National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 3.2016

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in Version 3.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 2.2016 include:

NSCL-18
- **Subsequent therapy; brain: Ceritinib added as a treatment option as a category 2A recommendation.**
- **Subsequent therapy: Alectinib added as a treatment option as a category 2A recommendation.**
- **Footnote "rr" modified: Patients who are intolerant to crizotinib may be switched to ceritinib *or alectinib.***

NSCL-20
- **The Performance Status groups of PS 0-1 and PS 2 combined with the recommendation of "chemotherapy." Specific regimens and categories noted on NSCL-F 3 of 4.**

NSCL-F 3 of 4
- **The combination regimen of cisplatin/gemcitabine/necitumumab was added as a first-line treatment option for patients with metastatic squamous cell carcinoma as a category 3 recommendation.**

NSCL-F 4 of 4
- **Reference added for new regimen.**

MS-1
- **The discussion section was updated to reflect the changes in the algorithm.**

Updates in Version 2.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 1.2016 include:

NSCL-17
- **Subsequent therapy: Osimertinib added as a treatment option as a category 2A recommendation.**
- **Footnote pp added: Osimertinib is approved for patients with metastatic EGFR T790M mutation-positive tumors, as determined by an FDA-approved test or other validated laboratory developed test performed in a CLIA-approved laboratory.**

MS-1 - The discussion section was updated to reflect the changes in the algorithm.

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Updates in Version 1.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2015 include:

DIAG-2
- Footnote f modified with the addition of this sentence: When a biopsy is not possible, a multidisciplinary evaluation should be done including radiation oncology, surgery, interventional pulmonology.

DIAG-A 1 of 2
- Bullet 1, sub-bullet 2 modified: A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by *core biopsy* or fine-needle aspiration (FNA).

DIAG-A 2 of 2
- Sub-bullet 3 of sub-bullet 3, entry 1 added: EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L and other hilar nodal stations if necessary.
- Sub-bullet 3 of sub-bullet 3, entry 2 modified: Esophageal ultrasound–guided biopsy provides additional access to stations ~~2L, 4L,~~ 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.

NSCL-2
- Footnote "i" added: Solid tumors <1 cm and purely non-solid tumors <3 cm that are CT and PET negative have a low likelihood of positive mediastinal lymph nodes and pre-resection pathologic mediastinal evaluation is optional.

NSCL-14
- Bullet 1, sub-bullet 1 modifed with the addition of the text from a previous footnote: Patients treated with chemotherapy ± RT who have residual abnormalities may require more frequent imaging.

NSCL-16
- Testing; bullet 3: EGFR and ALK testing should be conducted as part of ~~multiplex/next generation sequencing~~broad molecular profiling.

NSCL-17
- EGFR mutation discovered prior to first-line chemotherapy; First-line therapy: Gefitinib added as a category 1 recommendation.
- EGFR mutation discovered during first-line chemotherapy; First-line therapy:
  - Interrupt or complete planned chemotherapy, ~~start~~ *followed by* erlotinib or afatinib *or gefitinib*
  - The option of "May add erlotinib or afatinib to current chemotherapy (category 2B)" removed.
- Subsequent therapy: Gefitinib added as a treatment option as a category 2A recommendation.
- Subsequent therapy; brain: criteria of "isolated" and "multiple" lesions removed and treatment recommendations consolidated. Link added to the NCCN Guidelines for CNS Cancer.
- Subsequent therapy; Multiple lesions: "± erlotinib" removed as a treatment option.
- Footnote "pp" added: Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.
- Footnote removed: In areas of the world where gefitinib is available, it may be used in place of erlotinib. (also applies to NSCL-19-NSCL-20)
- Footnote removed: Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. J Clin Oncol 2012;30:2063-2069.
- Footnote removed: Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and on or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-538.

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Updates in Version 1.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2015 include:

NSCL-18

- ***ALK*** **rearrangement discovered during first-line chemotherapy; First-line therapy:**
  - **Interrupt or complete planned chemotherapy, ~~start~~ *followed by* crizotinib.**
- **Subsequent therapy; brain: criteria of "isolated" and "multiple" lesions removed and treatment recommendations consolidated. Link added to the NCCN Guidelines for CNS Cancer.**

NSCL-19

- **Systemic immune checkpoint inhibitors listed as preferred.**
- **Subsequent therapy, PS 0-2: Pembrolizumab added as a treatment option.**
- **Subsequent therapy, PS 0-2: Nivolumab changed from a category 2A to a category 1 recommendation.**
- **Subsequent therapy, PS 3-4: Afatinib and gefitinib added as treatment options for patients with sensitizing EGFR mutations.**
- **Subsequent therapy, PS 3-4: Crizotinib added as a treatment option for patients with a positive ALK rearrangement.**
- **Footnote "xx" added: Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.**
- **Footnote "bbb" modified: If not already given, options for PS 0-2 include erlotinib, nivolumab, *pembrolizumab*, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.**
- **Footnote removed: Chemotherapy preferred in this setting. Grassino M, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. Lancet Oncol 2013; 14:981-988. (also applies to NSCL-20)**

NSCL-20

- **Systemic immune checkpoint inhibitors listed as preferred.**
- **Subsequent therapy, PS 0-2: Pembrolizumab added as a treatment option.**
- **Subsequent therapy: Erlotinib removed as a treatment option for any performance status.**
- **Switch maintenance: Erlotinib removed as a treatment option.**
- **Footnote "xx" added: Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.**
- **Footnote "ccc" modified: If not already given, options for PS 0-2 include ~~erlotinib,~~ nivolumab, *pembrolizumab*, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include ~~erlotinib or~~ best supportive care. Options for further progression are best supportive care or clinical trial.**
- **Footnote removed: Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. Lancet Oncol 2014; 15:713-21.**

NSCL-A (2 of 4)

- **Immunohistochemical Staining; Bullet 1 added: Judicious use of immunohistochemistry is strongly recommended to preserve tissue for molecular testing. IHC should be utilized only after consideration of all data including routine H&E histology, clinical findings, imaging studies, and patient's history.**
- **Immunohistochemical Staining; Bullet 4; Sub-bullet 1 modified: *In patients for whom the primary origin of the carcinoma is uncertain,* an appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to the lung.**

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Updates in Version 1.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2015 include:

NSCL-A (2 of 4)
- Immunohistochemical Staining; Bullet 6; Sub-bullet 1 replaced: ~~The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) is made by using 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).~~ The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) can be made by correlation of the histology with the clinical impression, imaging studies, and a limited panel of immunomarkers if needed.

NSCL-B 1 of 4
- Evaluation, bullet 1, section of sentence highlighted: Determination of resectability, surgical staging, and ***pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice***.

NSCL-C (1 of 10)
- Heading modified: Early-Stage NSCLC (Stage I, *selected node negative Stage IIA)*
  - Bullet 3 added: A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery. This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
  - Bullet 4 modified: For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are *less preferred* alternatives.

NSCL-C (2 of 10)
- Locally Advanced NSCLC (Stage II-III)
  - Bullet 1 modified: The standard of care for patients with inoperable stage II *(node positive)* and stage III is concurrent chemotherapy/RT.
  - Bullet 2 modified: Accelerated RT regimens may be beneficial, particularly if ~~not~~ concurrent ~~with~~ chemotherapy *would not be tolerated* (ie, in a sequential or RT-only approach).
  - Bullet 3; Sub-bullet 2; sentence added: The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.
  - Bullet 3; Sub-bullet 3; sentence added: Up front multidisciplinary consultation is particularly important when considering surgical treatment of stage III NSCLC.

NSCL-C (4 of 10)
- Locally Advanced Stage/Conventionally Fractionated RT
  - Bullet 1 modified: ~~One~~ *Two* randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation. IFI is reasonable in order to optimize definitive dosing to the tumor.
  - Bullet 2 modified: While doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected, ~~preliminary~~ results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy, found that 74 Gy does not improve overall survival, ~~and therefore is not currently a standard dose~~ *and might be potentially harmful.*
  - Bullet 3 modified: Doses of 45 to ~~50~~*54* Gy in 1.8 to 2 Gy fractions are standard preoperative doses.

NSCL-C (6 of 10)
- RTOG definition modifed: Radiation Therapy Oncology Group *now part of NRG Oncology.*

NSCL-C (9 of 10)
- The following references were added: 13, 28, 29, 35

NSCL-C (10 of 10)
- The following references were added: 51, 60, 69, 71, 77

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Updates in Version 1.2016 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 7.2015 include:

NSCL-D
- The following regimen removed: Cisplatin 80 mg/m^2 days 1, 22, 43, 64; vinblastine 4 mg/m^2 days 1, 8, 15, 22, 29 then every 2 wks after day 43, every 21 days for 4 cycles
- References added:
  Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524.

NSCL-E
- Concurrent Chemotherapy/RT Regimens: Preferred removed from the following regimens:
  - Cisplatin 50 mg/m^2 on days 1, 8, 29, and 36; etoposide 50 mg/m^2 days 1–5, 29–33; concurrent thoracic RT
  - Cisplatin 100 mg/m^2 days 1 and 29; vinblastine 5 mg/m^2/weekly x 5; concurrent thoracic RT
- The following regimen aded to Concurrent Chemotherapy/RT Regimens: Paclitaxel 45–50 mg/m^2 weekly; carboplatin AUC 2, concurrent thoracic RT.
- Footnote "*" modified: Regimens can be used as neoadjuvant/*preoperative/induction* 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 2 cycles of full-dose platinum therapy after local treatment is completed.~~
- Footnote "**" added: Regimens can be used as adjuvant or definitive concurrent chemotherapy/RT.
- References added:
  Choy H, Gerber DE, Bradley JD, et al. Concurrent pemetrexed and radiation therapy in the treatment of patients with inoperable stage III non-small cell lung cancer: a systematic review of completed and ongoing studies. Lung Cancer 2015;87:232-240
  Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncol 2015;16:187-199.

NSCL-F modified, reorganized, and expanded to include specific regimens for first-line therapy for NSCLC based on histology.

NSCL-F (1 of 4)
- Advanced Disease, bullet 6 modified: Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib, *afatinib, or gefitinib* for *EGFR* mutation-positive *and crizotinib for ALK positive tumors of nonsquamous NSCLC or NSCLC NOS.*
- Subsequent Therapy, bullet 1, sub-bullet 2 added: Pembrolizumab improves overall response rate in PD-L1 positive tumors.

NSCL-F (2 of 4)
- First-line systemic therapy options listed for advanced or metastatic adenocarcinoma, large cell, NSCLC NOS.

NSCL-F (3 of 4)
- First-line systemic therapy options listed for advanced or metastatic squamous cell carcinoma.

NSCL-F (4 of 4)
- Reference list expanded.

NSCL-H
- Emerging Targeted Agents for Patients with Genetic Alterations
  - Dabrafenib + trametinib added as an available targeted regimen with activity against *BRAF* V600E mutation.
  - Cabozantinib changed from a category 2B to a category 2A recommendation.
  - *MET* amplification clarified as "*High level* MET amplification *or MET exon 14 skipping mutation*"
  - References 1, 2, 4,7,8 and 10 are new to the page.

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% to 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 for lung cancer from second-hand smoke exposure associated with living with a smoker (http://www.ncbi.nlm.nih.gov/books/NBK44324/).**
  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 using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the NCCN Guidelines for Lung Cancer Screening).**

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

Nodule suspicious for lung cancer

- **Multidisciplinary evaluation[a]**
- **Smoking cessation counseling**

RISK ASSESSMENT[b]

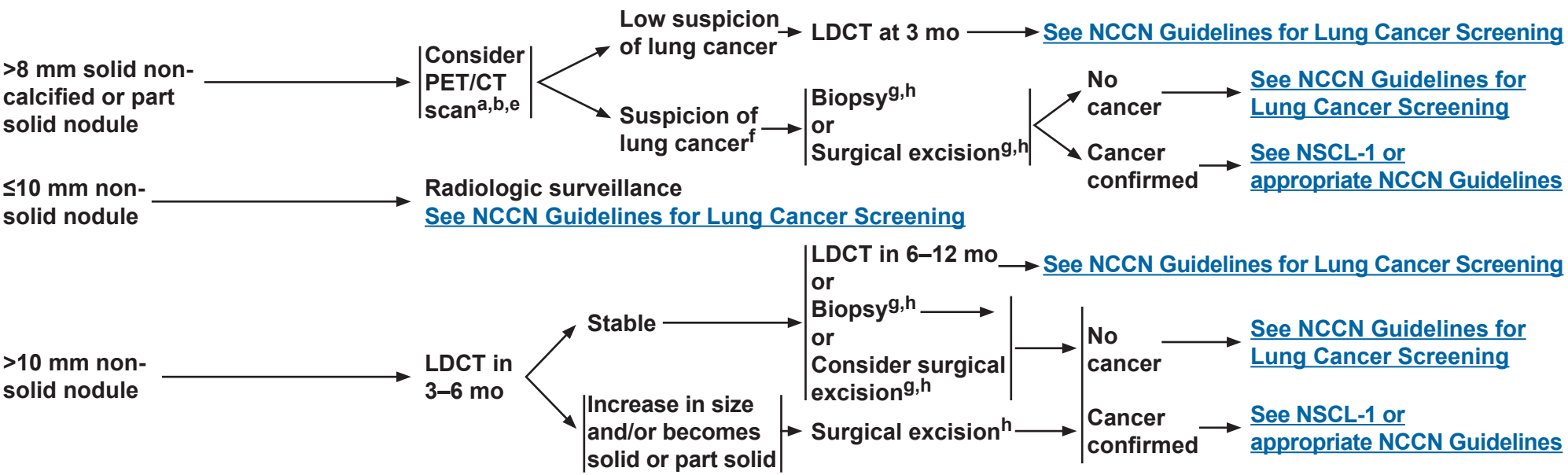
Patient factors
- **Age**
- **Smoking history**
- **Previous cancer history**
- **Family history**
- **Occupational exposures**
- **Other lung disease (chronic obstructive pulmonary disease [COPD], pulmonary fibrosis)**
- **Exposure to infectious agents (eg, endemic areas of fungal infections, tuberculosis) or risk factors or history suggestive of infection (eg, immune suppression, aspiration, infectious respiratory symptoms)**

Radiologic factors[c,d]
- **Size, shape, and density of the pulmonary nodule**
- **Associated parenchymal abnormalities (eg, scarring or suspicion of inflammatory changes)**
- **Fluorodeoxyglucose (FDG) avidity on PET imaging**

See Findings and Follow-up (DIAG-2)

[a]Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.
[b]Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.
[c]See Principles of Diagnostic Evaluation (DIAG-A 1 of 2).
[d]The most important radiologic factor is change or stability compared with a previous imaging study.

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.



[a]Multidisciplinary evaluation including thoracic surgeons, thoracic radiologists, and pulmonologists to determine the likelihood of a cancer diagnosis and the optimal diagnostic or follow-up strategy.

[b]Risk calculators can be used to quantify individual patient and radiologic factors but do not replace evaluation by a multidisciplinary diagnostic team with substantial experience in the diagnosis of lung cancer.

[c]See Principles of Diagnostic Evaluation (DIAG-A 1 of 2).

[d]The most important radiologic factor is change or stability compared with a previous imaging study.

[e]A positive PET result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (eg, nodal, parenchymal, pleural). A false-negative PET scan can be caused by a small nodule, low cellular density (nonsolid nodule or ground-glass opacity [GGO]), or low tumor avidity for FDG (eg, adenocarcinoma in situ [previously known as bronchoalveolar carcinoma], carcinoid tumor).

[f]Patients with a suspicion of lung cancer after PET/CT require histologic confirmation before any nonsurgical therapy. When a biopsy is not possible, a multidisciplinary evaluation should be done including radiation oncology, surgery, interventional pulmonology.

[g]The choice of biopsy or surgical excision should be based on the clinical suspicion of lung cancer, location of lesion (feasibility for surgical identification and resection by minimally invasive video-assisted thoracic surgery [VATS]), and patient preferences.

[h]Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.

Note: All recommendations are category 2A unless otherwise indicated.
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PRINCIPLES OF DIAGNOSTIC EVALUATION

- Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.
  - A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.
  - A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by core biopsy or fine-needle aspiration (FNA).
  - A preoperative biopsy may be appropriate if an intraoperative diagnosis appears difficult or very risky.
  - If a preoperative tissue diagnosis has not been obtained, then an intraoperative diagnosis (ie, wedge resection, needle biopsy) is necessary before lobectomy, bilobectomy, or pneumonectomy.
- Bronchoscopy should preferably be performed during the planned surgical resection, rather than as a separate procedure.
  - Bronchoscopy is required before surgical resection (see NSCL-2).
  - A separate bronchoscopy may not be needed for treatment decisions before the time of surgery and adds time, costs, and procedural risk.
  - A preoperative bronchoscopy may be appropriate if a central tumor requires pre-resection evaluation for biopsy, surgical planning (eg, potential sleeve resection), or preoperative airway preparation (eg, coring out an obstructive lesion).
- Invasive mediastinal staging is recommended before surgical resection for most patients with clinical stage I or II lung cancer (see NSCL-2).
  - Patients should preferably undergo invasive mediastinal staging as the initial step before the planned resection (during the same anesthetic procedure), rather than as a separate procedure.
  - A separate staging procedure adds time, costs, coordination of care, inconvenience, and an additional anesthetic risk.
  - Preoperative invasive mediastinal staging may be appropriate for a strong clinical suspicion of N2 or N3 nodal disease or when intraoperative cytology or frozen section analysis is not available.
- In patients with suspected non-small cell lung cancer (NSCLC), many techniques are available for tissue diagnosis.
  - Diagnostic tools that should be routinely available include:
    - ◊ Sputum cytology
    - ◊ Bronchoscopy with biopsy and transbronchial needle aspiration (TBNA)
    - ◊ Image-guided transthoracic needle core biopsy (preferred) or FNA
    - ◊ Thoracentesis
    - ◊ Mediastinoscopy
    - ◊ Video-assisted thoracic surgery (VATS) and open surgical biopsy
  - Diagnostic tools that provide important additional strategies for biopsy include:
    - ◊ Endobronchial ultrasound (EBUS)–guided biopsy
    - ◊ Endoscopic ultrasound (EUS)–guided biopsy
    - ◊ Navigational bronchoscopy

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 DIAGNOSTIC EVALUATION

- The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.
  - Factors to be considered in choosing the optimal diagnostic step include:
    - ◊ Anticipated diagnostic yield (sensitivity)
    - ◊ Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)
    - ◊ Adequate volume of tissue specimen for diagnosis and molecular testing
    - ◊ Invasiveness and risk of procedure
    - ◊ Efficiency of evaluation
      - – Access and timeliness of procedure
      - – Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion). Therefore, PET imaging is frequently best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced stage tumors.
    - ◊ Technologies and expertise available
    - ◊ Tumor viability at proposed biopsy site from PET imaging.
  - Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation should also include a pulmonologist or thoracic surgeon with expertise in advanced bronchoscopic techniques for diagnosis.
  - The least invasive biopsy with the highest yield is preferred as the first diagnostic study.
    - ◊ Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.
    - ◊ Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or TTNA.
    - ◊ Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.
      - – EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L and other hilar nodal stations if necessary.
      - – EUS–guided biopsy provides additional access to stations 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.
      - – TTNA and anterior mediastinotomy (ie, Chamberlain procedure) provide additional access to anterior mediastinal (station 5 and 6) lymph nodes if these are clinically suspicious.
    - ◊ EUS also provides reliable access to the left adrenal gland.
    - ◊ Lung cancer patients with an associated pleural effusion should undergo thoracentesis and cytology. A negative cytology result on initial thoracentesis does not exclude pleural involvement. An additional thoracentesis and/or thoracoscopic evaluation of the pleura should be considered before starting curative intent therapy.
    - ◊ Patients suspected of having a solitary site of metastatic disease should have tissue confirmation of that site if feasible.
    - ◊ Patients suspected of having metastatic disease should have confirmation from one of the metastatic sites if feasible.
    - ◊ Patients who may have multiple sites of metastatic disease—based on a strong clinical suspicion—should have biopsy of the primary lung lesion or mediastinal lymph nodes if it is technically difficult or very risky to biopsy a metastatic site.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2016
Non-Small Cell Lung Cancer

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PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

NSCLC →

- Pathology review[a]
- H&P (include performance status + weight loss)[b]
- CT chest and upper abdomen with contrast, including adrenals
- CBC, platelets
- Chemistry profile
- Smoking cessation advice, counseling, and pharmacotherapy
  - Use the 5 A's Framework: Ask, Advise, Assess, Assist, Arrange http://www.ahrq.gov/clinic/tobacco/5steps.htm
- Integrate palliative care[c] (See NCCN Guidelines for Palliative Care)

CLINICAL STAGE

Stage IA, peripheral[d] (T1ab, N0)	See Pretreatment Evaluation (NSCL-2)
Stage I, peripheral[d] (T2a, N0); central[d] (T1ab-T2a, N0); Stage II (T1ab-T2ab, N1; T2b, N0); stage IIB (T3, N0)[e] Stage IIIA (T3, N1)	See Pretreatment Evaluation (NSCL-2)
Stage IIB[f] (T3 invasion, N0); Stage IIIA[f] (T4 extension, N0-1; T3, N1)	See Pretreatment Evaluation (NSCL-4)
Stage IIIA[f] (T1-3, N2)	See Pretreatment Evaluation (NSCL-7)
Separate pulmonary nodule(s) (Stage IIB, IIIA, IV)	See Pretreatment Evaluation (NSCL-7)
Multiple lung cancers	See Treatment (NSCL-9)
Stage IIIB[f] (T1-3, N3) mediastinal CT positive Contralateral (lymph nodes ≥1 cm) or palpable supraclavicular lymph nodes	See Pretreatment Evaluation (NSCL-11)
Stage IIIB[f] (T4, N2-3) on CT	See Pretreatment Evaluation (NSCL-12)
Stage IV (M1a)[c] (pleural or pericardial effusion)	See Pretreatment Evaluation (NSCL-12)
Stage IV (M1b)[c] Limited sites with resectable lung lesion	See Pretreatment Evaluation (NSCL-13)
Stage IV (M1b)[c] disseminated metastases	See Systemic Therapy (NSCL-16)

[a] See Principles of Pathologic Review (NSCL-A).
[b] Enhanced frailty or geriatric assessments may predict complications better following treatment modalities, particularly surgery. A preferred frailty assessment system has not been established.
[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small cell lung cancer. N Engl J Med 2010;363:733-742.
[d] Based on the CT of the chest: Peripheral = outer third of lung. Central = inner two thirds of lung.
[e] T3, N0 related to size or satellite nodules.
[f] For patients considered to have stage IIB and stage III tumors, where more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.

