



National
Comprehensive
Cancer
Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Non-Small Cell Lung Cancer

Version 1.2012

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NCCN Guidelines™ Version 1.2012 Panel Members Non-Small Cell Lung Cancer

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

See [NCCN Categories of Evidence and Consensus](#)

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Updates in the 1.2012 version of the Non-Small Cell Lung Cancer guidelines from the 3.2011 version include:

PREV-1

- **Bullet 1 modified:** Lung cancer is a unique disease in that the *major* etiologic agent is *an addictive product that is made and promoted by an industry*.
- **Last bullet deleted and replaced with** “Lung cancer screening by low-dose CT decreases lung cancer mortality in certain high-risk individuals (age > 55 y and smoking ≥ 30 pk/year). Reference added.

NSCL-1

- **Clinical stage - footnote “e” related to pleural effusion deleted, as this is addressed on NSCL-10.**

NSCL-2

- **Footnote “e” was added to Pretreatment Evaluation:** Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.
- **Pretreatment Evaluation:** “and/or EBUS/EUS” added to Mediastinoscopy. EBUS/EUS changed from a category 2B to a 2A for stage IB (peripheral T2a, N0), stage I (central T1ab-T2a, N0), stage II (T1ab-2ab, N1; T2b, N0), stage IIB (T3, N0). (also applies to other pages)
- **Adjuvant treatment for stage IA (peripheral T1ab, N0), medically inoperable:** Definitive RT changed to Definitive RT or SABR.
- **Adjuvant treatment for stage IB (peripheral T2a, N0), I (central T1ab-T2a, N0), II (T1ab-2ab, N1; T2b, N0), IIB (T3, N0), medically inoperable:** Definitive RT changed to Definitive RT or SABR ± chemotherapy.

NSCL-3

- **Stage IB, IIA, adjuvant treatment:** RT + chemotherapy changed to RT ± chemotherapy for margins positive.
- **Stage IIA-IIB, adjuvant treatment:** “± RT” removed for margins negative.
- **Footnote “k” added to provide guidance regarding adjuvant chemoradiation:** The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections. (also applies to NSCL-7)

NSCL-3

- **Footnote “l” modified:** “High-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, Nx. *These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.*

NSCL-6

- **Separate pulmonary nodule, same lobe or ipsilateral lung - ipsilateral lung changed to ipsilateral non-primary lobe.**
- **The following stage added** “stage IV (N0, M1a): contralateral lung (multiple nodules).”
- **Extrathoracic added to clarify metastatic disease.**

NSCL-7

- **T1-3, N0-1 (including same lobe) modified to T1-3 (including T3 with multiple nodules in same lobe)**

NSCL-8

- **Stage IV (N0, M1a): contralateral lung (multiple nodules) added with direction to NSCL-13.**

NSCL-11

- **Brain:** “category 1 for one metastasis” was added to SRS + WBRT.
- **Adrenal, footnotes “w”:** “May include adrenalectomy or RT (including SABR)” and “x”: “Patients with N2 disease have a poor prognosis and systemic therapy may be considered” are new to the page.

NSCL-12

- **Surveillance:** NED defined as “no evidence of clinical or radiographic disease.”
- **Surveillance:** Chest CT interval changed from every 4-6 months to every 6-12 months and the use of contrast is now optional.
- **Resectable recurrence:** “preferred” added to the treatment option “resection.”

Updates in the 1.2012 version of the Non-Small Cell Lung Cancer guidelines from the 3.2011 version include:

NSCL-13

- Adenocarcinoma, large cell, NSCLC NOS: ALK testing added as a category 2A recommendation.
- ALK positive: crizotinib added as the recommended treatment option.
- Squamous cell carcinoma: “EGFR testing is not *routinely* recommended.”
- EGFR mutation positive discovered prior to first-line therapy: Erlotinib recommendation changed from a category 2A to a category 1.
- EGFR mutation positive discovered during chemotherapy: The qualifier “may” added and the erlotinib recommendation changed from a category 2A to a category 2B.
- Footnote “bb” - references updated.
- Footnote “ee” reference added: Janne PA, Wang XF, Socinski MA, et al. Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 7503.

NSCL-14

- First-line therapy: Chemotherapy clarified as “doublet chemotherapy.”
- First-line therapy, PS 2: Deleted the recommendation “cetuximab/vinorelbine/cisplatin (category 2B).”
- Maintenance therapy, continuation: Pemetrexed changed from a category 2B to a category 2A recommendation. Gemcitabine added as a category 2A recommendation.
- Maintenance therapy, switch: Erlotinib changed from a category 2B to a category 2A recommendation. “Docetaxel (category 3)” deleted.
- Previous footnote “ff”: “Full-dose cisplatin for PS 2 patients should be given selectively” deleted.
- Footnote “kk” reference added: Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 7507. (also applies to NSCL-15)

NSCL-15

- First-line therapy, PS 2: Deleted the recommendation “cetuximab/vinorelbine/cisplatin (category 2B).”
- Maintenance therapy, continuation: Gemcitabine added as a category 2A recommendation.
- Maintenance therapy, switch: Erlotinib changed from a category 2B to a category 2A recommendation. Docetaxel changed from a category 3 to a category 2B recommendation.

NSCL-16

- Second-line therapy, platinum doublet ± bevacizumab: adenocarcinoma changed to “nonsquamous.” The category recommendation changed from 2B to 2A.
- Third-line therapy, progression: Erlotinib deleted for PS 3-4.

NSCL-A 1 of 4 and NSCL-A 2 of 4

- Principles of Pathologic Review extensively revised. References 1, 5, 6, 7, 8, 9 are new to page NSCL-A 4.

NSCL-A 3 of 4

- First sub-bullet, the following sentence added: Crizotinib is an oral ALK inhibitor that was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK rearrangement mutation. (ie, ALK positive).
- Third sub-bullet deleted and replaced with the following: A new molecular diagnostic test that uses fluorescence in situ hybridization (FISH) has recently been approved by the FDA to determine which patients with NSCLC are positive for ALK rearrangements.

NSCL-B

- Principles of Radiation Therapy extensively revised and reorganized.

NSCL-C

- The following footnote was added to identify regimens that can be used for neoadjuvant chemoradiotherapy “These regimens can be used as neoadjuvant chemotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 3 cycles of full-dose platinum therapy after local treatment is completed.”

Updates in the 1.2012 version of the Non-Small Cell Lung Cancer guidelines from the 3.2011 version include:

[NSCL-D 1 of 5](#)

- **Bullet 7, sub-bullet 2: Bronchioloalveolar carcinoma (BAC) replaced with adenocarcinoma in situ (AIS) category 2B designations deleted from characteristics listed under peripheral nodule ≤ 2 cm.**

[NSCL-D 2 of 5](#)

- **The following bullets are new to the page: 2, 4, 5, 8**
Bullet 2: In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (pain, hospital length of stay, return to function) without compromise of cancer outcomes.
Bullet 4: T3 (extension) and T4 local invasion tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.
Bullet 5: Surgical pathologic correlation is critical to assess apparent close or positive margins as these may not represent true margins or may not truly represent areas of risk for local recurrence, (e.g. medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed, or pleural margin adjacent to aorta when no attachment to aorta is present).
Bullet 8: Complete resection requires free resection margins, systematic node dissection or sampling, no extracapsular nodal extension of the tumor, and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, extracapsular nodal extension, unremoved positive lymph nodes or positive pleural or pericardial effusions, the resection is defined as incomplete. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.

[NSCL-D 3 of 5](#)

- **The following bullets are new to the page:**
Bullet 5: It may be preferable to sample mediastinal lymph nodes by EBUS/EUS prior to initiating therapy, reserving mediastinoscopy and mediastinal lymph node dissection until the planned surgical resection.
Bullet 7: Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.

[NSCL-E](#)

- **The following footnote was added to identify regimens that can be used for neoadjuvant chemotherapy: “These regimens can be used as neoadjuvant chemotherapy. They are to be given for 3 cycles prior to localized therapy. See Discussion for further information and references.”**

[NSCL-F 1 of 3](#)

- **Advanced disease, bullet 1 added:** “The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.”
- **Advanced disease, bullet 6 deleted:** “No specific platinum-based cytotoxic combination is clearly superior.”
- **First-line therapy, bullet 2 modified:** “*Cetuximab + vinorelbine/cisplatin is an option for patients with performance status 0-1. indicated in PS 0-2 patients with advanced or recurrent NSCLC.*”
- **First-line therapy, bullet 3 modified:** Erlotinib is indicated as a *first-line therapy in patients with for EGFR mutations positive patients.*
- **First-line therapy, bullet 4 added:** “Crizotinib is indicated as first-line therapy for patients that are ALK positive.”
- **First-line therapy, bullet 6 added:** “There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.”

Updates in the 1.2012 version of the Non-Small Cell Lung Cancer guidelines from the 3.2011 version include:

NSCL-F 1 of 3

- First-line therapy, bullet 7 modified: Two drug regimens are preferred; a third cytotoxic drug *increases response rate but does not increase survival, with the exception of bevacizumab or cetuximab in treatment-naïve PS 0-1 NSCLC.*
- First-line therapy, bullet 9 deleted: Systemic chemotherapy is not indicated in PS 3 or 4 patients.
- First-line therapy, bullet 9 modified: In locally advanced NSCLC, *concurrent chemotherapy and thoracic irradiation is superior to radiation alone and sequential chemotherapy followed by radiation. chemoradiation is superior to radiation alone; concurrent chemoradiation appears to be better than sequential chemoradiation.*
- First-line therapy, previous bullet 11 deleted: 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).
- First-line therapy, bullet 10 modified by deleting irinotecan.
- First-line therapy, bullet 11 modified: New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, *gemcitabine/vinorelbine*)
- First-line therapy, previous bullet 14 deleted: If patient has a known KRAS mutation, therapy other than erlotinib should be considered first.

NSCL-F 2 of 3

- Maintenance Therapy, Continuation Maintenance modified: ~~Biologic agents given in combination with conventional chemotherapy~~ *Bevacizumab and cetuximab given in combination with 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 supporting their use. There are no randomized data supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.*
- Maintenance Therapy, Continuation Maintenance, 3rd sub-bullet modified: “Continuation of pemetrexed (category ~~2B-2A~~) after 4-6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma.

NSCL-F 2 of 3

- Maintenance Therapy, Continuation Maintenance, sub-bullet 4 added: Continuation of gemcitabine after 4-6 cycles of platinum-doublet chemotherapy.
- Maintenance Therapy, Switch Maintenance, sub-bullet 2 modified: Initiation of erlotinib (category ~~2B-2A~~) after 4-6 cycles of first-line platinum-doublet chemotherapy.
- Maintenance Therapy, Switch Maintenance, sub-bullet 3 modified: Initiation of docetaxel (category ~~3-2B~~) after 4-6 cycles of first-line platinum-doublet chemotherapy *in patients with squamous cell carcinoma.*
- Second-line therapy, sub-bullet 2 modified: Pemetrexed ~~has been shown to be is considered equivalent superior~~ to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
- Second-line therapy, sub-bullet 3 modified: “Erlotinib ~~has proven is superior to best supportive care. with significantly improved survival and delayed time to symptom deterioration.”~~
- Third-line therapy, bullet 1 modified: “Erlotinib ~~has proven statistically is superior to best supportive care. BSC with respect to survival.~~

New section added;

Continuation after Disease Progression

- With the exception of erlotinib in patients with EGFR mutations who have experienced objective regressions with erlotinib, no agent should be continued after disease progression has been documented. (see Discussion section)

NSCL-F 3 of 3

- Crizotinib added as a systemic therapy option for advanced or metastatic disease with supporting references.

LUNG CANCER PREVENTION AND SCREENING

- Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85-90% of cases are caused by voluntary or involuntary (second hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products and other tobacco control measures.
- Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life and reduced survival.
- Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from second-hand smoke exposure associated with living with a smoker (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf). Every person should be informed of the health consequences, addictive nature and mortal threat posed by tobacco consumption and exposure to tobacco smoke and effective legislative, executive, administrative or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke. www.who.int/tobacco/framework/final_text/en/.
- Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (www.ahrq.gov/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- Lung cancer screening by low-dose CT decreases lung cancer mortality in certain high-risk individuals (age > 55 y and smoking ≥ 30 pk/year).¹

¹National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.

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.

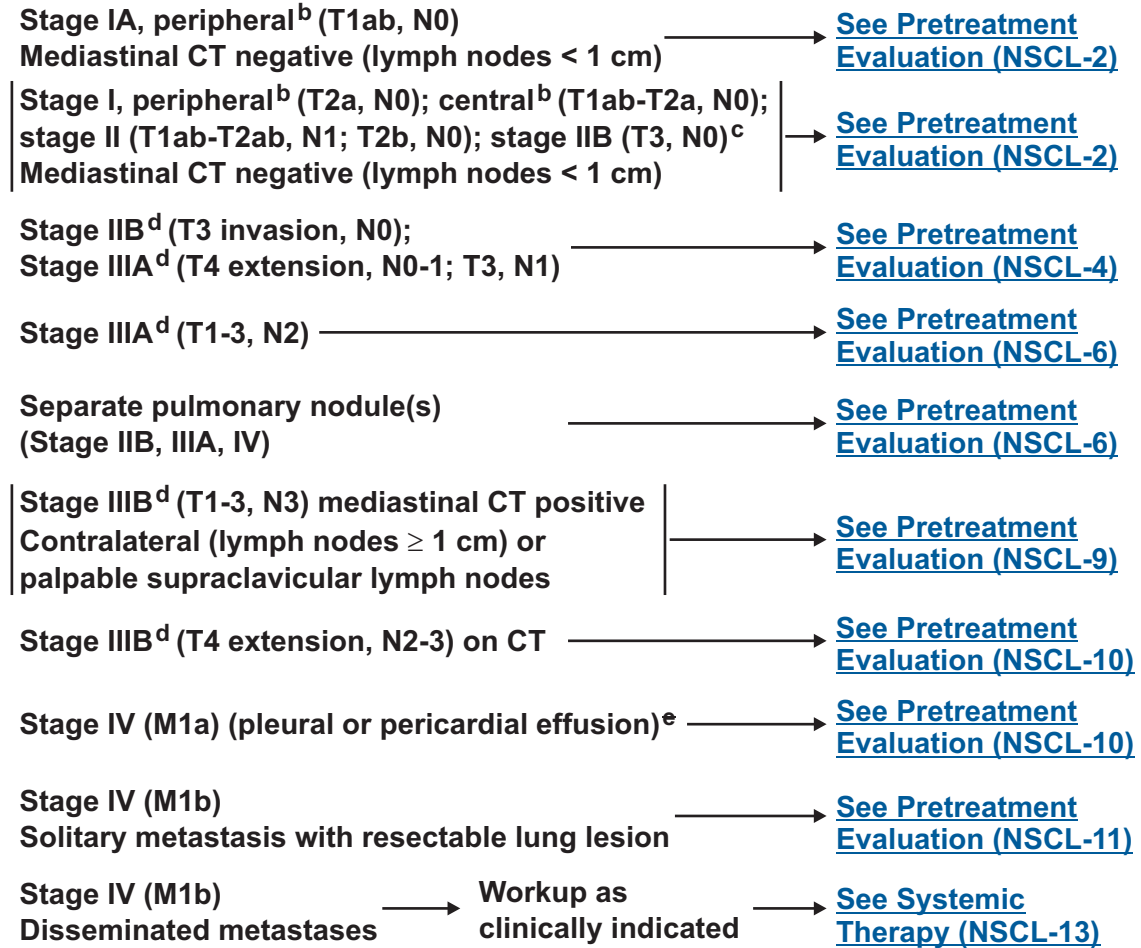
**PATHOLOGIC
DIAGNOSIS OF NSCLC**

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 advice, counseling and pharmacotherapy



^aSee [Principles of Pathologic Review \(NSCL-A\)](#).

^bBased on the CT of the chest:
Peripheral = outer third of lung.
Central = inner two thirds of lung.

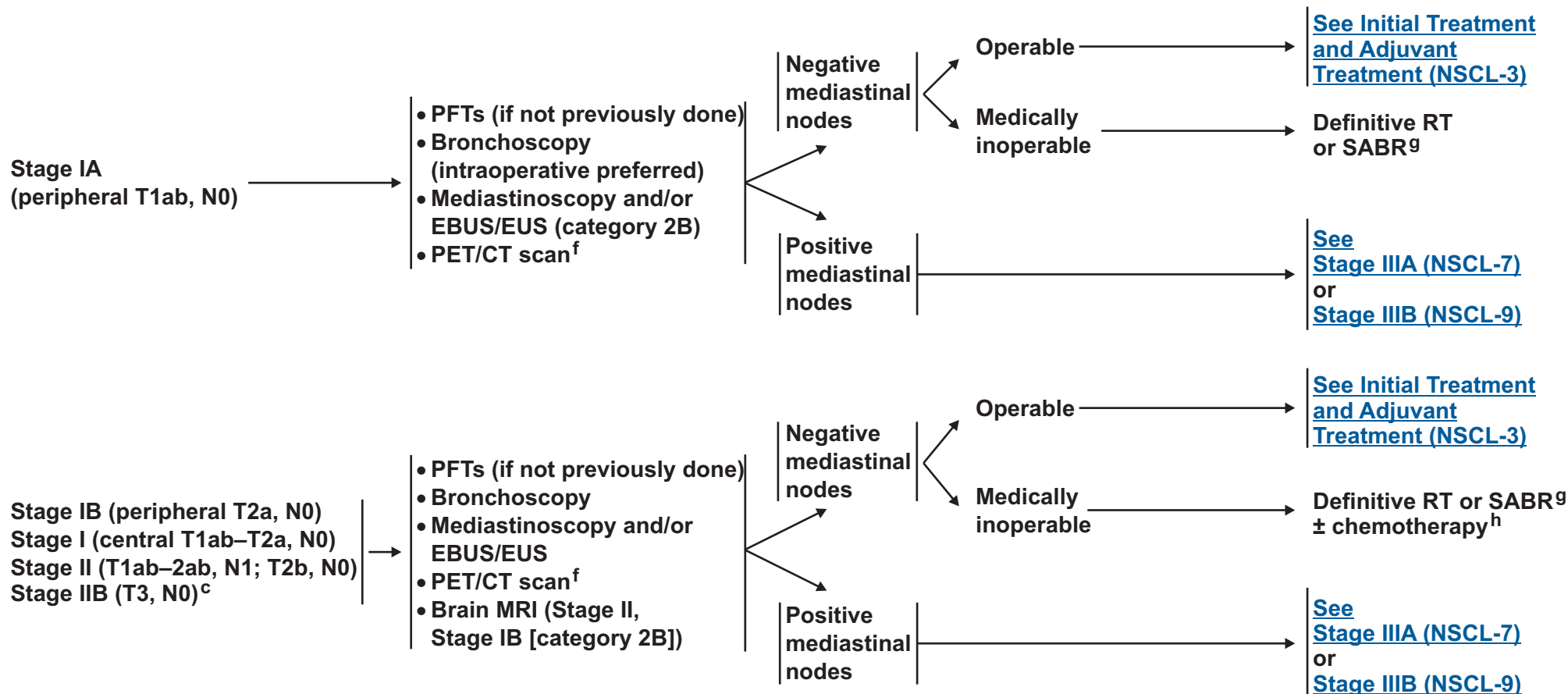
^cT3, N0 related to size or satellite nodules.

^dFor 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



^cT3, N0 related to size or satellite nodules.

^eTesting is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.

