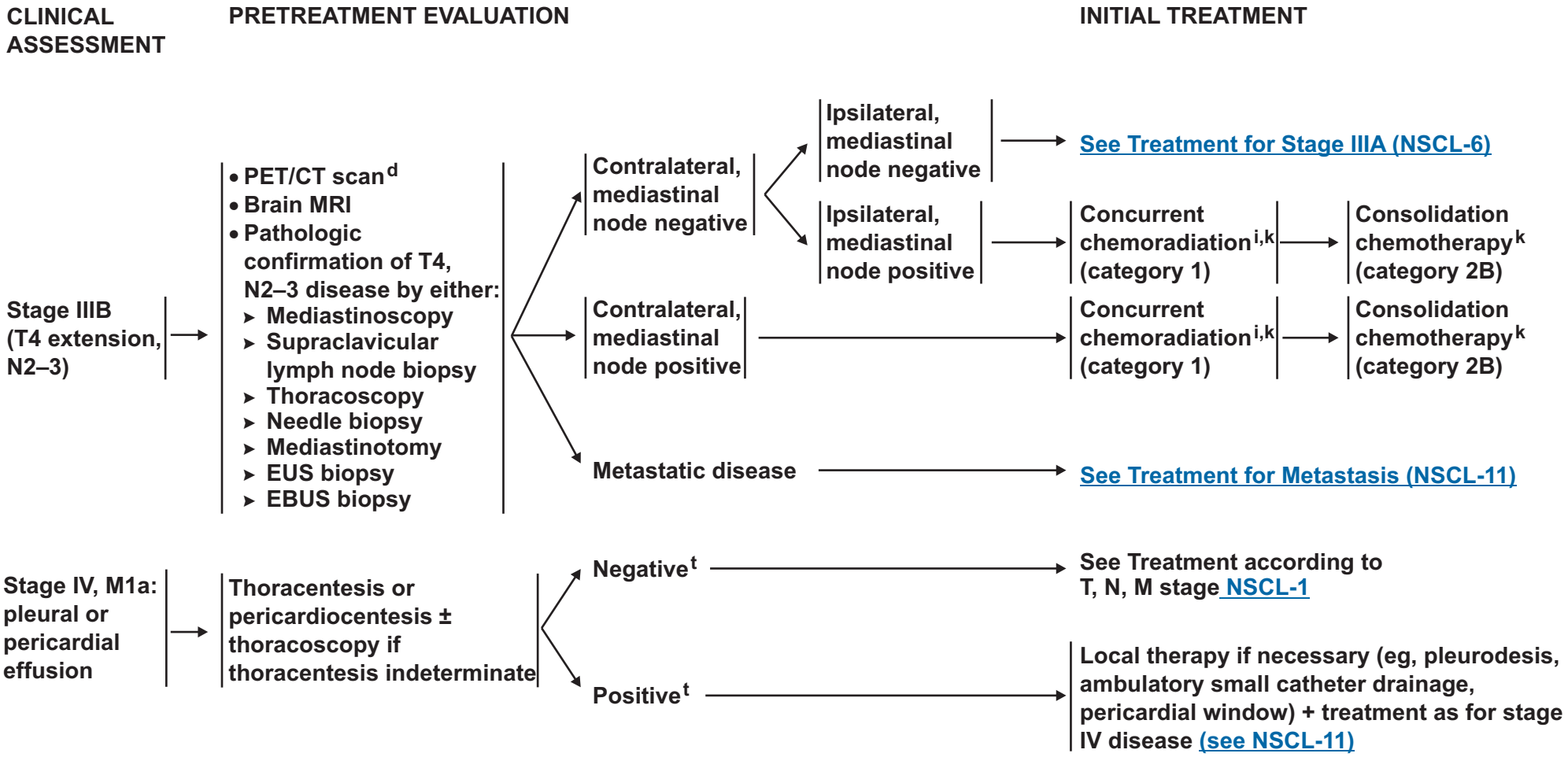

[d] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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