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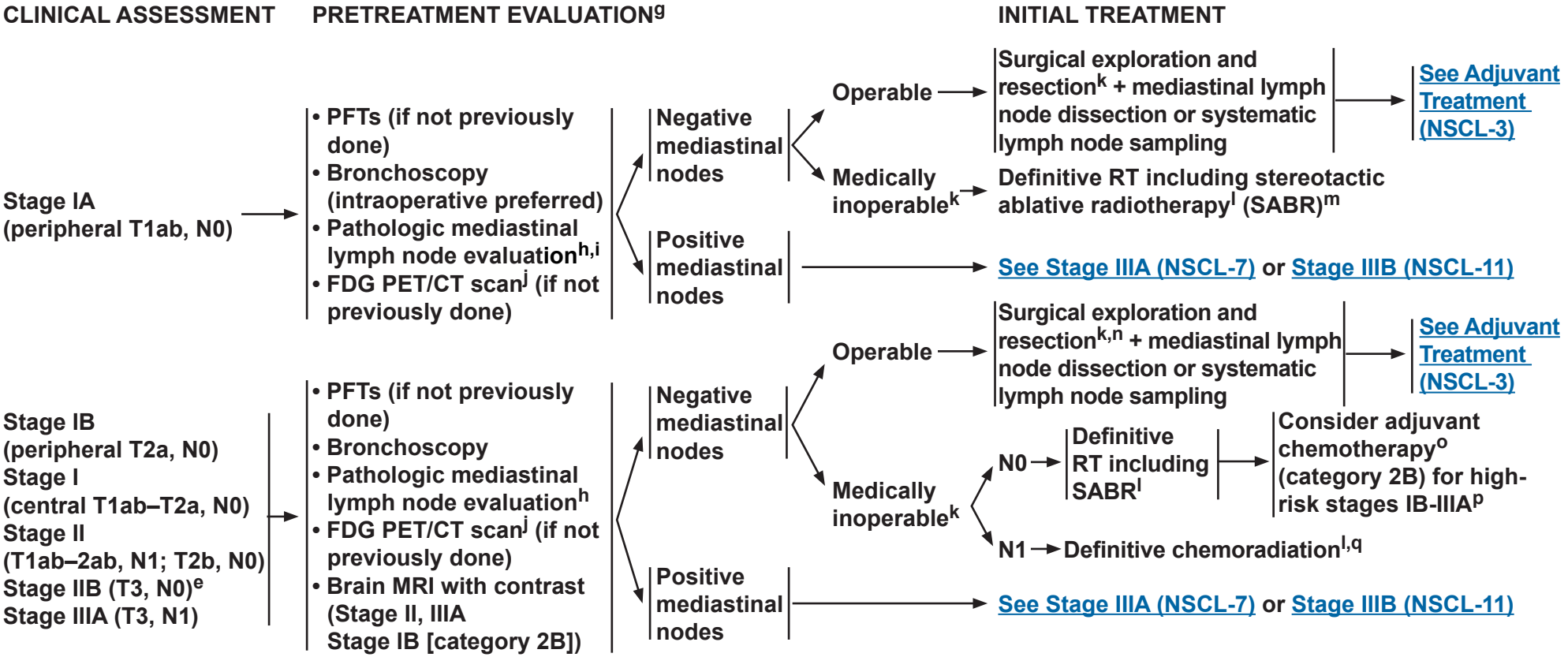

[e]T3, N0 related to size or satellite nodules.
[g]Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.
[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[i]Solid tumors <1 cm and purely non-solid tumors <3 cm that are CT and PET negative have a low likelihood of positive mediastinal lymph nodes and pre-resection pathologic mediastinal evaluation is optional.
[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[m]Interventional radiology ablation is an option for selected patients.
[n]After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.
[o]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[p]Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

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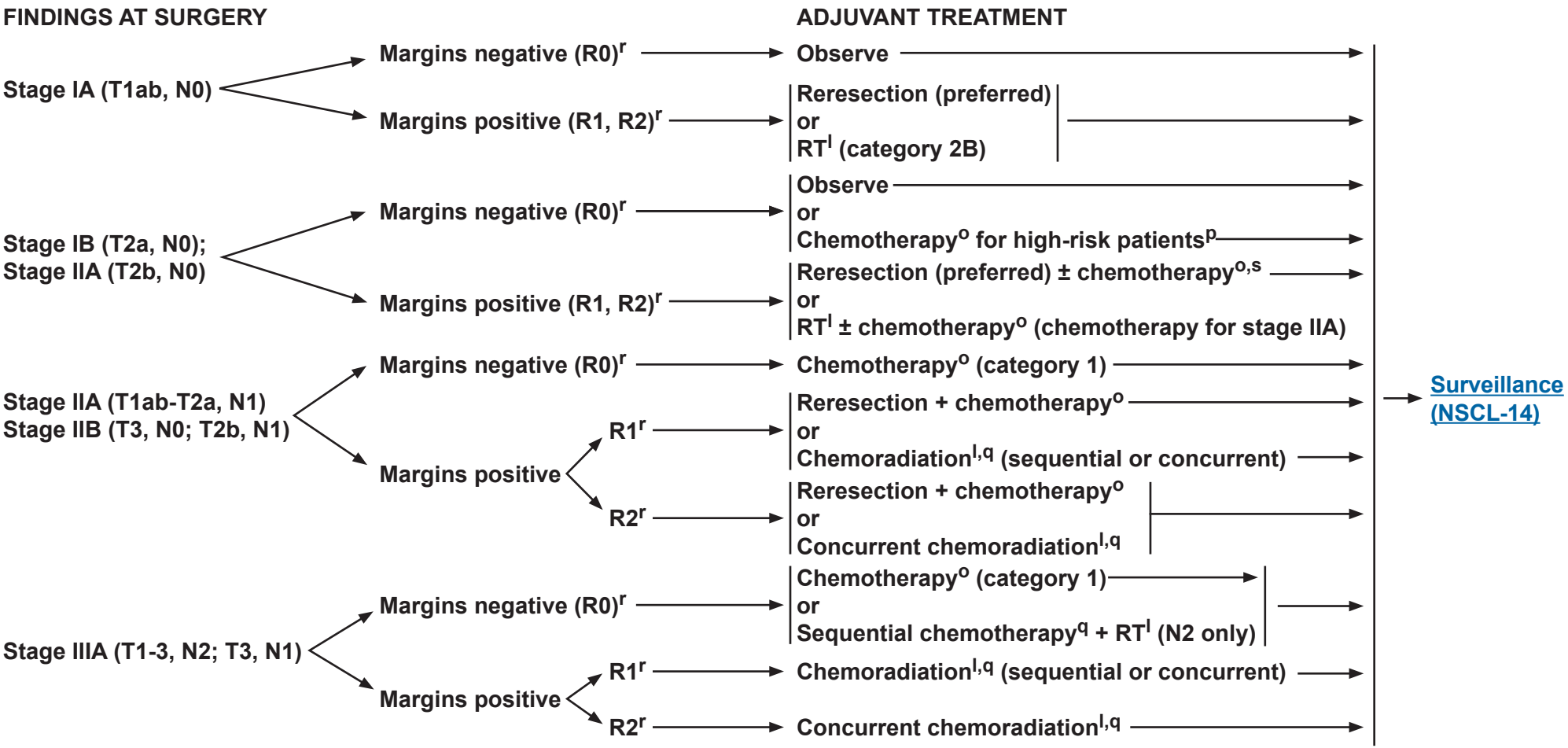

[l] See Principles of Radiation Therapy (NSCL-C).
[o] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
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[q] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[r] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[s] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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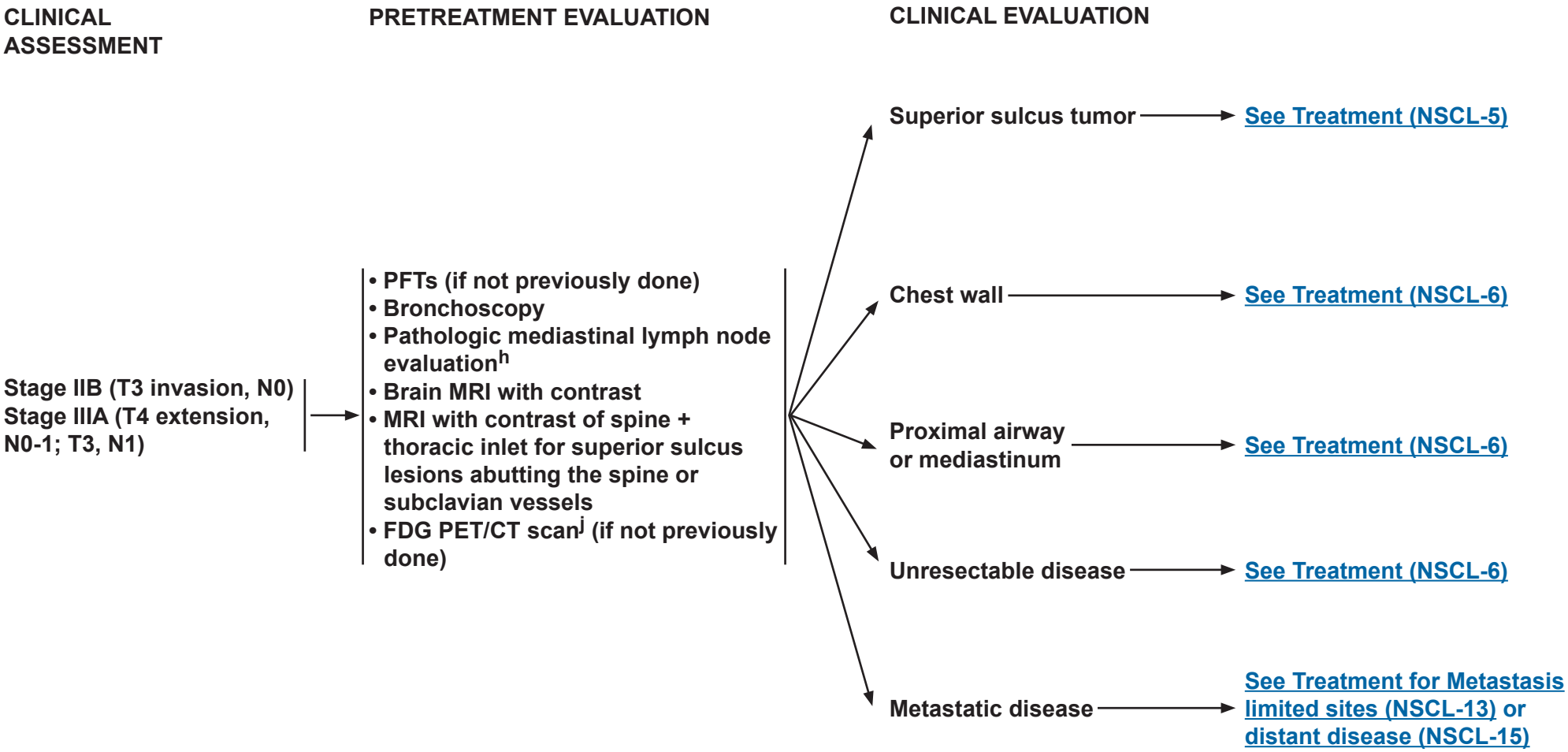

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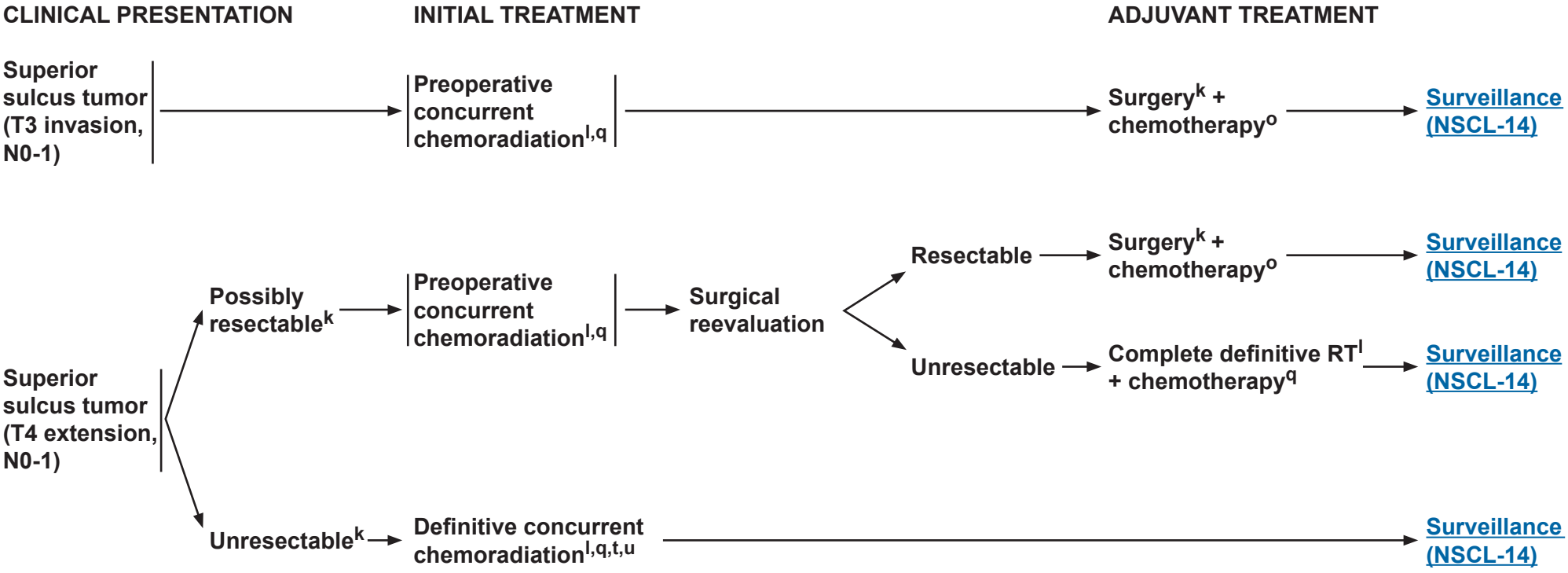

[k] See Principles of Surgical Therapy (NSCL-B).
[l] See Principles of Radiation Therapy (NSCL-C).
[o] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[q] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

[t] RT should continue to definitive dose without interruption if patient is not a surgical candidate.
[u] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

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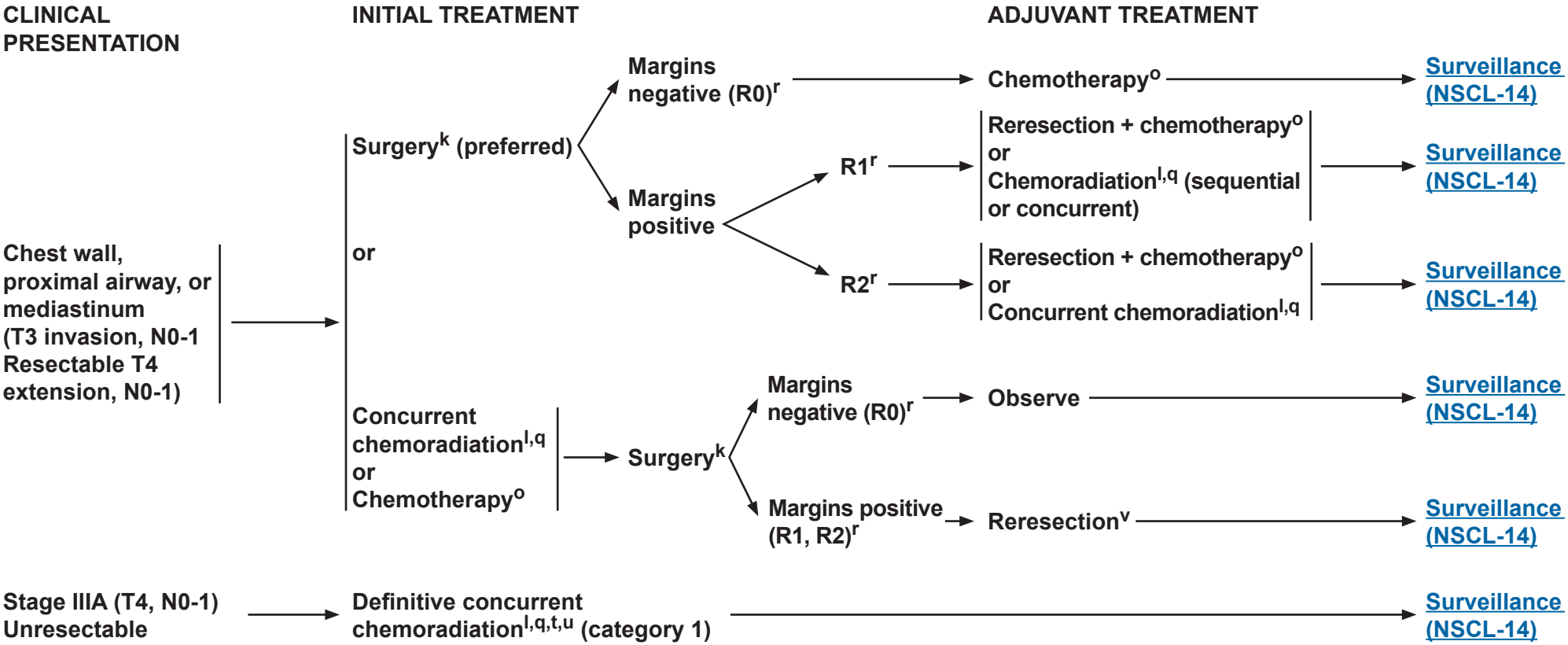

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[l] See Principles of Radiation Therapy (NSCL-C).
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[q] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
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[t] RT should continue to definitive dose without interruption if patient is not a surgical candidate.
[u] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.
[v] Consider RT boost if chemoradiation is given as initial treatment.