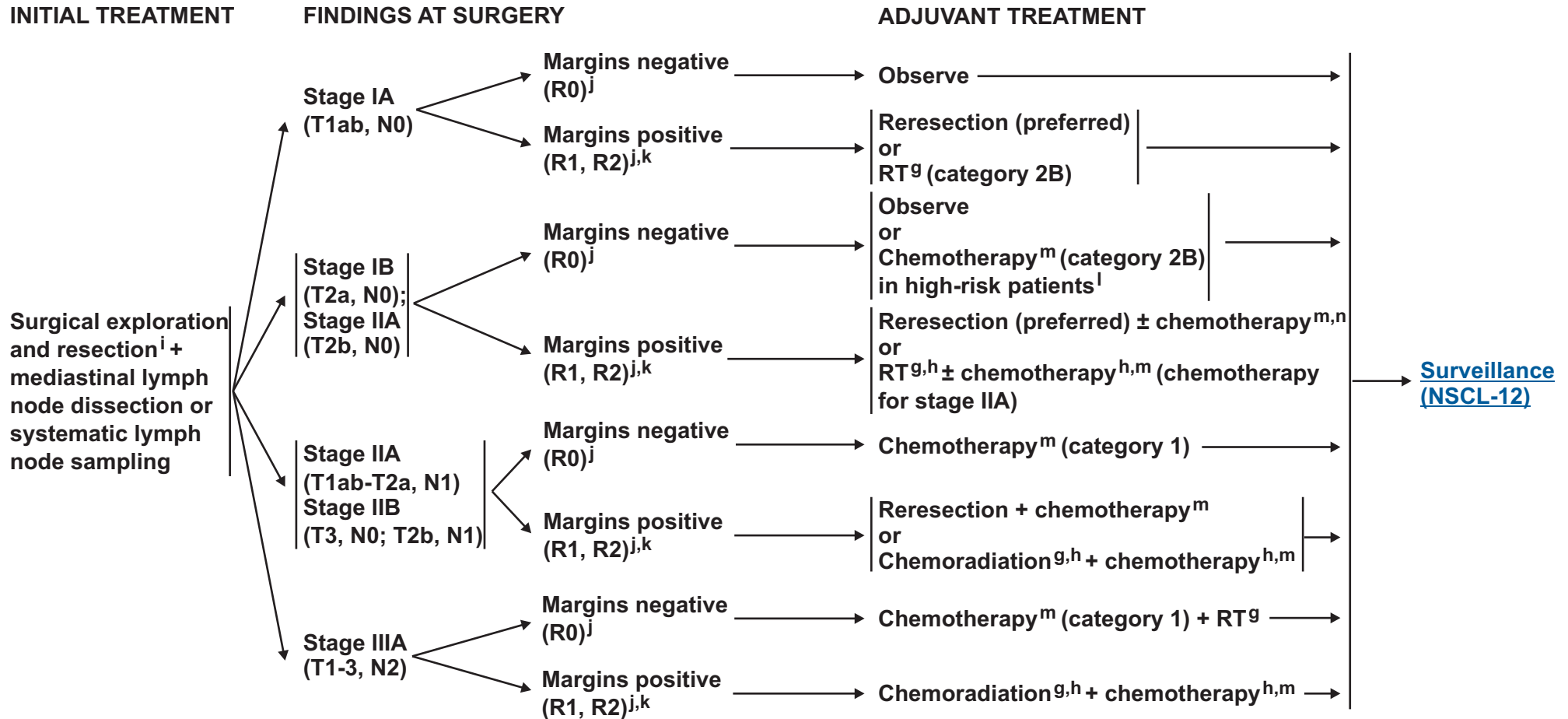
^fPositive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

^g[See Principles of Radiation Therapy \(NSCL-B\).](#)

^h[See Chemotherapy Regimens used with Radiation Therapy \(NSCL-C\).](#)

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

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^gSee Principles of Radiation Therapy (NSCL-B).

^hSee Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

ⁱSee Principles of Surgical Therapy (NSCL-D).

^jR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^kThe panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections.

^lHigh-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, Nx. These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy. (See Principles of Surgery NSCL-D)

^mSee Chemotherapy Regimens for Adjuvant Therapy (NSCL-E).

ⁿIncreasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

CLINICAL EVALUATION

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

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

Superior sulcus tumor → [See Treatment \(NSCL-5\)](#)

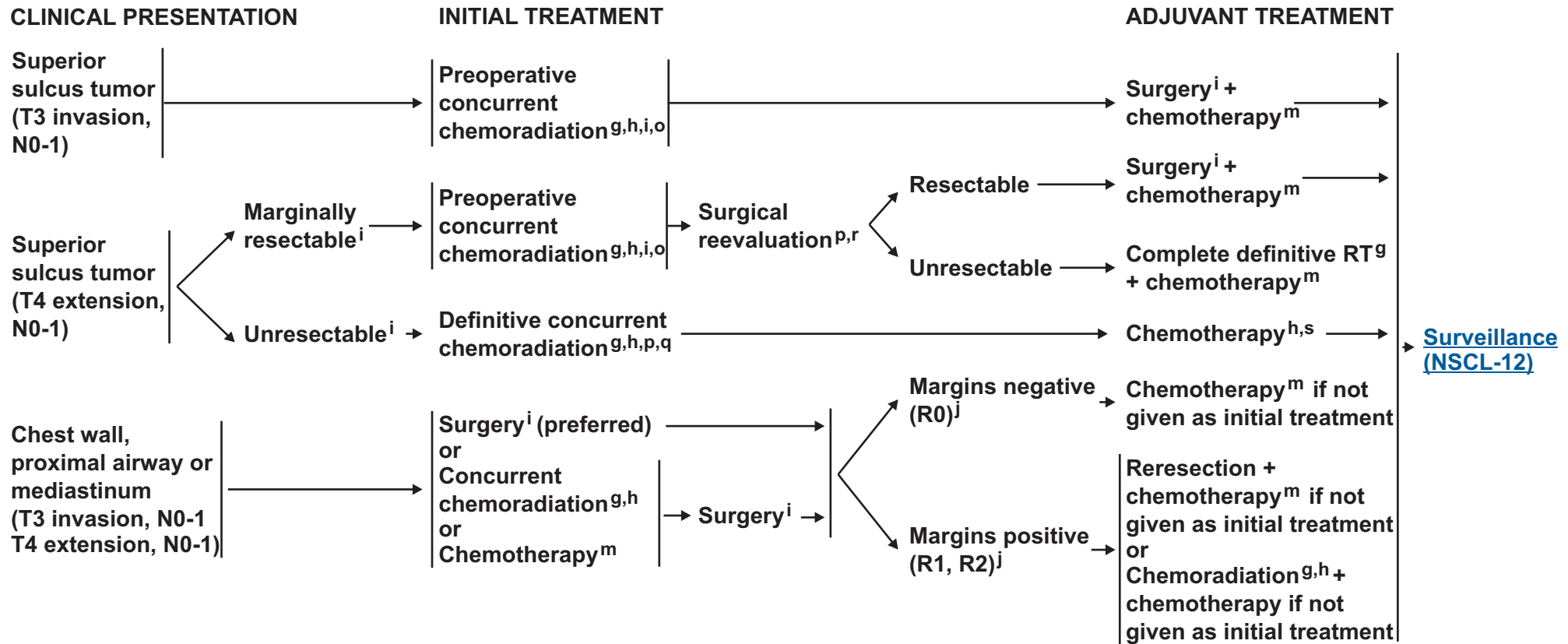
Chest wall → [See Treatment \(NSCL-5\)](#)

Proximal airway or mediastinum → [See Treatment \(NSCL-5\)](#)

Metastatic disease → [See Treatment for Metastasis solitary site \(NSCL-11\) or disseminated \(NSCL-13\)](#)

^fPositive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

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^gSee Principles of Radiation Therapy (NSCL-B).

^hSee Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

ⁱSee Principles of Surgical Therapy (NSCL-D).

^jR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^mSee Chemotherapy Regimens for Adjuvant Therapy (NSCL-E).

^oIn 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.

^pRT should continue to definitive dose without interruption if patient is not a surgical candidate.

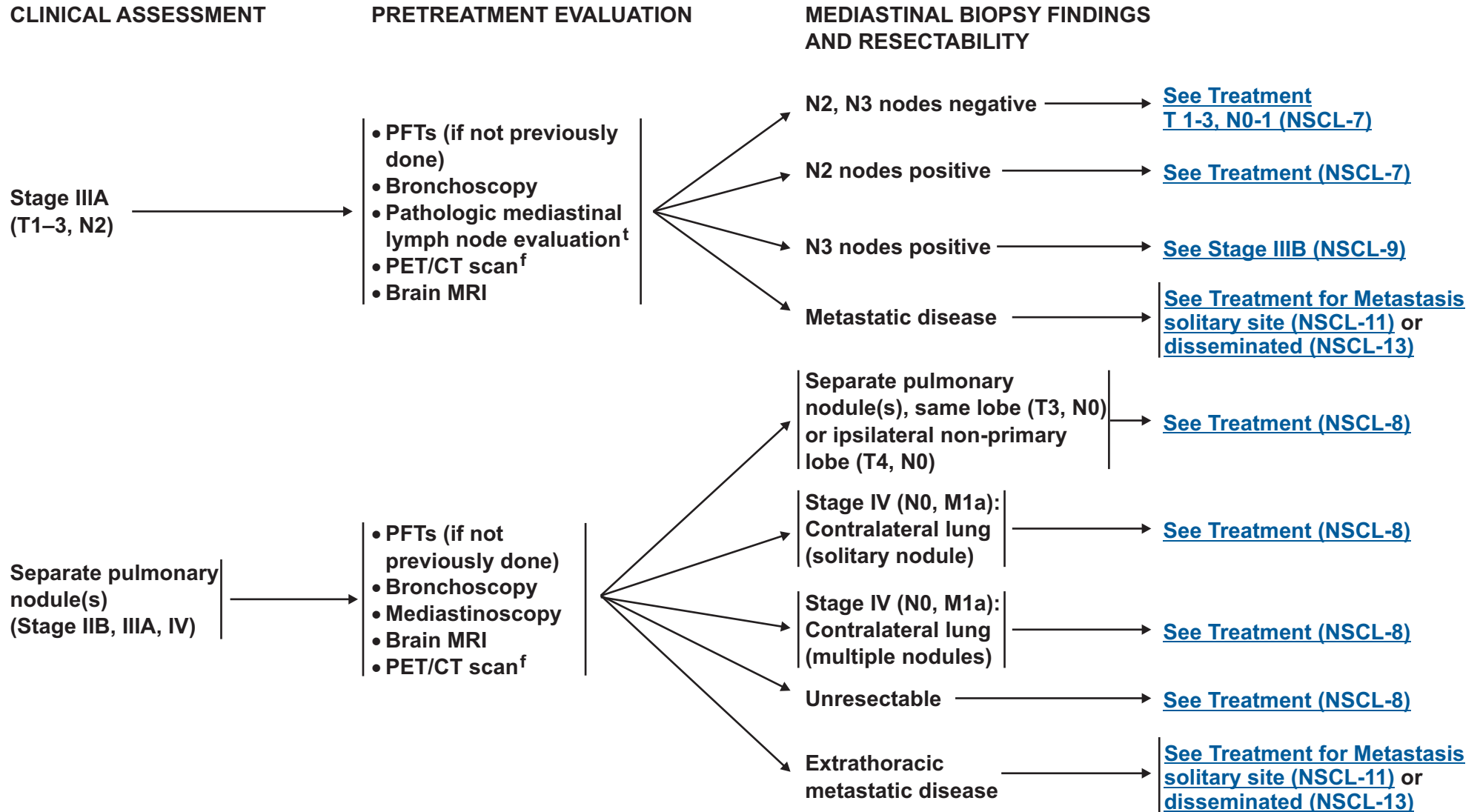
^qIn the definitive chemoradiation setting, a total dose of 60-70 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.

^rRusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). J Clin Oncol 2007;25:313-318.

^sIf full-dose chemotherapy not given concurrently with RT as initial treatment.

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

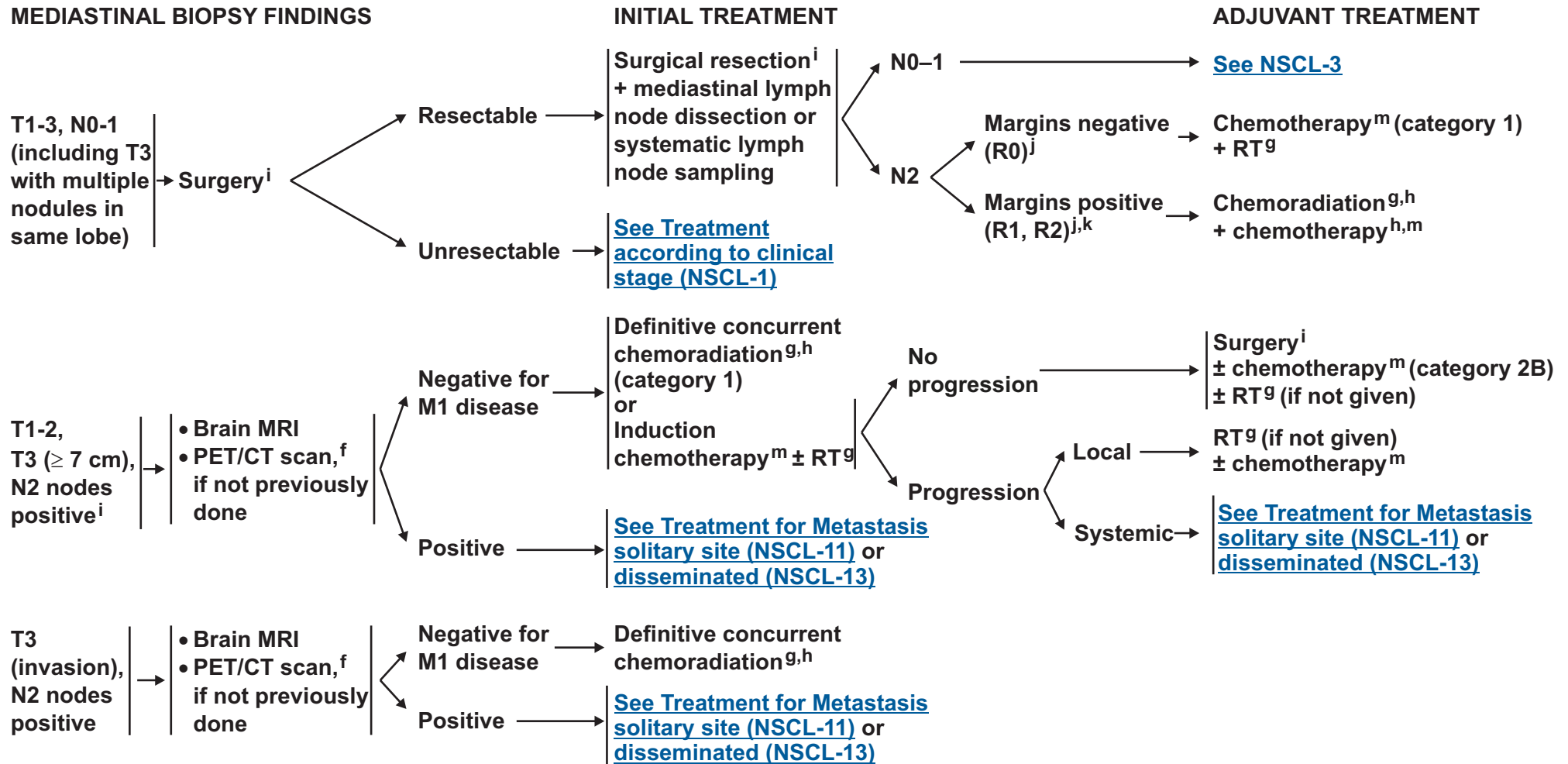
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^fPositive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

^tMethods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS and CT-guided biopsy.

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^g[See Principles of Radiation Therapy \(NSCL-B\).](#)

^h[See Chemotherapy Regimens used with Radiation Therapy \(NSCL-C\).](#)

ⁱ[See Principles of Surgical Therapy \(NSCL-D\).](#)

^jR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^kThe panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections.

^m[See Chemotherapy Regimens for Adjuvant Therapy \(NSCL-E\).](#)

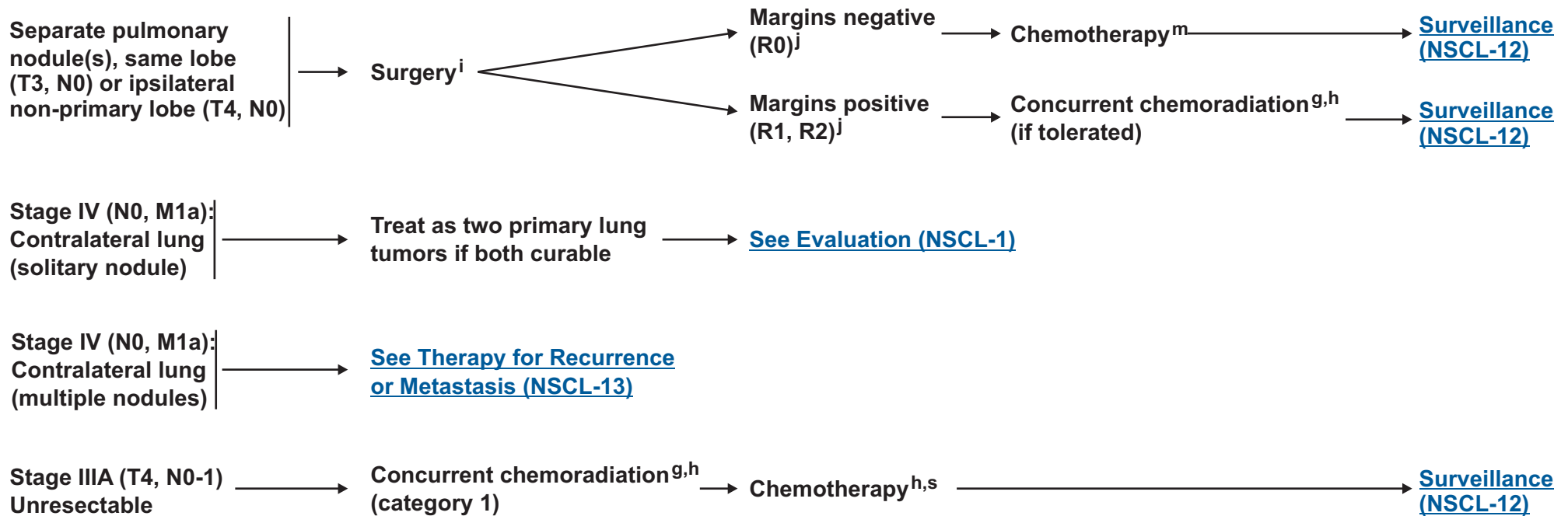
Note: All recommendations are category 2A unless otherwise indicated.

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

CLINICAL PRESENTATION

INITIAL TREATMENT

ADJUVANT TREATMENT



^gSee Principles of Radiation Therapy (NSCL-B).

^hSee Chemotherapy Regimens used with Radiation Therapy (NSCL-C).

ⁱSee Principles of Surgical Therapy (NSCL-D).

^jR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^mSee Chemotherapy Regimens for Adjuvant Therapy (NSCL-E).

^sIf full-dose chemotherapy not given concurrently with RT as initial treatment.

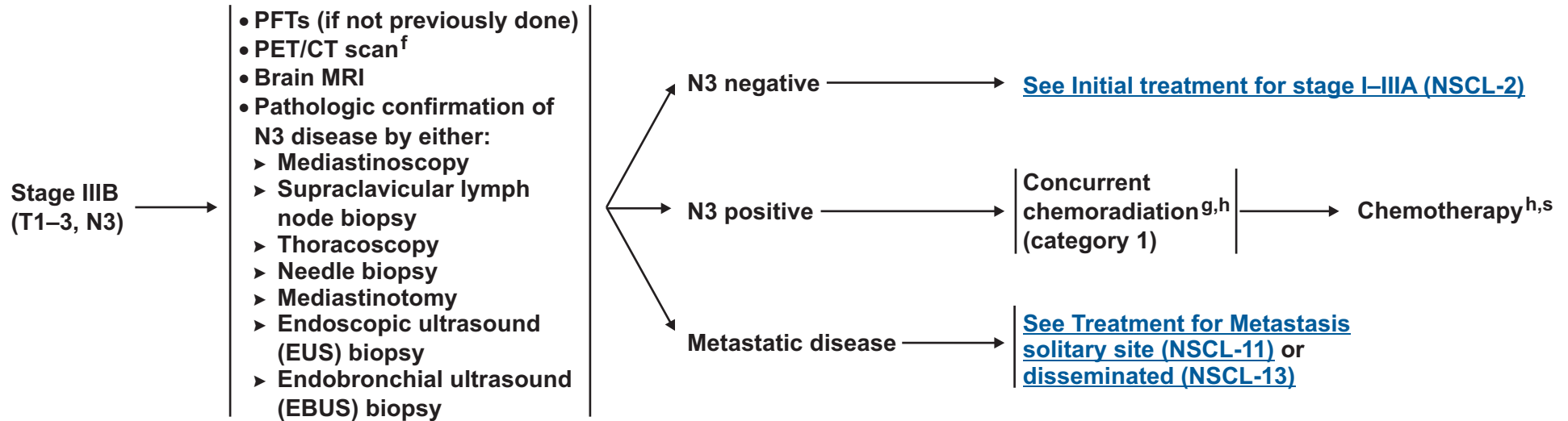
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**CLINICAL
ASSESSMENT**

PRETREATMENT EVALUATION

INITIAL TREATMENT



^fPositive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

^g[See Principles of Radiation Therapy \(NSCL-B\).](#)

^h[See Chemotherapy Regimens used with Radiation Therapy \(NSCL-C\).](#)

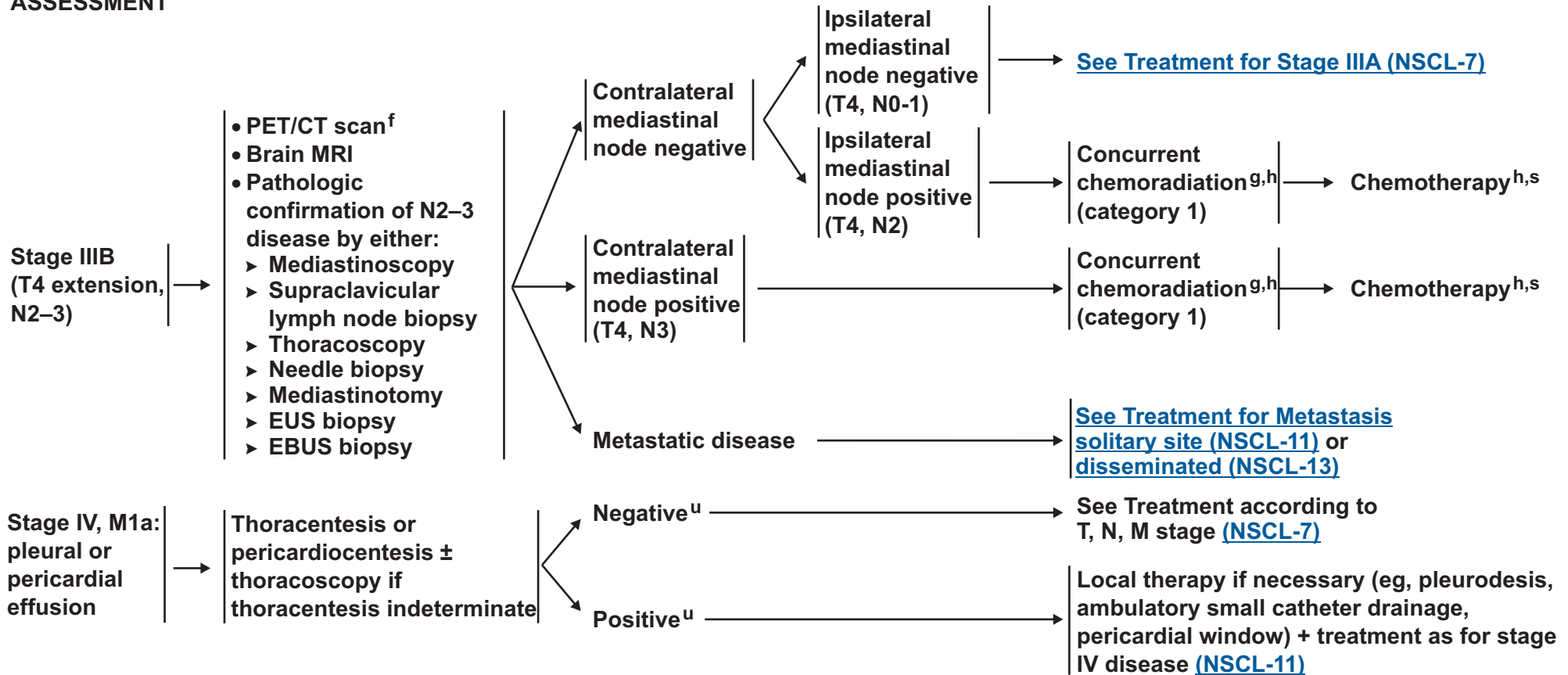
^sIf full-dose chemotherapy not given concurrently with RT as initial treatment.