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

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Non-Small Cell Lung Cancer

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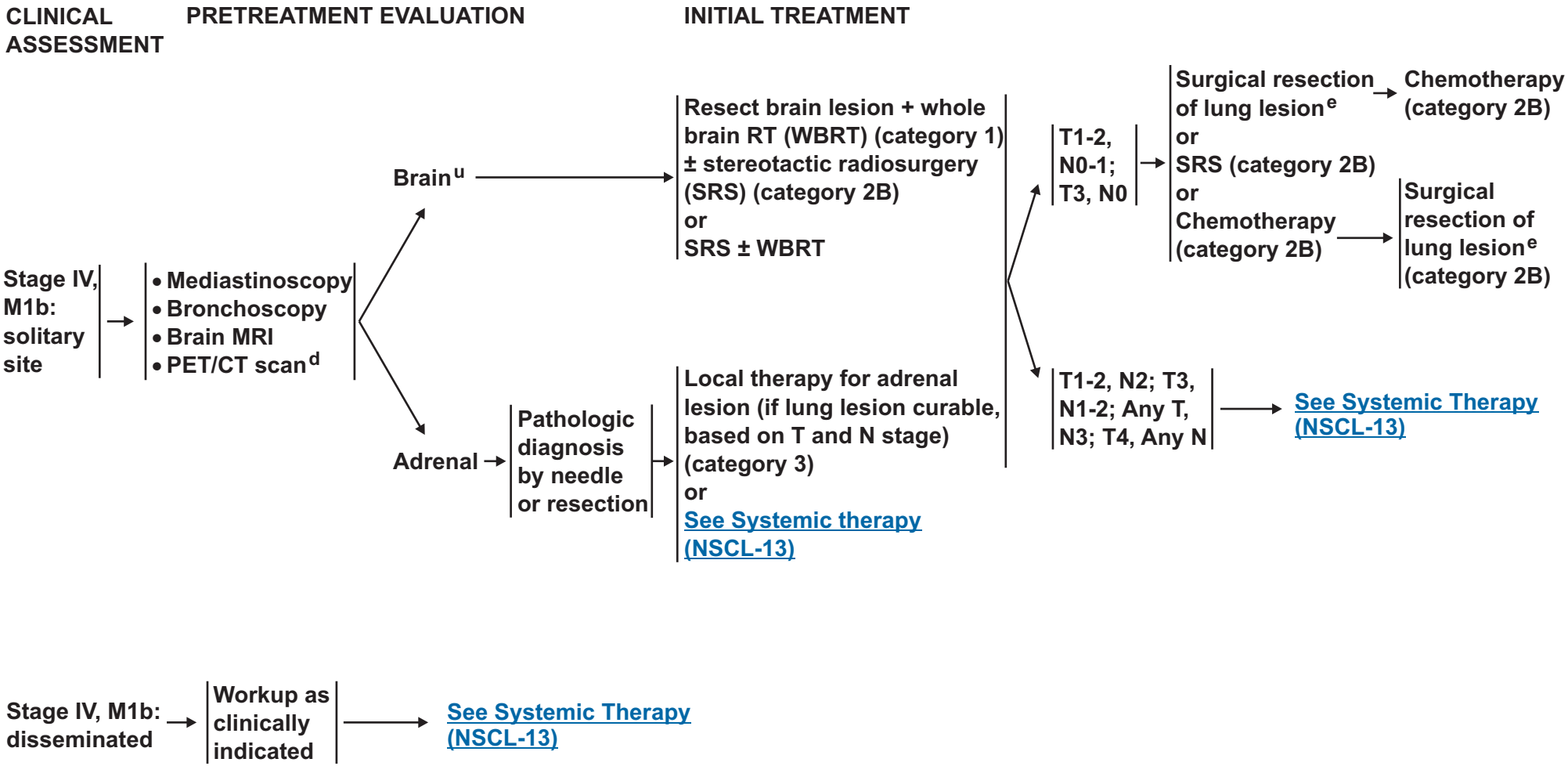

[d] Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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

[u] See NCCN CNS Guidelines.

Surveillance (NSCL-12)

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Non-Small Cell Lung Cancer

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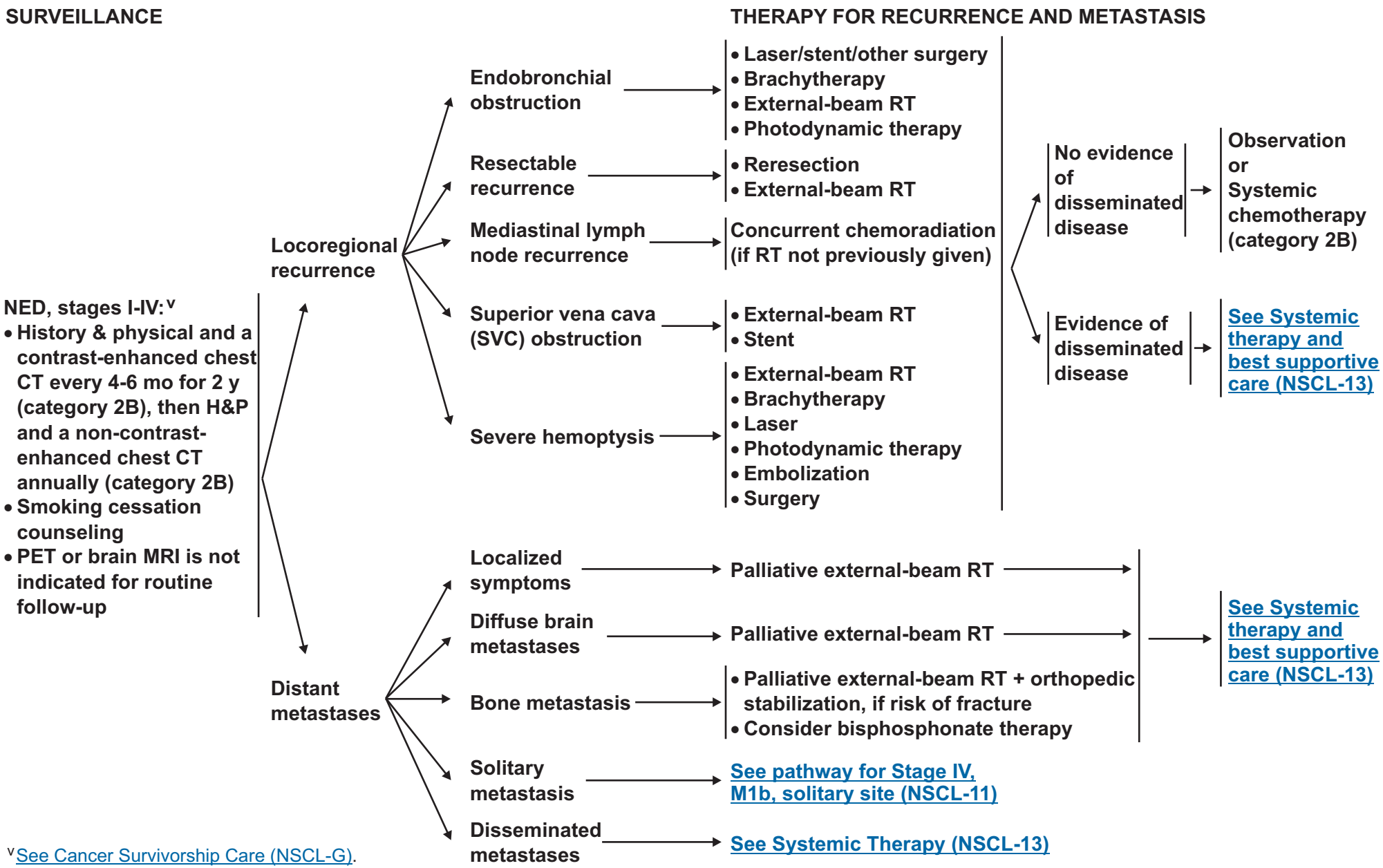