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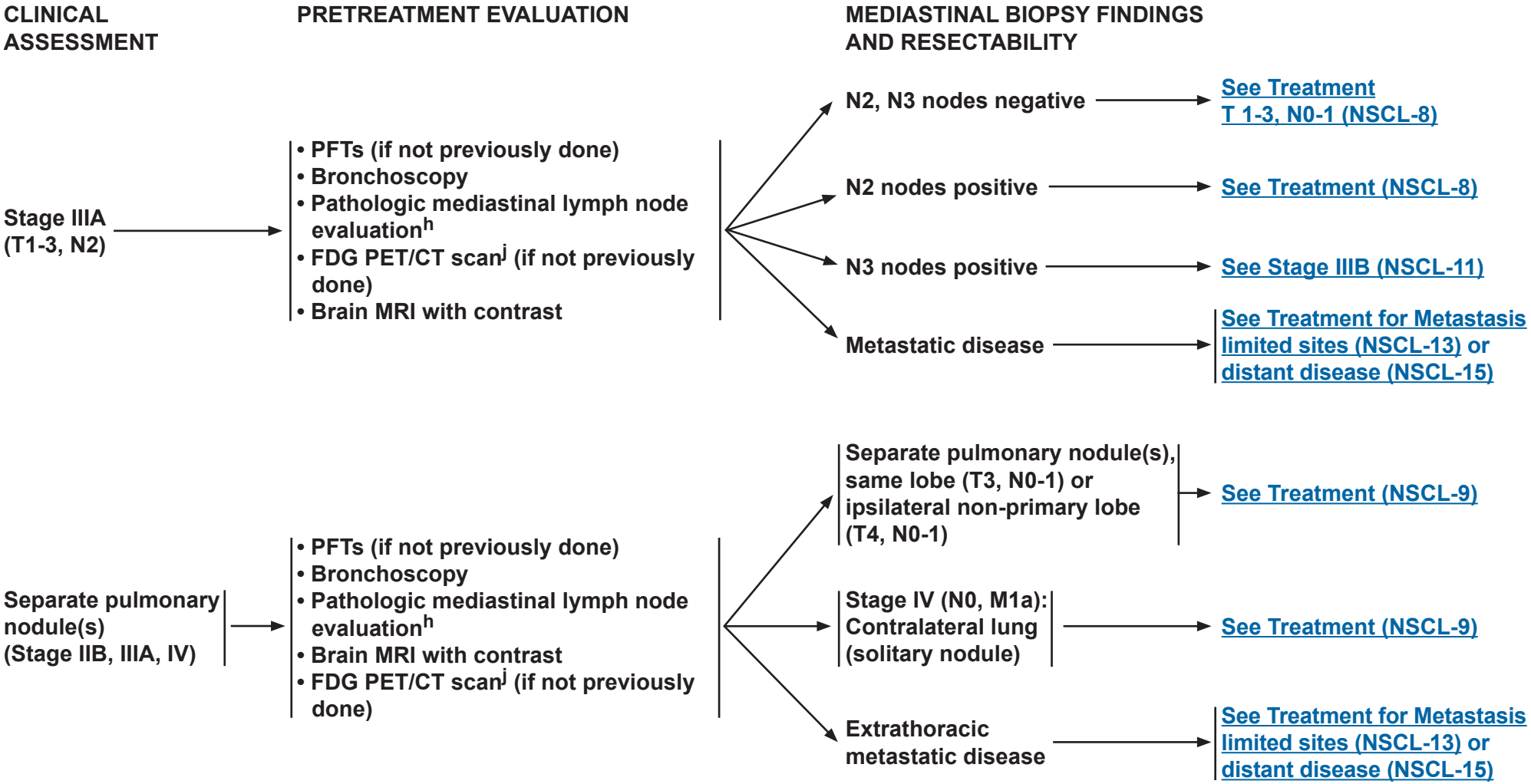

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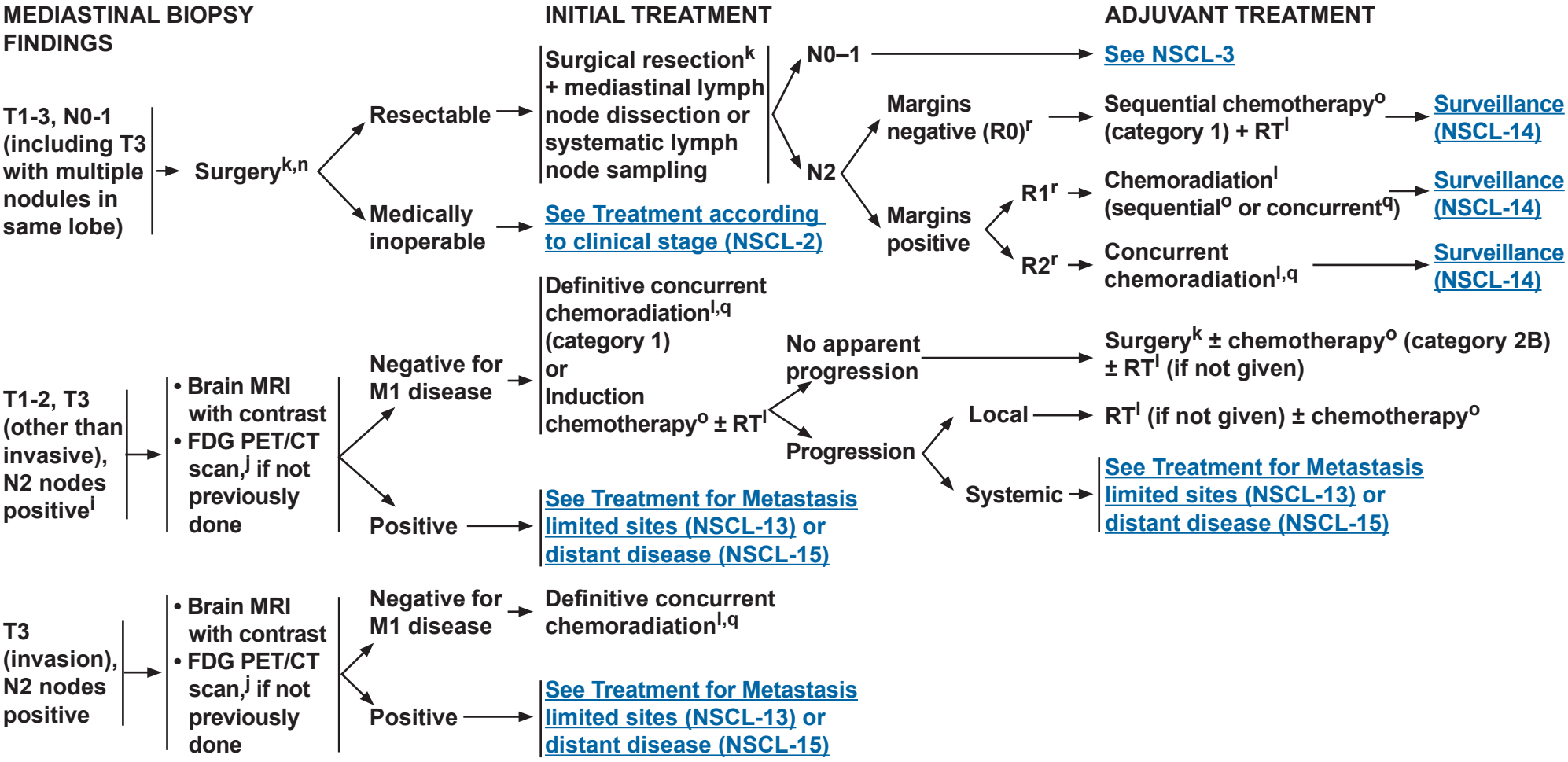

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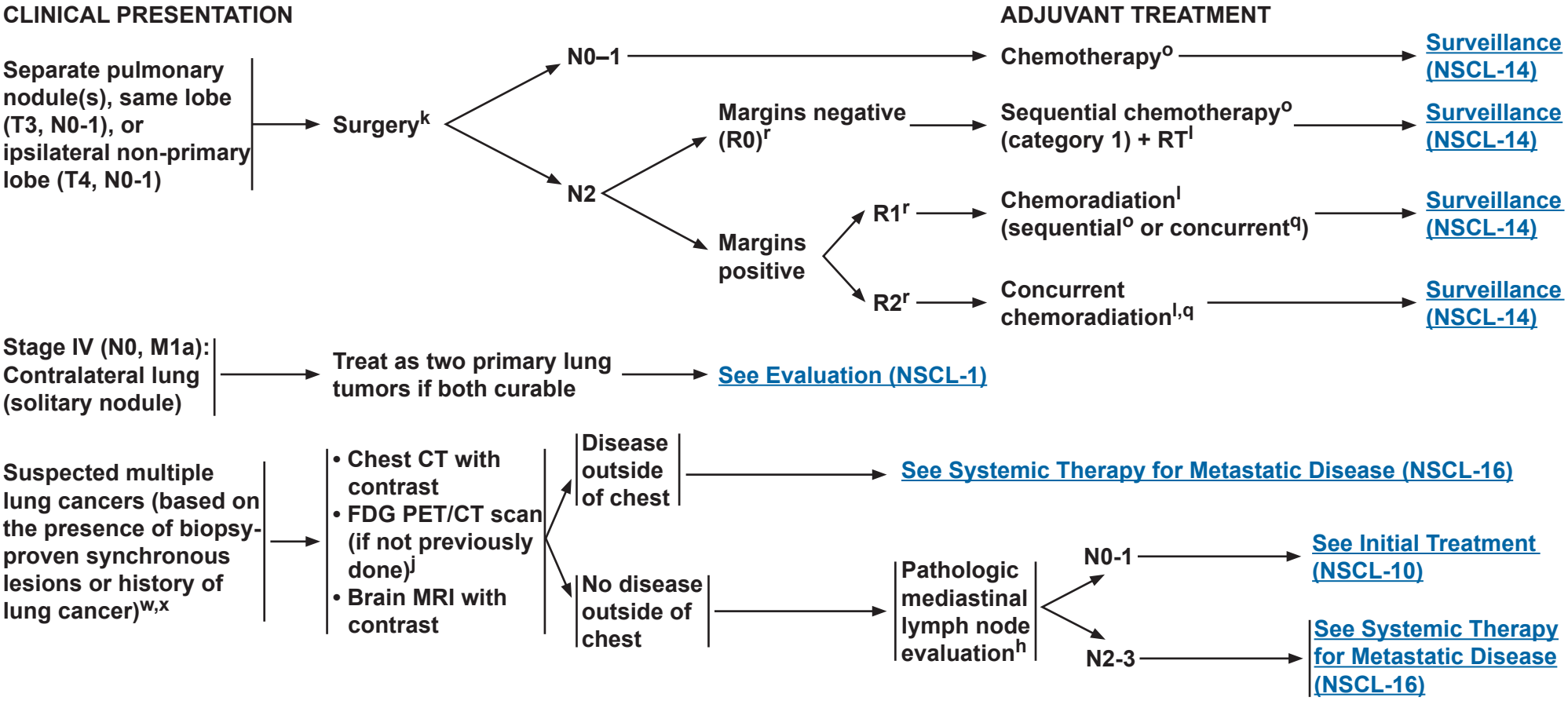

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[l]See Principles of Radiation Therapy (NSCL-C).

[o]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

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

[w]Lesions with different cell types (eg, squamous cell carcinoma, adenocarcinoma) may be different primary tumors. This analysis may be limited by small biopsy samples. However, lesions of the same cell type are not necessarily metastases.

[x]For guidance regarding the evaluation, workup, and management of subsolid pulmonary nodules, please see the diagnostic evaluation of a nodule suspicious for lung cancer (DIAG-1).

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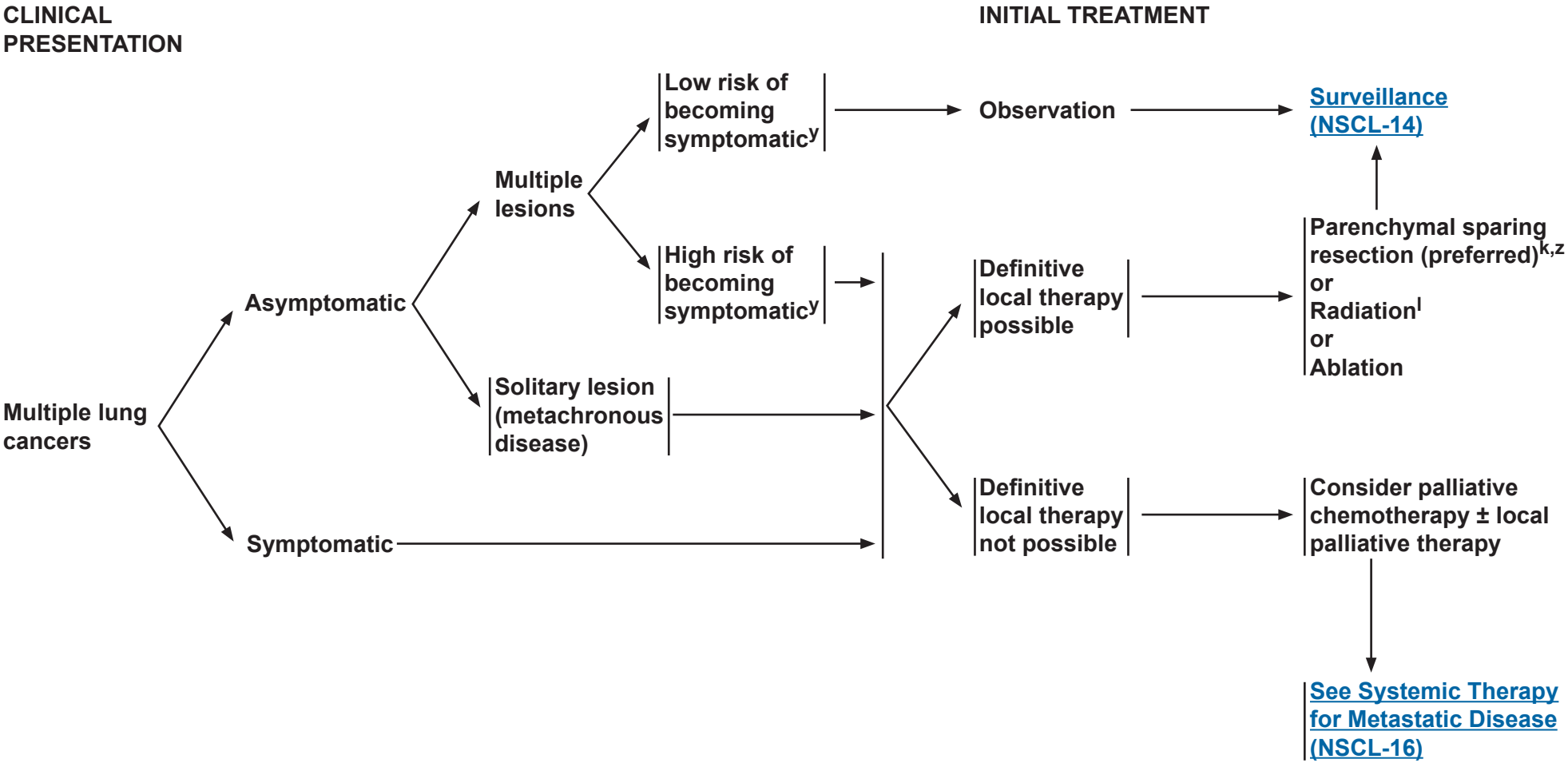

[k] See Principles of Surgical Therapy (NSCL-B).
[l] See Principles of Radiation Therapy (NSCL-C).
[y] Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms (eg, subsolid nodules with accelerating growth or increasing solid component or increasing FDG uptake, even while small), treatment should be considered.
[z] Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning.

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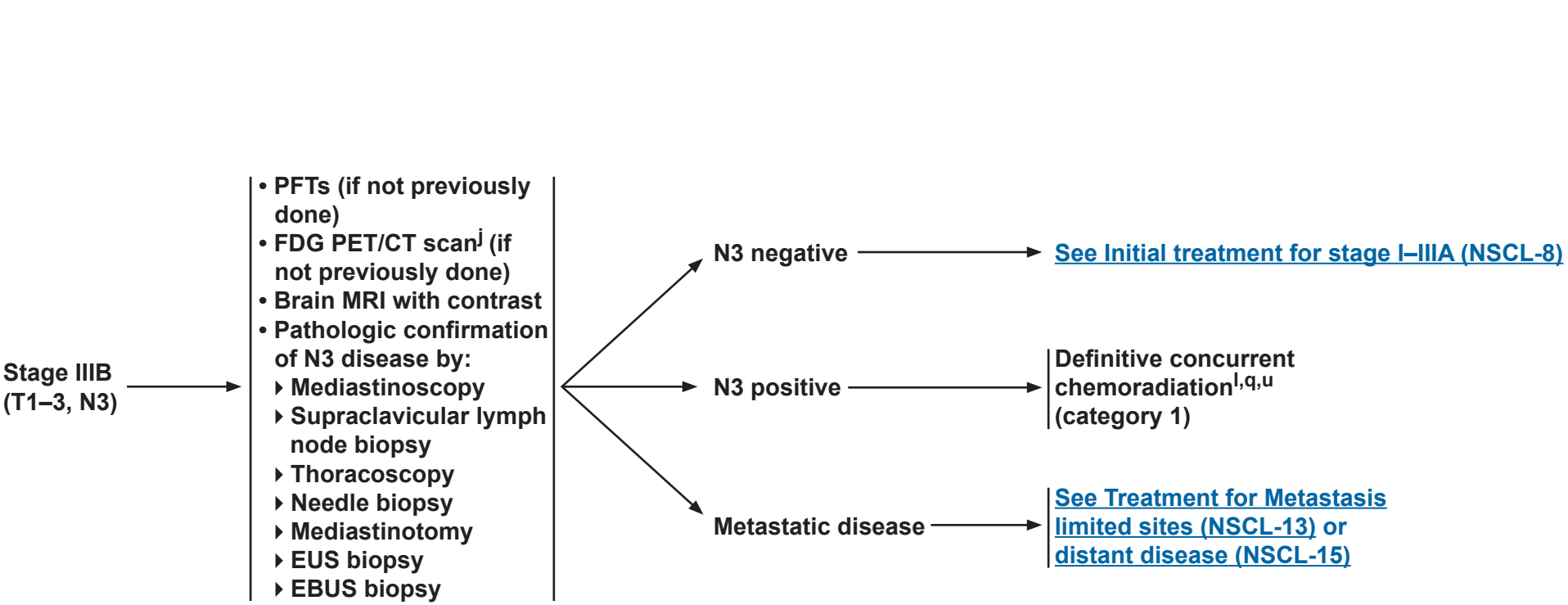

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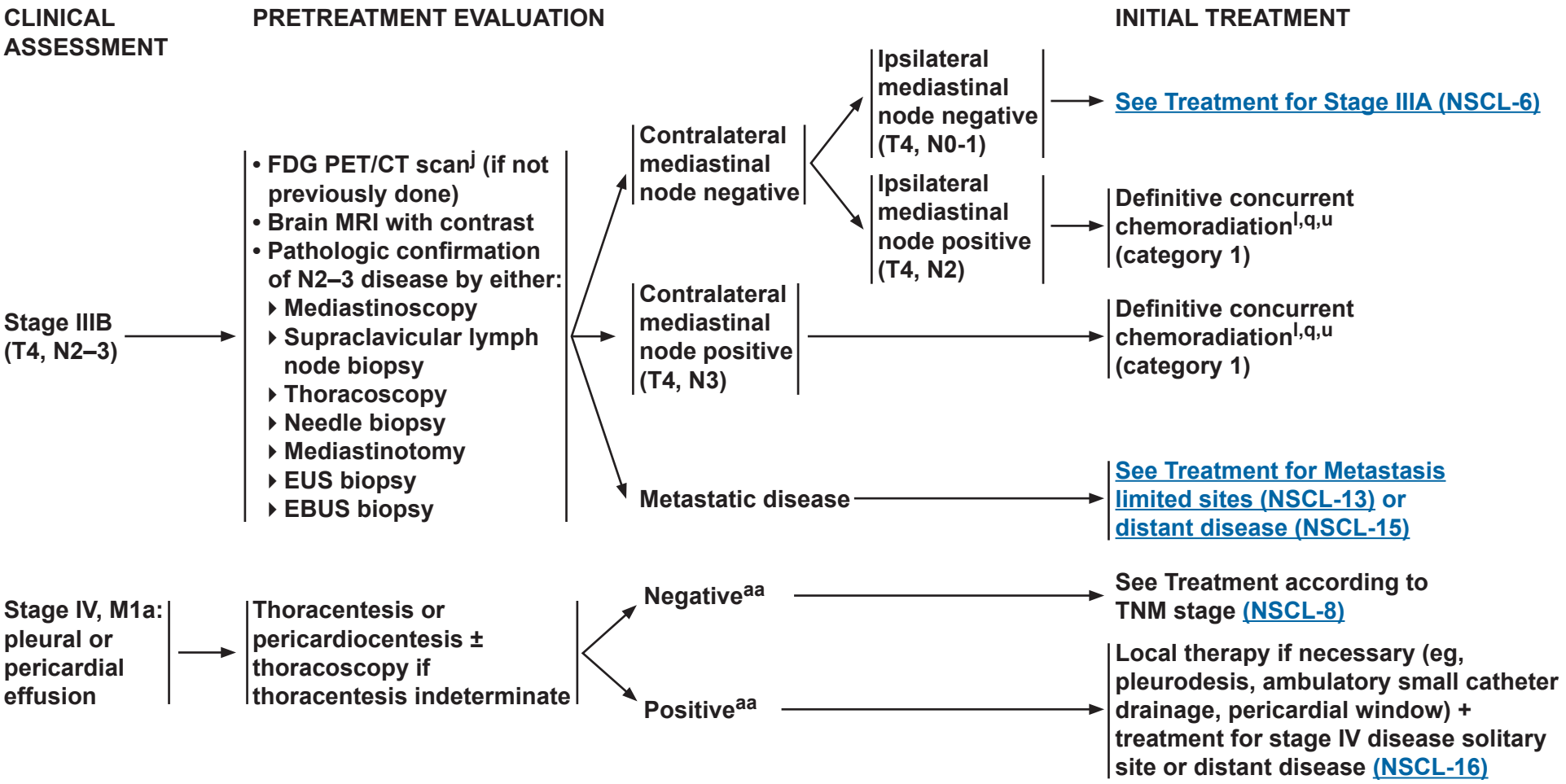

[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

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

[q]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

[u]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

[aa]While 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 that 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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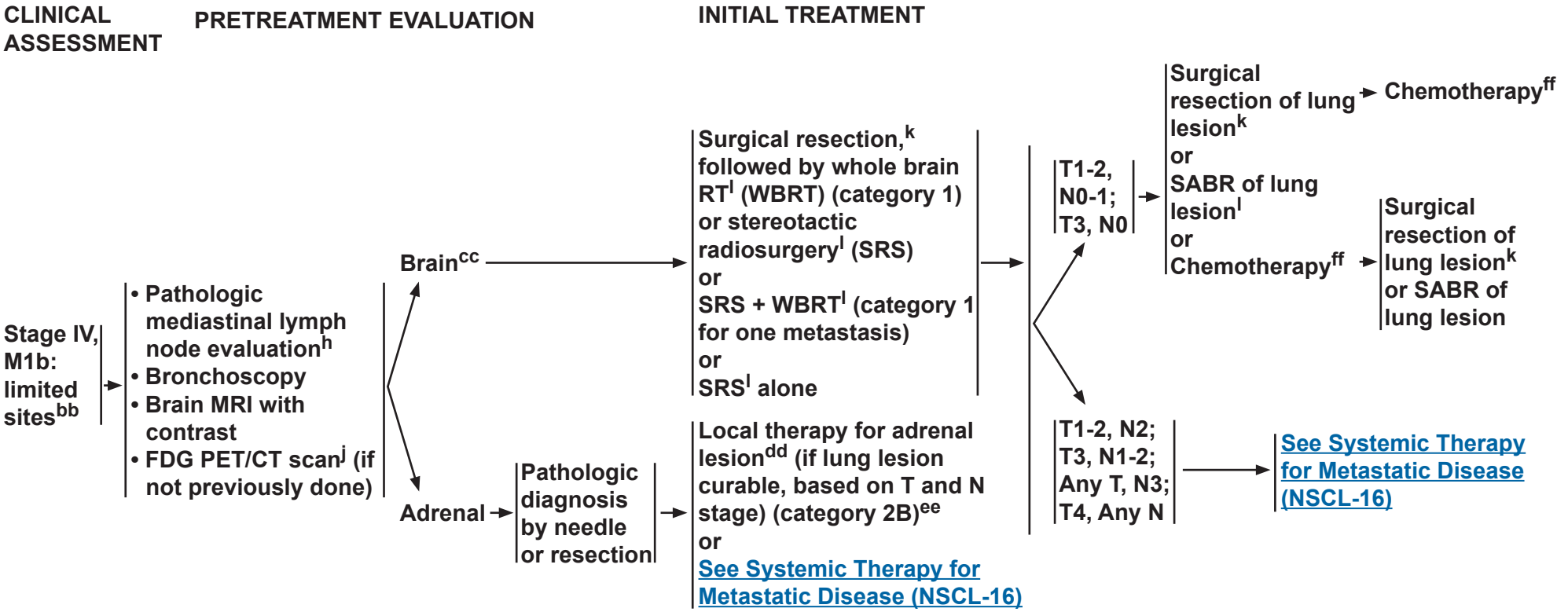

[h]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[j]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[k]See Principles of Surgical Therapy (NSCL-B).
[l]See Principles of Radiation Therapy (NSCL-C).
[bb]Aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease.
[cc]See NCCN Guidelines for Central Nervous System Cancers.
[dd]May include adrenalectomy or RT (including SABR).
[ee]Patients with N2 disease have a poor prognosis and systemic therapy should be considered.
[ff]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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SURVEILLANCE

No evidence of clinical/radiographic disease, stages I–IV:

- **H&P and chest CT ± contrast every 6–12 mo for 2 y, then H&P and a low-dose non-contrast-enhanced chest CT annually**
  - **Patients treated with chemotherapy ± RT who have residual abnormalities may require more frequent imaging**
- **Smoking cessation advice, counseling, and pharmacotherapy**
- **FDG PET/CT[hh] or brain MRI is not indicated**
- **See Cancer Survivorship Care (NSCL-G).**

Locoregional recurrence → **See Therapy for Recurrence and Metastasis (NSCL-15)**

Distant metastases → **See Therapy for Recurrence and Metastasis (NSCL-15)**

[gg]FDG PET/CT is currently not warranted in the routine surveillance and follow-up of patients with NSCLC. However, many benign conditions (such as atelectasis, consolidation, and radiation fibrosis) are difficult to differentiate from neoplasm on standard CT imaging, and FDG PET/CT can be used to differentiate true malignancy in these settings. However, if FDG PET/CT is to be used as a problem-solving tool in patients after radiation therapy, histopathologic confirmation of recurrent disease is needed because areas previously treated with radiation therapy can remain FDG avid for up to 2 years.