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CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



^fPositive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

^gSee [Principles of Radiation Therapy \(NSCL-B\)](#).

^hSee [Chemotherapy Regimens used with Radiation Therapy \(NSCL-C\)](#).

^sIf full-dose chemotherapy not given concurrently with RT as initial treatment.

^uWhile most pleural effusions associated with lung cancer are due to tumor, there are a 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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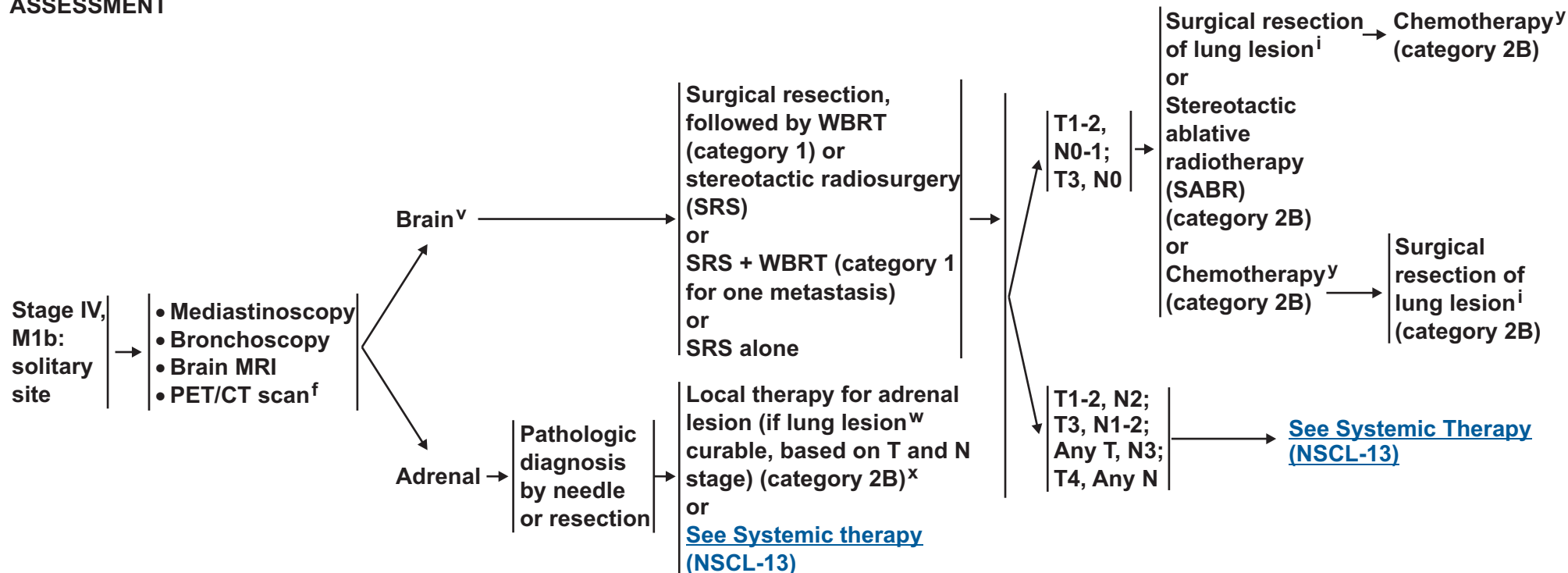
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



^fPositive 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 Surgical Therapy \(NSCL-B\).](#)

^v[See NCCN CNS Guidelines.](#)

^wMay include adrenalectomy or RT (including SABR).

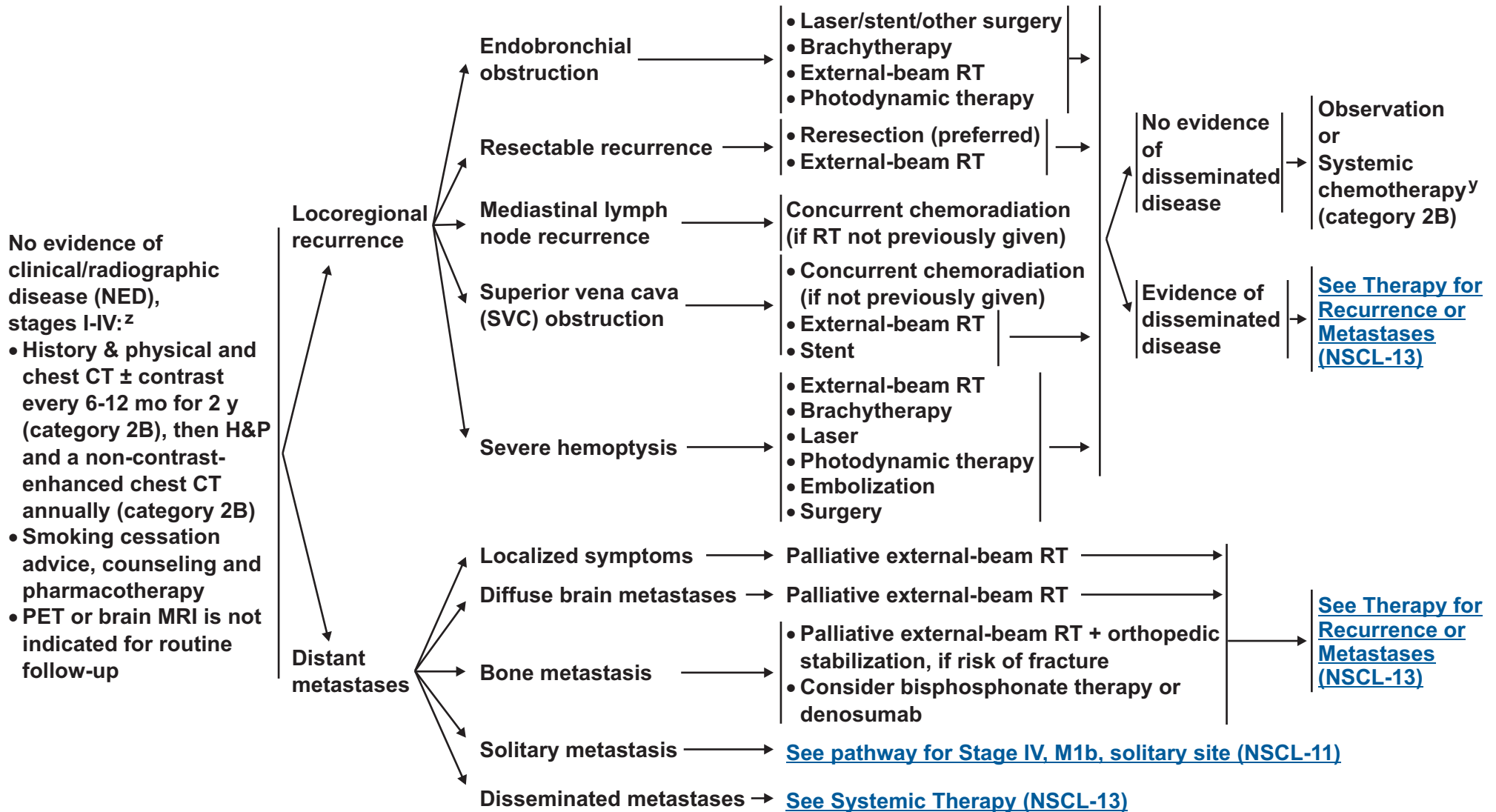
^xPatients with N2 disease have a poor prognosis and systemic therapy may be considered.

^y[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)

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SURVEILLANCE

THERAPY FOR RECURRENCE AND METASTASIS

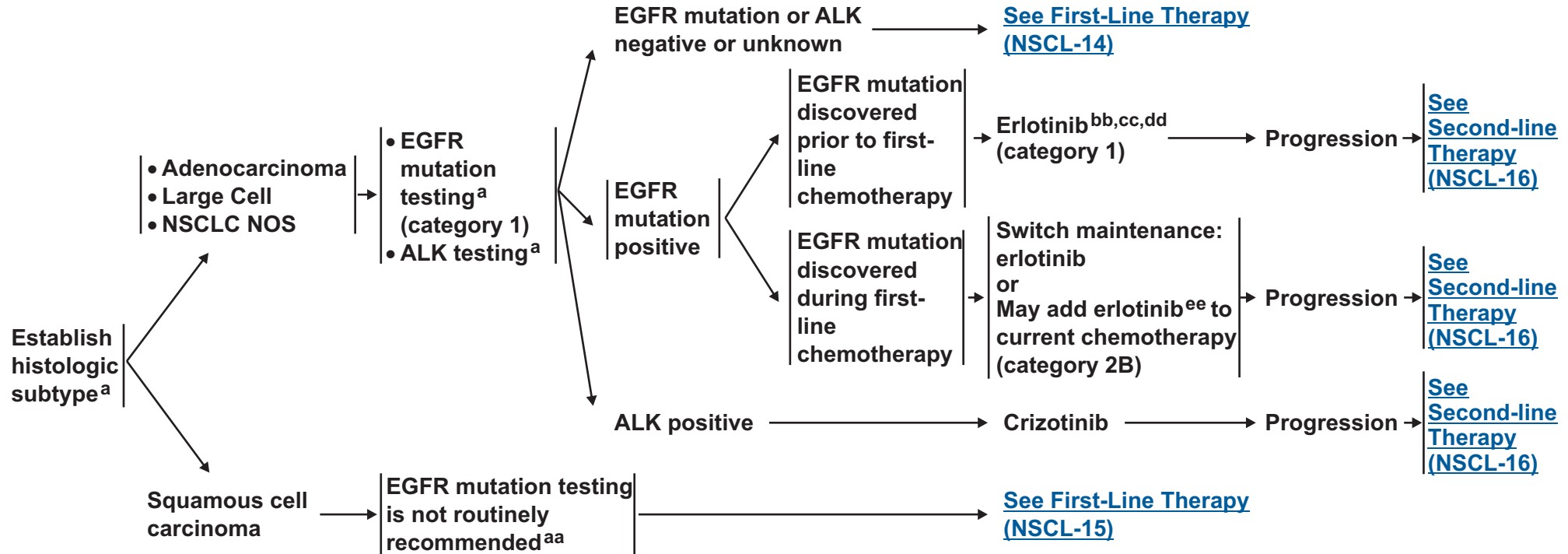


^ySee [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

^zSee [Cancer Survivorship Care \(NSCL-G\)](#).

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THERAPY FOR RECURRENCE OR METASTASES



^aSee Principles of Pathologic Review (NSCL-A).

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

^{bb}Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med. 2010;362(25):2380-2388. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol. 2010;11(2):121-128.

^{cc}For performance status 0-4.

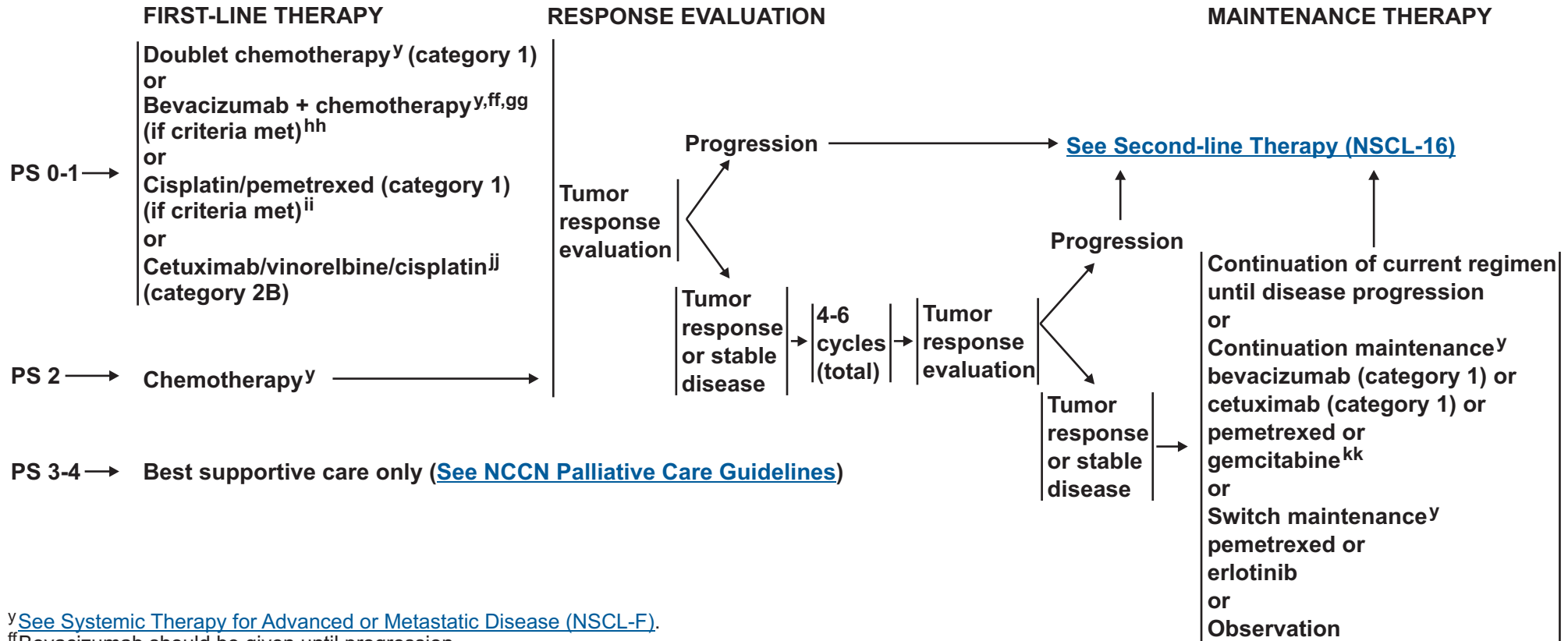
^{dd}In areas of the world where gefitinib is available, it may be used in place of erlotinib.

^{ee}Janne PA, Wang XF, Socinski MA, et al. Randomized phase II trial of erlotinib (E) alone or in combination with carboplatin/paclitaxel (CP) in never or light former smokers with advanced lung adenocarcinoma:CALGB 30406 [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 7503.

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



^ySee [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

^{ff}Bevacizumab should be given until progression.

^{gg}Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

^{hh}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.

ⁱⁱThere 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-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543-3551.

^{jj}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.

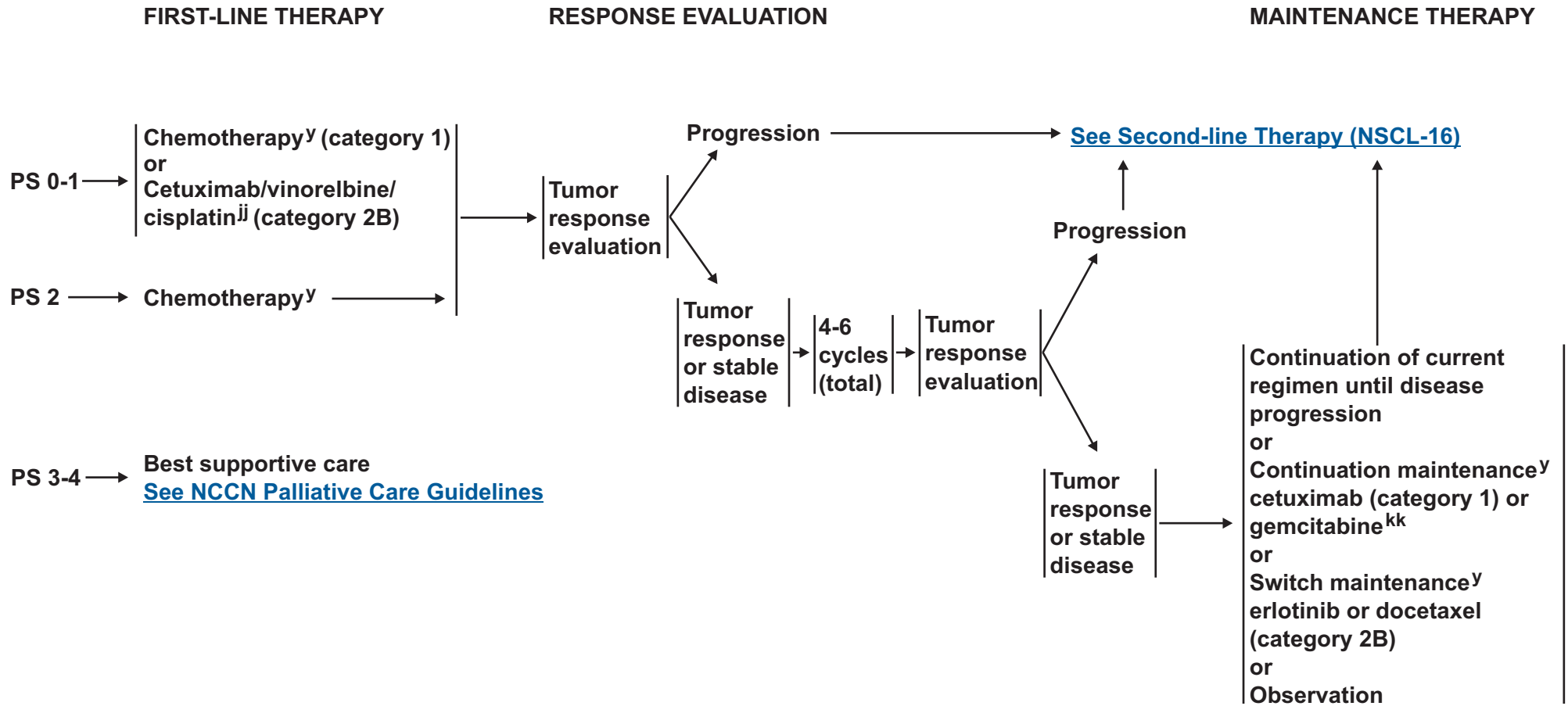
^{kk}Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. *J Clin Oncol* 2010;28 (Suppl 15):Abstract 7507.

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SQUAMOUS CELL CARCINOMA



^ySee [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

^{jj}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.