[v] See Cancer Survivorship Care (NSCL-G).

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Non-Small Cell Lung Cancer

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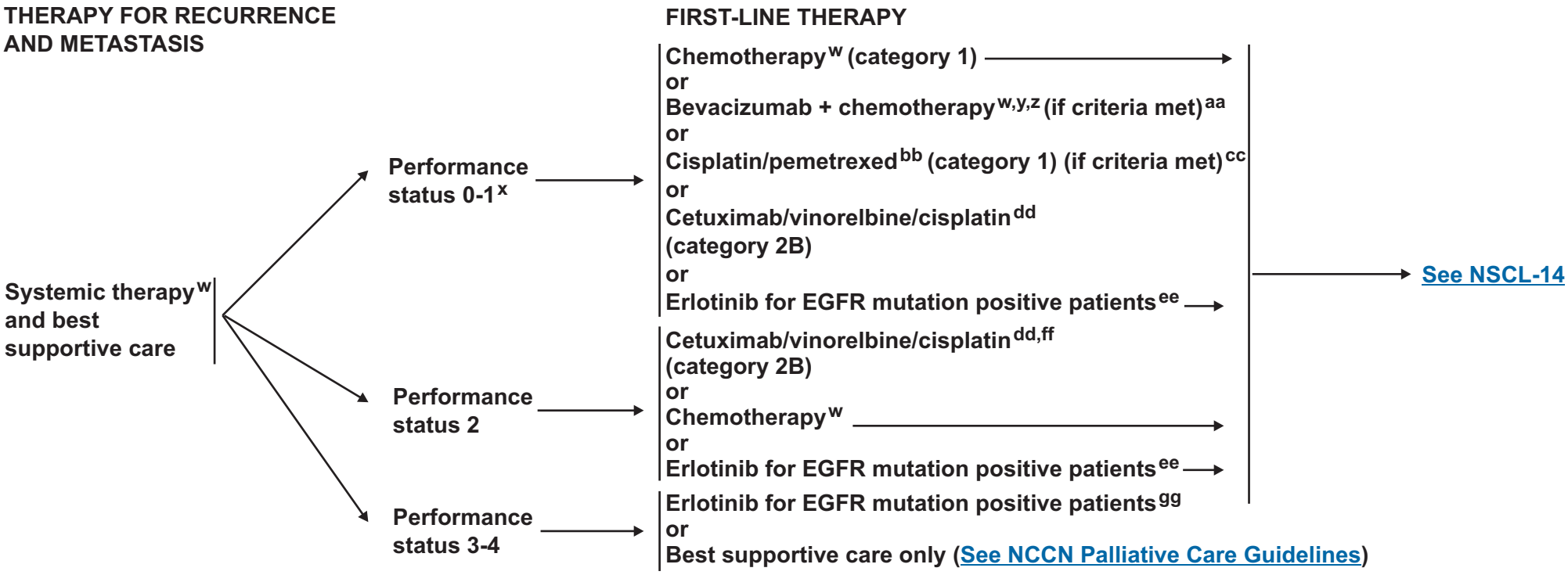

[w] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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

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

[z] Bevacizumab should be given until progression.

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

[bb] Pemetrexed is not recommended for squamous histology.

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

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

[ee] Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med 2009;361:947-57.

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

[gg] Inoue A, Kobayashi K, Usui K, et al. First-line gefitinib for patients with advanced non-small cell lung cancer harboring epidermal growth factor receptor mutations without indication for chemotherapy. J Clin Oncol 2009;27:1394-1400.