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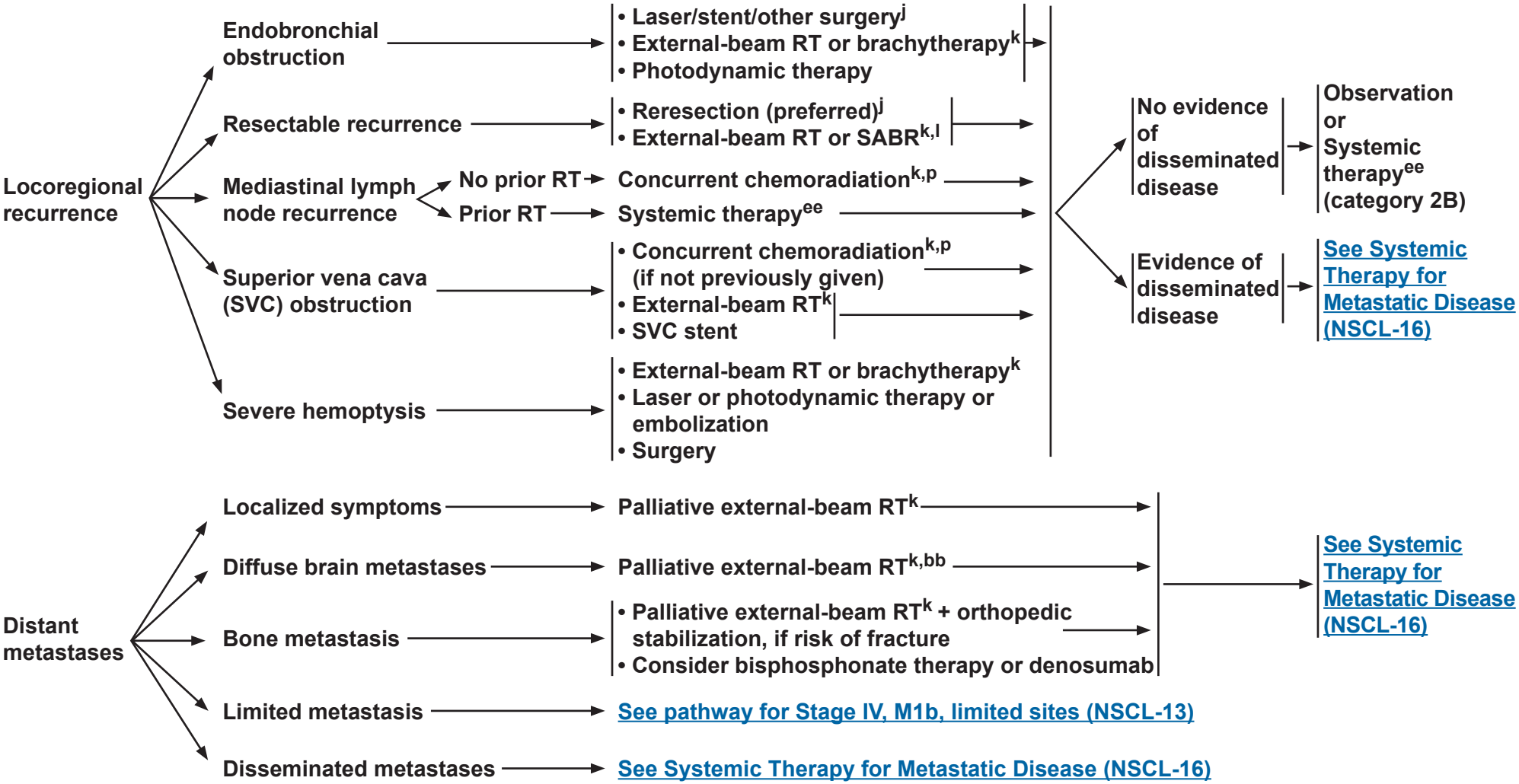
THERAPY FOR RECURRENCE AND METASTASIS



[j] See Principles of Surgical Therapy (NSCL-B).
[k] See Principles of Radiation Therapy (NSCL-C).
[l] Interventional radiology ablation is an option for selected patients.
[p] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[bb] See NCCN Guidelines for Central Nervous System Cancers.
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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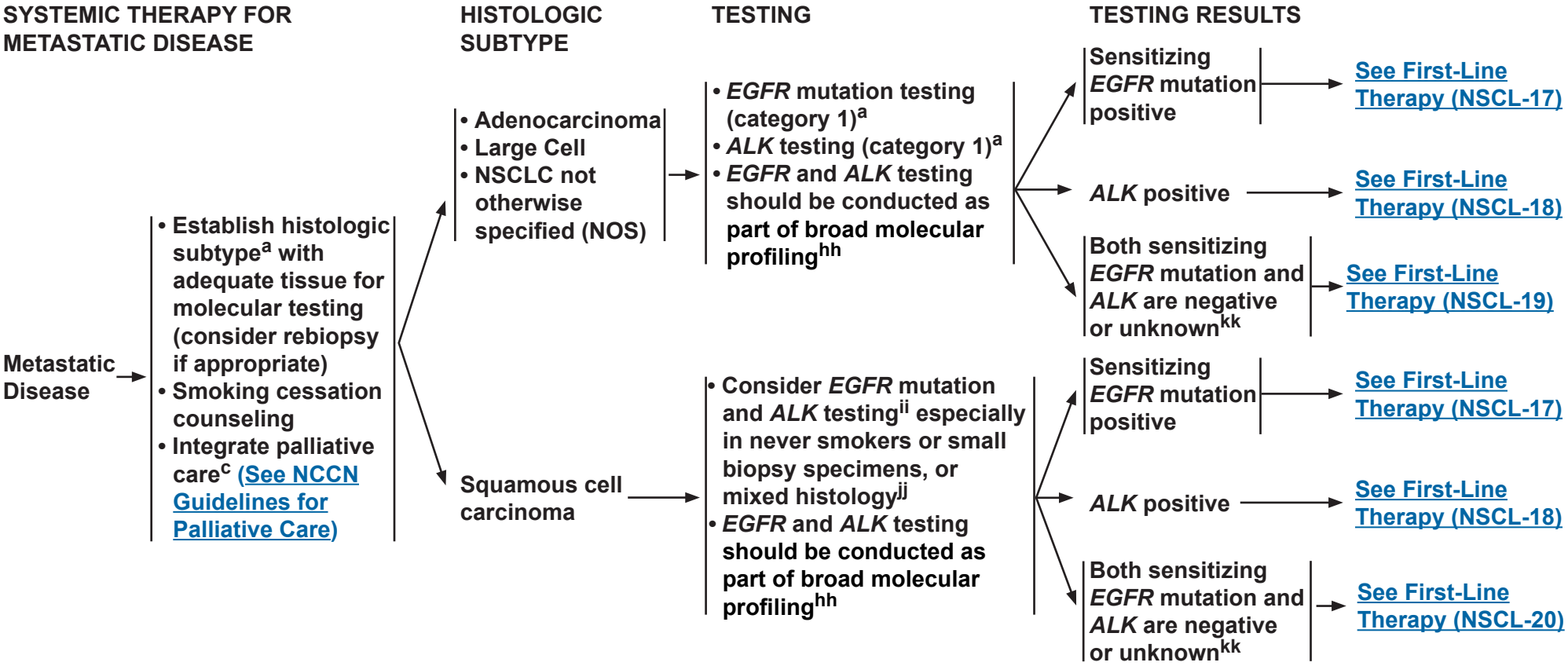

[a] See Principles of Pathologic Review (NSCL-A).

[c] Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742.

[hh] The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

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

[jj] Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with *EGFR* mutant advanced non-small cell lung cancers with a squamous or squamous-like component. Mol Cancer Ther 2012;11:2535-2540.

[kk] Consider ROS1 testing; if positive, may treat with crizotinib. Shaw AT, Ou S-HI, Bang Y-J, et al. Crizotinib in ROS1-rearranged non-small cell lung cancer. N Engl J Med 2014;371:1963-1971.

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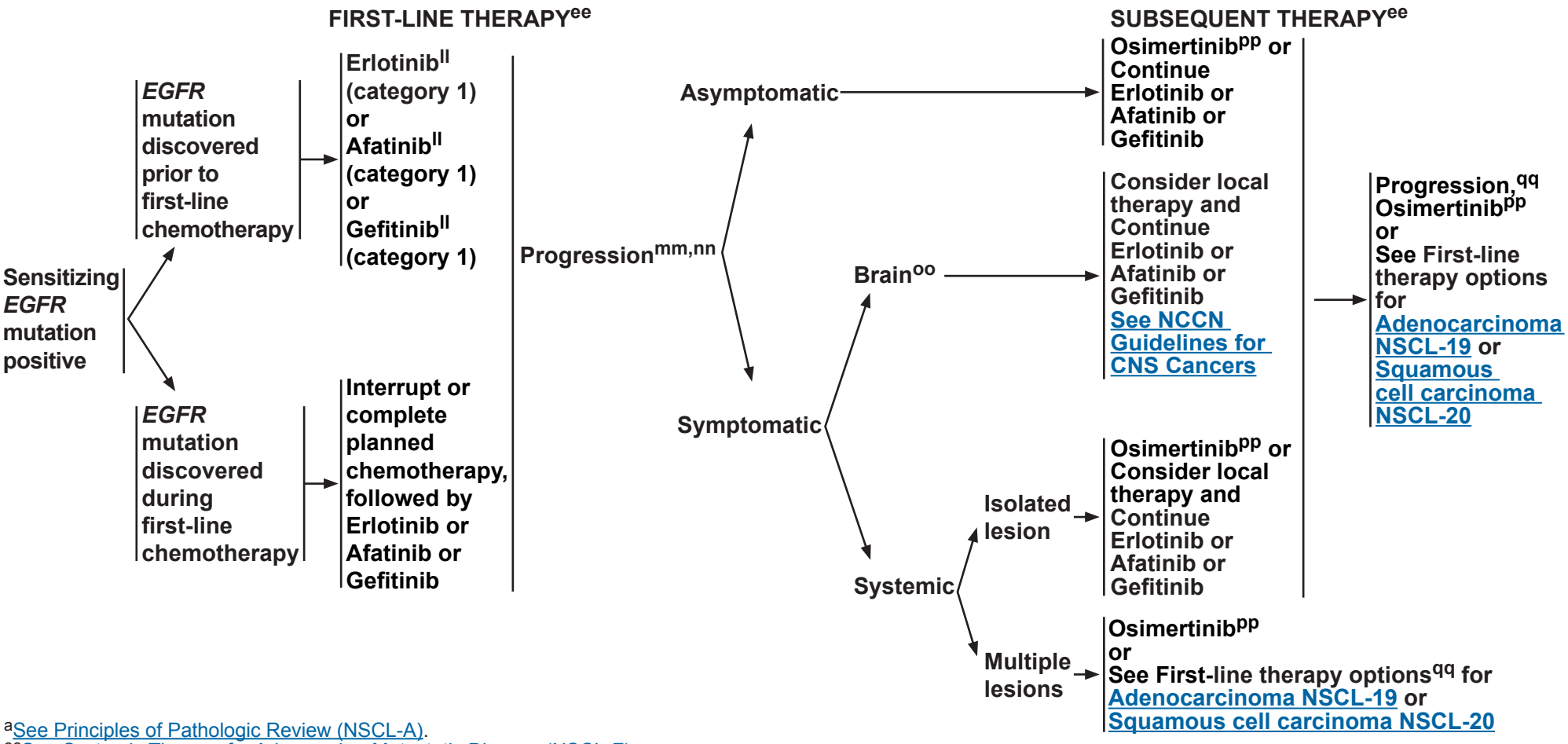
SENSITIZING EGFR MUTATION POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll] For performance status 0-4.
[mm] Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.
[nn] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[oo] Consider pulse erlotinib for carcinomatosis meningitis.
[pp] Osimertinib is approved for patients with metastatic EGFR T790M mutation-positive tumors, as determined by an FDA-approved test or other validated laboratory developed test performed in a CLIA-approved laboratory.
[qq] Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

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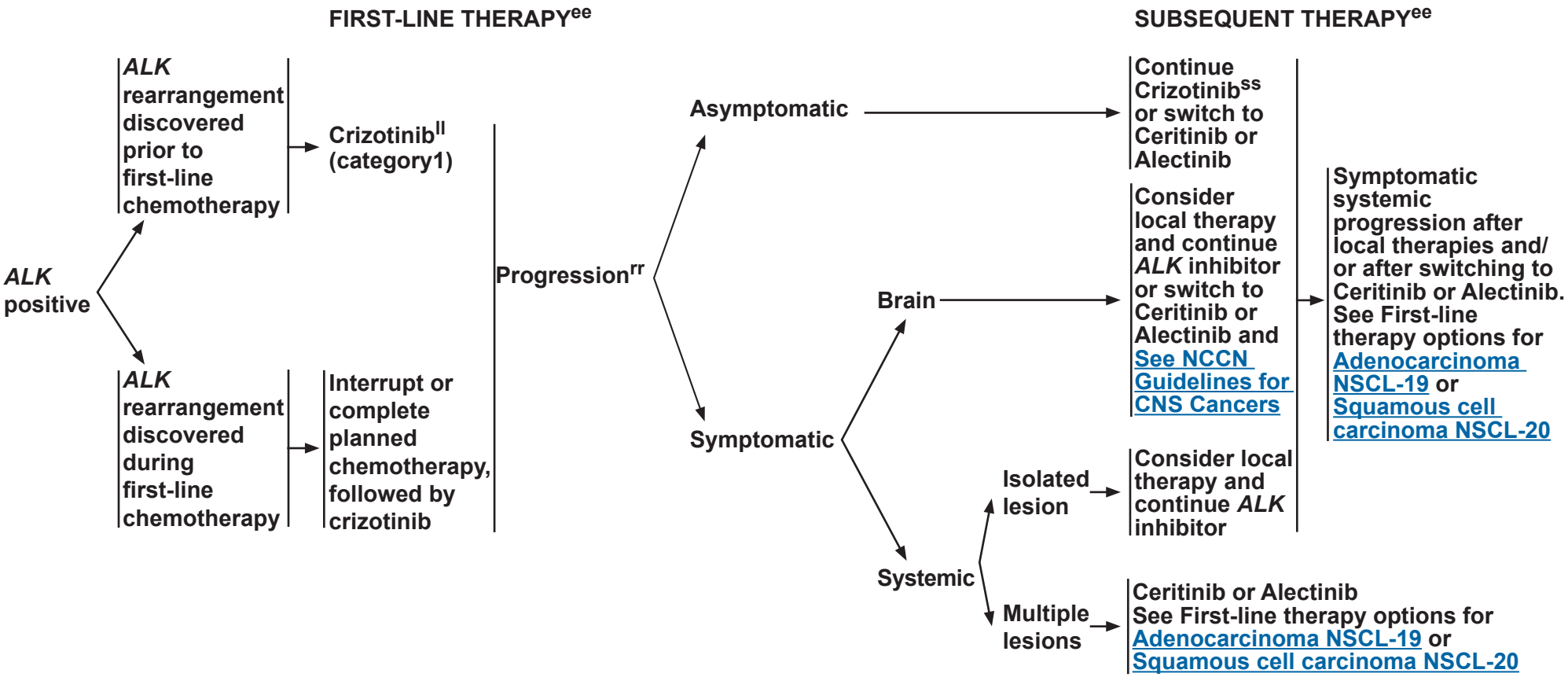
ALK POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[ee] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ll] For performance status 0-4.
[rr] Patients who are intolerant to crizotinib may be switched to ceritinib or alectinib.
[ss] For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

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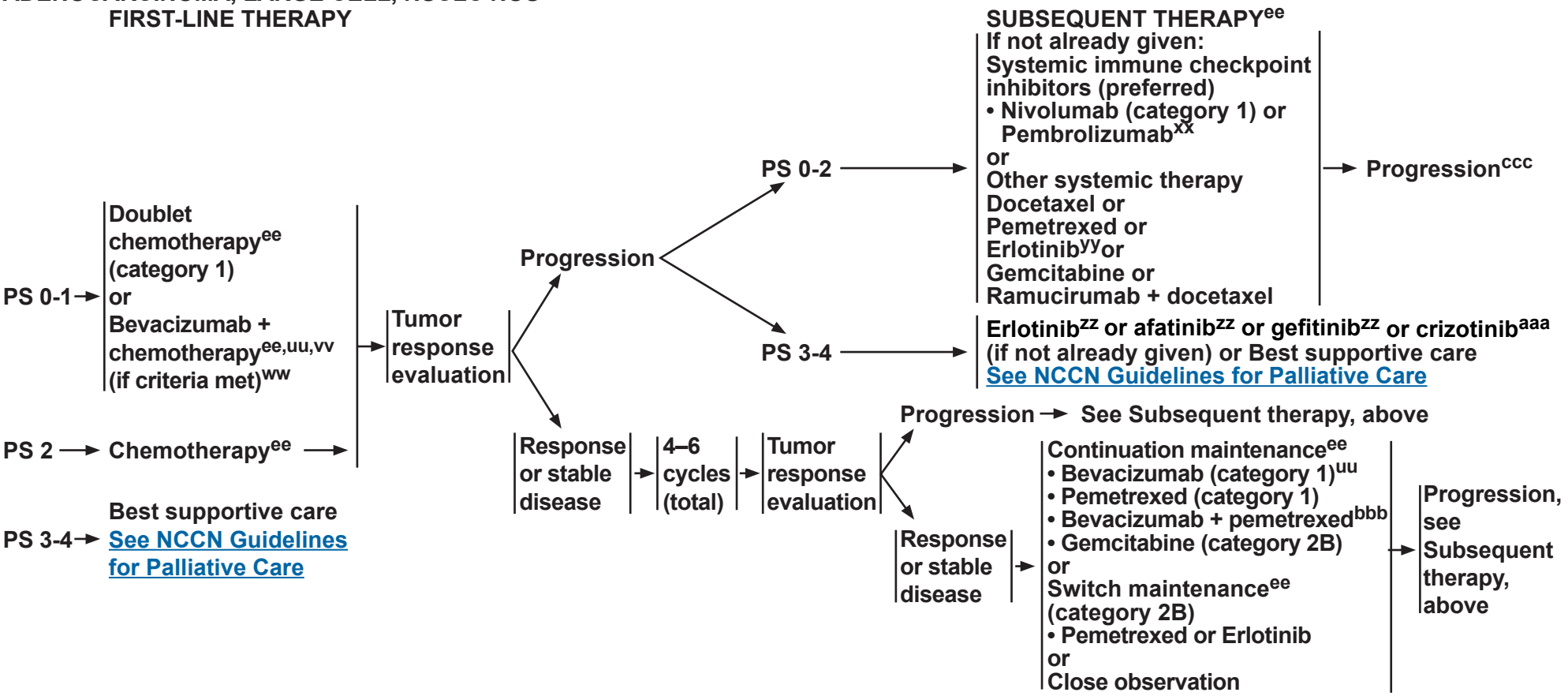
ADENOCARCINOMA, LARGE CELL, NSCLC NOS[tt]

FIRST-LINE THERAPY



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

[tt] Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).