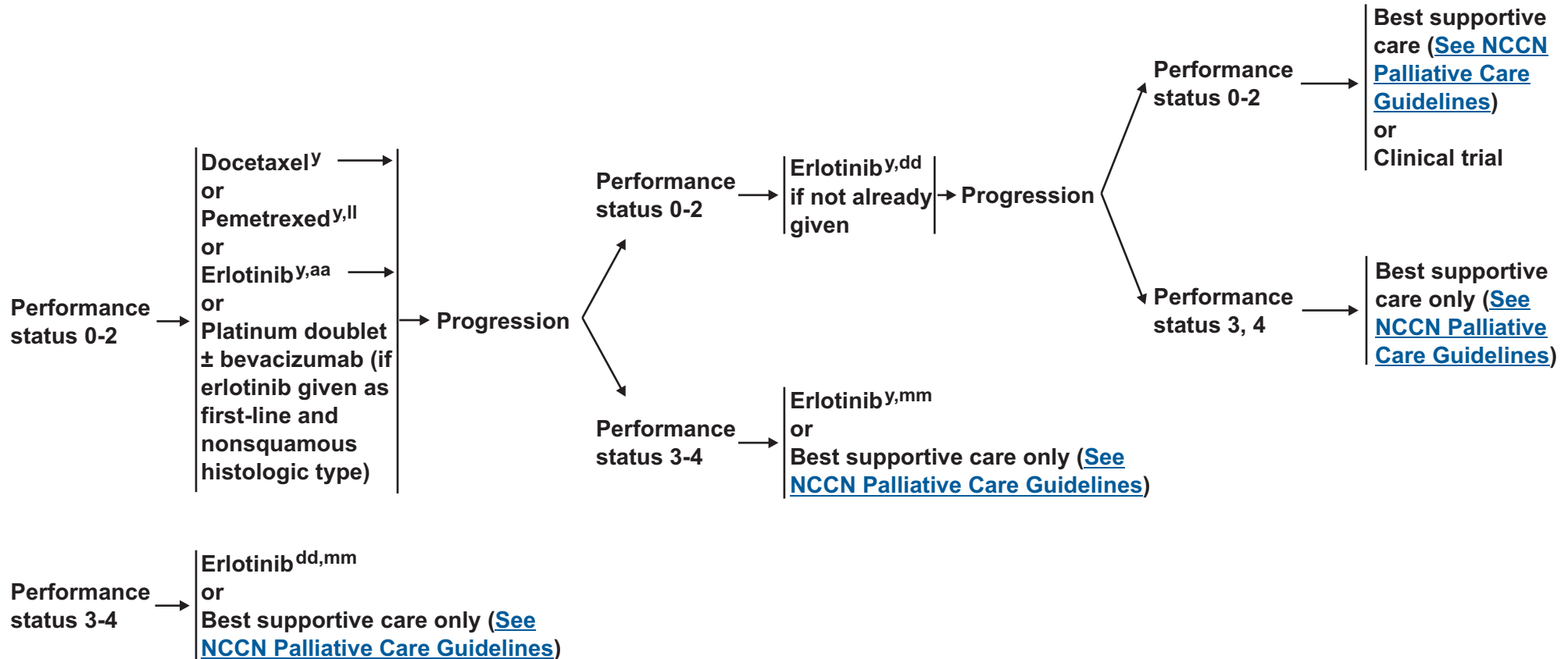
^{kk}Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. *J Clin Oncol* 2010;28 (Suppl 15):Abstract 7507.

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SECOND-LINE THERAPY

THIRD-LINE THERAPY



^ySee [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

^{dd}In areas of the world where gefitinib is available, it may be used in place of erlotinib.

^{ll}Pemetrexed is not recommended for squamous histology.

^{mm}Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Pathologic Evaluation

- The purpose of pathologic evaluation is to precisely classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC¹ including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis.² Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to a growing number of targeted therapies primarily tyrosine kinase inhibitors (see “Molecular Diagnostic Studies” in this section).^{3,4}
- The World Health Organization (WHO) tumor classification system has historically provided the foundation for the classification of lung tumors, including histologic types, clinical features, staging considerations as well as the molecular, genetic, and epidemiology aspects of lung cancer.^{2,5}
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung with squamous morphology, neuroendocrine differentiation, and other variant carcinomas. The recently published classification of adenocarcinoma should be used for this tumor subtype in resection specimens and small biopsies.⁶ Use of bronchioloalveolar carcinoma (BAC) terminology is strongly discouraged.
- The generic term non-small cell lung cancer (NSCLC) should be avoided except in those cases where extensive pathology workup fails to identify a specific lineage (ie, adenocarcinoma or squamous cell cancer).
- Whenever possible, acquisition of fresh cryopreserved tumor tissue for molecular studies is highly recommend especially in late stage disease. Formalin fixed paraffin embedded tumor may also be used for most analyses.
- Judicious use of ancillary immunohistochemical (IHC) studies in small tissue samples is encouraged, thereby preserving tumor tissue for molecular studies particularly in patients with advanced stage disease.

Adenocarcinoma Classification⁶

- Adenocarcinoma in situ (AIS; formerly BAC)- < 3 cm nodule, lepidic growth, mucinous, non-mucinous or, mixed mucinous/nonmucinous types.
- Minimally invasive adenocarcinoma (MIA)- < 3 cm nodule with < 5 mm of invasion, predominantly lepidic growth, mucinous, nonmucinous, or mixed mucinous/nonmucinous types.
- Invasive adenocarcinoma- lepidic predominant growth with > 5 mm of invasion, acinar, papillary, micropapillary, or solid with mucin
- Invasive adenocarcinoma variants-mucinous adenocarcinoma, colloid, fetal, and enteric morphologies.

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PRINCIPLES OF PATHOLOGIC REVIEW (2 of 4)

Immunohistochemical staining

Although the concordance between the histologic subtype and the immunophenotype seen in small biopsies compared with surgical resection specimens is generally good, caution is advised in attempting to subtype small biopsies with limited material or in those cases with an ambiguous immunophenotype.

- Immunohistochemistry should be used to differentiate primary pulmonary adenocarcinoma from squamous or large cell carcinoma, from metastatic carcinoma, and from malignant mesothelioma; and to determine whether neuroendocrine differentiation is present
- Primary pulmonary adenocarcinoma
 - ▶ An appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to lung.
 - ▶ 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 immunoreactivity is seen in primary pulmonary adenocarcinoma in the majority (70-100%) of nonmucinous adenocarcinomas subtypes. Metastatic adenocarcinoma to the lung is virtually always negative for TTF-1 except in metastatic thyroid malignancies.
 - ▶ Napsin A, an aspartic proteinase expressed in normal Type II pneumocytes and in proximal and distal renal tubules appears to be expressed in >80% of lung adenocarcinomas and may be a useful adjunct to TTF-1.⁷
 - ▶ Pulmonary adenocarcinoma of the lung is typically CK7+/ CK20- and therefore distinguishable from CK7-/CK20+ metastatic adenocarcinoma of the GI tract.
 - ▶ The panel of mucicarmine, p63, CK5/6, and high molecular weight cytokeratin (34βE12) can be used to distinguish adenocarcinoma solid variant from squamous cell cancer.⁸
 - ▶ The panel of TTF-1, Napsin A, p63, and CK5/6 may be useful in refining the diagnosis in small biopsy specimens previously generically classified as NSCLC.⁹
- Neuroendocrine differentiation
 - ▶ CD56, chromogranin and synaptophysin are used to identify neuroendocrine differentiation in lung tumors including poorly differentiated neuroendocrine (small cell) and large cell neuroendocrine cancer. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin, whereas small cell lung cancer is negative in 25% of cases.
- Malignant mesothelioma versus pulmonary adenocarcinoma
 - ▶ The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) can be daunting; however, a panel of markers including 2 with known immunopositivity in mesothelioma (but negative in adenocarcinoma) and 2 with known positivity in adenocarcinoma (but negative in mesothelioma) is suggested.
 - ▶ Immunostains relatively sensitive and specific for mesothelioma are WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma)
 - ▶ Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (negative in mesothelioma).

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

Molecular Diagnostic Studies in Lung Cancer

• EGFR and KRAS

- ▶ EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents critical biological factors for proper patient selection.
- ▶ There is a significant association between EGFR mutations — especially exon 19 deletion, exon 21 mutation (L858R), and exon 18 (G719X) — and response to TKIs.¹⁰⁻¹³
- ▶ EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.¹⁴
- ▶ KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy.¹⁵
- ▶ The prevalence of EGFR mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher EGFR mutation frequency in non-smokers, women, and non-mucinous tumors. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.¹⁶ The most common EGFR mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations more common in non-mucinous lung adenocarcinoma with BAC features and in lung adenocarcinoma with papillary (and or micropapillary) features.
- ▶ Resistance to TKI therapy is associated with KRAS mutation and specific acquired EGFR mutations, such as T790M.
- ▶ Because EGFR gene mutations are the best predictor of a patient's response to EGFR TKI, various DNA mutational assays have been reported in the literature.¹⁷

• EML4-ALK

- ▶ ALK-rearrangements in a subset of anaplastic large cell lymphomas (ALCL) have been recognized for over 15 years.¹⁸ The fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) has recently been identified in a subset of non-small cell lung cancers (NSCLCs). EML4-ALK NSCLC represents a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.¹⁹ Crizotinib is an oral ALK inhibitor that was recently approved by the FDA for patients with locally advanced or metastatic NSCLC who have the ALK rearrangement mutation. (ie, ALK positive).
- ▶ EML4-ALK NSCLC occurs most commonly in a unique clinical subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor EGFR mutations.^{20,21} However, for the most part, EML4-ALK and EGFR mutations are mutually exclusive.^{20,21-24} EML4-ALK translocations tend to occur in younger patients and those with more advanced NSCLC while this relationship has not been reported for EGFR mutant NSCLC.^{22,25}
- ▶ A new molecular diagnostic test that uses fluorescence in situ hybridization (FISH) has recently been approved by the FDA to determine which patients with NSCLC are positive for ALK rearrangements.

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

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PRINCIPLES OF RADIATION THERAPY (1 of 10)

General Principles (see Table 1. Commonly Used Abbreviations in Radiation Therapy)

- **Determination of the appropriateness of radiation therapy (RT) should be made by board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice.**
- **RT has a potential role in all stages of lung cancer, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients who may benefit from definitive local therapy, particularly those with absolute or relative contraindications to surgery as determined by a thoracic surgeon.**
- **To maximize tumor control and to minimize treatment toxicity, critical components of modern radiation therapy include appropriate simulation, accurate target definition, conformal RT planning, and ensuring accurate delivery of the planned treatment. A minimum standard is CT-planned 3DCRT.**
- **Use of more advanced technologies is appropriate when needed to deliver adequate tumor doses while respecting normal tissue dose constraints. Such technologies include (but are not limited to) 4DCT simulation, IMRT/VMAT, stereotactic ablative radiotherapy (SABR), IGRT, motion management strategies, and proton therapy. Daily IGRT is recommended to ensure accurate delivery when using highly conformal therapy or complex motion management techniques, and should be required for dose-intensified or hypofractionated therapy such as SABR. In non-randomized retrospective comparisons in patients with locally advanced NSCLC treated with concurrent chemotherapy, 4DCT planned IMRT significantly reduced rates of high grade pneumonitis and higher overall survival compared to 3DCRT,¹ and proton therapy reduced esophagitis and pneumonitis despite higher doses compared to 3DCRT or IMRT,² while a prospective clinical trial demonstrated favorable outcomes compared to historical results.³**
- **Of note, the higher complexity of advanced technologies increases the risk of errors, and the relatively higher cost of some raises concern about their cost-effectiveness. Thus, centers using these technologies should implement and document modality-specific quality assurance measures. Useful references include the ACR-ASTRO Practice Guidelines for Radiation Oncology.⁴ Minimum requirements for thoracic IMRT are specified in NCI Advanced Technology Consortium IMRT Guidelines,⁵ and safety considerations for contemporary RT are detailed in a series of ASTRO commissioned white papers.⁶ The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies.**

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**PRINCIPLES OF RADIATION THERAPY (2 of 10)****Early Stage Lung Cancer (Stage I)**

- **SABR (traditionally known as SBRT) is recommended for patients who are medically inoperable and is also an appropriate option for many older patients (eg, ≥ age 75). SABR has achieved high primary tumor control rates and favorable overall survival in prospective studies, comparable to surgery and higher than 3DCRT in non-randomized comparisons.⁷⁻¹⁰ An analysis of cost-effectiveness found SABR more cost-effective than 3DCRT and radiofrequency ablation, largely owing to its high efficacy.¹¹**
- **For patients with high surgical risk (able to tolerate sublobar resection but not lobectomy), SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control in non-randomized comparisons.^{12,13} A prospective randomized cooperative group trial of sublobar resection vs. SABR has been initiated (ACOSOG Z4099/RTOG 1021).**
- **For potentially operable patients who refuse surgical therapy despite a complete thoracic surgery consultation, SABR is recommended based on comparable outcomes in non-randomized retrospective comparisons, especially in older patients.^{10,14}**
- **For institutions without an established SABR program, more modestly hypofractionated or dose intensified conventionally fractionated 3DCRT regimens are recommended.¹⁵⁻¹⁷**
- **In patients treated with surgery, PORT is not recommended unless there are positive margins or upstaging to N2 (see Locally Advanced Lung Cancer below).**

Locally Advanced Lung Cancer (Stage II-III)

- **The standard of care for fit patients with inoperable stage II and stage III is concurrent chemoradiotherapy.^{18,19} Sequential chemoRT is appropriate for frail patients unable to tolerate concurrent therapy.^{20,21} In patients receiving conventionally fractionated RT with or without concurrent chemotherapy for curative intent, treatment interruptions and dose reductions for manageable acute toxicities should be avoided in favor of aggressive supportive care, including opiate pain medications and IV hydration. An integrated multidisciplinary care setting is recommended.**
- **Surgery with preoperative concurrent chemoRT or preoperative chemotherapy and postoperative RT are options for well selected patients with resectable stage IIIA (N2) ([See NSCL-D 2 of 5](#)). If pneumonectomy is anticipated, it is controversial whether neoadjuvant chemoradiation is appropriate ([See Principles of Surgical Resection - NSCL-D 4 of 5](#)).^{22,23} Preoperative concurrent chemoRT is recommended for resectable superior sulcus tumors.²⁴⁻²⁶ The determination of resectability in trimodality therapy should be made prior to initiation of all treatment.**
- **Postoperative radiotherapy (PORT) is not recommended for patients with pathologic stage N0-1 disease as it has been associated with increased mortality, at least when using older RT techniques.²⁷**
- **In patients with pathologic N2+ disease, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.^{28,29} Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients³⁰⁻³² and is recommended for positive resection margins. RT should start early as local recurrence is a prominent pattern of failure in this setting.**
- **Unlike for small cell lung cancer, prophylactic cranial irradiation (PCI) has not been shown to improve survival in locally advanced NSCLC, but it significantly reduces brain metastases.³³ In addition, it causes significant decline in memory but not in global cognitive function or quality of life.³⁴ PCI is not recommended standardly but its relative risks and potential benefits should be considered on an individual patient basis.**

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**PRINCIPLES OF RADIATION THERAPY (3 of 10)*****Advanced Lung Cancer (Stage IV)***

- RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction) from either primary or metastatic tumors.
- Definitive local therapy to isolated or limited metastatic sites (oligometastases)(including but not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease. Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved site.³⁵⁻³⁷
- See [NCCN CNS Guidelines](#) regarding RT for brain metastases.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints (See Tables 2-5 on NSCL-B 7 of 10 and NSCLB 8 of 10)

- ICRU reports 50 & 62^{38,39} detail the current definitions of target volumes for 3D RT (See Figure 1 on NSCL-B 8 of 10). GTV comprises the visible extent of disease (primary and nodal) on imaging and clinical exams, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a set-up margin for positioning and mechanical variability.
- Consistent delineation of normal structures is critical for evaluating plans for safety. An expert consensus atlas has been developed for contouring several thoracic OARs.⁴⁰
- Optimal prescription doses and normal tissue dose constraints are still under investigation, and a single standard cannot be recommended. Commonly used regimens are summarized in Tables 2-5. Normal tissue constraints are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.^{41,42} Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.⁴³⁻⁴⁷

Early stage/SABR

- The high dose intensity and conformity of SABR requires minimizing the target volume. Commonly, gross disease is explicitly targeted with the prescription dose, while microscopic extension is implicitly covered by intermediate doses.
- For SABR, intensive regimens of BED ≥ 100 Gy are associated with significantly better local control and survival than less intensive regimens.⁴⁸ In the United States, only regimens of ≤ 5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.^{48,49} Prospective evaluation and comparison of different regimens are ongoing in cooperative group studies.
- Treatment of centrally located tumors (defined as within 2 cm of the proximal bronchial tree) using the most intensive SABR regimens (i.e., 54-60 Gy in 3 fractions) is unsafe,⁵⁰ but modified/risk-adapted SABR regimens appear to be effective and safe.^{49,51} Normal organ dose limits for centrally located tumors are being studied prospectively in RTOG 0813.
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.⁵²
- Prescription doses incompletely describe the actual delivered doses, which also depend strongly on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.⁵³ All of these must be considered when interpreting or emulating a regimen from prior studies.

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

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

PRINCIPLES OF RADIATION THERAPY (4 of 10)

Locally advanced stage/conventionally fractionated RT

- Including elective nodal regions in the CTV for definitive RT remains controversial.⁵⁴ IFI omitting ENI allows tumor dose escalation, and is associated with a low risk of isolated nodal relapse compared to local and distant relapse rates, particularly in PET-CT staged patients.⁵⁵⁻⁵⁸ One randomized trial found improved survival for IFI vs. ENI, possibly because it enabled dose escalation.⁵⁹ IFI is reasonable in order to optimize definitive dosing to the tumor. In patients who receive induction chemotherapy for a large initial tumor volume, particularly those with compromised lung or cardiac function or other risk factors for increased normal tissue toxicity, the GTV can be limited to the post-chemotherapy volume to avoid excessive toxicity. Initially involved nodal regions (but not their entire pre-chemotherapy volume) should be covered.
- The most commonly prescribed doses for definitive RT are 60-70 Gy in 2 Gy fractions. Doses of at least 60 Gy should be given.⁶⁰ Dose escalation in RT alone,⁶¹ sequential chemoRT,⁶² or concurrent chemoRT⁶³ is associated with better survival in non-randomized comparisons. Doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected.⁶⁴⁻⁶⁸ However, it remains to be demonstrated in randomized trials that dose escalation beyond 60 Gy improves survival. The final results from RTOG 0617, comparing 60 vs. 74 Gy with concurrent chemotherapy, are pending.
- In preoperative RT, the CTV generally includes the highest risk elective nodal regions. Doses of 45-50 Gy in 1.8 to 2 Gy fractions are standard. Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,⁶⁹⁻⁷¹ but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high dose RT. When using higher doses, only involved fields are targeted.
- In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.⁷² Standard doses after complete resection are 50-54 Gy in 1.8-2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.^{30,31} Lung dose constraints should be more conservative as tolerance appears to be reduced after lung resection. The ongoing European LungART trial provides useful guidelines for PORT technique.⁷³

Advanced stage/palliative RT

- The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations to maximize quality of life. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment,⁷⁴⁻⁷⁷ and are favored for patients with poor performance status and/or shorter life expectancy. When higher doses (>30 Gy) are warranted, 3DCRT should be used to reduce normal tissue irradiation.

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PRINCIPLES OF RADIATION THERAPY (5 of 10)

Radiation Therapy Simulation, Planning, and Delivery

- **Simulation should be performed using CT scans obtained in the RT treatment position with appropriate immobilization devices. IV contrast with or without oral contrast is recommended for better target/organ delineation whenever possible in patients with central tumors or nodal disease. Since IV contrast can affect tissue heterogeneity correction calculations, density masking or use of a pre-contrast scan may be needed when intense enhancement is present.**
- **PET/CT significantly improves targeting accuracy,⁷⁸ especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT vs. CT only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.⁷⁹ Given the potential for rapid progression of NSCLC,^{80,81} PET/CT should be obtained preferably within 4 weeks and no more than 8 weeks before treatment, and should be repeated otherwise. The ideal is to obtain PET/CT in the treatment position.**
- **Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or ideally 4DCT. Centers using 4DCT should understand how to address potential artifacts, including by patient coaching/training.**
- **Photon beam energy can be individualized based the anatomic location of the tumors and beam paths. In general, photon energies between 4 to 10 MV are recommended for beams passing through low-density lung tissue before entering the tumor. When there is no air gap before the beam enters the tumor such as for some large mediastinal tumors or tumors attached to chest wall, higher energies may improve the dose distribution, especially when using a smaller number of fixed beam angles.**
- **Tissue heterogeneity correction and accurate dose calculation algorithms that account for build-up and lateral electron scatter effects in heterogeneous density tissues are recommended. Heterogeneity correction with simple pencil beam algorithms can result in substantial overestimates of actual delivered dose.**
- **Respiratory motion should be managed when motion is excessive, including but not limited to by forced shallow breathing with abdominal compression, accelerator beam gating with the respiratory cycle, dynamic tumor tracking, active breathing control (ABC), or coaching/biofeedback techniques. If motion is minimal or the ITV is small, motion-encompassing targeting is appropriate. A useful resource for implementation of respiratory motion management is the report of AAPM Task Group 76.⁸²**
- **IGRT, including but not limited to orthogonal pair planar imaging and volumetric imaging such as CBCT or CT on rails, is recommended when using highly conformal RT, including all SABR and 3DCRT/IMRT with steep dose gradients around the target, when OARs are in close proximity to high dose regions, and when using complex motion management techniques.**

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PRINCIPLES OF RADIATION THERAPY (6 of 10)

Table 1. Commonly Used Abbreviations in Radiation Therapy

RT	Radiation Therapy or Radiotherapy	IFI	Involved Field Irradiation
2DRT	2-Dimensional RT	IGRT	Image-Guided RT
3DCRT	3-Dimensional Conformal RT	IMRT	Intensity-Modulated RT
4DCT	4-Dimensional Computed Tomography	ITV*	Internal Target Volume
AAPM	American Association of Physicists in Medicine	MLD	Mean Lung Dose
ABC	Active Breathing Control	OAR	Organ at Risk
ACR	American College of Radiology	OBI	On-Board Imaging
ASTRO	American Society for Radiation Oncology	PCI	Prophylactic Cranial Irradiation
BED	Biologically Effective Dose	PORT	Post-operative RT
CBCT	Cone-Beam CT	PTV*	Planning Target Volume
CTV*	Clinical Target Volume	QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
DVH	Dose-Volume Histogram	RTOG	Radiation Therapy Oncology Group
ENI	Elective Nodal Irradiation	SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
GTV*	Gross Tumor Volume	V20	% Volume of an OAR receiving ≥ 20 Gy
ICRU	International Commission on Radiation Units and Measurements	VMAT	Volumetric Modulated Arc Therapy

*Refer to ICRU Reports 50 & 62 for detailed definitions.