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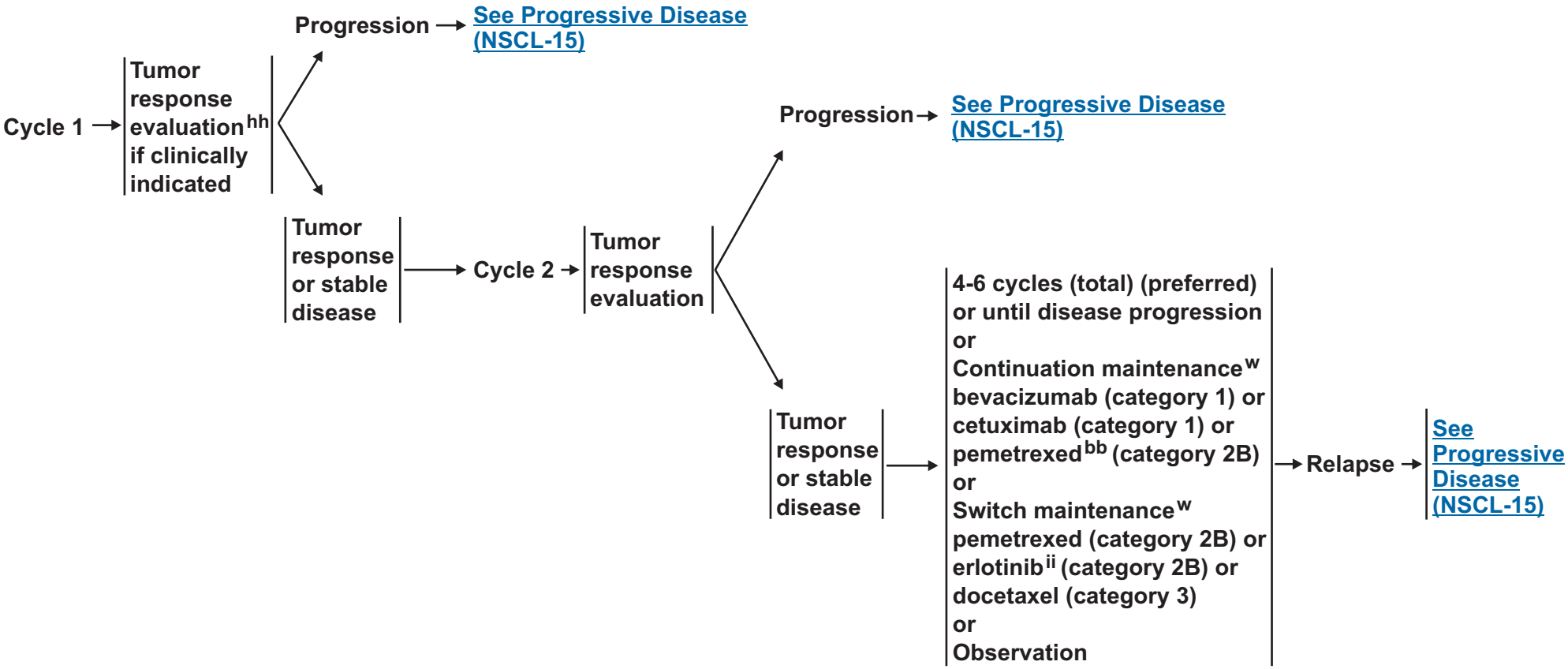
THERAPY FOR RECURRENCE AND METASTASIS



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

[bb] Pemetrexed is not recommended for squamous histology.

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

[ii] Cappuzzo F, et al. Efficacy and safety of erlotinib as first-line maintenance in NSCLC following non-progression with chemotherapy: results from the phase III SATURN Study. 13th World Conference on Lung Cancer 2009;Abstract A2.1

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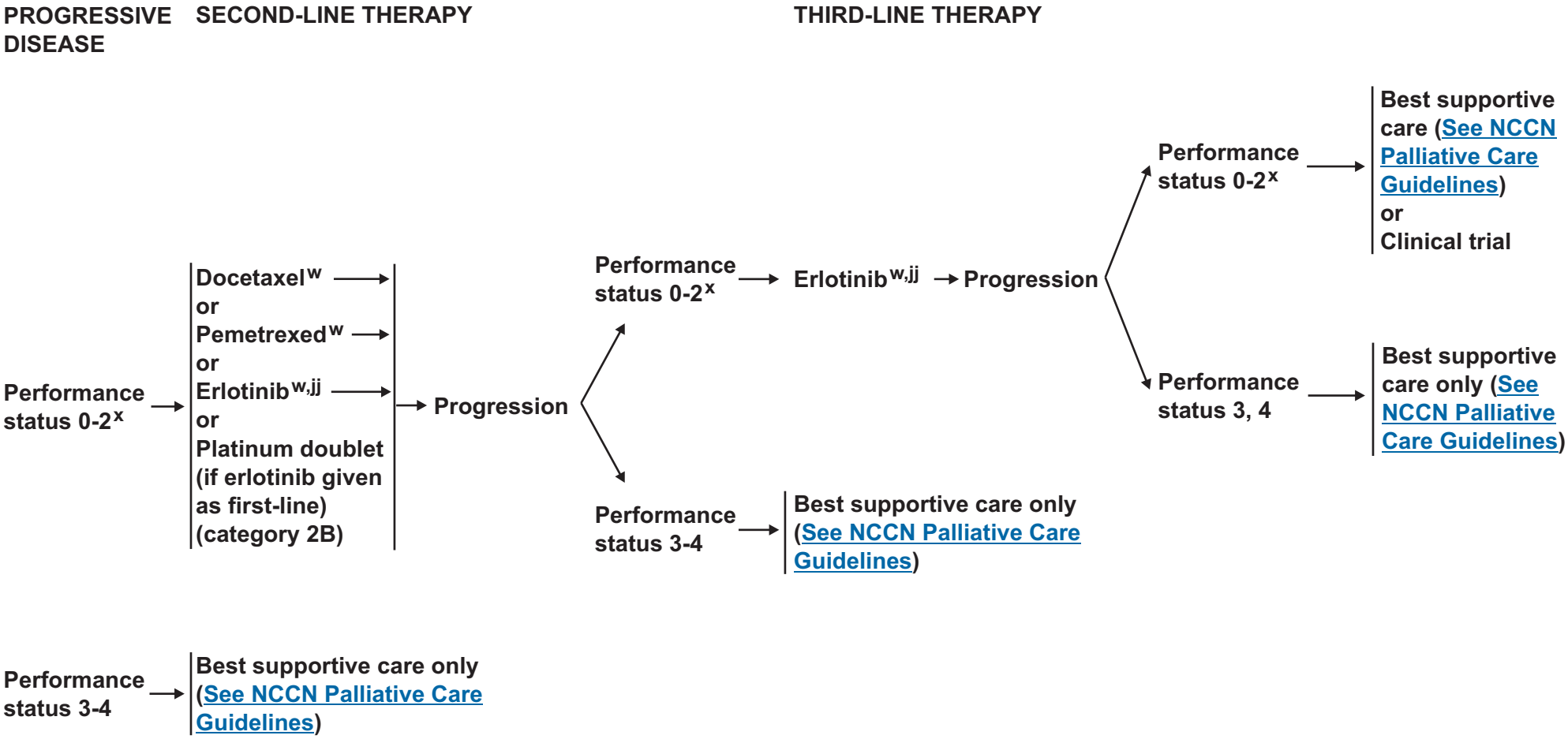