[uu] Bevacizumab should be given until progression.

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

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

[xx] Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.

[yy] Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a "poor" classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Lancet Oncol 2014; 15:713-21.

[zz] May be considered for PS 3 and 4 patients with sensitizing EGFR mutations.

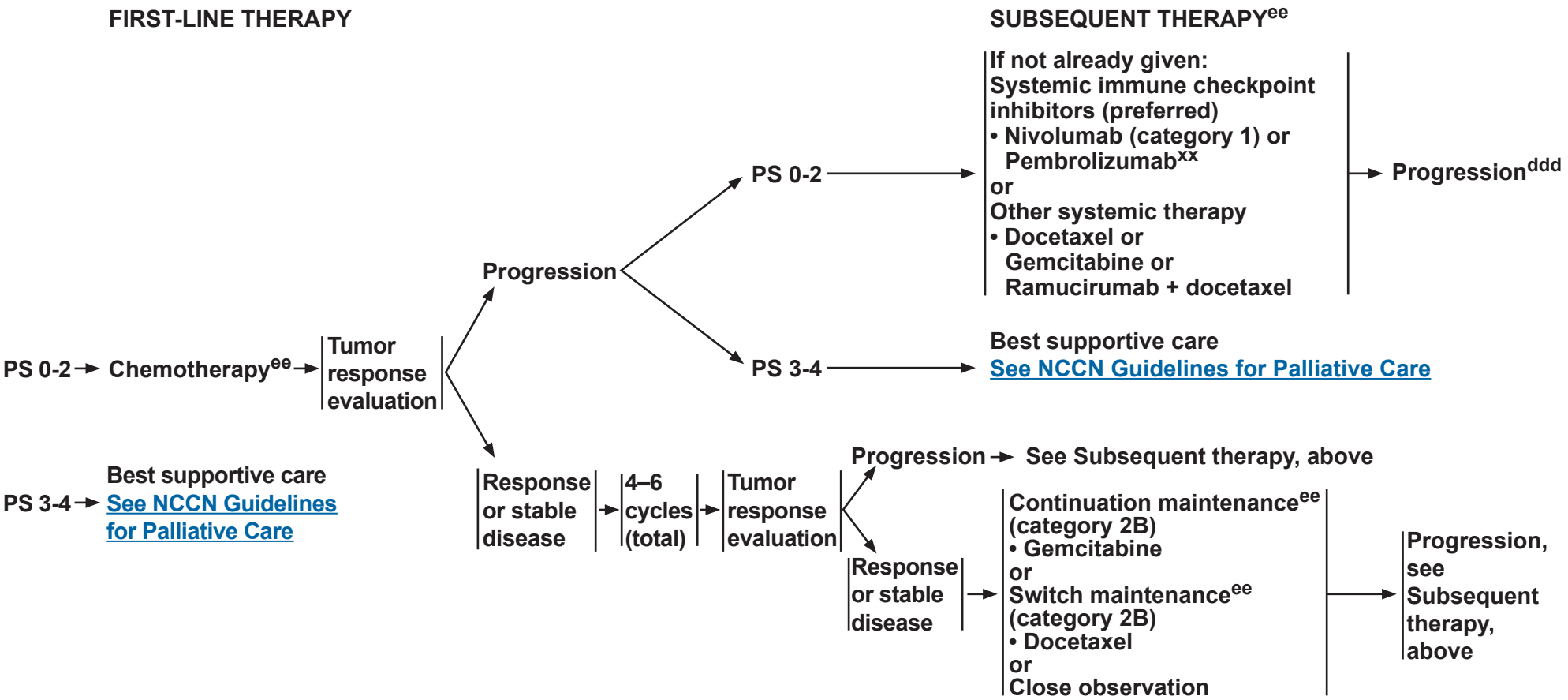
[aaa] May be considered for PS 3 and 4 patients if positive for the ALK rearrangement.

[bbb] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

[ccc] If not already given, options for PS 0-2 include erlotinib, nivolumab, pembrolizumab, docetaxel (category 2B), pemetrexed (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

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.

SQUAMOUS CELL CARCINOMA[tt]



[ee]See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[tt]Consider additional mutational testing if only EGFR and ALK were performed. See Emerging Targeted Agents for Patients With Genetic Alterations (NSCL-H).
[xx]Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression, as determined by an FDA-approved test for PD-L1 with use of pembrolizumab.
[ddd]If not already given, options for PS 0-2 include nivolumab, pembrolizumab, docetaxel (category 2B), gemcitabine (category 2B), or ramucirumab + docetaxel (category 2B); options for PS 3-4 include best supportive care. Options for further progression are best supportive care or clinical trial.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC,[1] including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis.[2,3] Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to an increasing number of drugable targets, primarily tyrosine kinase inhibitors (TKIs) (see *Molecular Diagnostic Studies in Lung Cancer* in this section).[4,5]
- The WHO tumor classification system has historically provided the foundation for the classification of lung tumors, including histologic types, clinical features, staging considerations, and the molecular, genetic, and epidemiologic aspects of lung cancer.[6,7]
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung. The recently published classification of adenocarcinoma should be used for this tumor subtype in resection specimens and small biopsies.[8] Use of bronchioloalveolar carcinoma (BAC) terminology is strongly discouraged.
- The generic term "non-small cell lung cancer (NSCLC)" should be avoided as a single diagnostic term. In small biopsies of poorly differentiated carcinomas where immunohistochemistry (IHC) is used, the following terms are acceptable: "NSCLC favor adenocarcinoma" or "NSCLC favor squamous cell carcinoma."[8] Mutational testing (eg, epidermal growth factor receptor [EGFR]) is strongly recommended in all NSCLC favor adenocarcinomas.
- Formalin-fixed paraffin-embedded tumor is acceptable for most molecular analyses.
- Limited use of IHC studies in small tissue samples is strongly recommended, thereby preserving critical tumor tissue for molecular studies, particularly in patients with advanced-stage disease. A limited panel of one squamous cell carcinoma marker (eg, p63, p40) and one adenocarcinoma marker (eg, TTF-1, napsin A) should suffice for most diagnostic problems.[8]

Adenocarcinoma Classification[8]

- Adenocarcinoma in situ (AIS; formerly BAC): ≤3 cm nodule, lepidic growth, mucinous, non-mucinous, or mixed mucinous/non-mucinous types.
- Minimally invasive adenocarcinoma (MIA): ≤3 cm nodule with ≤5 mm of invasion, lepidic growth, mucinous, non-mucinous, or mixed mucinous/non-mucinous types.
- Invasive adenocarcinoma, predominant growth pattern: lepidic >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

- Judicious use of immunohistochemistry is strongly recommended to preserve tissue for molecular testing. IHC should be utilized only after consideration of all data including routine H&E histology, clinical findings, imaging studies, and patient's history.
- Although the concordance is generally good between the histologic subtype and the immunophenotype seen in small biopsies compared with surgical resection specimens, caution is advised in attempting to subtype small biopsies with limited material or cases with an ambiguous immunophenotype.
- IHC should be used to differentiate primary pulmonary adenocarcinoma from the following: squamous cell carcinoma, large cell carcinoma, metastatic carcinoma, and malignant mesothelioma; to determine whether neuroendocrine differentiation is present.[9-11]
- Primary pulmonary adenocarcinoma
  - In patients for whom the primary origin of the carcinoma is uncertain, an appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to the lung.[12]
  - 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 non-mucinous adenocarcinoma subtypes.[13] Metastatic adenocarcinoma to the lung is virtually always negative for TTF-1 except in metastatic thyroid malignancies, in which case thyroglobulin is also positive.
  - 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.[12]
  - The panel of TTF-1 (or alternatively napsin A) and p63 (or alternatively p40) may be useful in refining the diagnosis to either adenocarcinoma or squamous cell carcinoma in small biopsy specimens previously classified as NSCLC NOS.[8]
- Neuroendocrine differentiation
  - CD56, chromogranin, and synaptophysin are used to identify neuroendocrine tumors.
- Malignant mesothelioma versus pulmonary adenocarcinoma
  - The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) can be made by correlation of the histology with the clinical impression, imaging studies, and a limited panel of immunomarkers if needed.[11]
    - ◊ Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma).[14,15]
    - ◊ Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, claudin-4 and TTF-1 (negative in mesothelioma).[8,11]

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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 a critical biological determinant for proper therapy selection in patients with lung cancer.**
  - **There is a significant association between** ***EGFR*** **mutations—especially exon 19 deletion and exon 21 (L858R, L861), exon 18 (G719X, G719), and exon 20 (S768I) mutations—and sensitivity to EGFR TKIs.[16-19]**
  - **The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.[20,21]**
  - **Overlapping** ***EGFR*** **and** ***KRAS*** **mutations occur in <1% of patients with lung cancer.[22]**
  - ***KRAS*** **mutations are associated with intrinsic EGFR TKI resistance, and** ***KRAS*** **gene sequencing could be useful for the selection of patients as candidates for EGFR TKI therapy.[23]** ***KRAS*** **testing may identify patients who may not benefit from further molecular diagnostic testing.**
  - **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 cancers.** ***KRAS*** **mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.[24] 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 are more common in non-mucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.**
  - **Primary resistance to EGFR TKI therapy is associated with** ***KRAS*** **mutation. Acquired resistance is associated with second-site mutations within the** ***EGFR*** **kinase domain (such as T790M), amplification of alternative kinases (such as** ***MET***), **histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).**
- ***ALK***
  - **Anaplastic lymphoma kinase (*ALK*) gene rearrangements represent the fusion between** ***ALK*** **and various partner genes, including echinoderm microtubule-associated protein-like 4 (*EML4*).[25] ALK fusions have been identified in a subset of patients with NSCLC and represent a unique subset of NSCLC patients for whom** ***ALK*** **inhibitors may represent a very effective therapeutic strategy.[26] Crizotinib and ceritinib are oral** ***ALK*** **inhibitors that are approved by the FDA for patients with metastatic NSCLC who have the** ***ALK*** **gene rearrangement (ie,** ***ALK*** **positive).**
  - ***ALK*** **NSCLC occurs most commonly in a unique subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor** ***EGFR*** **mutations.[27,28] However, for the most part,** ***ALK*** **translocations and** ***EGFR*** **mutations are mutually exclusive.[27, 29-31]**
  - **The current standard method for detecting** ***ALK*** **NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. The appropriate antibody and detection method for** ***ALK*** **protein expression can be used for rapid prescreening of ALK-rearranged lung adenocarcinomas and selection of cases that will subsequently be confirmed by FISH testing.[32]**

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

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PRINCIPLES OF SURGICAL THERAPY (1 of 4)

Evaluation

- **Determination of resectability, surgical staging, and *pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice*.**
- **CT and PET used for staging should be within 60 days before proceeding with surgical evaluation.**
- **Resection is the preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, and SABR). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where SABR is considered for high-risk patients, a multidisciplinary evaluation (including a radiation oncologist) is recommended.**
- **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 (eg, multidisciplinary clinic and/or tumor board).**

Resection

- **Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.**
- **Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.**
- **Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.**
- **Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:**
  - **Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy**
  - **Peripheral nodule[1] ≤2 cm with at least one of the following:**
    - **Pure AIS histology**
    - **Nodule has ≥50% ground-glass appearance on CT**
    - **Radiologic surveillance confirms a long doubling time (≥400 days)**
- **VATS or minimally invasive surgery (including robotic-assisted approaches) should be strongly considered 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 (ie, decreased pain, reduced hospital length of stay, more rapid return to function, fewer complications) without compromise of cancer outcomes.**
- **Lung-sparing anatomic resection (sleeve lobectomy) is preferred over pneumonectomy, if anatomically appropriate and margin-negative resection is achieved.**
- **T3 (invasion) and T4 local extension 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.**

Margins and Nodal Assessment (see NSCL-B 2 of 4)

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

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

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PRINCIPLES OF SURGICAL THERAPY (2 of 4)

Margins and Nodal Assessment

- 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 (eg, medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed; pleural margin adjacent to aorta when no attachment to aorta is present).
- N1 and N2 node resection and mapping should be a routine component of lung cancer resections—a 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, and the highest mediastinal node negative for tumor. The resection is defined as incomplete whenever there is involvement of resection margins, 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 a radiation oncologist for resected stage IIIA.

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

The role of surgery in patients with pathologically documented N2 disease remains controversial.[1] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[2,3] However, this population is heterogeneous and the panel believes that these trials did 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 lymph node dissection. If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option.
- The determination of the role of surgery in a patient with N2-positive lymph nodes 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 lymph nodes substantially increases the likelihood of positive N3 lymph nodes. Pathologic evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS are additional techniques for minimally invasive 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 lymph node involvement prior to a final treatment decision.

The Role of Surgery in Patients With Stage IIIA (N2) NSCLC is continued on NSCL-B 3 of 4 through NSCL-B 4 of 4

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PRINCIPLES OF SURGICAL THERAPY (3 of 4)

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

- 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 pretreatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.[5]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,6,7]
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[7,8]
- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[5,9] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[10] 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 those used for standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Treatment 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 of the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.[11,12] If a surgeon or center is uncertain about the feasibility or safety of resection after definitive doses of radiation, consider obtaining an additional surgical opinion from a high-volume specialized center. These operations may also benefit from additional considerations of soft tissue flap coverage in the radiation field at the time of resection.
- 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.[13-16] In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy.[17]

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

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PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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

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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 NSCLC, as either definitive or palliative therapy. Radiation oncology input as part of a multidisciplinary evaluation or discussion should be provided for all patients with NSCLC.
- The critical goals of modern RT are to maximize tumor control and to minimize treatment toxicity. A minimum technologic standard is CT-planned 3D-CRT.[1]
- More advanced technologies are appropriate when needed to deliver curative RT safely. These technologies include (but are not limited to) 4D-CT and/or PET/CT simulation, IMRT/VMAT, IGRT, motion management, and proton therapy (https://www.astro.org/Practice-Management/Reimbursement/Model-Policies.aspx). Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.[2-4]
- Centers using advanced technologies should implement and document modality-specific quality assurance measures. The ideal is external credentialing of both treatment planning and delivery such as required for participation in RTOG clinical trials employing advanced technologies. Useful references include the ACR-ASTRO Practice Guidelines for Radiation Oncology (http://www.acr.org/~/media/ACR/Documents/PGTS/toc.pdf).

Early-Stage NSCLC (Stage I, selected node negative Stage IIA)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.[5-10]
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.[10-12]
- A combined analysis of two randomized trials (that individually did not complete accrual) of SABR vs. lobectomy in operable patients found similar cancer-specific outcomes and improved toxicity profile and survival for SABR compared to surgery.[13] This analysis does not provide sufficient data to change the standard of care for good surgical candidates but strengthens the indication for SABR in patients with relative contraindications for surgery or who refuse surgery.
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are less preferred alternatives.[14-15]
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC*).

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 (2 of 10)

Locally Advanced NSCLC (Stage II-IIII)

- The standard of care for patients with inoperable stage II (node positive) and stage III is concurrent chemotherapy/RT.[16-18] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf) RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemotherapy/RT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.[19,20] (http://www.acr.org/~/media/ACR/Documents/AppCriteria/OncologyNonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf) Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).[21,22]
- RT has a role before or after surgery.
  http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf
  - Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[23] and is recommended for resectable superior sulcus tumors.[24,25]
  - Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.[26,27] The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.[28,29]
  - The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Up front multidisciplinary consultation is particularly important when considering surgical treatment of stage III NSCLC.
  - In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.[30,31] 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 patients[32-34] and is recommended for positive resection margins.[35]
  - PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.[36]

Advanced/Metastatic NSCLC (Stage IV)

- RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction).
- 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 sites.[37,38]
- See the NCCN Guidelines for Central Nervous System Cancers regarding RT for brain metastases.

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PRINCIPLES OF RADIATION THERAPY (3 of 10)

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

- ICRU Reports 62 and 83 detail the current definitions of target volumes for 3D-RT and IMRT. GTV comprises the known extent of disease (primary and nodal) on imaging and pathologic assessment, CTV includes regions of presumed microscopic extent or dissemination, and PTV comprises the ITV (which includes margin for target motion) plus a setup margin for positioning and mechanical variability. http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx
- PTV margin can be decreased by immobilization, motion management, and IGRT techniques.
- Consistent delineation of normal structures is critical for evaluating plans for safety. The RTOG consensus lung-contouring atlas is a useful resource. http://www.rtog.org/CoreLab/ContouringAtlases/LungAtlas.aspx
- Commonly used prescription doses and normal tissue dose constraints are summarized in Tables 2 through 5. These are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.[39,40] Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.[41-45]

Node-Negative Early-Stage SABR

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[46] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SABR, but slightly more protracted regimens are appropriate as well.[46,47] For centrally located tumors (defined as within 2 cm of the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,[48,49] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[51] The dose for 5-fraction regimens is 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.[50,51]
- Prescription doses incompletely describe the actual delivered doses, which also strongly depend 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.[52,53] All of these must be considered when interpreting or emulating regimens from prior studies.

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PRINCIPLES OF RADIATION THERAPY (4 of 10)

Locally Advanced Stage/Conventionally Fractionated RT

- IFI omitting ENI allows tumor dose escalation and is associated with a low risk of isolated nodal relapse, particularly in PET/CT–staged patients.[54-58] Two randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[59] IFI is reasonable in order to optimize definitive dosing to the tumor.[60]
- The most commonly prescribed doses for definitive RT are 60 to 70 Gy in 2 Gy fractions. Doses of at least 60 Gy should be given.[61] Dose escalation in RT alone,[62] sequential chemoRT,[63] or concurrent chemoRT[64] is associated with better survival in non-randomized comparisons. While doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected,[65-68] results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy, found that 74 Gy does not improve overall survival, and might be potentially harmful.[69] A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,[70] and individualized accelerated RT dose intensification is now being evaluated in a randomized trial (RTOG 1106).
- Doses of 45 to 54 Gy in 1.8 to 2 Gy fractions are standard preoperative doses.[71] Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,[72-75] but require experience in thoracic surgical techniques to minimize the risk of surgical complications after high-dose RT.
- In PORT, the CTV includes the bronchial stump and high-risk draining lymph node stations.[76] Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.[30,31,77] Lung dose constraints should be more conservative as tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.[78]

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. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment,[79-82] and are preferred for patients with poor performance status and/or shorter life expectancy. For palliation of thoracic symptoms, higher dose/longer-course thoracic RT (eg, ≥30 Gy in 10 fractions) is associated with modestly improved survival and symptoms, particularly in patients with good performance status.[83] When higher doses (>30 Gy) are warranted, 3D-CRT 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. Because 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,[84] especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT versus 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.[85] Given the potential for rapid progression of NSCLC,[86,87] PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal 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, 4D-CT.
- Photon beam energy should be individualized based on 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 buildup and lateral electron scatter effects in heterogeneous density tissues are recommended. Heterogeneity correction with simple pencil beam algorithms is not recommended.[55]
- Respiratory motion should be managed when motion is excessive. This includes (but is not limited to) 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.[88]
- IGRT—including (but not limited to) orthogonal pair planar imaging and volumetric imaging (such as CBCT or CT on rails)—is recommended when using SABR and 3D-CRT/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
2D-RT	2-Dimensional RT
3D-CRT	3-Dimensional Conformal RT
4D-CT	4-Dimensional Computed Tomography
AAPM	American Association of Physicists in Medicine
ABC	Active Breathing Control
ACR	American College of Radiology
ASTRO	American Society for Radiation Oncology
BED	Biologically Effective Dose
CBCT	Cone-Beam CT
CTV*	Clinical Target Volume
ENI	Elective Nodal Irradiation
GTV*	Gross Tumor Volume
ICRU	International Commission on Radiation Units and Measurements
IFI	Involved Field Irradiation
IGRT	Image-Guided RT
IMRT	Intensity-Modulated RT
ITV*	Internal Target Volume
OAR	Organ at Risk
OBI	On-Board Imaging
PORT	Postoperative RT
PTV*	Planning Target Volume
QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
RTOG	Radiation Therapy Oncology Group now part of NRG Oncology
SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
VMAT	Volumetric Modulated Arc Therapy

*Refer to ICRU Report 83 for detailed definitions.