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Table 2. Commonly Used Doses for SABR

Nominal Dose	# Fractions	Example Indications
25-34 Gy	1	Peripheral, small (< 2 cm) tumors, esp. > 1 cm from chest wall
45-60 Gy	3	Peripheral tumors, esp. > 1 cm from chest wall
48-50 Gy	4	Central or peripheral tumors < 4-5 cm, esp. < 1 cm from chest wall
50-55 Gy	5	Central or peripheral tumors, esp. < 1 cm from chest wall
60-70 Gy	8-10	Central tumors

Table 3. Normal Tissue Dose-Volume Constraints for SABR*

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 & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	31.2 Gy (7.5 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)

*Based on constraints used in recent and ongoing RTOG SABR trials (RTOG 0618, 0813, & 0915).

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Table 4. Commonly Used Doses for Conventionally Fractionated and Palliative RT

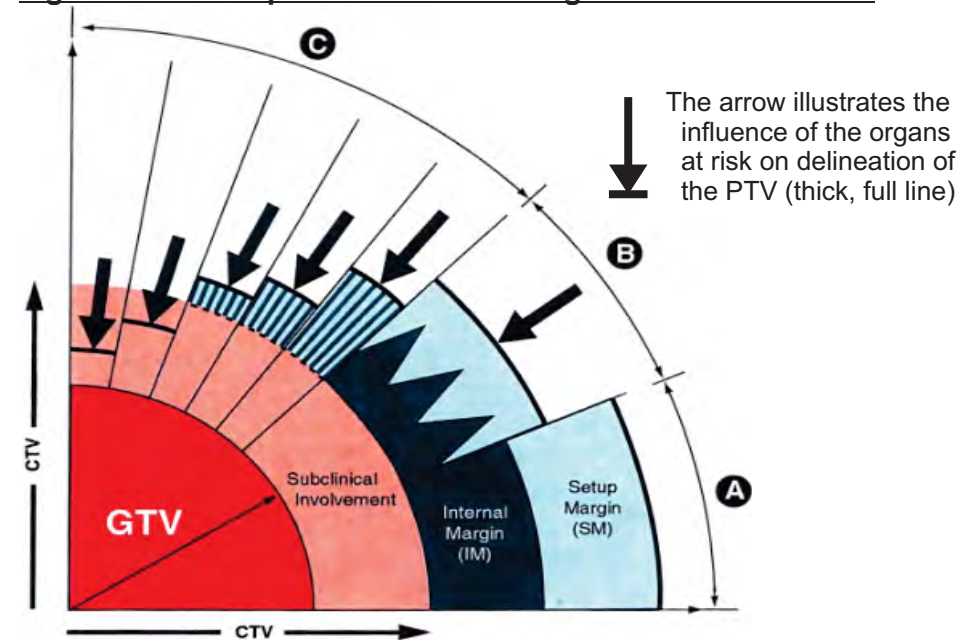
Treatment type	Total dose	Fraction size	Treatment duration
Definitive RT with or without chemotherapy	60-74 Gy	2 Gy	6-7.5 weeks
Preoperative RT	45-50 Gy	1.8-2 Gy	5 weeks
Postoperative RT			
• Negative margins	50-54 Gy	1.8-2 Gy	5-6 weeks
• Extracapsular nodal extension or microscopic positive margins	54-60 Gy	1.8-2 Gy	6 weeks
• Gross residual tumor	60-70 Gy	2 Gy	6-7 weeks
Palliative RT			
• Obstructive disease (SVC syndrome or obstructive pneumonia)	30-45 Gy	3 Gy	2-3 weeks
• Bone metastases with soft tissue mass	20-30 Gy	4-3 Gy	1-2 weeks
• Bone metastases without soft tissue mass	8-30 Gy	8-3 Gy	1 day-2 weeks
• Brain metastases	CNS GLs 17 Gy	CNS GLs 8.5 Gy	CNS GLs 1-2 weeks
• Symptomatic chest disease in patients with poor PS			
• Any metastasis in patients with poor PS	8-20 Gy	8-4 Gy	1 day-1 week

Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

OAR	Constraints in 30-35 Fractions
Spinal cord	Max ≤ 50 Gy
Lung	V20 ≤ 30-35%; V5 ≤ 70%; MLD ≤ 20 Gy
Heart	V40 ≤ 80 %; V45 ≤ 60%; V60 ≤ 30%; Mean ≤ 35 Gy
Esophagus	Mean ≤ 34 Gy; Max ≤ 105% of prescription dose
Brachial plexus	Max ≤ 66 Gy

Vxx = % of the whole OAR receiving ≤ xx Gy.

Figure 1. ICRU Report 62 schema of target volume definitions



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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 USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens*

- Cisplatin 50 mg/m² on day 1, 8, 29, and 36; etoposide 50 mg/m² days 1-5, 29-33; concurrent thoracic RT^a (preferred)**
- Cisplatin 100 mg/m² day 1, 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT^b (preferred)
- Paclitaxel 45-50 mg/m² weekly over 1 hour; carboplatin AUC = 2 mg/mL/min over 30 min weekly; concurrent thoracic RT^c (category 2B)**

Sequential Chemotherapy/RT Regimens

- Cisplatin 100 mg/m² on day 1, 29; vinblastine 5 mg/m²/weekly on days 1, 8, 15, 22, 29; followed by RT^b
- Paclitaxel 200 mg/m² every 3 weeks over 3 hours, 2 cycles; carboplatin AUC 6, 2 cycles followed by thoracic RT^c

Concurrent Chemotherapy/RT Followed by Chemotherapy

- Cisplatin 50 mg/m² on day 1, 8, 29, 36; etoposide 50 mg/m² days 1-5, 29-33; concurrent thoracic RT followed by cisplatin 50 mg/m² and etoposide 50 mg/m² x 2 additional cycles (category 2B)^a
- Paclitaxel 45-50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6^c (category 2B)

*There are data that support full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

**These regimens can be used as neoadjuvant chemoradiotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 3 cycles of full-dose platinum therapy after local treatment is completed.

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PRINCIPLES OF SURGICAL THERAPY (1 of 5)

- **Determination of resectability should be performed by Board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
- **Resection, including wedge resection, is a preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, stereotactic radiation). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where stereotactic RT is considered for high-risk patients, a multidisciplinary evaluation including a radiation oncologist is recommended.**
- **Surgical staging and pulmonary resection should be performed by Board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.**
- **The overall plan of treatment as well as needed imaging studies should be determined before any non-emergency treatment is initiated.**
- **Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (e.g. multidisciplinary clinic and/or Tumor Board).**
- **Anatomic pulmonary resection is preferred for the majority of patients with non-small cell lung cancer.**
- **Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥ 2 cm or \geq 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 nodule¹ ≤ 2 cm with at least one of the following:**
 - ◊ **Pure adenocarcinoma in situ (AIS) histology**
 - ◊ **Nodule has $\geq 50\%$ ground glass appearance on CT**
 - ◊ **Radiologic surveillance confirms a long doubling time (≥ 400 days)**

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

The Role Surgery in Patients with Stage IIIA (N2) NSCLC
(see [NSCL-D 3 of 5](#) through [NSCL-D 5 of 5](#))

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

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PRINCIPLES OF SURGICAL THERAPY (2 of 5)

- **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.**
- **In high-volume centers with significant VATS experience, VATS lobectomy in selected patients results in improved early outcomes (pain, hospital length of stay, return to function) without compromise of cancer outcomes.**
- **Lung-sparing anatomic resection (sleeve lobectomy) preferred over pneumonectomy, if anatomically appropriate and margin-negative resection achieved.**
- **T3 (extension) and T4 local invasion tumors require en-bloc resection of the involved structure with negative margins. If a surgeon or center is uncertain about potential complete resection, consider obtaining an additional surgical opinion from a high-volume specialized center.**
- **Surgical pathologic correlation is critical to assess apparent close or positive margins as these may not represent true margins or may not truly represent areas of risk for local recurrence (e.g. medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed, or pleural margin adjacent to aorta when no attachment to aorta is present).**
- **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.**
- **Complete resection requires free resection margins, systematic node dissection or sampling, no extracapsular nodal extension of the tumor, and the highest mediastinal node negative for tumor. The resection is defined as incomplete, whenever there is involvement of resection margins, extracapsular nodal extension, unremoved positive lymph nodes or positive pleural or pericardial effusions. A complete resection is referred to as R0, microscopically positive resection as R1, and macroscopic residual tumor as R2.**
- **Patients with pathologic stage II or greater should be referred to medical oncology for evaluation.**
- **Consider referral to medical oncologist for resected stage IB, and consider referral to radiation oncologist for resected stage IIIA.**

**The Role Surgery in Patients with Stage IIIA (N2) NSCLC
(see [NSCL-D 3 of 5](#) through [NSCL-D 5 of 5](#))**

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PRINCIPLES OF SURGICAL THERAPY (3 of 5)

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

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

- The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. (NSCL-1, NSCL-2, and NSCL-6)
- Patients with occult positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal LN dissection.
- The determination of the role of surgery in a patient with N2 positive LNs should be made prior to the initiation of any therapy, by a multidisciplinary team, including a board-certified thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.⁴
- The presence of N2 positive LNs substantially increases the likelihood of positive N3 LNs. Pathological evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS have provided additional techniques for pathologic mediastinal staging that are complementary to mediastinoscopy. Even when these modalities are employed it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral LN involvement prior to a final treatment decision.
- It may be preferable to sample mediastinal lymph nodes by EBUS/EUS prior to initiating therapy, preserving mediastinoscopy and mediastinal lymph node dissection until the planned surgical resection.
- Patients with a single LN smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.^{1,5,6}
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.^{6,7}
- Radiographic methods have poor positive and negative predictive values in the evaluation of the mediastinum after neoadjuvant therapy.⁸ Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (+/- EUS) in the initial pre-treatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.⁹

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PRINCIPLES OF SURGICAL THERAPY (4 of 5)

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

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

A questionnaire was submitted to the NCCN institutions in 2010 regarding their approach to patients with N2 disease. Their responses indicate the patterns of practice when approaching this difficult clinical problem.

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

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PRINCIPLES OF SURGICAL THERAPY (5 of 5)

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

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CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY

Published Chemotherapy Regimens

- Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles*^a
- Cisplatin 100 mg/m² on day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22; every 28 days for 4 cycles*^{b,c}
- Cisplatin 75-80 mg/m² day 1; vinorelbine 25-30 mg/m² days 1 + 8, every 21 days for 4 cycles*
- Cisplatin 100 mg/m² on day 1; etoposide 100 mg/m² days 1-3, every 28 days for 4 cycles^b
- Cisplatin 80 mg/m² on day 1, 22, 43, 64; vinblastine 4 mg/m² days 1, 8, 15, 22 then every 2 wks after day 43, every 21 days for 4 cycles^b

Other Acceptable Cisplatin-based Regimens

- Cisplatin 75 mg/m² on day 1; gemcitabine 1250 mg/m² on days 1, 8 every 21 days*
- Cisplatin 75 mg/m²; docetaxel 75 mg/m² every 21 days*^d
- Pemetrexed 500 mg/m² on day 1; cisplatin 75 mg/m² 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

Paclitaxel 200 mg/m² on day 1, carboplatin AUC 6 on day 1, every 21 days*^e

*These regimens can be used as neoadjuvant chemotherapy. They are to be given for 3 cycles prior to localized therapy. See Discussion for further information and references.

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

ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, Performance status, and 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 (\approx 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.
- 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 an option for patients with performance status 0-1.
- Erlotinib is indicated as a first-line therapy in patients with EGFR mutation.
- Crizotinib is indicated as a first-line therapy in patients that are ALK positive.
- There is superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- There is superior efficacy for cisplatin/gemcitabine in patients with squamous histology, in comparison to cisplatin/pemetrexed.
- Two drug regimens are preferred; a third cytotoxic drug increases response rate but not survival.
- Single agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- In locally advanced NSCLC, concurrent chemotherapy and thoracic irradiation is superior to radiation alone and sequential chemotherapy followed by radiation.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).

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

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

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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:** Bevacizumab and cetuximab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
 - › 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.
 - › Continuation of gemcitabine after 4-6 cycles of platinum-doublet chemotherapy.
- **Switch Maintenance:** Two recent studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4-6 cycles of therapy.
 - › Initiation of pemetrexed after 4-6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma.
 - › Initiation of erlotinib after 4-6 cycles of first-line platinum-doublet chemotherapy.
 - › Initiation of docetaxel after 4-6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
 - › 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 is superior to vinorelbine or ifosfamide.
 - › Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
 - › Erlotinib is superior to best supportive care.

Third-line therapy

- Erlotinib is superior to best supportive care.

Continuation after Disease Progression

- With the exception of erlotinib in patients with EGFR sensitizing mutations who have experienced objective regressions with erlotinib, no agent should be continued after disease progression has been documented. (refer to discussion section)

[See Specific Systemic Agents on page NSCL-F \(3 of 3\)](#)

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

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

- **Cisplatin**¹⁻⁹
- **Carboplatin**^{4,6-11}
- **Paclitaxel**^{1,4,6,8-11}
- **Docetaxel**^{5,7,8,12,13}
- **Vinorelbine**^{7,9,10}
- **Gemcitabine**^{3,5,6,8,9,13}
- **Etoposide**⁴
- **Irinotecan**⁹
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**¹²
- **Pemetrexed**^{14,15}
- **Erlotinib**¹⁶
- **Bevacizumab**¹⁷
- **Cetuximab**¹⁸
- **Albumin-bound paclitaxel**^{19,20 †}
- **Crizotinib**²¹

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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.

CANCER SURVIVORSHIP CARE

NSCLC Long-term Follow-up Care

• Cancer Surveillance

- ▶ History and Physical and a chest CT scan ± contrast every 6-12 months for 2 years, then H&P and a non-contrast-enhanced chest CT scan annually
- ▶ 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 Wellness²

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

Additional Health Monitoring

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

Resources

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

Cancer Screening Recommendations^{2,3}

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

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

¹ACS 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)

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

³American Cancer Society Guidelines for Early Detection of Cancer:

http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 24, 2009)

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

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

**Table 6. Definitions for T, N, M***

T	Primary Tumor	N	Regional Lymph Nodes
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	NX	Regional lymph nodes cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis
Tis	Carcinoma in situ	N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
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	N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
T1a	Tumor ≤ 2 cm in greatest dimension	N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
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	M	Distant Metastasis
	Involves main bronchus, ≥ 2 cm distal to the carina	MX	Distant metastasis cannot be assessed
	Invades visceral pleura	M0	No distant metastasis
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung	M1	Distant metastasis
T2a	Tumor > 3 cm but ≤ 5 cm in greatest dimension	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion ^c
T2b	Tumor > 5 cm but ≤ 7 cm in greatest dimension	M1b	Distant metastasis
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		

^aThe 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.

^bT2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm

^cMost 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.



NCCN Guidelines™ Version 1.2012 Staging Non-Small Cell Lung Cancer

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

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

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

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

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 01/07/11

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Lung cancer is the leading cause of cancer death in the United States. An estimated 222,500 new cases (116,750 in men and 105,770 in women) of lung and bronchial cancer will be diagnosed in 2010, and 157,300 deaths (86,200 in men, 71,100 in women) are estimated to occur due to the disease.¹ Only 15.6% of all lung cancer patients are alive 5 years or more after diagnosis (<http://seer.cancer.gov/statfacts/html/lungb.html>). Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.

The primary risk factor for lung cancer is smoking, which accounts for more than 85%-90% of all lung cancer-related deaths.² The risk of lung cancer increases with the number of cigarettes smoked per day and

with the number of years spent smoking. Exposed nonsmokers also have an increased relative risk of developing lung cancer from “secondhand smoke”.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 U.S. Environmental Protection Agency (EPA) estimates that radon is the main cause of lung cancer in nonsmokers; however, secondhand smoke is also a major factor (<http://www.epa.gov/radon/healthrisks.html>). The decay of radon leads to the production of substances that emit alpha-particles, which may cause cell damage and, therefore, increase the potential for malignant transformation. Data suggest that postmenopausal women who smoke or are former smokers should not receive hormone replacement therapy, because it increases the risk of death from non-small cell lung cancer (NSCLC).⁵

Asbestos, a mineral compound that breaks into small airborne shards, is a known carcinogen that increases the risk of lung cancer in people exposed to airborne fibers, especially in individuals who smoke. It is estimated that about 3% to 4% of lung cancers are caused by asbestos exposure.⁶ In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (i.e., bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds).^{7, 8}

Prevention and Screening

Approximately 85%-90% of cases of lung cancer are caused by voluntary or involuntary secondhand cigarette smoking. Active smoking and secondhand smoke both cause lung cancer (see Reports from the Surgeon General, which are the next 2 links). There is a causal relationship between active smoking and lung cancer and also with other cancers, such as esophageal, oral cavity, laryngeal, pharyngeal,

bladder, pancreatic, gastric, kidney, and cervical cancers as well as other diseases and conditions (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf). Smoking harms nearly every organ in the body. Those who live with someone who smokes have a 20% to 30% increased risk for lung cancer (<http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf>).

Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance. Oncologists should encourage smoking cessation, especially in patients with cancer (<http://www.smokefree.gov/>). Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA [Food and Drug Administration]) can be very useful (see *Treating Tobacco Use and Dependence: 2008 Update*, which is published by the Agency for Healthcare Research and Quality [AHRQ]) (http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf).

Agents that can be used to promote smoking cessation include nicotine replacement (e.g., gum, inhaler, nasal spray, and patch), bupropion, and varenicline. Studies have shown that varenicline is better than bupropion for smoking cessation.^{9, 10} However, almost 30% of patients had nausea while using varenicline.¹¹ The effectiveness of varenicline for preventing relapse has not been clearly established.¹² The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms (<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm>).

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.^{13, 14} Because localized cancer can be managed curatively and because survival in other solid tumors (e.g., breast, cervix, colon, and prostate) appears to be increased by screening and early detection, lung cancer would be an appropriate candidate for a population-based screening approach. Pilot trials of spiral computed tomography (CT) in lung cancer screening are promising with a frequency of stage I detectable lung cancer in more than 80% of newly diagnosed cases.¹⁵⁻¹⁷

The National Lung Screening Trial (NLST, ACRIN Protocol A6654) is a randomized, controlled study involving more than 53,000 current or former heavy smokers; this trial assessed the risks and benefits of low-dose spiral CT scans compared with chest x-rays for detecting lung cancer.¹⁸ A press release from the NLST (November 4, 2010) reported that screening high-risk patients with low-dose spiral CT decreases the mortality rate from lung cancer by 20% when compared with chest x-ray (<http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease>). High-risk patients were either current or former smokers with a 30-pack year smoking history (former smokers had quit 15 years ago), were 55-74 years old, and had no evidence of lung cancer.^{19, 20} However, the complete data from the NLST have not been published yet in a peer-reviewed journal. Additional information on NLST can be found at <http://www.cancer.gov/nlst>.

The International Early Lung Cancer Action Program (I-ELCAP) has been assessing whether annual screening by spiral CT scan increases the detection of early-stage lung cancer in patients at risk for cancer. Data from I-ELCAP showed that stage I lung cancer can be detected using annual low-dose CT screening. The 10-year survival rate was 92% for stage I patients whose cancers were promptly removed;

however, all stage I patients who chose not to be treated died within 5 years.²¹ 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. A recent press release from the NLST suggests that screening decreases the mortality rate.

The NCCN NSCLC panel met in July 2010 to update the guidelines for 2011. At that time, the recent results from the NLST (about lung cancer screening with low-dose CT) were not available. In addition, the complete data regarding screening for lung cancer from the NLST have not been published yet in a peer-reviewed journal. Previously, the NCCN NSCLC panel did not recommend (category 3) the routine use of screening for lung cancer with low-dose CT, although there was major disagreement among panel members and some believe that screening is appropriate. An NCCN panel is currently assessing lung cancer screening.

Previous published data about screening²¹⁻²⁴ are conflicting,^{25, 26} thus, conclusive data from ongoing trials are necessary to define the benefits and risks associated with screening for lung cancer with low-dose CT (see also the NCCN NSCLC algorithm). Patients should discuss the risks and benefits with an expert at a center of excellence before having a screening CT.²⁷ Data show that a CT screening clinic detected a malignant tumor in 3% of patients; many patients (45%) did not complete followup.²⁸

Classification and Prognostic Factors

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

than 85% of all lung cancer cases, and it includes 2 major types: (1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types); and (2) squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring cell type in nonsmokers. Gene expression profiling (using DNA microarrays) has identified subtypes of lung adenocarcinomas (i.e., bronchioid, squamoid, magnoid), which correlate with stage-specific survival and metastatic pattern. Bronchioid tumors were associated with increased survival in early-stage disease, whereas, squamoid tumors were associated with increased survival in advanced disease.²⁹

Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status ([PS] Eastern Cooperative Oncology Group 0, 1, or 2), no significant weight loss (not more than 5%), and female gender.³⁰ Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (*p53*), the activation of proto-oncogene Kirsten-Rous sarcoma virus (*K-ras*), and other biologic markers, may have significant value in predicting a poor prognosis.^{31, 32} Patients with stage I lung adenocarcinoma who have specific genetic abnormalities, such as *k-ras* oncogene activation, have a poor prognosis and disease-free survival.