[w] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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

[jj] 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 and 4 patients with EGFR mutation.

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Non-Small Cell Lung Cancer

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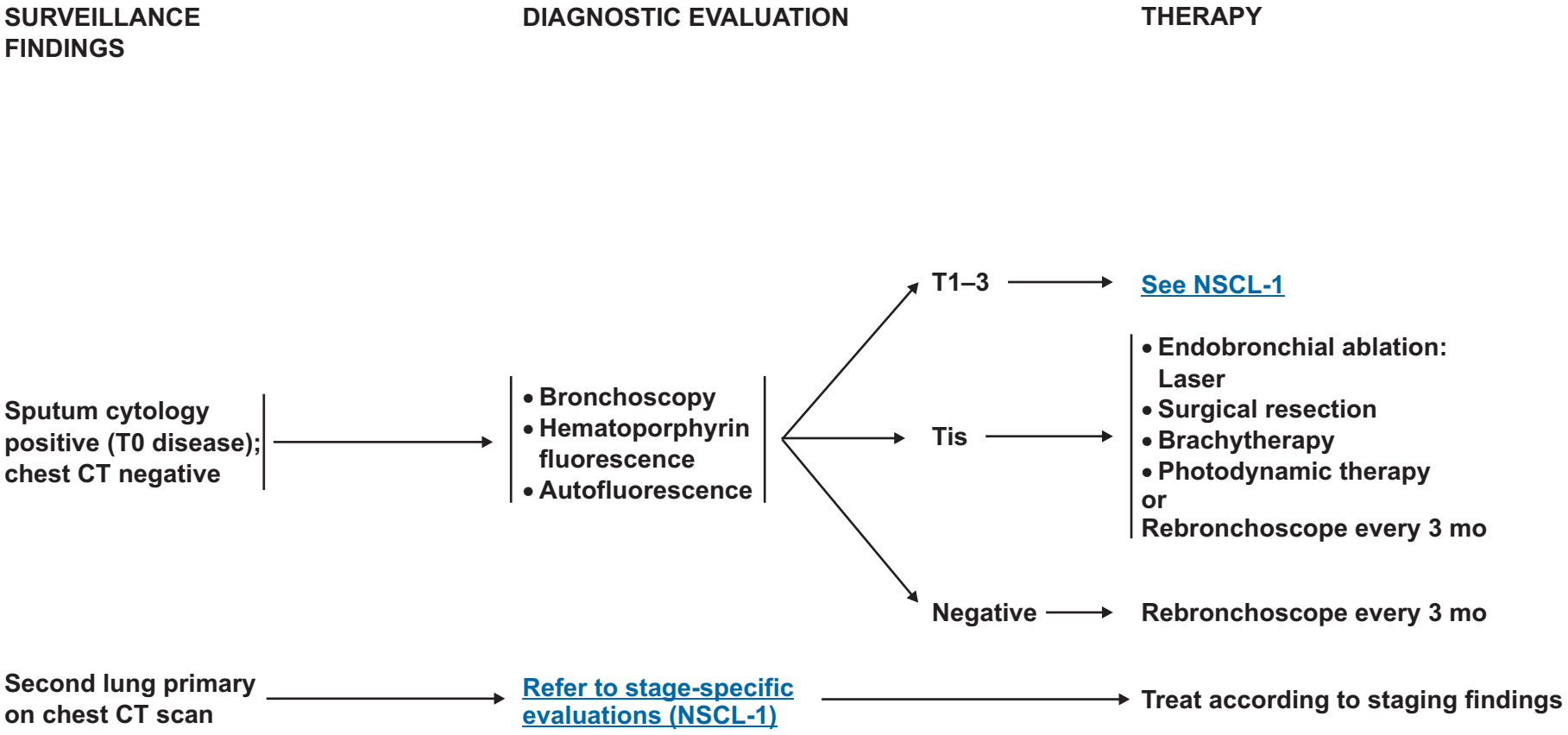

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 2)

Pathologic Evaluation

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

Bronchioloalveolar carcinoma (BAC)