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Table 2. Commonly Used Doses for SABR

Total 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 and >1 cm from chest wall
48–50 Gy	4	Central or peripheral tumors <4–5 cm, especially <1 cm from chest wall
50–55 Gy	5	Central or peripheral tumors, especially <1 cm from chest wall
60–70 Gy	8–10	Central tumors

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	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	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	105% of PTV prescription^
Brachial Plexus	17.5 Gy	24 Gy (8 Gy/fx)	27.2 Gy (6.8 Gy/fx)	32 Gy (6.4 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	105% of PTV prescription^
Great Vessels	37 Gy	NS	49 Gy (12.25 Gy/fx)	105% of PTV prescription^
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	105% of PTV prescription^
Rib	30 Gy	30 Gy (10 Gy/fx)	40 Gy (10 Gy/fx)	NS
Skin	26 Gy	24 Gy (8 Gy/fx)	36 Gy (9 Gy/fx)	32 Gy (6.4 Gy/fx)
Stomach	12.4 Gy	NS	27.2 Gy (6.8 Gy/fx)	NS

*Based on constraints used in recent RTOG SABR trials (RTOG 0618, 0813, & 0915).
^for central tumor location. NS = not specified

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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	60–70 Gy	2 Gy	6–7 weeks
Preoperative RT	45–54 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*	CNS GLs*	CNS GLs*
• Symptomatic chest disease in patients with poor PS	17 Gy	8.5 Gy	1–2 weeks
• Any metastasis in patients with poor PS	8–20 Gy	8–4 Gy	1 day–1 week

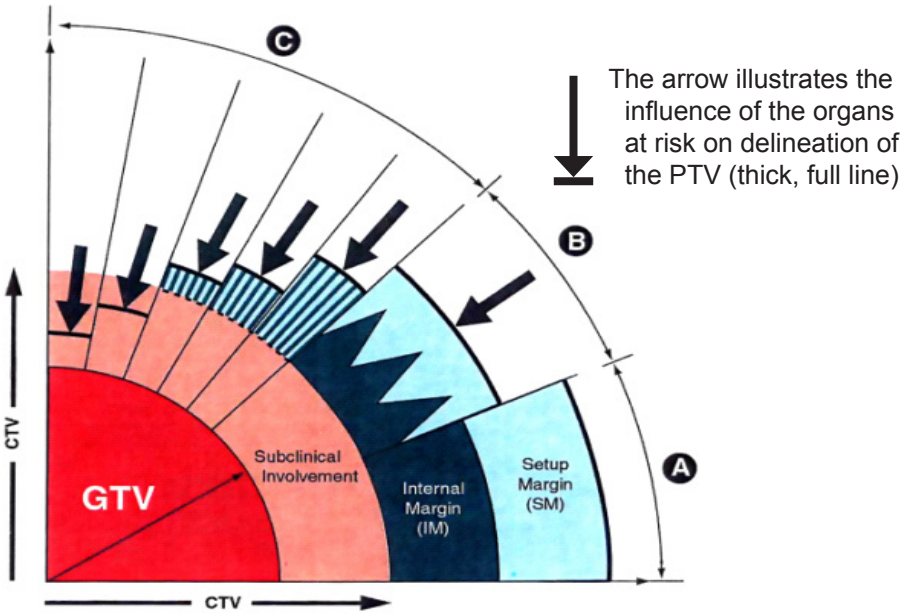
*NCCN Guidelines for Central Nervous System Cancers

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

OAR	Constraints in 30–35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; 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



©Journal of the ICRU. Report 62 Prescribing, Recording and Reporting Photon Beam Therapy (Supplement to ICRU Report 50) 1999, Figure 2.16 from p 16.

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

CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- **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 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 day 1; etoposide 100 mg/m² days 1–3, every 28 days for 4 cycles[b]**
- **Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles[d]**
- **Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[e]**
- **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for nonsquamous (without specific histologic subtype) every 21 days for 4 cycles[f]**

Chemotherapy Regimens for Patients with Comorbidities or Patients Not Able to Tolerate Cisplatin

Paclitaxel 200 mg/m² day 1, carboplatin AUC 6 day 1, every 21 days[g]

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

Concurrent Chemotherapy/RT Regimens*,**

- **Cisplatin 50 mg/m² on days 1, 8, 29, and 36; etoposide 50 mg/m² days 1–5, 29–33; concurrent thoracic RT[a,b]**
- **Cisplatin 100 mg/m² days 1 and 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT[b]**
- **Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT[c] (nonsquamous)**
- **Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT[d] (nonsquamous)**
- **Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT[e]**

Sequential Chemotherapy/RT Regimens (Adjuvant)

- **Cisplatin 100 mg/m² on days 1 and 29; vinblastine 5 mg/m²/weekly on days 1, 8, 15, 22, and 29; followed by RT[b]**
- **Paclitaxel 200 mg/m² over 3 hours on day 1; carboplatin AUC 6 over 60 minutes on day 1 every 3 weeks for 2 cycles followed by thoracic RT[f]**

Concurrent Chemotherapy/RT Followed by Chemotherapy**

- **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[f]**
- **Cisplatin 50 mg/m² on days 1, 8, 29, and 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]**

*Regimens can be used as neoadjuvant/preoperative/induction chemoradiotherapy.
**Regimens can be used as adjuvant or definitive concurrent chemotherapy/RT.

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 4)

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 (≈ 25%–35%), time to progression (4–6 mo), median survival (8–10 mo), 1-year survival rate (30%–40%), and 2-year survival rate (10%–15%) in fit patients.**
- **Unfit patients of any age (performance status 3–4) do not benefit from cytotoxic treatment, except erlotinib, afatinib, or gefitinib for *EGFR* mutation-positive and crizotinib for *ALK* positive tumors of nonsquamous NSCLC or NSCLC NOS.**

First-line Therapy

- **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 may be appropriate in select patients.**
- **Response assessment after 1-2 cycles, then every 2-4 cycles.**

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.

Subsequent Therapy

- **In patients who have experienced disease progression either during or after first-line therapy, the following are established second-line agents.**
  - **Nivolumab improves survival when compared with docetaxel.**
  - **Pembrolizumab improves overall response rate in PD-L1 positive tumors.**
  - **Docetaxel is superior to vinorelbine or ifosfamide.**
  - **Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.**
  - **Ramucirumab + docetaxel improves survival when compared to docetaxel alone.**
  - **Erlotinib is superior to best supportive care.**

See First-line Systemic Therapy options for Adenocarcinoma, Large cell, NSCLC NOS on NSCL-F (2 of 4)

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 of 4)†

First-line Systemic Therapy options

Adenocarcinoma, Large cell, NSCLC NOS (PS 0-1)

- Bevacizumab/carboplatin/paclitaxel (category 1)[1]
- Bevacizumab/carboplatin/pemetrexed[2]
- Bevacizumab/cisplatin/pemetrexed[3]
- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/pemetrexed (category 1)[10]
- Carboplatin/vinorelbine (category 1)[11]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[12]
- Cisplatin/gemcitabine (category 1)[9,13]
- Cisplatin/paclitaxel (category 1)[14]
- Cisplatin/pemetrexed (category 1)[13]
- Cisplatin/vinorelbine (category 1)[5,9,15]
- Gemcitabine/docetaxel (category 1)[16]
- Gemcitabine/vinorelbine (category 1)[17]

Adenocarcinoma, Large cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel[18]
- Carboplatin/albumin-bound paclitaxel[19,20]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/pemetrexed[10]
- Carboplatin/vinorelbine
- Docetaxel[21,22]
- Etoposide[23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[16]
- Gemcitabine/vinorelbine[17]
- Irinotecan[27,28]
- Paclitaxel[29-31]
- Pemetrexed[32]
- Vinorelbine[21]

See First-line Systemic Therapy options for Squamous Cell Carcinoma on NSCL-F (3 of 4)

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

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 of 4)†

First-line Systemic Therapy options

Squamous cell carcinoma (PS 0-1)

- Carboplatin/albumin-bound paclitaxel (category 1)[4]
- Carboplatin/docetaxel (category 1)[5]
- Carboplatin/etoposide (category 1)[6,7]
- Carboplatin/gemcitabine (category 1)[8]
- Carboplatin/paclitaxel (category 1)[9]
- Carboplatin/vinorelbine (category 1)[11]
- Cisplatin/docetaxel (category 1)[5]
- Cisplatin/etoposide (category 1)[12]
- Cisplatin/gemcitabine (category 1)[9,13]
- Cisplatin/gemcitabine/necitumumab (category 3)[33]
- Cisplatin/paclitaxel (category 1)[14]
- Cisplatin/vinorelbine (category 1)[5,9,15]
- Gemcitabine/docetaxel (category 1)[16]
- Gemcitabine/vinorelbine (category 1)[17]

Squamous cell carcinoma (PS 2)

- Albumin-bound paclitaxel[18]
- Carboplatin/albumin-bound paclitaxel[19-20]
- Carboplatin/docetaxel[5]
- Carboplatin/etoposide[6,7]
- Carboplatin/gemcitabine[8]
- Carboplatin/paclitaxel[9]
- Carboplatin/vinorelbine
- Cisplatin/gemcitabine/necitumumab (category 3)[33]
- Docetaxel[21-22]
- Etoposide[23]
- Gemcitabine[24-26]
- Gemcitabine/docetaxel[16]
- Gemcitabine/vinorelbine[17]
- Irinotecan[27-28]
- Paclitaxel[29-31]
- Vinorelbine[21]

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

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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (4 of 4)

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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
  - H&P 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
  - Herpes zoster vaccine
  - Pneumococcal vaccination with revaccination as appropriate

Counseling Regarding Health Promotion and Wellness[1]

- 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:
  See NCCN Guidelines for Colorectal Cancer Screening
- Prostate Cancer:
  See NCCN Guidelines for Prostate Cancer Early Detection
- Breast Cancer:
  See NCCN Guidelines for Breast Cancer Screening

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[3]American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed September 24, 2014)

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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.

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
BRAF* V600E mutation	**vemurafenib[1,2]** **dabrafenib[2,3]** **dabrafenib + trametinib[4]**
High level *MET* amplification or MET exon 14 skipping mutation	**crizotinib[5,6,7,8]**
***RET* rearrangements**	**cabozantinib[9,10]**
***ROS1* rearrangements**	**crizotinib[11]**
***HER2* mutations**	**trastuzumab[12] (category 2B)** **afatinib[13] (category 2B)**

*Non-V600E mutations have variable kinase activity and response to these agents.

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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.

Table 1. Definitions for T, N, M*

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

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

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

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

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

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

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

Table 2. Anatomic Stage and Prognostic Groups

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0

Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original and primary source for this information is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science+Business Media, LLC (SBM). (For complete information and data supporting the staging tables, visit www.springer.com.) Any citation or quotation of this material must be credited to the AJCC as its primary source. The inclusion of this information herein does not authorize any reuse or further distribution without the expressed, written permission of Springer SBM, on behalf of the AJCC.

Table 3. Descriptors, T and M Categories, and Stage Grouping*

6th Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (<2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤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

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.

Table of Contents

Overview

Lung cancer is the leading cause of cancer death in the United States. In 2015, an estimated 221,200 new cases (115,610 in men and 105,590 in women) of lung and bronchial cancer will be diagnosed, and 158,040 deaths (86,380 in men and 71,660 in women) are estimated to occur because of the disease.[1] Only 17.4% of all patients with lung cancer are alive 5 years or more after diagnosis.[2] However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), targeted therapies, and immunotherapies.[3-6] Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease.[7]

The NCCN Guidelines® for Non-Small Cell Lung Cancer (NSCLC) are updated at least once a year by the NCCN Panel (eg, there were 7 updates for 2015). These NCCN Guidelines were first published in 1996.[8] The *Summary of the Guidelines Updates* describes the most recent revisions to the algorithms, which have been incorporated into this updated Discussion text. By definition, the NCCN Guidelines cannot incorporate all possible clinical variations and are not intended to replace good clinical judgment or individualization of treatments.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for NSCLC, an electronic search of the PubMed database was performed to obtain key literature in NSCLC, published between June 1, 2014 and July 1, 2015 using the following search term: NSCLC. The PubMed database was chosen, because it is the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase 2; Clinical Trial, Phase 3; Clinical Trial, Phase 4; Guideline; Meta-Analysis; Randomized Controlled Trial; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 245 citations and their potential relevance was examined. The data from key PubMed articles selected by the NCCN Panel for review during the NCCN Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the NCCN Panel, have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). If high-level evidence is lacking, recommendations are based on the panel's review of lower-level evidence and expert opinion. The complete details of the development and update of the NCCN Guidelines are available on the NCCN webpage.

Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths.[9-13] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[12,14] The risk for lung cancer increases with the number of packs of cigarettes smoked per day and with the number of years spent smoking (ie, pack-years of smoking history). Exposed nonsmokers also have an increased relative risk (RR = 1.24) of developing lung cancer from *secondhand smoke*; other studies have reported a modest risk (hazard ratio [HR] = 1.05).[10,14-17]

Other possible risk factors for lung cancer include disease history (eg, COPD), cancer history, family history of lung cancer, and exposure to other carcinogens (see the NCCN Guidelines for Lung Cancer

Screening, available at NCCN.org).[18,19] The International Agency for Research on Cancer lists several agents known to cause lung cancer, including arsenic, chromium, asbestos, nickel, cadmium, beryllium, silica, and diesel fumes.[20-22] Asbestos is a known carcinogen that increases the risk for 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.[23] Asbestos also causes malignant pleural mesothelioma (see the NCCN Guidelines for Malignant Pleural Mesothelioma, available at NCCN.org). Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.

It is not clear whether hormone replacement therapy (HRT) affects the risk for lung cancer in women. More than 20 studies have been published, but the results have been inconsistent. In a large randomized controlled study,[24] no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT; however, the risk of death from NSCLC increased.[24] In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.[25]

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[11] Active smoking and secondhand smoke both cause lung cancer. There is a causal relationship between active smoking and lung cancer and also between other cancers (eg, esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, ovarian cancer, colorectal, and cervical cancers) and other diseases and conditions.[11] Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.[26] Those who live with someone who smokes have an increased risk for lung cancer.[15] Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer.[27-30] The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).[31] It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.[32] Some surgeons will not operate on a current smoker. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful.[33] For example, the American Cancer Society (ACS) has a *Guide to Quitting Smoking* as well as The E-Quit Study, which uses email to help smokers quit smoking.

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline.[34,35] A recent study suggests that cytisine is more efficacious than nicotine replacement therapy, although more side effects were reported with cytisine such as nausea, vomiting, and sleep disorders.[36] Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.[37-39] The effectiveness of varenicline for preventing relapse has not been clearly established.[40] The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms. Varenicline has also been associated with other disorders (eg, visual disturbances, movement disorders, unconsciousness, cardiovascular disorders) and, therefore, is banned in truck and bus drivers, pilots, and air traffic controllers.[41-44] Other side effects with varenicline include nausea, abnormal dreams, insomnia, and headache.[39,45,46] Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.[47] However, in spite of the

potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[47]

Lung Cancer Screening

Lung cancer is the leading cause of cancer death worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes.[48,49] Because localized cancer can be managed with curative intent, and because the mortality rate in other solid tumors (eg, cervix, colon) seems to be decreased by screening and early detection, lung cancer is an appropriate candidate for a population-based screening approach.

The National Lung Screening Trial (NLST) (ACRIN Protocol A6654) was a randomized controlled study involving more than 53,000 current or former heavy smokers that assessed the risks and benefits of low-dose CT scans compared with chest radiographs for detecting lung cancer.[50] Data from the NLST showed that screening individuals with high-risk factors using low-dose CT decreased the mortality rate from lung cancer by 20%.[51] Individuals with high-risk factors were either current or former smokers with a 30 or more pack-year smoking history (former smokers had quit up to 15 years before enrollment), were 55 to 74 years of age, and had no evidence of lung cancer.[50,52] The NCCN, ACS, U.S. Preventive Services Task Force, American College of Chest Physicians, European Society for Medical Oncology (ESMO), and other organizations recommend lung cancer screening using low-dose CT for select high-risk current and former smokers (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).[53-56] It is important to note that low-dose CT screening and follow-up is not a substitute for smoking cessation; patients should be offered smoking cessation counseling (see NCCN Guidelines for Smoking Cessation, available at NCCN.org).

Classification and Prognostic Factors

The 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 the NCCN Guidelines for Small Cell Lung Cancer, available at NCCN.org). NSCLC accounts for more than 83% of all lung cancer cases, and it includes 2 major types: 1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types); and 2) squamous cell (epidermoid) carcinoma.[2] Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring histology in nonsmokers. In 2011, an international panel revised the classification of lung adenocarcinoma (see the *Pathologic Evaluation of Lung Cancer* in this Discussion).[57] Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status (PS) (ECOG 0, 1, or 2), no significant weight loss (not more than 5%), and female gender.[58]

Diagnostic Evaluation of Lung Nodules

Because lung cancer screening is now recommended for early diagnosis, algorithms for evaluating suspicious lung nodules are included in the NCCN Guidelines (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[59] The diagnostic algorithm for pulmonary nodules in the NCCN Guidelines for NSCLC incorporates information from the NCCN Guidelines for Lung Cancer Screening. Risk assessment is used to determine which individuals are at high risk for lung cancer and thus are candidates for low-dose CT.

Solid and subsolid nodules are the 2 main types of pulmonary nodules that may be seen on low-dose CT scans. The Fleischner Society has recommendations for patients with solid and subsolid nodules.[60,61]

Subsolid nodules include 1) nonsolid nodules also known as ground-glass opacities (GGOs) or ground-glass nodules (GGNs); and 2) part-solid nodules, which contain both ground-glass and solid components.[60,62-64] Nonsolid nodules are mainly adenocarcinoma in situ (AIS) or minimally invasive adenocarcinoma (MIA), formerly known as bronchioloalveolar carcinoma (BAC) (see *Adenocarcinoma* in this Discussion); patients have 5-year disease-free survival of 100% if these nonsolid nodules are completely resected.[57,60,62,63,65,66] Data suggest that many nonsolid nodules discovered incidentally on CT imaging will resolve and many of those that persist may not progress to clinically significant cancer.[67,68] Solid and part-solid nodules are more likely to be invasive, faster-growing cancers, factors that are reflected in the increased suspicion and follow-up of these nodules (see *Follow-up* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[59-61]

All findings and patient factors need to be carefully evaluated in a multidisciplinary diagnostic team before establishing a diagnosis of lung cancer and before starting treatment. The NCCN Guidelines recommend biopsy or surgical excision for highly suspicious nodules seen on low-dose CT scans or further surveillance for nodules with a low suspicion of cancer depending on the type of nodule and a multidisciplinary evaluation of other patient factors (see *Risk Assessment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients having repeat scans, the most important radiologic factor is change or stability of a nodule when compared with a previous imaging study. False-positive results (eg, benign intrapulmonary lymph nodes, noncalcified granulomas) frequently occurred with low-dose CT when using the original cutoffs for nodule size deemed suspicious for malignancy from the NLST.[51] However, it is anticipated that the revised cutoff values for suspicious nodules recently recommended by the American College of Radiology will decrease the false-positive rate from low-dose CT.[69,70]

Larger Tumors

The NCCN Guidelines recommend that the diagnostic strategy should be individualized for each patient depending on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (eg, comorbidities), and local expertise. The diagnostic strategy needs to be decided in a multidisciplinary setting. Decisions regarding whether a biopsy (including what type of biopsy) or surgical excision is appropriate depend on several factors as outlined in the NSCLC algorithm (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For example, a preoperative biopsy may be appropriate if an intraoperative diagnosis seems to be difficult or very risky. The preferred biopsy technique depends on the site of disease and is described in the NSCLC algorithm (see *Principles of Diagnostic Evaluation*). For example, radial endobronchial ultrasound (EBUS; also known as endosonography), navigational bronchoscopy, or transthoracic needle aspiration (TTNA) are recommended for patients with suspected peripheral nodules.[71] PET imaging is useful before selecting a biopsy site, because it is better to biopsy the site that will confer the highest stage. Patients with suspected nodal disease should be assessed by endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA), EBUS–guided transbronchial needle aspiration (EBUS-TBNA), navigational bronchoscopy, or mediastinoscopy (see *Mediastinoscopy* in this Discussion and *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer). EBUS provides access to nodal stations 2R/2L, 4R/4L, 7, 10R/10L, and other hilar nodal stations. EUS provides access to nodal stations 5, 7, 8, and 9.

If pathology results from biopsy or surgical excision indicate a diagnosis of NSCLC, then further evaluation and staging need to be done so that the patient's health care team can determine the most appropriate and effective treatment plan (see *Pathologic Evaluation of Lung Cancer* and *Staging* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer). Diagnosis, staging, and planned resection (eg, lobectomy) are ideally one operative procedure for patients with early-stage disease (see the *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A preoperative or intraoperative tissue diagnosis of lung cancer should be established before doing a lobectomy.

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the histologic type of 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 (ie, positive or negative margins), and do molecular diagnostic studies to determine whether certain gene alterations are present (eg, epidermal growth factor receptor [EGFR] mutations) (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[72] Data show that targeted therapy is potentially very effective in patients with specific gene mutations or rearrangements (see *EGFR Mutations* and *ALK Gene Rearrangements* in this Discussion).[5,73-78] Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, sputum, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.[71,79] Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;[80,81] however, diagnosis may be more difficult when using small biopsies and cytology.[65] The mediastinal lymph nodes are systematically sampled to determine the staging and therapeutic options. Other lung diseases also need to be ruled out (eg, tuberculosis, sarcoidosis).[82,83]

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 WHO histologic classification for carcinomas of the lung.[84] In 2011, the classification for lung adenocarcinoma was revised by an international panel (see *Adenocarcinoma* in this Discussion).[57] The revised classification requires immunohistochemical, histochemical, and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[85] In addition, the revised classification recommends that use of general categories (eg, NSCLC) should be minimized, because more effective treatment can be selected when the histology is known.