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the lung cancer, determine the extent of invasion, determine whether it is primary lung cancer or metastatic cancer, establish the cancer involvement status of the surgical margins (i.e., positive or negative margins), and do molecular diagnostic studies to determine whether certain gene

mutations are present (e.g., epidermal growth factor receptor [EGFR] mutations). Data show that targeted therapy is potentially very effective in patients with specific gene mutations (see sections on “EGFR Mutations” and “EML4-ALK Mutations”).³³⁻³⁶ 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 systematically sampled to assess the staging and therapeutic options.

Lobectomy or pneumonectomy specimens are evaluated intraoperatively to determine the surgical resection margin status, diagnose incidental nodules discovered at the time of surgery, or evaluate the regional lymph nodes. Postoperative evaluation provides the pathology characteristics necessary for the classification of tumor type, staging, and prognostic factors. The surgical pathology report should include the histologic classification published by the WHO for carcinomas of the lung.³⁷ Note that the “Principles of Pathologic Review” are listed in the NCCN NSCLC algorithm.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important type of pulmonary adenocarcinoma, because reports suggest that EGFR mutations are common in patients with nonmucinous BAC, which is one of 3 subtypes of BAC.³⁸ EGFR inhibitors, such as gefitinib and erlotinib, are useful for patients with BAC.³⁹⁻⁴¹ However, mucinous BAC typically are negative for EGFR mutations and positive for K-ras mutations.^{42, 43} The different subtypes of BAC and methods for distinguishing the subtypes are described in the NCCN NSCLC algorithm (see “Principles of Pathologic Review”).⁴⁴⁻⁴⁶

Immunohistochemical Staining

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung (e.g., breast and prostate), to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the NCCN NSCLC algorithm (see “Principles of Pathologic Review”). Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma. The stains that are positive for adenocarcinoma, include CEA (carcinoembryonic antigen), B72.3, Ber-EP4, MOC31, and TTF-1; these stains are negative for mesothelioma.⁴⁷ Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40,⁴⁸ and cytokeratin 5/6. A panel of 4 markers can be used to distinguish mesothelioma from adenocarcinoma—2 are positive in mesothelioma and 2 are positive in adenocarcinoma but negative in mesothelioma—including calretinin, cytokeratin 5/6 (or WT1), CEA, and MOC-31 (or B72.3, Ber-EP4, or BG-8).⁴⁹

TTF-1 is a transcription factor that regulates tissue-specific expression of surfactant apoprotein A (SPA), surfactant apoprotein B (SPB), surfactant apoprotein C (SPC), Clara cell antigen, and T1α. TTF-1 is very important in distinguishing primary from metastatic adenocarcinoma, because most primary carcinomas are TTF-1 positive. However, TTF-1 is positive in tumors from patients with thyroid cancer.⁵⁰ In addition, thyroglobulin is present in tumors from patients with thyroid cancer, while it is negative in lung cancer tumors.

Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- whereas metastatic adenocarcinoma of the colorectum is usually CK7- and CK20+. CDX-2 is a marker for metastatic gastrointestinal malignancies that can be used to differentiate them from primary lung

tumors. All typical and atypical carcinoid tumors are positive for chromogranin and synaptophysin, whereas small cell lung carcinoma is negative in 25% of the cases.

Most 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.⁵¹ Recent data suggest that microRNAs (miRNA) expression can be used to distinguish SCLC from NSCLC.⁵²

Staging

The international staging system for lung cancer has been revised and adopted by the American Joint Committee on Cancer (AJCC) and by the Union Internationale Contre le Cancer.⁵³⁻⁵⁶ Recently, the lung cancer staging system was revised by the International Association of the Study of Lung Cancer (IASLC).^{57, 58} This new revised staging is available from the AJCC (7th edition). These NCCN guidelines use the revised AJCC (7th edition) staging.⁵⁹ The revised stage grouping is summarized in Table 6 of the staging tables. The descriptors of the TNM classification scheme are summarized in Table 7 (note that the cells in bold indicate a change from the 6th edition for a particular TNM category).

The TNM staging revisions (AJCC 7th edition) became effective for all new cases diagnosed after January 1, 2010.⁵⁹ With the new staging, locally advanced disease is now stage III; advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging: for example, 1) T2bN0M0 is upstaged from stage IB to

stage IIA; 2) T2aN1M0 is downstaged from stage IIB to stage IIA; 3) T4N0-N1M0 is downstaged from stage IIIB to stage IIIA; and 4) wet IIIB (i.e., malignant pleural effusions) is upstaged to stage IV.⁶⁰ These new changes reflect the prognosis of patients with these different tumors.

Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (i.e., thoracotomy, examination of lymph nodes using mediastinoscopy).⁵³

For 1999-2006, the overall 5-year relative survival rate for lung cancer was 15.8% (from 17 SEER [Surveillance, Epidemiology, and End Results] geographic areas in the United States). Of lung and bronchial cancer cases, 15% were diagnosed while the cancer was still confined to the primary site (localized stage); 22% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 56% were diagnosed after the cancer had already metastasized (distant stage); and for the remaining 8%, the staging information was unknown. The corresponding 5-year relative survival rates were: 52% for localized, 24% for regional, 3.6% for distant, and 8.1% for unstaged (<http://seer.cancer.gov/statfacts/html/lungb.html>). However, these data include small cell lung cancer, which has a poorer prognosis.

Five-year survival after lobectomy for pathologic stage I NSCLC ranges from 45% to 65%, depending on whether the patient has stage 1A or 1B disease and on the location of the tumor.⁶¹ Another study in stage I patients (n=19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; however, for untreated stage I NSNCL, 5-year overall survival was only 6%.⁶² Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Prognostic and Predictive Biomarkers

Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, the evidence is strongest for epidermal growth factor receptor (EGFR), the 5' endonuclease of the nucleotide excision repair complex (ERCC1), the k-ras oncogene, the regulatory subunit of ribonucleotide reductase (RRM1), and the EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]). A *prognostic* biomarker is a biomolecule that is indicative of patient survival independent of the treatment received; that is, the biomolecule is an indicator of the innate tumor aggressiveness. A *predictive* biomarker is a biomolecule that is indicative of therapeutic efficacy; that is, there is an interaction between the biomolecule and therapy on patients' outcome.

The presence of the EGFR exon 19 deletion (LREA) or exon 21 L858R mutation does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.⁶³ However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitors (EGFR-TKI) therapy.^{40, 64} High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.^{65, 66} High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy.^{66, 67} The presence of K-ras mutations is prognostic of poor survival for patients with NSCLC when compared to absence of K-ras mutations, independent of therapy.³¹ K-ras mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.^{40, 68} High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression,

independent of therapy.^{69, 70} High levels of RRM1 expression are also predictive of poor response to gemcitabine-based chemotherapy.^{67, 71, 72}

The EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]) is a new predictive biomarker that has been identified in a small subset of patients with NSCLC (see the section on “EML4-ALK Mutations” and the NCCN NSCLC algorithm).

EGFR Mutations

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

The most commonly found EGFR mutations in patients with NSCLC are deletions in exon 19 (E19del [LREA deletion] in 45% of patients) and a mutation in exon 21 (L858R in 40%). Both mutations result in activation of the tyrosine kinase domain, and both are associated with sensitivity to the small molecule TKIs, erlotinib and gefitinib. These drug-sensitive mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.⁷³ Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).⁷⁴ The T790M mutation is associated with resistance to TKI therapy and has been reported in about 50% of patients with disease progression.⁷⁵⁻⁷⁷

DNA mutational analysis is the preferred method to assess for EGFR status, although fluorescence in situ hybridization ([FISH] to determine

gene copy number) and immunohistochemistry (to determine level of expression) have been used.⁷⁸⁻⁸⁰ Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18-21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.^{73, 79, 81-83} It may be better to assess EGFR mutation status on the primary tumor before therapy and not on the metastasis, although no consensus has been reached.

The prognostic effect of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—is not clear, because most reports are limited to patients receiving active therapy. Tsao and colleagues determined mutations in 177 patients who participated in a randomized trial of second-line gefitinib versus placebo.⁶³ Mutations were found in 40 patients, and 20 had E19del (LREA deletions) or L858R. They did not find a correlation between mutational status and gene copy number or expression by standard immunohistochemistry. In the placebo-treated group, 19 patients had any EGFR mutation, and their overall survival was apparently not different from the 44 patients without mutations. A retrospective study of patients treated with first-line chemotherapy with or without erlotinib found that the median overall survival for all patients with mutations (N=11) was significantly better (>20 months, $P<.001$) than overall survival for patients without mutations (N=45, 10 months).³⁴ It has been reported that in patients with EGFR mutations who receive TKIs, those with E19del (LREA deletion) have increased survival when compared with L858R mutations; those with wild-type EGFR have poorer outcomes.⁸⁴

The predictive effects of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib or gefitinib. The initial retrospective reports suggested that approximately 90% of

patients with a tumor response to these drugs had mutations, whereas unresponsive patients did not have mutations.^{85, 86} Subsequent retrospective studies have demonstrated an objective response rate of approximately 80% with a median progression-free survival of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and an EGFR mutation.⁴⁰ A prospective study has demonstrated that the objective response rate in North American patients with non-squamous cell histology and EGFR mutations (53% E19del [LREA deletion], 26% L858R, 21% other mutations) is 55% with a median progression-free survival of 9.2 months.⁶⁴ In patients treated with first-line chemotherapy with or without erlotinib, EGFR mutations were predictive of a better response in patients receiving erlotinib (53% in patients with mutations versus 18% in those without mutations).³⁴ The response rates in the group of patients receiving only chemotherapy were 21% for those with mutations and 27% for those without mutations.

EML4-ALK Mutations

Estimates are that 2%-7% of patients have EML4-ALK mutations, about 10,000 patients in the United States.³⁶ These patients are resistant to EGFR TKIs but are otherwise similar to those with EGFR mutations (i.e., adenocarcinoma, nonsmokers or light smokers). In these selected populations, estimates are that about 30% of patients will have EML4-ALK mutations.⁸⁷ Mutations for EGFR and EML4-ALK are generally mutually exclusive.⁸⁸ Currently, no standard method is available for detecting EML4-ALK mutations, although a FISH probe set (for ALK-rearranged anaplastic large cell lymphomas) appears to be better than immunohistochemistry tests (see the NCCN NSCLC algorithm).^{89, 90}

PF-02341066 (crizotinib) is an inhibitor of ALK and MET tyrosine kinases.⁹¹ Recently, crizotinib has been shown to yield very high

disease control rates (about 90%) when used in patients with advanced NSCLC who have EML4-ALK mutations and have progressed on previous therapy.³⁶ Crizotinib is orally active with few side effects (5% of patients had elevations in aminotransferases). Patients have responded rapidly to crizotinib. Some patients have developed resistance to crizotinib,⁹² however, other EMLK4-ALK inhibitors are in development.^{93, 94} A randomized phase III trial (PROFILE-1007) is comparing crizotinib with standard second-line chemotherapy.

ERCC1 Level of Expression

ERCC1 is the 5' endonuclease of the nucleotide excision repair complex. It is found in all tumor cells, and its level of expression varies widely. In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, *ERCC1* mRNA levels were prognostic of survival. Patients whose tumors had high levels (N=26, relative *ERCC1* expression above the cohort median of 50) lived significantly longer than patients whose tumors had low levels (N=25, relative expression below 50).⁶⁵ These results were independently confirmed in a similar cohort of patients (N=372) using standard immunohistochemistry. Patients with high tumoral ERCC1 expression had a median overall survival of 55 months compared to 42 months for patients with low ERCC1 expression.⁶⁶

Multiple translational investigations have provided evidence for the predictive use of ERCC1 levels to assess the efficacy of platinum-based chemotherapies in NSCLC; high levels are associated with resistance, while low levels are associated with sensitivity. Olausson and colleagues found that ERCC1 protein expression, as determined by standard immunohistochemistry, was predictive of benefit from adjuvant cisplatin-based therapy in a large group of patients with surgically resected NSCLC who participated in the International Adjuvant Lung Trial (IALT).⁶⁶ In this study, only patients

with low tumoral ERCC1 protein levels benefited from adjuvant chemotherapy (adjusted hazard ratio for death, 0.65; 95% CI, 0.50 to 0.86; $P=.002$). In a community-based randomized phase III clinical trial, Bepler and colleagues reported that in situ ERCC1 protein levels (in tumor specimens collected prospectively) were significantly and inversely correlated with disease response to carboplatin/gemcitabine or gemcitabine alone ($P=.003$, $r=-0.39$); that is, response was better in patients with low levels of ERCC1 expression.^{71, 72}

K-ras Mutations

K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, K-ras is constitutively active, able to transform immortalized cells, and promote cell proliferation and survival. Initially, K-ras was described as mutated in codon 12 in 5/10 adenocarcinomas, 0/15 squamous, and 0/10 large cell carcinomas.⁹⁵ Current data suggest that approximately 25% of adenocarcinomas in a North American population have K-ras mutations.^{34, 40, 68} K-ras mutation prevalence is associated with cigarette smoking.⁹⁶

K-ras mutational status is prognostic of survival. Patients with K-ras mutations have a shorter survival than patients with wild-type K-ras. Slebos and colleagues determined K-ras codon 12 mutations in 69 patients with completely resected adenocarcinomas who did not receive additional therapy.³¹ They found that disease-free and overall survival were significantly ($P=.038$ and $P=.002$, respectively) shorter in the 19 patients with mutations compared to the 50 patients without mutations. These data were independently confirmed in a cohort of 66 patients (11 with K-ras codon 12 mutations; $P=.03$ for overall survival difference) by Mitsudomi and colleagues.⁹⁷ However, Tsao and colleagues did not find a significant difference ($P=.40$) in survival by ras mutational status on the observation arm of the Canadian adjuvant chemotherapy trial (JBR10).⁶⁸ In this report, the authors investigated

codons 12, 13, and 61 of all 3 ras genes and categorized patients as ras mutated if any mutation was detected.

K-ras mutational status is also predictive of therapeutic efficacy from EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy. In a retrospective study of 101 patients with a bronchioloalveolar variant of adenocarcinoma, K-ras codon 12 and 13 mutations were found in 23% (18/80) of patients.⁴⁰ All patients had been treated with first-line single-agent erlotinib. None of the patients with K-ras mutations responded (0/18), while 20 without K-ras mutations responded (20/62, 32%). This difference was statistically significant ($P<.01$). In patients treated with first-line chemotherapy plus erlotinib or chemotherapy plus placebo (the TRIBUTE trial), K-ras codon 12 and 13 mutations were present in 51/264 and 4/264 patients respectively.³⁴ Patients with K-ras mutations had a response rate of 8% in the chemotherapy plus erlotinib arm (2/25) and 23% in the chemotherapy only arm (7/30). Patients without K-ras mutations had a response rate of 26% in the chemotherapy plus erlotinib arm (27/104) and 26% in the chemotherapy only arm (27/103). In this report, time-to-progression and overall survival were also shortest in the group of patients with K-ras mutations receiving chemotherapy plus erlotinib, which suggests that the addition of erlotinib to chemotherapy in patients with K-ras mutations may adversely interfere with chemotherapeutic efficacy.

Tsao and colleagues identified 88 patients with and 333 without any ras mutation (codons 12, 13, and 61 of K-ras, N-ras, H-ras) in the Canadian adjuvant chemotherapy trial (JBR10).⁶⁸ They found that patients with ras mutations did not derive benefit from adjuvant cisplatin/vinorelbine (hazard ratio of death for chemotherapy versus observation 0.95, CI, 0.53-1.71; $P=.87$), while those without ras mutations (N=333) benefited significantly (hazard ratio of death for chemotherapy versus observation

0.69, CI, 0.49-0.97; $P=.03$) from adjuvant therapy. However, when taking both the treatment arm and the ras mutational status into account (i.e., when testing for interaction), the P -value did not reach statistical significance ($P=.29$).

RRM1 Level of Expression

RRM1 is the gene that encodes the regulatory subunit of ribonucleotide reductase, and it is crucial for production of deoxynucleotides from nucleotides.^{98, 99} *RRM1* is found in all tumor cells, and its level of expression varies widely over a continuous range.

In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, *RRM1* mRNA levels were prognostic of survival. Patients whose tumors had high levels (N=39, relative *RRM1* expression above the cohort median of 12.2) lived significantly longer than patients whose tumors had low levels (N=38, relative expression below 12.2).⁶⁹ These results were independently confirmed in a cohort of 187 patients with stage I disease. Patients with high tumoral *RRM1* expression had a median overall survival of greater than 120 months compared to 60.2 months for patients with low *RRM1* expression.⁷⁰

In a community-based randomized phase III clinical trial, Bepler and colleagues reported that in situ *RRM1* protein levels (in tumor specimens collected prospectively) were significantly and inversely correlated with disease response to gemcitabine or carboplatin/gemcitabine ($P=.001$, $r=-0.41$); that is, response was better in patients with low levels of *RRM1* expression.^{71, 72}

Treatment Approaches

Surgery, radiation therapy (RT), and chemotherapy are the 3 modalities commonly used to treat patients with NSCLC. They can be used either

alone or in combination depending on the disease status. In the following sections, the clinical trials are described that have led to the standard treatments.

Surgery

In general, for patients with stage I or stage II disease, surgery provides the best chance for cure. However, thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated.

The “Principles of Surgical Therapy” are described in the NCCN NSCLC algorithm and are summarized here. Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who should participate in multidisciplinary clinics and/or Tumor Boards for lung cancer patients. Patients with pathologic stage II or greater disease should be referred to medical oncology for evaluation. For patients with stage IB, consider referral to medical oncologist. For stage IIIA, consider referral to radiation oncologist. If stereotactic body RT (SBRT) is considered for high-risk patients, a multidisciplinary evaluation is recommended (including a radiation oncologist). Treatment delays, because of poor coordination among specialists, should be avoided.

The surgical procedure used depends on the extent of disease and on the cardiopulmonary reserve of the patient. Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and if margin-negative resection can be achieved; otherwise, lobectomy or pneumonectomy should be done if physiologically feasible.^{100, 101} Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select

patients; the parenchymal resection margins are defined in the NCCN NSCLC algorithm (see “Principles of Surgical Therapy”).^{102, 103}

Resection (including wedge resection) is preferred over ablation.¹⁰¹ However, 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.^{101, 104, 105} SBRT may be more appropriate for these patients.¹⁰⁶

Lymph Node Dissection

The American College of Surgeons Oncology Group randomized trial (ACOSOG Z0030) compared mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with N0 (no demonstrable metastasis to regional lymph nodes) or N1 (metastasis to lymph nodes in the ipsilateral peribronchial and/or hilar region, including direct extension) NSCLC disease. This study is evaluating whether complete mediastinal lymph node dissection results in better overall survival when compared to mediastinal lymph node sampling in the patient undergoing resection for N0 or non-hilar N1 NSCLC. Initial results indicate that morbidity is not increased with complete lymphadenectomy.^{107, 108} Recent data from this study indicate that systematic lymph node sampling is appropriate during pulmonary resection; one or more nodes should be sampled from all mediastinal stations. For right-sided cancers, an adequate mediastinal lymphadenectomy should include stations 2R, 4R, 7, 8, and 9. For left-sided cancers, stations 4L, 5, 6, 7, 8, and 9 should be sampled.¹⁰⁹ Data on survival are not available yet.

Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection. Note that the IASCL (International Association for the Study of Lung Cancer) has proposed



a new lymph node map.¹¹⁰ Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because it would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients (see the NCCN NSCLC algorithm): 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features (category 2B for low-risk features). Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins either 1) 2 cm or more, or 2) the size of the nodule or more.

Stage IIIA N2 Disease

The role of surgery in patients with pathologically documented stage IIIA (N2) disease is discussed in the NCCN NSCLC algorithm (see the “Principles of Surgical Therapy”) and is summarized here; note that this is a new section for the NCCN NSCLC guidelines. Before treatment, it is essential to carefully evaluate for N2 disease using radiologic and invasive staging (i.e., endobronchial ultrasound-guided procedures, mediastinoscopy, thorascopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team (which should include a board-certified thoracic surgeon).¹¹¹ Randomized controlled trials suggest that surgery does not increase survival in these patients.^{112, 113} However, one of these trials (EORTC) only enrolled unresectable patients.¹¹³

Most clinicians agree that resection is appropriate for patients with a negative preoperative mediastinum and with a single positive node (< 3 cm) found at thoracotomy.¹¹⁴ Neoadjuvant therapy is recommended for

select patients. In N2 patients, 50% of the NCCN institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.¹¹⁵ Clinicians also agree that resection is not appropriate for patients with multiple pathologically proven malignant lymph nodes greater than 3 cm; definitive chemoradiotherapy is recommended for these patients.