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

Immunohistochemical staining

- Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma and to determine the neuroendocrine status of tumors.
- Differentiation between primary pulmonary adenocarcinoma and metastatic adenocarcinoma
  - TTF-1 is a homeodomain-containing nuclear transcription protein of the Nkx2 gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid.
  - TTF-1 is important in distinguishing primary from metastatic adenocarcinoma: the majority of primary lung carcinomas is positive for TTF-1 whereas metastatic adenocarcinoma to the lung is virtually always negative.
  - Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum.
  - CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies, that could help distinguish from primary lung tumors. Prostate specific antigen, prostatic acid phosphatase and gross cystic disease fluid protein 15 may identify metastatic adenocarcinoma of prostate and breast origin, respectively.
- Determining neuroendocrine status of tumors
  - Chromogranin and synaptophysin are used to diagnose neuroendocrine tumors of the lung. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin whereas small cell lung cancer is negative in 25% of cases.
- Distinguishing between malignant mesothelioma and lung adenocarcinoma
  - A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) is used routinely.
  - The stains negative in mesothelioma, but positive in adenocarcinoma are CEA, B72.3, Ber-EP4 and MOC31.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40[7,8] and cytokeratin 5/6.

Continued NSCL-A 2 of 2

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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 exon 21 mutation, and response to TKIs.[9-12]**
- **EGFR and k-ras mutations are mutually exclusive in patients with lung cancer.[13]**
- **K-ras mutations are associated with intrinsic TKI resistance, and k-ras gene sequencing could be useful for the selection of patients as candidates for TKI therapy.[14]**

[1] Fossella FV, Putnam JB & Komaki R. Lung Cancer. New York: Springer, 2003.

[2] Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib.J Clin Oncol. 2005;23:5900-9.

[3] Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:423-9.

[4] Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-68.

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

[6] Goldstein NS & Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001;116:319-25.

[7] Chirieac LR, et al. Modern Pathology 2006;19:305A 1422.

[8] Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-80.

[9] Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.

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

[11] Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-8.

[12] Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-95.

[13] Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-62.

[14] 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 THERAPY

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

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

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PRINCIPLES OF RADIATION THERAPY (1 of 7)

General Principles

- Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical oncologists, radiation oncologists, medical oncologists, pulmonologists, pathologists, and diagnostic radiologists.
- Radiation therapy can be offered as an adjunct for operable patients with resectable diseases, as the primary local treatment for patients with medically inoperable or unresectable diseases, and as an important palliative modality for patients with incurable diseases. The terminology and abbreviations for radiation therapy are summarized in Table 1. Commonly Used Radiation Therapy Abbreviations NSCL-C 5 of 7.
- For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy followed by postoperative radiotherapy is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established[1-3]
- For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiotherapy is recommended if the patient is medically fit.[4,5] Radiation therapy should start earlier as local recurrence is the most common failure in this group of patients.[6]
- Conformal radiation therapy ± chemotherapy should be offered to patients with stage I, II, and III NSCLC who are medically inoperable but of reasonable performance status and life expectancy. Modern technology can be applied as indicated. Both treatment outcome and cost should be considered.
- In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (i.e. Grade 3 esophagitis or hematologic toxicities) should be minimized by conformal treatment planning and aggressive supportive care.
- Radiation therapy can be offered to primary or distant sites as palliative care for stage IV patients with extensive metastasis.

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

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

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

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

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PRINCIPLES OF RADIATION THERAPY (2 of 7)

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

- The dose recommendations for definitive and palliative radiation are summarized in Table 2. Recommended Doses for Conventionally Fractionated Radiation Therapy NSCL-C 5 of 7. Tissue heterogeneity correction should be used in radiation treatment planning for all patients.
- Preoperatively, a dose of 45-50 Gy in 1.8 to 2 Gy fraction size is recommended.[7] Doses greater than 50 Gy in the preoperative setting have been reported to be safe and achieved favorable survival outcome.[8-10] However, this should only be performed with an experienced team.
- Postoperative radiation dose should be based on margin status.[2,4] Lung tolerance to radiation after surgery is remarkably smaller than those with the presence of both lungs. Every effort should be made to minimize the dose of radiation therapy. More conservative consideration should be applied for the dose constraints of normal lungs.
- For definitive radiation therapy, the commonly prescribed dose is 60-70 Gy.[11,12] Limited evidence suggested that a dose $\geq$ 74 Gy is significantly associated with better survival in patients treated with radiation alone or sequential chemoradiation.[13] Radiation dose may be one significant factor for overall survival in stage I-II after radiation alone[14] or stage III disease treated with concurrent chemoradiation.[15] When radiation is given concurrently with chemotherapy, a dose up to 74 Gy may be delivered safely,[16-18] if the dose to normal structures are strictly limited (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7). The role of high dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).
- For treatment volume consideration, PTV should be defined per ICRU-62 guidelines, based on GTV, plus CTV margin for microscopic diseases, ITV margins for target motion, and margins for daily set-up errors. GTV should be confined to visible tumors (include both primary and nodal diseases) on CT or PET-CT.
- Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial[19] and should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. Involved field radiation to high dose without ENI has been shown to allow higher dose radiation with acceptable toxicity and low risk of isolated nodal relapse.[11,13,20-23]
- In patients who receive postoperative radiotherapy, CTV should consist of the bronchial stump and high-risk draining lymph node stations.[24]
- It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the lungs, heart, esophagus, brachial plexus, and spinal cord (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7) to minimize normal tissue toxicity. These limits are largely empirical.[25-32]
- For patients receiving postoperative radiation therapy, more strict DVH parameters should be considered for the lung. The exact limit is unknown for lobectomy cases; mean lung dose should be limited to less than 8.5 Gy in pneumonectomy patients.