Adenocarcinoma

In the revised classification for adenocarcinoma, the categories of BAC or mixed subtype adenocarcinoma are no longer used.[57] If necessary, *former BAC* can be used. The categories for adenocarcinoma include: 1) AIS (formerly BAC), which is a preinvasive lesion; 2) MIA; 3) invasive adenocarcinoma (includes formerly nonmucinous BAC); and 4) variants of invasive adenocarcinoma (includes formerly mucinous BAC). Both AIS and MIA are associated with excellent survival if they are resected. The international panel and NCCN recommend that all patients with adenocarcinoma be tested for EGFR mutations; the NCCN Panel also recommends that these patients be tested for anaplastic lymphoma kinase (ALK) gene rearrangements and other genetic alterations. The

terms---*AIS*, *MIA*, and *large cell carcinoma*---should not be used for small samples because of challenges with cytology specimens.[57]

Immunohistochemical Staining

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung (eg, breast, prostate, colorectal), to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the NSCLC algorithm (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). However, limited use of IHC in small tissue samples is recommended to conserve tumor tissue for molecular studies, especially in patients with advanced disease.[81,86] For the 2016 update, the NCCN Panel added a recommendation that IHC should be judiciously used to preserve tissue for molecular testing. Before using IHC, all findings should be assessed including routine H&E histology, clinical findings, imaging studies, and the patient's history. Although cytology can be used to distinguish adenocarcinomas from squamous cell carcinomas, IHC is also useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens.[57,87] Squamous cell carcinomas are often TTF-1 negative and p63 positive, whereas adenocarcinomas are usually TTF-1 positive.[57] These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[57,87] Other markers (eg, p40, Napsin A) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[88,89]

Immunohistochemistry (IHC) is valuable for distinguishing between malignant mesothelioma and lung adenocarcinoma.[90,91] However, the NCCN Panel feels that malignant mesothelioma and lung adenocarcinoma can be distinguished using clinical impression, imaging, and a limited panel of immunomarkers (if needed) to preserve tissue for molecular testing. The stains that are positive for adenocarcinoma include carcinoembryonic antigen (CEA), B72.3, Ber-EP4, MOC-31, CD15, claudin-4, and TTF-1; these stains are negative for mesothelioma.[92] Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin antibody),[93] HMBW-1, and cytokeratin 5/6.[90,91] If needed, 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 WT-1), CEA, and MOC-31 (or B72.3, Ber-EP4, or BG-8).[90,91,94]

An appropriate panel of immunohistochemical stains is recommended to rule out metastatic carcinoma to the lung if the primary origin of the carcinoma is uncertain. TTF-1 is very important for distinguishing primary lung adenocarcinoma from metastatic adenocarcinoma, because most primary adenocarcinomas are TTF-1 positive. TTF-1 is typically negative for squamous cell carcinoma.[87] However, TTF-1 is positive in tumors from patients with thyroid cancer.[95] 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+. CDX2 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 SCLC is negative in 25% of cases.

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC.[71,87,96] However, many patients with SCLC have characteristic CT and clinical findings (eg, massive lymphadenopathy, mediastinal invasion). Most SCLCs are immunoreactive for TTF-1; they are typically negative for CK34βE12

and p63.[97,98] Many SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule, and synaptophysin. However, these markers alone cannot be used to distinguish SCLC from NSCLC, because approximately 10% of NSCLCs are immunoreactive for at least one of these neuroendocrine markers.[99] Data suggest that microRNA expression can be used to distinguish SCLC from NSCLC.[100]

Staging

The NCCN Guidelines use the AJCC (7th edition) staging system for lung cancer.[101] The definitions for TNM and the stage grouping are summarized in Tables 1 and 2 of the staging tables (see *Definitions for T,N,M* and *Staging* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The descriptors of the TNM classification scheme are summarized in Table 3 of the staging tables (see *Staging*). The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)[102,103] and was adopted by the AJCC.[104,105] With the AJCC staging, locally advanced disease is stage III; advanced disease is stage IV. Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, and imaging) and other invasive staging procedures (eg, thoracotomy, examination of lymph nodes using mediastinoscopy).[101]

From 2005 to 2011, the overall 5-year relative survival rate for lung cancer was 17.4% in the United States.[2] Of lung and bronchial cancer cases, 16% were diagnosed while the cancer was still confined to the primary site; 22% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 57% were diagnosed after the cancer had already metastasized; and for the remaining 5% the staging information was unknown. The corresponding 5-year relative survival rates were 54.8% for localized, 27.4% for regional, 4.2% for distant, and 7.5% for unstaged.[2] However, these data include SCLC, which has a poorer prognosis.

Five-year survival after lobectomy for pathologic stage I NSCLC ranges from 45% to 65%, depending on whether the patient has stage 1A or 1B disease and on the location of the tumor.[106] Another study in patients with stage I disease (n = 19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; however, for untreated stage I NSCLC, 5-year overall survival was only 6%.[107] Of patients with stage I disease who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Predictive and Prognostic Biomarkers

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. A *predictive* biomarker is indicative of therapeutic efficacy, because there is an interaction between the biomarker and therapy on patient outcome. A *prognostic* biomarker is indicative of patient survival independent of the treatment received, because the biomarker is an indicator of the innate tumor aggressiveness (see *KRAS Mutations* at the end of this section).

Predictive biomarkers include the ALK fusion oncogene (fusion between ALK and other genes [eg, echinoderm microtubule-associated protein-like 4]) and sensitizing EGFR mutations (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Emerging biomarkers include HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and high-level MET amplification or MET exon 14 skipping mutation (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The presence

of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy; therefore, these mutations are referred to as *sensitizing* EGFR mutations (see *EGFR Mutations* in this Discussion).[108,109] However, the presence of EGFR exon 19 deletions (LREA) or exon 21 L858R mutations does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.[110] The ALK fusion oncogene (ie, ALK gene rearrangement) is a predictive biomarker that has been identified in a small subset of patients with NSCLC (see *ALK Gene Rearrangements* in this Discussion and *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Other gene rearrangements (ie, gene fusions) have recently been identified (such as ROS1, RET) that are susceptible to targeted therapies.[111-116]

Testing for ALK gene rearrangements and EGFR mutations is recommended (category 1) in the NSCLC algorithm for patients with nonsquamous NSCLC or NSCLC not otherwise specified (NOS) so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as erlotinib, gefitinib, afatinib, crizotinib, ceritinib, and alectinib (see *Targeted Therapies* in this Discussion and in the NCCN Guidelines for Non-Small Cell Lung Cancer).[117-121] Although rare, patients with ALK rearrangements or sensitizing EGFR mutations can have mixed squamous cell histology.[122,123] Therefore, testing for ALK rearrangements and EGFR mutations can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. EGFR, KRAS, and ALK genetic alterations do not usually overlap.[124,125]

Patients with NSCLC may have other genetic alterations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[73,126,127] Mutation screening assays for detecting multiple biomarkers simultaneously (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) have been developed that can detect more than 50 point mutations, including EGFR.[128,129] However, these multiplex polymerase chain reaction (PCR) systems do not detect gene rearrangements, because they are not point mutations. ALK gene rearrangements can be detected using fluorescence in situ hybridization (FISH) (see *ALK Gene Rearrangements* in this Discussion). Broad molecular profiling systems, such as next-generation sequencing (NGS) (also known as massively parallel sequencing), can detect panels of mutations and gene rearrangements if the NGS platforms have been designed and validated to detect these genetic alterations.[130-137] It is important to recognize that NGS requires quality control as much as any other diagnostic technique; because it is primer dependent, the panel of genes and abnormalities detected with NGS will vary depending on the design of the NGS platform. For example, some NGS platforms can detect both mutations and gene rearrangements, as well as copy number variation, but they are not uniformly present in all NGS assays being conducted either commercially or in institutional laboratories.

Other driver mutations and gene rearrangements (ie, driver events) are being identified such as HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and high-level MET amplification or MET exon skipping mutation.[111,112,114,116,138-147] Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they are FDA approved for other indications (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[135,148] Thus, the NCCN Panel strongly endorses broader molecular profiling (also known as precision medicine) to identify rare driver mutations to ensure that patients receive the most appropriate

treatment; patients may be eligible for clinical trials for some of these targeted agents.[120] Several online resources are available that describe NSCLC driver events such as DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment)[149] and *My Cancer Genome*.[128,150] The KRAS oncogene is a prognostic biomarker. The presence of KRAS mutations is prognostic of poor survival for patients with NSCLC when compared to the absence of KRAS mutations, independent of therapy (see *KRAS Mutations* in this Discussion).[151] KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.[108,152,153] EGFR, KRAS, and ALK genetic alterations do not usually overlap.[124,125] TKI therapy is not effective in patients with KRAS mutations and ALK gene rearrangements.

EGFR Mutations

In patients with NSCLC, the most commonly found EGFR mutations are deletions in exon 19 (Exon19del [with conserved deletion of the LREA sequence] in 45% of patients with EGFR mutations) 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, such as erlotinib, gefitinib, and afatinib (see *Targeted Therapies* in this Discussion).[154] Thus, these mutations are referred to as sensitizing EGFR mutations. Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was recently re-approved by the FDA based on a phase 4 study and is now available in the United States.[118] Afatinib is an oral TKI that inhibits the entire ErbB/HER family of receptors including EGFR and HER2.[155,156] The FDA has approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.[157,158]

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.[159] Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).[160] Primary resistance to TKI therapy is associated with KRAS mutations and ALK gene rearrangements. Patients with exon 20 insertion mutations are also resistant to TKIs.[161-164] The EGFR T790M mutation is associated with acquired resistance to TKI therapy and has been reported in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib.[134,165-171] Most patients with sensitizing EGFR mutations become resistant to erlotinib, gefitinib, or afatinib after about 8 to 16 months of TKI therapy.[166] However, studies suggest the T790M mutation may also occur in patients who have not previously received TKI therapy, although this is a rare event.[172] For the 2016 update, the NCCN Panel added a recommendation for osimertinib as second-line and beyond (subsequent) therapy for patients with EGFR T790M mutations who have progressed on sensitizing EGFR TKI therapy (eg, erlotinib, gefitinib, afatinib) (see *Osimertinib* in this Discussion). Acquired resistance may be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[173-175]

DNA mutational analysis is the preferred method to assess for EGFR status.[176-178] Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells.[179] Direct sequencing of DNA corresponding to exons 18 to 21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.[159,177,180-182] Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot®

Multiplex System) can detect more than 50 point mutations, including EGFR.[129] NGS can also be used to detect EGFR mutations.[136]

The predictive effects of the drug-sensitive EGFR mutations—Exon19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib, gefitinib, or afatinib.[154] Retrospective studies have shown an objective response rate of approximately 80% with a median progression-free survival (PFS) of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and a sensitizing EGFR mutation.[108] A prospective study has shown that the objective response rate in North American patients with non-squamous NSCLC and sensitizing EGFR mutations (53% Exon19del [LREA deletion], 26% L858R, and 21% other mutations) is 55% with a median PFS of 9.2 months.[109] EGFR mutation testing is not usually recommended in patients with pure squamous cell carcinoma unless they never smoked, if only a small biopsy specimen (ie, not a surgical resection) was used to assess histology, or if the histology is mixed.[122] Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.[122]

Recent data suggest that erlotinib, gefitinib, or afatinib (instead of standard first-line chemotherapy) should be used as first-line systemic therapy in patients with sensitizing EGFR mutations documented before first-line therapy.[158,183-187] Data show that PFS is improved with use of EGFR TKI in patients with sensitizing EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.[158,183,188] Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.[183,189] A recent phase 4 trial showed that gefitinib is safe and effective in patients with sensitizing EGFR mutations.[118] Based on these data and the FDA approvals, erlotinib and gefitinib are recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.[118,183] In a phase 3 randomized trial, patients receiving afatinib had decreased cough, decreased dyspnea, and improved health-related quality of life when compared with those receiving cisplatin/pemetrexed.[189] Based on these data and the FDA approval, afatinib is also recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.[158] However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.[158] A combined analysis (LUX 3 and LUX 6) reported a survival advantage in patients with exon 19 deletions who received afatinib when compared with chemotherapy.[190]

ALK Gene Rearrangements

Estimates are that 2% to 7% of patients with NSCLC have ALK gene rearrangements, about 10,000 of whom live in the United States.[78] Patients with ALK rearrangements are resistant to EGFR TKIs but have similar clinical characteristics to those with EGFR mutations (ie, adenocarcinoma histology, never smokers, light smokers) except they are more likely to be men and may be younger.[127] In these selected populations, estimates are that about 30% of patients will have ALK rearrangements.[127,191] ALK rearrangements are not routinely found in patients with squamous cell carcinoma. Although rare, patients with ALK gene rearrangements can have mixed squamous cell histology.[123] It can be challenging to accurately determine histology in small biopsy specimens; thus, patients may have mixed squamous cell histology (or squamous components) instead of pure squamous cell. The NCCN Panel recommends testing for ALK rearrangements if small biopsy specimens were used to assess histology, mixed histology was reported, or patients never smoked. A molecular diagnostic test (using

FISH) has been approved by the FDA for detecting ALK rearrangements and is a prerequisite before treatment with crizotinib. Studies suggest that IHC can be used to screen for ALK rearrangements; if positive, FISH analysis can be done to confirm ALK positivity.[121,125,192-199] NGS can also be used to assess whether ALK rearrangements are present, if the platform has been appropriately designed and validated to detect ALK rearrangements.[200,201]

Crizotinib—an inhibitor of ALK, ROS1, and some MET tyrosine kinases (high-level MET amplification or MET exon 14 skipping mutation)—is approved by the FDA for patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements (ie, ALK-positive disease).[111,202-206] Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements, including those with brain metastases.[78,202,207-209] Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).[208,210,211] However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.[204] Patients have responded rapidly to crizotinib with improvement in symptoms (eg, cough, dyspnea, pain); median time to progression on crizotinib is about 7 months to 1 year.[212,213] Randomized phase 3 trials have compared crizotinib with standard second-line (ie, subsequent) chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014).[5,202,214] First-line therapy with crizotinib improved PFS, response rate (74% vs. 45%; $P < .001$), lung cancer symptoms, and quality of life when compared with chemotherapy (pemetrexed with either cisplatin or carboplatin).[202] Based on this trial, crizotinib is recommended (category 1) for first-line therapy in patients with ALK-positive NSCLC (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Subsequent therapy with crizotinib improved PFS (7.7 vs. 3.0 months; $P < .001$) and response rate (65% vs. 20%; $P < .001$) when compared with single-agent therapy (either docetaxel or pemetrexed) in patients with ALK-positive NSCLC who had progressed after first-line chemotherapy.[203] Based on this trial, crizotinib is recommended as subsequent therapy in patients with ALK-positive disease. The phrase *subsequent* therapy was recently substituted for the terms *second-line or beyond* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents.

For patients who progress on crizotinib, New ALK inhibitors include ceritinib and alectinib; others are in development.[117,215-223] Ceritinib is an orally active TKI of ALK, which also inhibits the insulin-like growth factor--1 (IGF-1) receptor but not MET. A recent expanded phase 1 trial showed that ceritinib was very active in 122 patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements.[217] The overall response rate to ceritinib was 56% in patients who had previously received crizotinib; the median PFS was 7 months. Based on this study, ceritinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who progress on or are intolerant to crizotinib. The NCCN Panel recommends ceritinib for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib based on the data from Shaw et al and the recent FDA approval.[217]

Alectinib is another oral TKI of ALK, which also inhibits RET but not MET or ROS1. A recent phase II trial in 138 patients with ALK rearrangements showed that alectinib was very active in those who had progressed on crizotinib.[117] Patients on alectinib had a response rate of 50% (95% CI, 41% to 59%), and median duration of response of 11.2 months (95% CI, 9.6 mo to not reached). For CNS disease, the control rate was 83% (95% CI, 74% to 91%), and the median duration of response was 10.3 months (95% CI, 7.6 to 11.2 mo). Of patients with

baseline CNS metastases, 10 (43%) had a complete CNS response to alectinib. Most adverse events were only grade 1 to 2 (constipation, fatigue, and peripheral edema; 4 patients (3%) had grade 3 dyspnea. Based on this study, alectinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who progress on or are intolerant to crizotinib. The NCCN Panel recommends alectinib (category 2A) for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib based on the data from Ou et al and the recent FDA approval.[117]

ALK rearrangements and sensitizing EGFR mutations are generally mutually exclusive.[125,224,225] Thus, erlotinib, gefitinib, and afatinib are not recommended as subsequent therapy in patients with ALK rearrangements who relapse on crizotinib (see *ALK Positive*: *Subsequent Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[126,127] Likewise, crizotinib, ceritinib, and alectinib are not recommended for patients with sensitizing EGFR mutations who relapse on erlotinib, gefitinib, or afatinib. For patients who progress on crizotinib, subsequent treatment for ALK-positive NSCLC includes ceritinib or alectinib (see *Ceritinib* and *Alectinib* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer).[117,208,226,227] Continuing crizotinib may also be appropriate for patients who progress on crizotinib.[228]

KRAS Mutations

Data suggest that approximately 25% of patients with adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation.[76,108,135,148,153] KRAS mutation prevalence is associated with cigarette smoking.[229] Patients with KRAS mutations appear to have a shorter survival than patients with wild-type KRAS; therefore, KRAS mutations are prognostic biomarkers.[151,153,230] KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.[76,108,152] Overlapping EGFR and KRAS mutations generally do not occur (<1%).[124,125,231] Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.[120,152] Targeted therapy is not currently available for patients with KRAS mutations, although MEK inhibitors are in clinical trials.[148,216,232]

Treatment Approaches

Surgery, RT, and systemic therapy are the 3 modalities most 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 II disease, surgery provides the best chance for cure.[233] 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. It is essential to determine whether patients can tolerate surgery or whether they are medically inoperable; some patients deemed inoperable may be able to tolerate minimally invasive surgery and/or sublobar resection.[233-237] Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.[238-240]

The *Principles of Surgical Therapy* are described in the NSCLC algorithm and are summarized here (see the NCCN Guidelines for Non-Small Cell Lung Cancer). 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 patients with lung cancer. Surgery may be appropriate for select patients with uncommon types of lung cancer (eg, superior sulcus, chest wall involvement) (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[241] Patients with pathologic stage II or greater disease can be referred to a medical oncologist for evaluation. For resected stage IIIA, consider referral to 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; lobectomy or pneumonectomy should be done if physiologically feasible.[233,242,243] Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[244-248] Resection (including wedge resection) is preferred over ablation.[233,243] Wide wedge resection may improve outcomes.[249] Patients with medically inoperable disease may be candidates for SABR, also known as stereotactic body RT (SBRT).[250] If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).[251-253]

Lymph Node Dissection

A randomized trial (ACOSOG Z0030) compared systematic mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with either 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. In patients with early-stage disease who had negative nodes by systematic lymph node dissection, complete mediastinal lymph node dissection did not improve survival.[254,255] Thus, 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.[254] Patients should have N1 and N2 node resection and mapping (American Thoracic Society map) with a minimum of 3 N2 stations sampled or a complete lymph node dissection. The lymph node map from the IASLC may be useful.[256] 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 sampling would substantially increase the surgical risk.

Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer): 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features. Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins that are: 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 described in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer) and summarized here. Before treatment, it is essential to

carefully evaluate for N2 disease using radiologic and invasive staging (ie, EBUS-guided procedures, mediastinoscopy, thorascopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team (which should include a board-certified thoracic surgeon).[257,258] Randomized controlled trials suggest that surgery does not increase survival in these patients.[259,260] However, one of these trials (EORTC) only enrolled patients with unresectable disease.[260] Most clinicians agree that resection is appropriate for patients with negative preoperative mediastinal nodes and with a single positive node (<3 cm) found at thoracotomy.[261] Neoadjuvant therapy is recommended for select patients. The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and controversial.[262,263] In patients with N2 disease, 50% of the NCCN Member Institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.[264] However, there is no evidence that adding RT to induction regimens improves outcomes for patients with stage IIIA (N2) disease when compared with using chemotherapy alone.[263] 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 *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[257,265] However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.[259,265-271] Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.[265,272]

Thorascopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also known as thorascopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[273,274] Published studies suggest that thorascopic lobectomy has several advantages over standard thoracotomy.[275-279] Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.[280,281] Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[282-286] Thoracoscopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.[287-290]

In patients with stage I NSCLC 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.[291-295] Thorascopic lobectomy has also been shown to improve discharge independence in older populations and patients at high risk.[296,297] Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[298,299] Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy (including robotic-assisted approaches) is recommended in the 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* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[300-303] Robotic VATS seems to be more expensive with longer operating times than conventional VATS.[304,305]

Radiation Therapy

The *Principles of Radiation Therapy* in the NSCLC algorithm include the following: 1) general principles for early-stage, locally advanced, and advanced NSCLC; 2) target volumes, prescription doses, and normal tissue dose constraints for early-stage, locally advanced, and advanced NSCLC; and 3) RT simulation, planning, and delivery.[306-311] These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery (SRS) for brain metastases are also discussed in this section. The abbreviations for RT are defined in the NSCLC algorithm (see Table 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

General Principles

Treatment recommendations should be made by a multidisciplinary team. Because RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy, input from board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice should be part of the multidisciplinary evaluation or discussion for all patients with NSCLC. Uses of RT for NSCLC include: 1) definitive therapy for locally advanced NSCLC, generally combined with chemotherapy; 2) definitive therapy for early-stage NSCLC in patients with contraindications for surgery; 3) preoperative or postoperative therapy for selected patients treated with surgery; 4) therapy for limited recurrences and metastases; and/or 5) palliative therapy for patients with incurable NSCLC.[253,312-319] The goals of RT are to maximize tumor control and to minimize treatment toxicity. Advanced technologies such as 4D-conformal RT simulation, intensity-modulated RT/volumetric modulated arc therapy (IMRT/VMAT), image-guided RT, motion management strategies, and proton therapy have been shown to reduce toxicity and increase survival in nonrandomized trials.[320-324] CT-planned 3D-conformal RT is now considered to be the minimum standard.