The NCCN panel believes that surgery may be appropriate for select patients with N2 disease, especially those who respond to induction chemotherapy (see the NCCN NSCLC algorithm).¹¹⁶ However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.^{112, 116-121} Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.^{116, 122}

Thorascopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also referred to as thorascopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.^{123, 124}

Published studies suggest that thorascopic lobectomy has several advantages over the standard thoracotomy (or pleurotomy).¹²⁵⁻¹²⁹ Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires shorter length of hospitalization.¹³⁰

Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.¹³¹⁻¹³⁵ Recent analyses show that thorascopic lobectomy is associated with less morbidity than lobectomy by thoracotomy.^{136, 137}

In stage I NSCLC patients who had thorascopic lobectomy 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.¹³⁸⁻¹⁴⁰ Thorascopic lobectomy has also been shown to improve discharge independence in older populations and in high-risk patients as well.^{141, 142} Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.^{143, 144} Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy is included in the NCCN NSCLC algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as standard principles of thoracic surgery are not compromised (see “Principles of Surgical Therapy”).

Radiation Therapy

General Principles

Radiation therapy can be used as 1) adjuvant therapy for patients with resectable NSCLC who have no contraindications for surgery; 2) the primary local treatment (i.e., definitive RT for patients with medically inoperable or unresectable NSCLC; and/or 3) palliative therapy for patients with incurable NSCLC. Treatment recommendations should be made by a multidisciplinary team. The NCCN NSCLC algorithm contains a “Principles of RT” section, which includes the following: 1) general principles; 2) dose, volume and normal tissue constraints for conventionally fractionated RT; 3) radiation simulation, planning and delivery; 4) SBRT; and 5) prophylactic cranial irradiation (PCI).¹⁴⁵⁻¹⁵⁰ These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery for brain metastases are also discussed in this section. The terminology and abbreviations for RT are described in the NCCN NSCLC algorithm (see Table 1).

For stage IV patients with extensive metastases, palliative RT can be used for primary or distant sites. Definitive chemoradiation is recommended for patients with stage II-III disease who are medically inoperable. For patients with pN2 and positive or negative resection

margins, the RT recommendations are described in “Principles of RT” section in the NCCN NSCLC algorithm (see “General Principles”). To avoid postoperative pulmonary toxicity, preoperative chemoradiotherapy should be avoided if at all possible, if pneumonectomy is required.^{151, 152} Surgery in a field that has had 60 Gy is difficult, because the landmarks disappear with high doses of radiation. Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 Gy, especially patients who have received RT doses of more than 60 Gy (i.e., patients who have received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. Radiation therapy should continue to definitive dose without interruption if the patient is not a surgical candidate.

Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated RT

The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in “Principles of RT” section in the NCCN NSCLC algorithm (see “Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy” and see also Table 2).^{146, 148, 153-156} After surgery, lung tolerance to RT is much less than for patients with intact lungs. Thus, every effort should be made to minimize the [postoperative] dose of RT. Although the dose volume constraints for normal lungs are a useful guide (see Table 3), more conservative constraints should be used for postoperative RT. For definitive RT, the commonly prescribed dose is 60-70 Gy.¹⁵⁷ The use of higher RT doses is discussed in “Principles of RT” section in the NCCN NSCLC algorithm (see “Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy”).¹⁵⁸⁻¹⁶³ The role of high-dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).^{163, 164}

For treatment volume consideration, planning target volume (PTV) should be defined using the ICRU-62 (International Commission on Radiation Units and Measurements Report 62) guidelines, based on gross tumor volume (GTV), plus clinical target volume (CTV) margins for microscopic diseases, internal target volume (ITV) margins for target motion, and margins for daily set-up errors.¹⁶⁵ Additional volume considerations are described in the NCCN NSCLC algorithm.^{157,158,166-171}

It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the spinal cord, lungs, heart, esophagus, and brachial plexus to minimize normal tissue toxicity (see Table 3).¹⁷² These limits are mainly empirical.¹⁷³⁻¹⁸⁰ For patients receiving postoperative RT, more strict DVH parameters should be considered for lung. The exact limit is unknown for lobectomy cases; the mean lung dose should be limited to 8.5 Gy or less in pneumonectomy patients.¹⁸¹⁻¹⁸³

Radiation Simulation, Planning, and Delivery

Treatment planning should be based on CT scans obtained in the treatment position. IV contrast CT scans are recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal diseases. PET/CT is recommended for select patients (i.e., those with significant atelectasis, when IV contrast is contraindicated). PET-CT can significantly improve the target accuracy.¹⁸⁴ In the “Principles of RT” section of the NCCN NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or intensity modulated radiotherapy (IMRT) (see “Radiation Simulation, Planning and Delivery”).¹⁸⁵⁻¹⁹⁰

Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the AAPM Task Group 76 guideline, are described in the “Principles of RT” section of the NCCN NSCLC algorithm (see “Radiation Simulation, Planning and Delivery”).¹⁹¹

Stereotactic Body Radiation Therapy (SBRT)

SBRT, which is also known as stereotactic ablative radiotherapy (SABR), uses short courses of very high dose RT that are precisely delivered to the target.¹⁹² Studies have shown that SBRT is very useful for patients with inoperable stage I NSCLC.¹⁹³ With conventional treatment, 3-year survival is only about 20%-35% in these patients.¹⁹⁴ There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SBRT.¹⁹⁵ In patients with stage I NSCLC, SBRT provides a significantly longer 5-year survival than 3-D conformal RT.¹⁹⁰ SBRT yields median survival of 32 months and 3-year overall survival of about 43% in patients with stage I disease; patients with T1 tumors survive longer than those with T2 tumors (39 versus 25 months).¹⁹⁶

SBRT can also be used for patients with limited lung metastases and for palliative therapy.^{197,198} A recent study suggests that SBRT increases survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment.¹⁹⁹ SBRT is discussed in the “Principles of RT” section of the NCCN NSCLC algorithm; fractionation regimens and normal tissue constraints are also provided (see Tables 4 and 5; Figure 1; “Stereotactic Body Radiation Therapy”).^{193,196,200-205} Decisions about whether to recommend SBRT should be based on multidisciplinary discussion.

Radiofrequency Ablation

Studies suggest that radiofrequency ablation (RFA) may be an option for node-negative patients who either refuse surgery or cannot tolerate surgery because of poor PS, significant cardiovascular risk, poor pulmonary function, and/or comorbidities. Optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm; RFA can be used for previously irradiated tissue and for palliation.²⁰⁶ A study with RFA in 33 patients with NSCLC yielded overall survival of 70% (95% CI, 51%–83%) at 1 year and 48% (30%–65%) at 2 years. A 2-year overall survival of 75% (45%–92%) was reported in patients with stage I NSCLC (n=13) who received RFA.²⁰⁷ The procedure specific 30-day mortality rate is reported to be 2.6%.²⁰⁸

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.²⁰⁹ Surgery followed by whole brain RT is recommended (category 1) for select patients (those with good PS) with a single brain metastasis (see the NCCN NSCLC algorithm).^{210–213} Stereotactic radiosurgery (SRS) is another option after surgical resection, although there are only a few retrospective case series supporting this option.²¹⁰ Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with or without whole brain RT.^{209, 214, 215} Note that recent data suggest that erlotinib may be useful to manage brain metastases.^{216, 217}

Decisions about whether to recommend surgery, whole brain RT, SRS, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.^{210, 218} Treatment should be individualized for patients with recurrent or progressive brain lesions.²¹⁹

There have been concerns that whole brain RT adversely affects neurocognition. However, a study in 208 patients with brain metastases found that patients who responded (with tumor shrinkage) after whole brain radiation had improved neurocognitive function and that tumor progression affects neurocognition more than whole brain radiation.²²⁰ In 132 patients with 1–4 brain metastases who received SRS with or without whole brain RT, survival was similar in both groups.²¹⁵ In a subset of 92 of these patients who received SRS with or without whole brain RT, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function.²²¹ However, a study in 58 patients found that patients who received SRS plus whole brain radiation had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SRS alone.²²² Some have suggested that using resection with SRS (instead of resection with WBRT) will decrease neurocognitive problems.²²³

Prophylactic Cranial Irradiation

Prophylactic cranial irradiation (PCI) does not appear to improve survival in patients with NSCLC. Although it closed early because of poor accrual, a randomized phase III trial (RTOG 0214) of PCI for patients with stage III NSCLC showed that the incidence of brain metastases was decreased in patients who received PCI (18% versus 7.7%); however, overall survival was not improved.²²⁴ Impaired memory (immediate and delayed recall) was reported in these patients receiving PCI.²²⁵

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease who are medically fit and can tolerate surgery. In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.^{226–228} Currently, concurrent chemoradiation

appears superior to sequential therapy for patients with unresectable stage III disease.²²⁹⁻²³¹

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.²³²⁻²³⁵ Of interest, recent data show that early palliative care combined with standard care improves quality of life, mood, and survival in patients with metastatic NSCLC, even though these patients had less aggressive therapy when compared with those receiving standard care alone.²³⁶ Surgery is rarely done for patients with stage IV disease. However, surgical resection of a solitary brain metastasis may improve survival in selected patients with stage IV disease and is recommended in the NCCN NSCLC algorithm (see also the NCCN CNS guidelines).²³⁷ Surgical resection of a solitary metastasis located in sites other than the brain remains controversial. The trials supporting the recommendations for combined modality therapy are discussed in this section.

Surgery Followed by Chemotherapy: Trial Data

In the NCCN guidelines for stage IA disease, adjuvant chemotherapy is not recommended based on the following trials. Adjuvant chemotherapy is only recommended for high-risk margin-negative stage IB disease (see the NCCN NSCLC algorithm). Recommended chemotherapy regimens for adjuvant therapy are provided in the NCCN NSCLC algorithm (see “Chemotherapy Regimens for Adjuvant Therapy”).

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.²²⁶ The study included 1867 patients with surgically resected lung cancer who were randomly assigned either to cisplatin-based adjuvant chemotherapy or to observation, with a median follow-up duration of 56 months. A significantly higher survival rate (44.5% versus 40.4% at 5

years; hazard ratio for death, 0.86; 95% confidence interval [CI], 0.76 to 0.98; $P<.03$) and disease-free survival rate (39.4% versus 34.3% at 5 years; hazard ratio, 0.83; 95% CI, 0.74 to 0.94; $P<.003$) were observed for patients assigned to chemotherapy when compared with observation. IALT data suggest that cisplatin-based adjuvant chemotherapy improves survival 5 years after treatment in patients with completely resected NSCLC. However, after 7.5 years of followup, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.²³⁸ But, data show that adjuvant chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA (Adjuvant Navelbine International Trialist Association) trial compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in early-stage NSCLC. In the JBR.10 trial, 482 patients (ECOG PS of 0-1) with completely resected stage IB (T2, N0) or stage II (T1, N1, or T2, N1) NSCLC were randomly assigned either to vinorelbine plus cisplatin (242 patients) or to observation (240 patients).²²⁷ The median age was 61 years in both groups. Chemotherapy was not excessively toxic. Adjuvant chemotherapy significantly prolonged overall survival (94 versus 73 months, hazard ratio for death, 0.69, $P=.04$) and relapse-free survival (not reached versus 46.7 months, hazard ratio for recurrence, 0.60; $P<.001$) when compared with observation alone. The 5-year survival rates were 69% and 54%, respectively ($P=.03$).

However, recent updated data from JBR.10 after 9 years of followup show that when compared with observation alone, adjuvant chemotherapy is beneficial for stage II but not for stage IB patients.²³⁹ In stage II patients receiving adjuvant chemotherapy, median survival is 6.8 versus 3.6 years in those who were only observed. Of note, patients receiving chemotherapy did not have an increased death rate. In the

2010 NCCN update, some chemotherapy options for early-stage disease were deleted.

In the ANITA trial, 840 patients (median age, 59 years) with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned either to adjuvant vinorelbine plus cisplatin or to observation.²²⁸ 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.²²⁸ Adjuvant chemotherapy significantly improved the 5-year overall survival in patients with completely resected stage II and IIIA disease, although no benefit was observed in stage I. Some clinicians consider vinorelbine/cisplatin to be the preferred regimen for completely resected early-stage NSCLC based on the number of trials and the amount of use.

A meta-analysis in 4,584 patients (the Lung Adjuvant Cisplatin Evaluation) found that postoperative cisplatin-based chemotherapy increased survival over 5 years (absolute benefit of 5.4%); there was no difference among the chemotherapy regimens (vinorelbine, etoposide, others).²⁴⁰ The benefit was greater in patients with stage II and III disease and good PS.

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;²⁴¹ updated results have been reported.^{242, 243} In this trial, 344 patients (34-81 years) were randomly assigned either to paclitaxel and carboplatin or to observation within 4-8 weeks of resection with a median follow-up duration of 54 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 4 years was not significantly different, although 3-year survival was significant (79% versus 70%, $P=.045$).^{242, 243} The original results from CALGB suggested

that the paclitaxel and carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors greater than 4 cm). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin (see the NCCN NSCLC algorithm).²⁴⁴

Chemoradiation: Trial Data

The major controversies in NSCLC relate to the management of patients with stage IIIA disease (see “the Role of Surgery in Patients with Stage IIIA (N2) NSCLC” in the “Principles of Surgery” section in the NCCN NSCLC algorithm). 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.²⁴⁵⁻²⁴⁹ For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.^{245, 246, 248, 249} However, concurrent chemoradiation appears to be superior to sequential therapy.²²⁹⁻²³¹ Concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. 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 “Chemotherapy Regimens Used with Radiation Therapy” in the NCCN NSCLC algorithm).^{230,250,251} Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.²⁵²

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.²⁵³ Results

from SWOG 9504 have shown a median survival of 26 months and a 5-year survival rate of 29%.²⁵⁴ However, results from a phase III trial in patients with unresectable stage III NSCLC assessing consolidation docetaxel after cisplatin/etoposide with concurrent chemoradiation did not show improved survival with docetaxel and did show increased toxicity.^{255, 256} A randomized controlled trial in 203 unresectable patients with either stage IIIA or IIIB NSCLC assessed induction chemotherapy followed by either radiotherapy alone or chemoradiation using paclitaxel; median survival was 14.1 months versus 18.7 months ($P=.091$), respectively.²⁵⁷

Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS, benefit from chemotherapy, usually with a platinum-based regimen.²³²⁻²³⁴ Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, etoposide, pemetrexed, the camptothecin analogs (irinotecan), and gemcitabine (see the NCCN NSCLC algorithm). Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, cisplatin/pemetrexed, and docetaxel/cisplatin.^{244, 258-261} Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.^{262, 263} The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;^{258, 264-266} gemcitabine/docetaxel is another option.²⁶⁷ In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor.

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel for patients 1) who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or 2) in whom the standard premedications (i.e., dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.^{268, 269}

Targeted Therapies

Specific targeted therapies have been developed for the treatment of advanced lung cancer.^{270, 271} Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor of EGFR. Cetuximab is a monoclonal antibody that targets EGFR.

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. The Eastern Cooperative Oncology Group (ECOG) recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase II-III clinical trials (ECOG 4599).²⁷² To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC and no history of hemoptysis. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab. For patients with nonsquamous NSCLC and PS 0-1 who are EGFR mutation negative or unknown, bevacizumab in combination with chemotherapy is one of the recommended options (see the NCCN NSCLC algorithm).

Erlotinib was approved by the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib is also recommended



as first-line therapy in patients with advanced, recurrent, or metastatic nonsquamous NSCLC who have known active EGFR mutation or gene amplification regardless of their PS (see the NCCN NSCLC algorithm).^{34, 273-275} This recommendation is based on the results of a phase III randomized trial (Iressa Pan-Asia study [IPASS]) in which patients with EGFR mutations who received gefitinib had increased progression-free survival (25% versus 7%), response rate (71%), and quality of life and fewer side effects (e.g., neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).²⁷⁴

An analysis of 5 clinical trials in mainly Western patients (n = 223) with advanced NSCLC (stage IIIB or IV) found that patients with EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.⁸⁴ The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced nonsquamous NSCLC.²⁷⁶ Survival was increased in patients with wild type EGFR who received first-line chemotherapy compared with those who receive erlotinib first followed by second-line chemotherapy (10.8 versus 7.7 months). Erlotinib is an orally active agent that is very well tolerated by most patients.

A large phase III randomized trial (FLEX) assessed cisplatin/vinorelbine with or without cetuximab for patients with advanced NSCLC (most patients had stage IV disease).²⁷⁷ Adding cetuximab slightly increased overall survival (11.3 versus 10.1 months, $P = .04$).

Cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC, regardless of histology (see the NCCN NSCLC algorithm). However, because the benefits are very slight, the cetuximab/cisplatin/vinorelbine regimen has a category 2B recommendation in the NCCN guidelines.

Maintenance Therapy

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

For continuation maintenance therapy, targeted agents (which were initially given in combination with conventional chemotherapy) should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. Bevacizumab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., platinum-doublet chemotherapy given with bevacizumab) in patients with nonsquamous histology.^{272, 278} Cetuximab (category 1) may be continued beyond 4-6 cycles of initial therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown) or those with squamous histology (i.e., cisplatin, vinorelbine, and cetuximab therapy).²⁷⁷ Pemetrexed (category 2B) may also be given as continuation maintenance therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown).²⁷⁸ There are no randomized trials supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.²⁷⁹

A recent phase III randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Data show that continuation maintenance therapy with gemcitabine increased PFS to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).²⁸⁰ However, currently,

there is no evidence that continuation maintenance therapy improves overall survival or quality of life.^{279, 281, 282}

For switch maintenance therapy, 2 recent studies have shown a benefit in progression-free survival and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4-6 cycles) in patients without disease progression.^{283, 284} Pemetrexed may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy, in patients with histologies other than squamous cell carcinoma who are EGFR mutation negative (or with unknown mutation status).²⁸⁴ The FDA has approved maintenance therapy with pemetrexed (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021462s021lbl.pdf). Likewise, erlotinib (category 2B) or docetaxel (category 3) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy in this same patient population.²⁸³

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients with advanced NSCLC.²⁸⁵ The data showed that erlotinib alone was associated with fewer side effects in patients with EGFR mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to switch to maintenance therapy with erlotinib in patients found to have EGFR mutations during chemotherapy (see the NCCN NSCLC algorithm). The FDA has approved maintenance therapy with erlotinib (http://www.osip.com/pdf/Tarceva_PI_042010.pdf).

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC (see the NCCN NSCLC algorithm). The clinical stage is initially determined from disease history (i.e., cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests (see the NCCN NSCLC

algorithm). The panel also recommends that smoking cessation counseling be made available to patients (<http://www.smokefree.gov/expert.aspx>). Based on the initial evaluation, the clinical stage is determined and the patient is assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. Although PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (i.e., the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease), CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.²⁸⁶⁻²⁸⁸

Mediastinoscopy is the gold standard for evaluating mediastinal nodes. Thus, mediastinoscopy is encouraged as part of the initial evaluation, particularly if the results of imaging are not conclusive and the probability of mediastinal involvement is high (based on tumor size and location). Therefore, mediastinoscopy is appropriate for patients with T2-T3 lesions even if the PET/CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive PET/CT scan. In contrast, because of the low prior probability of lymph node involvement in patients with peripheral T1ab, N0 lesions,²⁸⁹ some NCCN institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2a, central T1ab, or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy is recommended (see the NCCN NSCLC algorithm).

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.²⁹⁰ 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.²⁹¹

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

Other Imaging Studies

As previously mentioned, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer.²⁸⁶ PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN guideline panel reviewed the diagnostic performance of CT and PET scans. Panel members assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.²⁹² Depending on the

clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported. Seely and coworkers reported on the number of metastatic lymph nodes discovered on routine mediastinoscopy and chest CT scan in patients with the most favorable tumors (i.e., T1 cancer).²⁹³ 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.²⁹⁴ 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%.²⁹⁵ Kernstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.^{296, 297} The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% versus 65%). PET/CT has been shown to be useful in restaging patients after adjuvant therapy.^{298, 299}

The NCCN panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, for example, in identifying stage I (peripheral and central T1-2, N0), stage II, stage III, and stage IV diseases.^{300, 301} However, PET/CT is even more sensitive and is now recommended by NCCN.³⁰²⁻³⁰⁴ When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.³⁰² However, positive PET/CT scans findings need pathologic or other radiologic confirmation (e.g., MRI of bone). If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Precisely how PET/CT scans will fit into

the overall staging and surveillance of NSCLC will become clearer as newer studies mature.

Transesophageal endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound–guided transbronchial needle aspiration (EBUS-TBNA) have proven useful to stage patients or to diagnose mediastinal lesions; these techniques can be used instead of invasive staging procedures in select patients.³⁰⁵ 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.³⁰⁶ In patients with positive nodes on CT or PET, EBUS-TBNA can be used to clarify the results.^{307, 308} However, in patients with negative findings on EBUS-TBNA, conventional mediastinoscopy can be done to confirm the results.^{308, 309}

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, III, and IV disease to rule out metastatic disease if aggressive combined-modality therapy is being considered.³¹⁰

Initial Therapy

It is strongly recommended that determination of tumor resectability be made by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice (see “Principles of Surgical Therapy” in the NCCN NSCLC algorithm).

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

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2, N1) tumors are generally candidates for surgical resection and mediastinal node mapping. In some instances, positive mediastinal nodes (N2) are discovered at

surgery; in this setting, an additional assessment of staging and tumor resectability must be made, and the treatment (i.e., inclusion of mediastinal lymph node dissection) must be modified accordingly. Therefore, the NCCN NSCLC algorithm includes 2 different tracks for T1–3, N2 disease: 1) T1–3, N2 disease discovered unexpectedly at surgical exploration; and 2) T1–3, N2 disease confirmed before thoracotomy. In the second case, an initial brain MRI and PET/CT scan (if not previously done) are recommended to rule out metastatic disease.