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

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PRINCIPLES OF RADIATION THERAPY (3 of 7)

Radiation Simulation, Planning and Delivery

- Treatment planning should be performed by CT scans obtained in the treatment position. IV contrast should be used for better target delineation whenever possible, especially in patients with central tumors or with nodal disease. PET-CT is preferable in cases with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improve the target accuracy.[33]
- In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume, and the cone-down fields should cover the post-chemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the post-chemotherapy volume can be used to avoid excessive pulmonary toxicity.
- Photon beam energy should be individualized based on the anatomic location of the tumors and beam angles. In general, photon beam energy between 4 to 10 MV is recommended for beams passing through low density lung tissue before entering the tumor. For large mediastinal tumors or tumors attached to chest wall, 15 MV or 18 MV energies can be considered for more optimal dose arrangement.
- In certain situations where there is a large volume of normal lung being irradiated or where tumors are located close to critical structures (i.e. spinal cord), intensity modulated radiotherapy (IMRT) may be considered for high-dose radiation to avoid overdose to normal tissues. Significantly lower risk of radiation pneumonitis and improved overall survival have been observed with IMRT compared to 3-D conformal radiation therapy for lung cancer.[34] When IMRT is used, the NCI IMRT guideline (http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf) should be followed. Under strictly defined protocols, proton therapy may be allowed.[35-39] When IMRT and proton therapy are used, daily image guidance at delivery should be used for quality assurance. The modality of IGRT should be based on the institutional experience and the treatment accuracy.
- Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per *AAPM Task Group 76* guideline, include: 1) Motion-encompassing methods such as slow CT scanning, inhale and exhale breath-hold CT, four-dimensional (4-D) respiration-correlated CT, 2) Respiratory gating methods using an external respiration signal or using internal fiducial markers, 3) Breath-hold methods by deep-inspiration breath-hold, active-breathing control (ABC) device, self breath-hold without respiratory monitoring, 4) Forced shallow breathing with abdominal compression, and 5) Real-time tumor-tracking methods.

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

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

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PRINCIPLES OF RADIATION THERAPY (4 of 7)

Stereotactic Body Radiation Therapy (SBRT)

- SBRT provides statistically significantly higher 5-year survival than 3DCRT in stage I NSCLC.[40] SBRT can be considered for inoperable stage I patients with node negative peripheral lesions (See Figure 1. Schema of Central and Peripheral Locations NSCL-C 6 of 7) that are less than 5 cm in maximal dimension[41,42] or limited lung metastasis.[43]
- SBRT fractionation regimens range from one single fraction[44] to 3 fractions,[45,46] 4 fractions,[47] and 5 fractions[48,49] (See Table 4. SBRT Regimens and Indications NSCL-C 6 of 7). While the optimal number of fractionation may be estimated based on the tumor size and total dose,[50] an accumulative BED of ≥100 Gy is associated with better survival.[51] RTOG 0915 is ongoing to compare the outcomes between one single fraction and 4 fractions.
- SBRT Normal tissue dose constraints should be strictly followed (See Table 5. Normal Tissue Dose Volume Constraints for SBRT NSCL-C 6 of 7).

Prophylactic Cranial Irradiation (PCI)

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

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PRINCIPLES OF RADIATION THERAPY (5 of 7)

Table 1. Commonly Used Radiation Therapy Abbreviations

3DCRT	3-D Conformal Radiation Therapy
GTV	Gross Tumor Volume
CTV	Clinical Target Volume
PTV	Planning Target Volume
ITV	Internal Target Volume
BED	Biological Equivalent Dose
OAR	Organ At Risk
V20	% Volume an OAR Receiving ≥ 20 Gy
MLD	Mean Lung Dose
ABC	Active Breathing Control
IMRT	Intensity Modulated Radiation Therapy
OBI	On Board Image
IGRT	Image Guided Radiation Therapy
SBRT	Stereotactic Body Radiation Therapy
4DCT	4 Dimensional Computerized Tomography
CBCT	Cone Beam Computerized Tomography

Table 2. Recommended Doses for Conventionally Fractionated Radiation Therapy

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

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

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

*The limits are consistent with those of the ongoing phase III trial RTOG 0617.
Vxx refers to the percentage of whole organ receiving more or equal to xx Gy.
Lung V20 refers to the percentage of both lungs with subtraction of overlapping CTV receiving ≥ 20 Gy, MLD=mean total lung dose.

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PRINCIPLES OF RADIATION THERAPY (6 of 7)

Table 4. SBRT Regimens and Indications for Lung Tumors

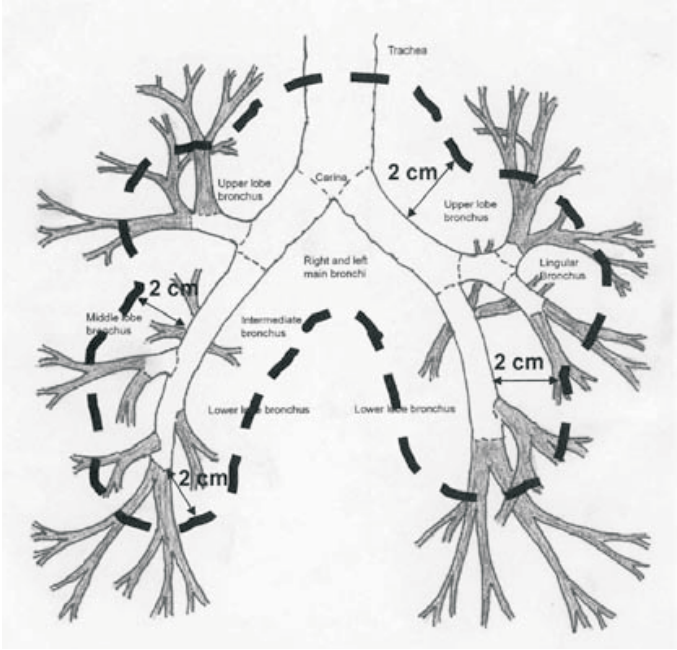
Regimen	Indications
30-34 Gy x 1	Peripheral small (< 2 cm) tumors, > 1 cm from chest wall
15-20 Gy x 3	Peripheral < 5 cm tumors, > 1 cm from chest wall
12-12.5 Gy x 4	Peripheral tumors, particularly those < 1 cm from chest wall
10-11 Gy x 5	Peripheral tumors, particularly those < 1 cm from chest wall

Table 5. Normal Tissue Dose Volume Constraints for SBRT*

OAR	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great vessels	37 Gy	39 Gy 13 Gy/fx	49 Gy 12.25 Gy/fx	55 Gy 11 Gy/fx
Trachea/ Large Bronchus	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	40 Gy (8 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	32 Gy (7.8 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy 10 Gy/fx	36 Gy (9 Gy/fx)	40 Gy 8 Gy/fx
Stomach	12.4 Gy	27 Gy 9 Gy/fx	30 Gy (7.5 Gy/fx)	35 Gy 7 Gy/fx

*The limits are the maximum point doses, based on a combined consideration of recommendations from ongoing multicenter trials (RTOG 0618 and RTOG 0915).

Figure 1. Schema of Central and Peripheral Locations
Peripheral tumors are those located ≥ 2 cm in all directions around the proximal bronchial tree.



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

PRINCIPLES OF RADIATION THERAPY - References (7 of 7)

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CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY

Published Chemotherapy Regimens	Schedule
Cisplatin 50 mg/m^2 days 1 and 8 Vinorelbine 25 mg/m^2 days 1, 8, 15, 22	Every 28 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 75 mg/m^2 on day 1 Gemcitabine 1250 mg/m^2 on days 1, 8	Every 21 days
Cisplatin 75 mg/m^2 Docetaxel 75 mg/m^2	Every 21 days [e]
Pemetrexed 500 mg/m^2 on day 1 Cisplatin 75 mg/m^2 on day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype)	Every 21 days for 4 cycles

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

See Chemoradiation on page NSCL-E

[a] Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. N Engl J Med 2005;352:2589-2597.
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Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens*
Cisplatin 50 mg/m^2 on 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 support full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

Concurrent Chemotherapy/RT Followed by Chemotherapy
Cisplatin 50 mg/m^2 on day 1, 8, 29, 36 Etoposide 50 mg/m^2 days 1-5, 29-33 Concurrent thoracic RT (total dose, 61 Gy) followed by cisplatin 50 mg/m^2 and etoposide 50 mg/m^2 x 2 additional cycles (category 2B)[a] or followed by docetaxel started 4-6 wks after chemoradiation at an initial dose of 75 mg/m2 x 3 doses every 3 weeks (category 3)[d]
Paclitaxel 45-50 mg/m^2 weekly Carboplatin AUC 2, concurrent thoracic RT 63 Gy followed by 2 cycles of paclitaxel 200 mg/m^2 and carboplatin AUC 6[c] (category 2B)

[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).

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

ADVANCED DISEASE:

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

First-line therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Cetuximab + vinorelbine/cisplatin is indicated in PS 0-2 patients with advanced or recurrent NSCLC.
- Erlotinib is indicated for EGFR mutation positive patients.
- There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- Two drug regimens are preferred; a third cytotoxic drug does not increase survival, with the exception of bevacizumab or cetuximab in treatment-naïve PS 0-1 NSCLC.
- Single agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Systemic chemotherapy is not indicated in PS 3 or 4 patients.
- In locally advanced NSCLC, chemoradiation is superior to radiation alone: concurrent chemoradiation appears to be better than sequential chemoradiation.
- Cisplatin-based combinations have been proven superior to best supportive care in advanced, incurable disease, with improvement in median survival of 6-12 wks, and a doubling of one-year survival rates (absolute 10-15% improvement).
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, pemetrexed.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel).
- If patient has a known KRAS mutation, therapy other than erlotinib should be considered first.

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

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

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

Maintenance Therapy

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

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

Second-line therapy

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

Third-line therapy

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

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

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

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

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

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

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

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[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

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[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 2007;18:317-323..

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[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.

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

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

CANCER SURVIVORSHIP CARE

Cancer Survivorship[1]

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

NSCLC long term follow-up care

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

Counseling Regarding Health Promotion and Wellness[2]

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

Additional Health Monitoring

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

Resources

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

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

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

NON-SMALL CELL LUNG CANCER SURVIVORSHIP

Cancer Screening Recommendations[3,4]

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

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

[3]Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed November 24, 2009)
[4]American Cancer Society Guidelines for Early Detection of Cancer:
http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 24, 2009)

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

Staging

Table 6. Definitions for T, N, M*

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

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

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

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

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

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

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

Staging

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

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

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

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

Discussion To view the most up-to-date discussion, click here.

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.