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

For patients with clinical stage IIB (T3, N0) and stage IIIA tumors who have different treatment options (surgery, RT, or chemotherapy), a multidisciplinary evaluation should be performed. For the subsets of stage IIB (T3, N0) and stage IIIA (T3-4, N1) tumors, treatment options are organized according to the location of the tumor (i.e., the superior sulcus, chest wall, and proximal airway or mediastinum). For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see “Principles of Surgical Therapy” in the NCCN NSCLC algorithm).

For patients with resectable tumors (T3 invasion, N0-1) in the superior sulcus, the panel suggests concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see the NCCN NSCLC algorithm). Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.^{153, 155, 311-314} The overall 5-year survival rate is approximately 40%.¹⁵³ Patients with marginally resectable superior sulcus tumors should undergo concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T4 extension, N0-1) in the superior sulcus, definitive RT with chemotherapy (i.e., definitive concurrent chemoradiation) is

recommended followed by chemotherapy if full-dose chemotherapy was not given initially.^{251, 253} Note that “Principles of RT” is in the NCCN NSCLC algorithm. In addition, the NCCN NSCLC algorithm also provides recommendations for chemotherapy (see “Chemotherapy Regimens for Adjuvant Therapy,” “Chemotherapy Regimens Used with Radiation Therapy,” and “Systemic Therapy for Advanced or Metastatic Disease”).

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

For patients with stage IIIA disease and positive mediastinal nodes (T1-3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (see the NCCN NSCLC algorithm). Patients with negative mediastinal biopsy findings are candidates for surgery, with additional assessment of resectability at the time of thoracotomy. For those patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the surgery. Those individuals found to have unresectable lesions should be treated according to pathologic stage (see the NCCN NSCLC algorithm). For patients with (T1-2 or T3) node-positive disease, an additional brain MRI and PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see the NCCN NSCLC algorithm).²²⁹ Induction chemotherapy with (or without) RT is another option for patients with T1-3, N2 disease.¹¹³ Recommended therapy for metastatic disease is described in the NCCN NSCLC algorithm.

When a lung metastasis is present, it usually occurs in patients with other systemic metastases; the prognosis is poor; therefore, many of these patients are not candidates for surgery. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery.³¹⁵ Patients with separate pulmonary nodule(s) in the same lobe or ipsilateral lung without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.³¹⁶ Intrapulmonary metastases have been downstaged in the recent TNM revised staging (i.e., AJCC 7th edition).^{60, 316, 317} After surgery, concurrent chemoradiation (if tolerated) is recommended for those with positive margins and chemotherapy is recommended for those with negative margins (see the NCCN NSCLC algorithm).

For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy (category 3) (see the NCCN NSCLC algorithm).²⁵⁴⁻²⁵⁶ In patients with synchronous nodules (contralateral lung), the guidelines suggest treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the NCCN NSCLC algorithm).

Stage IIIB tumors comprise 2 groups including 1) tumors with contralateral mediastinal nodes (T1-3, N3); and 2) tumors with T4 extension and N2-3 disease, which are unresectable. Surgical resection is not recommended in patients with T1-3, N3 disease. However, in patients with suspected N3 disease, the guidelines recommend pathologic confirmation of nodal status (see the NCCN NSCLC algorithm).^{318, 319} In addition, PET/CT scans and brain MRI should also be included in the pretreatment evaluation. If these tests are negative, then treatment options for the appropriate nodal status should be followed (see the NCCN NSCLC algorithm). If N3 disease is confirmed,

concurrent chemoradiation (category 1) is recommended followed by chemotherapy if full-dose chemotherapy was not given initially.^{251, 254, 256} For metastatic disease that is confirmed by PET/CT scan and brain MRI, treatment is described in the NCCN NSCLC algorithm.

For patients with T4 extension, N2-3 disease (stage IIIB), surgical resection is not generally recommended. The initial work-up includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0-1) disease (see the NCCN NSCLC algorithm). If either the contralateral or ipsilateral mediastinal node is positive, concurrent chemoradiation therapy is recommended (category 1) followed by chemotherapy if full-dose chemotherapy was not given initially (see the NCCN NSCLC algorithm).^{251, 254-256}

Stage IV Disease

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised AJCC staging (7th edition), T4 with effusion has been reclassified as stage IV, M1a (see Table 7).⁶⁰ Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (e.g., obstructive pneumonia), an exudate or sanguinous effusion is considered malignant no matter what the results of cytologic examination. If the pleural effusion is considered negative, the NCCN NSCLC algorithm tracks back to the confirmed T and N stage (see the NCCN NSCLC algorithm). However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.³²⁰ In patients with effusions that are positive

for malignancy, the tumor is treated as M1a with local therapy (i.e., ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see the NCCN NSCLC algorithm).

The NCCN NSCLC algorithm for patients with distant metastases (i.e., stage IV, M1b) depends on the location of the metastases—a solitary nodule in the brain or adrenal—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, PET/CT scan, and brain MRI. The increased sensitivity of PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. However, positive PET/CT scan findings need pathologic or other radiologic confirmation. If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.

Patients with solitary brain metastases may benefit from surgical resection (see NCCN NSCLC algorithm).²⁰⁹ The 5-year survival rates with such an approach range from 10% to 20%;^{270, 321} median survival is about 40 weeks.²¹³ Follow-up whole brain RT (category 1) or SRS may be used.^{220, 322} SRS alone or followed by whole brain radiation are additional treatment options.²¹⁵ Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.³²³ After their brain lesions are treated, further treatment options for these patients with T1-2, N0-1 NSCLC or for those with T3, N0 then include 1) surgical resection of the lung lesion followed by chemotherapy (category 2B for chemotherapy); 2) SBRT (category 2B); or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B). Systemic therapy is an option after surgery for patients with higher stage NSCLC.



Adrenal metastases from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. If an adrenal metastasis is found and if the lung lesion is curable, the resection of the adrenal lesion has produced some long-term survivors (category 2B) (see the NCCN NSCLC algorithm).^{324, 325} Some panel members feel that resection of adrenal metastases only makes sense if the synchronous lung disease is stage I or maybe stage II (i.e., resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Treatment options for patients with stage IA (T1ab, N0 disease) and with positive surgical margins (R1, R2) include 1) re-resection (preferred); or 2) RT (category 2B). Observation is recommended for patients with T1ab, N0 tumors and with negative surgical margins (R0). Patients with T2ab, N0 tumors with negative surgical margins are usually observed; chemotherapy (category 2B) is recommended as adjuvant treatment for patients with high-risk features, such as poorly differentiated tumor, vascular invasion, wedge resection, minimal margins, tumors greater than 4 cm, visceral pleural involvement, and Nx (see the NCCN NSCLC algorithm). If the surgical margins are positive in patients with T2ab, N0 tumors, these patients should have either 1) re-resection with or without chemotherapy; or 2) RT and chemotherapy.

Note that in the update for the NCCN NSCLC guidelines, the postoperative chemoradiation recommendation was deleted for stage

IA margin-positive disease because there are no data to support this recommendation (see the UPDATES pages in the NCCN NSCLC algorithm). Likewise, the postoperative chemoradiation plus chemotherapy recommendations were also removed from the guidelines for stage IB and IIA (T2b,N0) margin-positive disease and for stage IIA and IIB margin-negative disease based on the lack of data.

The panel recommends chemotherapy (category 1) with or without RT (category 3 for RT) for patients with negative surgical margins and stage II disease 1) T1ab-2a, N1; 2) T2b, N1; or 3) T3, N0 disease.²⁴⁰ If surgical margins are positive in these patients, options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with T1-3, N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy (see the NCCN NSCLC algorithm). Patients with negative margins may be treated with chemotherapy (category 1) and RT.²⁴⁰

Panel members disagreed about the use of chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.¹⁴⁶ 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 was less than 40%, some NCCN panel members feel that survival rates may increase with newer chemotherapeutic agents and with higher doses of radiation. For example, a phase II trial (RTOG 9705) (n = 88) using concurrent paclitaxel/carboplatin yielded a median survival of 56.3 months with 3-year survival of 61% in patients with resected stage II



and IIIA disease.¹⁴⁸ A phase II trial in 42 patients had similar results (5-year survival, 68%) except those with adenocarcinoma had poorer survival (only 28%).¹⁴⁹

As with stage IB and stage II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in stage III NSCLC patients who have had surgery (see the NCCN NSCLC algorithm). In the case of marginally resectable superior sulcus tumors (T4 extension, N0-1), if the lesion converts to a resectable status following concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN NSCLC algorithm). If the lesion does not convert (i.e., it remains unresectable), the full course of definitive RT followed by chemotherapy is administered as an adjuvant treatment. Among patients with chest wall lesions with T3 invasion-4 extension, N0-1 disease, those that are initially treated with surgery (preferred) may receive chemotherapy alone if the surgical margins are negative; when surgical margins are positive, they may receive either chemoradiation and chemotherapy or re-resection with chemotherapy. A similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3-4, N0-1).

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

In patients with separate pulmonary nodules in the same lobe or ipsilateral lung, surgery is recommended (see the NCCN NSCLC algorithm). If the margins are negative, adjuvant chemotherapy is recommended. If the resection margins are positive, concurrent chemoradiation is recommended (if tolerated).

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease obviously present but undetectable at diagnosis. The timing of this chemotherapy varies, with no one clear preference. Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients.

On the basis of clinical studies on adjuvant chemotherapy for NSCLC,²²⁶⁻²²⁸ the panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with gemcitabine, pemetrexed, or docetaxel (see the NCCN NSCLC algorithm).^{244, 258, 261} For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used.²⁴⁴ A recent phase III randomized trial in elderly (70-89 years) patients with advanced NSCLC reported that combined therapy with weekly paclitaxel and monthly carboplatin improved survival when compared with single-agent therapy using either gemcitabine or vinorelbine (10.4 versus 6.2 months).³²⁶

A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery.³²⁷⁻³²⁹ Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.³³⁰⁻³³³ 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.^{332, 333} 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. However, the induction chemotherapy-surgery approach needs to be compared with induction chemotherapy-RT in large, randomized clinical trials.

Radiation Therapy

NCCN panel members disagreed (category 2B) about using RT alone as adjuvant treatment for T1ab, N0 tumors based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).³³⁴ This study showed that postoperative radiotherapy is detrimental to patients with early-stage, completely resected NSCLC and should not be given routinely to such patients. However, the guideline panelists found several flaws in the meta-analysis, including:

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

An assessment of postoperative radiation in 7,465 patients with resected stage II or III NSCLC found that postoperative radiation

increased survival in patients with N2 disease but not in those with N1 or N0 disease.³³⁵ The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.¹⁴⁷ Adjuvant chemotherapy (category 1) with RT is recommended for T1-3, N2 patients with negative margins (see the NCCN NSCLC algorithm).

Surveillance and Treatment of Recurrences and Metastases

Surveillance

The surveillance guidelines are described in the NCCN NSCLC algorithm. A spiral contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years (category 2B); a non-contrast-enhanced chest CT is recommended annually thereafter (category 2B), although the panel disagreed about these recommendations for spiral chest CT scans.¹⁵ Information about smoking cessation (e.g., advice, counseling, and therapy) should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients (<http://www.smokefree.gov/>).

The NCCN NSCLC guidelines include an algorithm for long-term followup care of NSCLC survivors (see “Cancer Survivorship Care”). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening.

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (e.g., endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the NCCN

NSCLC algorithm. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life.³³⁶ After the treatment for the locoregional recurrence, observation or systemic chemotherapy (category 2B for chemotherapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic chemotherapy or best supportive care are recommended. The type of systemic therapy depends on the histologic type, EGFR mutation status, and PS (see the NCCN NSCLC algorithm).

Management of distant metastases (e.g., localized symptoms; diffuse brain, bone, solitary, or disseminated metastases) is described in the NCCN NSCLC algorithm. For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT.³³⁷ Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis.^{338, 339} Note that denosumab can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. The FDA recently approved the use of denosumab in patients with bone metastases from solid tumors.

For patients with recurrent and metastatic disease, the NCCN NSCLC guidelines now recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see the NCCN NSCLC algorithm).²⁶¹ EGFR mutation testing is recommended in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell, or NSCLC not otherwise specified), because erlotinib is recommended for patients who are positive for EGFR mutations (see section on “EGFR Mutations”).^{34, 43, 274, 340} However, very few patients with squamous cell carcinoma have EGFR

mutations (< 4%); therefore, routine testing is not recommended in these patients.^{341, 342}

Treatment recommendations and eligibility criteria for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) are described in the NCCN NSCLC algorithm. Treatment recommendations and eligibility criteria for patients with squamous histology are described in the NCCN NSCLC algorithm. These recommendations are briefly summarized in the following paragraph. Data supporting these recommendations are described in the following section (see “Trial Data”).

Cisplatin/pemetrexed is recommended (category 1) for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met.²⁶¹

Bevacizumab/chemotherapy is another option for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met.³⁴³ Previously patients with brain metastases were excluded from receiving bevacizumab because of concerns about CNS hemorrhage; however, data suggest that bevacizumab can be used in patients with treated CNS metastases.³⁴⁴ Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on PS and other factors (see next section “Trial Data”). Panel members disagreed (category 2B) about using cetuximab with cisplatin and vinorelbine, because data only showed a slight improvement in survival with the addition of cetuximab (11.3 versus 10.1 months, $P = .04$).²⁷⁷ Note that full-dose cisplatin may not be appropriate for some PS 2 patients.

Cisplatin/gemcitabine is an option for patients with squamous cell carcinoma.²⁶¹ Another option is cetuximab with cisplatin and vinorelbine, although this is a category 2B recommendation.²⁷⁷

Trial Data

In a phase II/III trial (ECOG 4599), 842 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.^{272, 345} 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.²⁷² However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 24% versus 16.4%, grade 3/4 hemorrhage: 4.5% versus 0.7%, hemoptysis: 1.9% versus 0.2%, and hypertension: 6.0% versus 0.7%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (9 patients) than with paclitaxel and carboplatin (2 patients).

A recent analysis of ECOG 4599 found that adenocarcinoma histology was associated with improved survival in patients receiving bevacizumab/paclitaxel/carboplatin compared with chemotherapy alone (14 versus 10 months).³⁴³ Of interest, a trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab.^{346, 347} A noninferiority trial in 1745 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine

compared with cisplatin plus pemetrexed.²⁶¹ Patients with either adenocarcinoma or large cell histology (i.e., nonsquamous) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 versus 10.9 months). Patients with squamous cell histology had improved survival with the cisplatin/gemcitabine regimen (10.8 versus 9.4 months). When compared with the cisplatin/gemcitabine regimen, the cisplatin/pemetrexed regimen had significantly lower rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$). Treatment-related deaths were similar for both regimens (cisplatin plus pemetrexed, 9 patients [1.0%]; cisplatin plus gemcitabine, 6 patients [0.7%]).

In the FLEX trial, 1125 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) were randomly assigned to either 1) cetuximab in combination with vinorelbine and cisplatin; or 2) vinorelbine and cisplatin alone.²⁷⁷ The response rate was increased with cetuximab (36% versus 29%, $P = .012$); there was no difference in progression-free survival. Overall survival was slightly better in patients receiving cetuximab (11.3 versus 10.1 months, $P = .04$). However, there was increased grade 3 or 4 febrile neutropenia in patients receiving cetuximab (22% versus 15%, $P < .05$); patients also had grade 2 acne-like rash. Treatment-related deaths were similar in both groups (3% versus 2%).

Data show that cisplatin-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Patients receiving cisplatin-based therapy had an improvement in median survival of 6-12 weeks and a doubling of 1-year survival rates (10%-15% improvement). Cisplatin or carboplatin have been proven effective in combination with any of the following agents: docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, pemetrexed, vinblastine, and vinorelbine.^{244, 258-261, 264, 265} New agent/non-platinum regimens are

reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel).²⁶⁷ As yet, there is no evidence that one platinum-based regimen is better than any other.^{262, 263} A recent meta-analysis reported that the objective response rate is higher with cisplatin therapy when compared with carboplatin therapy (30% versus 24%).³⁴⁸ For patients with advanced, incurable NSCLC, many clinicians prefer to give carboplatin-based regimens because they are better tolerated.

Maintenance Therapy

Patients receiving therapy should be evaluated for tumor response with a CT scan. 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 of chemotherapy³⁴⁹ or until the disease progresses. A meta-analysis suggests that continuing the initial regimen beyond 4-6 cycles is associated with increased PFS; however, patients have more adverse events.³⁵⁰ Another review suggests that there is no benefit to continuing chemotherapy beyond 4-6 cycles; however, it is important to note that many patients assigned to longer duration of therapy did not receive the planned number of cycles.²⁷⁹

For patients with nonsquamous NSCLC who are EGFR mutation negative (or unknown mutation status), continuation maintenance therapy regimens include bevacizumab (category 1), cetuximab (category 1), or pemetrexed (category 2B) (see the NCCN NSCLC algorithm).^{272, 277} Switch maintenance therapy regimens for these patients include pemetrexed, erlotinib (category 2B), or docetaxel (category 3).^{283, 284} Observation is another option.

For patients with squamous cell histology, cetuximab (category 1) can be used as a continuation maintenance therapy regimen (see the

NCCN NSCLC algorithm). Switch maintenance therapy for these patients includes erlotinib (category 2B) or docetaxel (category 3). Observation is another option.

A phase III randomized trial (n = 663) assessed the effect of best supportive care with or without maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but had not progressed.²⁸⁴ In patients with nonsquamous NSCLC, overall survival was increased with pemetrexed when compared with placebo (13.4 versus 10.6 months, $P=.012$).

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

Patients may continue to derive benefit from erlotinib or gefitinib after disease progression; discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).³⁵¹ This strategy mirrors the experience in other oncogene-addicted cancers, particularly *HER2*-amplified breast cancer. In women with *HER2*-amplified breast cancer who have had progression of disease on trastuzumab, improved radiographic response rate, time to progression, and overall survival are observed when conventional chemotherapy is added to trastuzumab.³⁵² Data support the continued use of erlotinib or gefitinib in patients with lung adenocarcinoma with *EGFR* mutations after development of acquired resistance to erlotinib or gefitinib when conventional chemotherapy is initiated.

There is accumulating data about how cancers become resistant to EGFR inhibitors. The most common known mechanism is the acquisition of a secondary mutation in EGFR, T790M, that renders the kinase resistant to erlotinib and gefitinib.^{353, 354} Amplification of the MET oncogene is another validated resistance mechanism. Activation of the

IGF-1R pathway has been observed in laboratory models. To overcome all 3 types of resistance, EGFR must still be inhibited. In the case of MET amplification and IGF-1R activation, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely and colleagues demonstrate that when cancers that were once sensitive to EGFR inhibitors start to progress, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.³⁵¹ In total, it is likely that continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.

Second-Line Chemotherapy

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, and erlotinib are recommended as single-agent second-line chemotherapy regimens for patients with PS of 0-2 and who have experienced disease progression during or after first-line therapy (see the NCCN NSCLC algorithm).³⁵⁵⁻³⁵⁸ Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.^{355,356} When compared with docetaxel, pemetrexed has similar median survival but less toxicity.^{357, 359} Pemetrexed is recommended in patients with adenocarcinoma or large cell histology (i.e., nonsquamous NSCLC).²⁸⁴ Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.³⁵⁸ Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with PS of 3-4 who have the EGFR mutation (see the NCCN NSCLC algorithm). A platinum doublet with or without bevacizumab is an option (category 2B) for patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell, NSCLC NOS) who have progressed after first-line therapy with erlotinib.²⁷²

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.³⁵⁸ Median age was 61.4 years. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group ($P<.001$). Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (hazard ratio, 0.70; $P<.001$). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (hazard ratio, 0.61, adjusted for stratification categories; $P<.001$). However, 5% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first- or second-line chemotherapy. A randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel.³⁶⁰

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 the NCCN Palliative Care Guidelines).

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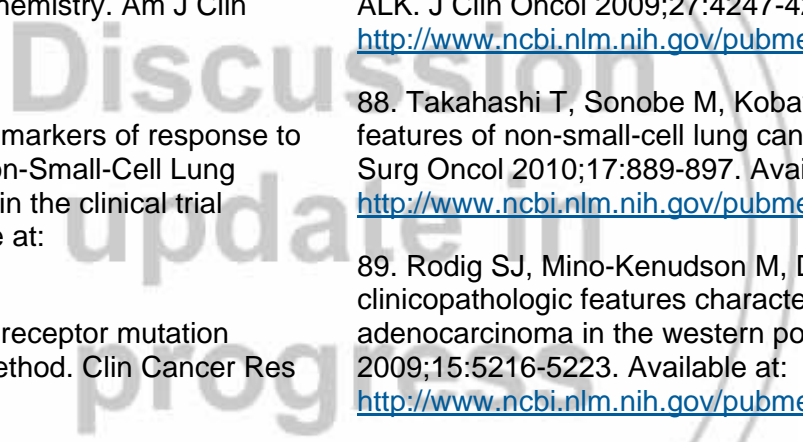
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