Definitive RT, particularly SABR, is recommended for patients with early-stage NSCLC (ie, stage I-II, N0) who are medically inoperable or those who refuse surgery (see *Stereotactic Ablative Radiotherapy* in this Discussion).[250,253,319,325] Interventional radiology ablation is an option for selected patients who are medically inoperable.[233,326,327] By extrapolation from surgical data, adjuvant chemotherapy (category 2B) may be considered after definitive RT/SABR in patients with high-risk factors for recurrence (eg, large tumors >4 cm in size).[251,328] SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy (eg, major medical comorbidity or severely limited lung function). However, resection is recommended for patients with early-stage NSCLC who are medically fit (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[329] Definitive chemoradiation is recommended for patients with stage II to III disease who are not appropriate surgical candidates.[330] Involved-field RT (also known as involved-field irradiation or IFI) is an option for treating nodal disease in patients with locally advanced NSCLC; IFI may offer advantages over elective nodal irradiation (ENI).[331-334]

For patients with advanced lung cancer (ie, stage IV) with extensive metastases, systemic therapy is recommended; palliative RT can be used for symptom relief and potentially for prophylaxis at primary or distant sites.[319,335-337] Shorter courses of palliative RT are preferred for patients with symptomatic chest disease who have poor PS and/or shorter life expectancy (eg, 17 Gy in 8.5 Gy fractions) (see Table 4 in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Higher dose and longer course thoracic RT (eg, ≥30 Gy in 10 fractions) are associated with modestly improved survival and symptoms, especially in patients with good PS.[335] The RT

recommendations for patients with stages I to IV are described in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

The indications for using preoperative or postoperative chemoradiation or RT alone are described in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with clinical stage I or II NSCLC who are upstaged to N2+ after surgery, postoperative chemotherapy can be administered followed by postoperative RT (also known as PORT) depending on the margin status (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[308,338] For clinical stage III NSCLC, definitive concurrent chemoradiation is recommended (category 1). However, the optimal management of patients with potentially operable stage IIIA NSCLC is controversial and is discussed in detail in the algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[257,259,270,339] For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some oncologists prefer chemotherapy alone rather than chemoradiotherapy for the preoperative treatment;[263] RT should generally be given postoperatively if not given preoperatively. For the 2016 update, the NCCN Panel revised the preoperative RT dose to 45 to 54 Gy based on a recent study;[262] previously, the dose had been 45 to 50 Gy. NCCN Member Institutions are evenly split in their use of neoadjuvant chemotherapy versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.[257] Similarly, some consider the need for pneumonectomy to be a contraindication to a combined modality surgical approach given the excess mortality observed in clinical trials,[259] but NCCN Member Institutions are split on this practice as well.

Surgery is associated with potentially greater risk of complications, particularly stump breakdown and bronchopleural fistula, in a field that has had high-dose RT (eg, 60 Gy). Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 to 50 Gy, especially patients who have received definitive doses of concurrent chemoradiation (ie, ≥60 Gy) preoperatively. Soft tissue flap coverage and reduced intraoperative fluid administration and ventilator pressures can reduce the risk of these complications.[340-342] When giving preoperative RT to less than definitive doses (eg, 45 Gy), one should be prepared up front to continue to a full definitive dose of RT without interruption if the patient does not proceed to surgery for some reason. For these reasons, when considering trimodality therapy, the treatment plan---including assessment for resectability and the type of resection---should be decided before initiation of any therapy.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints

The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in the *Principles of Radiation Therapy* in the NSCLC algorithm (see Table 4 in the NCCN Guidelines for Non-Small Cell Lung Cancer).[307,309,316,340-343] After surgery, lung tolerance to RT is much less than for patients with intact lungs. Although the dose volume constraints for conventionally fractionated RT for normal lungs are a useful guide (see Table 5 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer), more conservative constraints should be used for postoperative RT.

For definitive RT, the commonly prescribed dose is 60 to 70 Gy in 2 Gy fractions over 6 to 7 weeks.[344,345] The use of higher RT doses is discussed in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[346-351] Doses

up to 74 Gy can be given if normal tissue constraints are respected.[352] However, results from a phase 3 randomized trial (RTOG 0617) suggest that high-dose radiation using 74 Gy with concurrent chemotherapy does not improve survival, and might be harmful, when compared with a standard dose of 60 Gy.[351,353-355] At higher RT doses, normal tissue constraints become even more important; the absolute numbers in the RT tables may need revising depending on several factors such as location of the tumor, pulmonary function tests, and PS.[354]

Reports 50, 62, and 83 from the International Commission on Radiation Units and Measurements provide a formalism for defining RT target volumes based on grossly visible disease, potential microscopic extension, and margins for target motion and daily positioning uncertainty (see Figure 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer);[356,357] the ACR-ASTRO guidelines are also a helpful reference.[320,358,359] It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the organs at risk (such as spinal cord, lungs, heart, esophagus, and brachial plexus) to minimize normal tissue toxicity (see Table 5 in *Principles of Radiation Therapy*).[360] These constraints are mainly empirical and have for the most part not been validated rigorously.[361-368] However, the QUANTEC review provides the most comprehensive estimates from clinical data of dose-response relationships for normal tissue complications.[369-373] As previously mentioned, for patients receiving postoperative RT, stricter DVH parameters should be considered for the lungs.

Radiation Simulation, Planning, and Delivery

Treatment planning should be based on CT scans obtained in the treatment position. Intravenous contrast CT scans are recommended for better target delineation whenever possible, especially in patients with central tumors or nodal involvement. FDG PET/CT can significantly improve target delineation accuracy, especially when there is atelectasis or contraindications to intravenous CT contrast.[374] In the NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or IMRT (see *Radiation Therapy Simulation, Planning, and Delivery* in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[323,375-379] Respiratory motion should be managed. The report from the AAPM Task Group 76 is a useful reference for implementing a broad range of motion management strategies as described in the NSCLC algorithm (see *Radiation Therapy Simulation, Planning, and Delivery* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[380]

Stereotactic Ablative Radiotherapy

SABR (also known as SBRT) uses short courses of very conformal and dose-intensive RT precisely delivered to limited-size targets.[381-383] Studies, including prospective multi-institutional trials, have demonstrated the efficacy of SABR for patients with inoperable stage I NSCLC or for those who refuse surgery.[253,384-387] With conventionally fractionated RT, 3-year survival is only about 20% to 35% in these patients, with local failure rates of about 40% to 60%.[250] In prospective clinical trials, local control and overall survival appear to be considerably increased with SABR, generally more than 85% and about 60% at 3 years (median survival, 4 years), respectively, in patients who are medically inoperable.[233,250,327,329,379,386,388-393] Substantially higher survival has been observed in patients with potentially operable disease who are treated with SABR; survival is comparable in population-based comparisons to surgical outcomes.[329,385,394-398] However, it is not yet clear that use of SABR for medically operable patients provides long-term outcomes equivalent to surgery. Late recurrences have been reported more than 5 years after SABR, highlighting the need for careful

surveillance.[399] If possible, biopsy should confirm NSCLC before use of SABR.[400]

SABR is recommended in the NSCLC algorithm for patients with stage I and II (T1-3,N0,M0) NSCLC who are medically inoperable; SABR is a reasonable alternative to surgery for patients with potentially operable disease who are high risk, elderly, or refuse surgery after appropriate consultation (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[233,387,389,401,402] Recently, a combined analysis of 2 randomized trials (that did not complete accrual) assessed SABR compared with lobectomy in operable patients.[401] Although the analysis does not alter the fact that lobectomy is the standard of care for operable patients, it strengthens the indication for SABR for patients with relative contraindications for surgery or those who refuse surgery. SABR can also be used for patients with limited lung metastases or limited metastases to other body sites.[381,387,403-409] After SABR, assessment of recurrences by imaging can be challenging because of benign inflammatory/fibrotic changes that can remain FDG-PET avid for 2 or more years after treatment, emphasizing the importance of follow-up by a team with experience interpreting such post-treatment effects.[410,411] This is particularly relevant, because selected patients with localized recurrences after SABR may benefit from surgery or re-treatment with SABR.[412-416]

SABR fractionation regimens and normal tissue constraints are provided in the NSCLC algorithm (see Tables 2 and 3 in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[384,386,393,417-426] Although none of these dose constraints have been validated as maximally tolerated doses, outcomes of clinical trials to date suggest that they are safe constraints. The bronchial tree, esophagus, and brachial plexus are critical structures for SABR. Centrally located tumors include those within 2 cm in all directions of any mediastinal critical structure including the bronchial tree, esophagus, heart, brachial plexus, major vessels, spinal cord, phrenic nerve, and recurrent laryngeal nerve. Aggressive local therapy of oligometastatic disease in the adrenal gland remains controversial and thus is a category 2B recommendation; SRS or SABR for oligometastases to the brain or other body sites, respectively, may be useful in these settings (see *Stage IV, M1b: Limited Sites/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[241,387,427,428] However, local therapy combined with targeted therapy is a category 2A recommendation for patients with ALK rearrangements or sensitizing EGFR mutations.[429,430] Decisions about whether to recommend SABR should be based on multidisciplinary discussion. Hypofractionated or dose-intensified conventional 3D-conformal RT is an option if an established SABR program is not available.[431] Current nonrandomized clinical data indicate that local tumor control with SABR is higher than with interventional radiology ablation techniques. However, interventional radiology ablation may be appropriate for selected patients for whom local control is not necessarily the highest priority.[233,253,327]

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.[7,432] Options for treatment of single brain metastases include surgery followed by whole brain RT (category 1) for selected patients (eg, with symptomatic metastases or when tumor tissue is needed), surgery followed by SRS, SRS followed by WBRT (category 1), or SRS alone (see the NCCN Guidelines for Non-Small Cell Lung Cancer and for Central Nervous System Cancers, available at NCCN.org).[406,432-439] 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.[433,440-442] Treatment should be individualized for patients with recurrent or progressive brain lesions.[443]

For multiple metastases (eg, >3), WBRT is a standard option, although SRS is also an option (see the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).[444-446] WBRT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.[447-449] On the other hand, control of brain metastases confers improved neurocognitive function.[450,451] For limited metastases, randomized trials have found that the addition of WBRT to SRS decreases intracranial recurrence but does not improve survival and may increase the risk of cognitive decline.[451,452] Thus, an approach of SRS alone may strike an appropriate balance in patients with limited volume metastases.[453] Similarly, some have suggested that resection followed by SRS to the cavity (instead of resection followed by WBRT) will decrease the risk of neurocognitive problems.[454,455] A recent study suggests that using IMRT to avoid the hippocampus may help decrease memory impairment after WBRT.[456]

Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or II disease who are medically fit and can tolerate surgery. However, SABR can be considered for patients with unresectable stage I or II disease or those who refuse surgery if their disease is node negative (see *Stereotactic Ablative Radiotherapy* in this Discussion and see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.[457-459] Some studies suggested that neoadjuvant chemotherapy (also referred to as preoperative chemotherapy or induction chemotherapy) is as effective as and better tolerated than adjuvant chemotherapy (see *Neoadjuvant Chemotherapy Followed by Surgery: Trial Data* in this Discussion).[257,460-466] A recent randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.[467] The NCCN Guidelines state that patients with stage II or IIIA (T3, N1) disease may be treated with induction chemotherapy before surgery if they are candidates for adjuvant therapy after surgery.[233,468] Concurrent chemoradiation is superior to sequential therapy for patients with unresectable stage III disease.[469-472]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.[473-478] 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.[479] Patients should receive treatment for debilitating symptoms.[7,480,481] A recent study also suggests that social support, such as being married, is as effective as chemotherapy.[482] Surgery is rarely recommended 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 Guidelines (see the NCCN Guidelines for Non-Small Cell Lung Cancer and for Central Nervous System Cancers, available at NCCN.org).[483] Local therapy of a solitary metastasis located in sites other than the brain remains controversial and thus is a category 2B recommendation; however, SRS or SABR may be useful in these settings (see *Stage IV, M1b: Solitary Site/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[241,387] The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

Surgery Followed by Chemotherapy: Trial Data

In the NSCLC algorithm for stage IA disease, adjuvant chemotherapy is not recommended based on the trials described in the following paragraphs. Adjuvant chemotherapy may be considered for high-risk, margin-negative, stage IB disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Recommended chemotherapy regimens for neoadjuvant and adjuvant therapy are provided in the NCCN Guidelines.

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.[457] 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 (45% vs. 40% at 5 years; HR for death, 0.86; 95% CI, 0.76–0.98; $P < .03$) and disease-free survival rate (39% vs. 34% at 5 years; HR, 0.83; 95% CI, 0.74–0.94; $P < .003$) 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 follow-up, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.[484] Data show that adjuvant chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA trial compared the effectiveness of adjuvant vinorelbine/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/cisplatin or to observation.[458] Adjuvant chemotherapy significantly prolonged overall survival (94 vs. 73 months, HR for death, 0.69, $P = .04$) and relapse-free survival (not reached vs. 47 months, HR for recurrence, 0.60; $P < .001$) when compared with observation alone. The 5-year survival rates were 69% and 54%, respectively ($P = .03$). When compared with observation alone, adjuvant chemotherapy is beneficial for patients with stage II disease but not for stage IB disease as shown by updated data from JBR.10 after 9 years of follow-up.[485] In patients with stage II disease 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 ANITA trial, 840 patients with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned either to adjuvant vinorelbine/cisplatin or to observation.[459] Grade 3/4 toxicities were manageable in the chemotherapy group; however, 7 toxic deaths were reported. After a median follow-up of 76 months, median survival was 66 months in the chemotherapy group and 44 months in the observation group.[459] Adjuvant chemotherapy significantly improved (8.6%) 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;[486] however, most clinicians in the United States prefer to use regimens with less toxicity.[487,488]

A meta-analysis of 4,584 patients (LACE) 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, and others).[489] A subgroup analysis found that cisplatin/vinorelbine also increased survival.[486] The benefit was greater in patients with stage II and III disease and with good PS.

Postoperative adjuvant chemotherapy benefited elderly patients up to 80 years of age.[236,490]

The CALGB 9633 trial assessed paclitaxel/carboplatin in patients with T2, N0, M0, stage IB lung cancer;[491] updated results have been reported.[492,493] In this trial, 344 patients were randomly assigned either to paclitaxel/carboplatin or to observation (within 4–8 weeks of resection) with a median follow-up duration of 74 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 6 years was not significantly different, although 3-year survival was significant (80% vs. 73%, *P* = .02).[492,493] The original results from CALBG suggested that the paclitaxel/carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors 4 cm or more). Thus, the carboplatin/paclitaxel regimen is only recommended for early-stage disease if patients cannot tolerate cisplatin (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[494] However, it is important to note that the CALGB trial was underpowered for patients with stage 1B disease.[495]

Neoadjuvant Chemotherapy Followed by Surgery: Trial Data

Data from adjuvant clinical trials in patients with resected NSCLCs indicate that delivery of chemotherapy is an important problem. In the postoperative setting, significant comorbidities and incomplete recovery after surgery often make it difficult for patients to tolerate therapy. This problem was demonstrated in the NATCH phase 3 trial (which compared surgery alone to preoperative or postoperative chemotherapy with paclitaxel/carboplatin), because 90% of the preoperative cohort completed 3 cycles of chemotherapy but only 61% of the postoperative cohort completed chemotherapy; however, survival was equivalent among all 3 arms.[465] A recent randomized trial found no difference in 3-year overall survival (67.4% vs. 67.7%) with preoperative versus postoperative chemotherapy in patients with early-stage NSCLC; response rate and quality of life were similar in both arms.[467] Postoperative chemotherapy is considered the standard of care for early-stage disease.[233]

Several trials suggest that neoadjuvant therapy is beneficial in patients with N2 disease.[257,263,464] Other trials suggest that neoadjuvant therapy is beneficial in patients with earlier stage disease.[461,462,466] A follow-up, randomized intergroup trial (SWOG 9900) evaluated neoadjuvant paclitaxel/carboplatin in 354 patients with stage IB to IIIA (but not N2) disease versus surgery alone. The trial closed prematurely because of practice changes and was therefore not appropriately powered. However, this SWOG trial did show a trend toward improved PFS (33 vs. 20 months) and overall survival (62 vs. 41 months) with neoadjuvant chemotherapy, and no difference in resection rates between the 2 arms.[466]

Scagliotti et al published a phase 3 trial of preoperative cisplatin/gemcitabine versus surgery alone in 270 patients with stage IB to IIIA disease. Although the trial closed early, a significant survival benefit was seen in patients with stages IIB and IIIA disease who received chemotherapy (HR, 0.63).[461] Song et al published a meta-analysis of all available randomized clinical trials evaluating preoperative chemotherapy in resectable NSCLCs. This meta-analysis evaluated 13 randomized trials and found improvement in overall survival in the neoadjuvant chemotherapy arm when compared with the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92; *P* = .0001).[460] These results are similar to those recently reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; *P* = .02).[461] The benefit from neoadjuvant

chemotherapy is similar to that attained with postoperative chemotherapy.[461,467,489]

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 *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer]). 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.[496-500] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[496,497,499,500] Concurrent chemoradiation is superior to sequential chemoradiation.[469-472] However, concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential chemoradiation. Selection of patients should be based not only on the response to therapy but also on how well the patient tolerates therapy. Frail patients may not be able to tolerate concurrent chemoradiation.[234,501]

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[353,469,471,502-505] For non-squamous NSCLC, additional concurrent chemoradiation regimens may be used including carboplatin/pemetrexed and cisplatin/pemetrexed.[506-508] For the 2016 update, a weekly paclitaxel/carboplatin regimen was added as another chemoradiation option.[353] In addition, the different options for neoadjuvant/preoperative/induction, definitive, and adjuvant chemotherapy/RT were clarified. The NCCN Panel removed the *preferred* designation for the cisplatin/etoposide and cisplatin/vinblastine regimens based on preliminary data from a phase 3 randomized trial and a recent retrospective assessment of the Veterans Administration data for the 2016 update.[505,509]

Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.[475-477] Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, albumin-bound paclitaxel, and docetaxel), vinorelbine, etoposide, pemetrexed, and gemcitabine (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For the 2016 update, the NCCN Guidelines now provide lists of all of the combination systemic therapy regimens and single agents that are recommended for patients with metastatic NSCLC depending on histology and PS to clarify use of the agents (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For the 2016 update, the NCCN Panel deleted ifosfamide, mitomycin, and vinblastine from the NCCN Guidelines because these agents are rarely used; however, vinblastine/cisplatin/RT regimens are still recommended. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents.[494,510-513] In the United States, frequently used first-line regimens for non-squamous NSCLC include: 1) cisplatin (or carboplatin)/pemetrexed; or 2) carboplatin/paclitaxel with (or without) bevacizumab.[514,515] Gemcitabine/cisplatin is used for patients with squamous cell carcinoma.[513-516] These regimens are recommended based on phase 3 randomized trials (eg, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).[513,517]

For the 2016 update, the NCCN Panel added the necitumumab/cisplatin/gemcitabine regimen (category 3) for patients with metastatic squamous cell NSCLC. This category 3 recommendation reflects the fact that the NCCN Panel does not prefer the addition of necitumumab to the regimen based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine. A recent phase 3 randomized trial only showed a slight improvement in overall survival (11.5 months [95% CI, 10.4-12.6] vs. 9.9 months [8.9-11.1]).[518] The stratified HR was only 0.84 (95% CI, 0.74-0.96; *P*=.01). In addition, there were more grade 3 or higher adverse events in patients receiving the necitumumab regimen (388 [72%] of 538 patients) than in patients receiving only gemcitabine/cisplatin (333 [62%] of 541). Although a recent paper suggests that adding necitumumab to cisplatin/gemcitabine adds value and is cost effective, the NCCN Panel does not agree.[519]

Recently, many oncologists have been using pemetrexed-based regimens for adenocarcinomas (if patients are not candidates for targeted therapy), because taxane-based regimens are associated with more toxicity (eg, neurotoxicity).[513,520] There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.[521] The POINTBREAK trial showed that carboplatin/pemetrexed/bevacizumab is a reasonable option and confirmed that taxane-based regimens are more toxic than pemetrexed-based regimens.[522] However, the POINTBREAK trial showed that both regimens are similar in regard to overall survival rates; therefore, oncologists may return to using taxane-based regimens, which are well established. A retrospective cohort study suggests that the addition of bevacizumab (to carboplatin/paclitaxel) does not increase survival in older patients (≥65 years) with advanced non-squamous NSCLC.[523] However, another retrospective cohort study reported increased survival in older patients.[524] A combined analysis of the ECOG 4599 and POINTBREAK trials found survival benefit with the addition of bevacizumab (to carboplatin/paclitaxel) in patients younger than 75 years but no benefit in those older than 75 years.[525]

For patients with advanced NSCLC who have a PS of 2 (ie, poor PS), single-agent chemotherapy or platinum-based combinations are recommended in the NCCN Guidelines.[526] Single-agent chemotherapy includes vinorelbine, gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.[527-529] However, patients with a PS of 2 are often just treated with one chemotherapy agent because of concerns about toxicity.[530] Results from a recent trial reported that treatment with carboplatin/pemetrexed increased median overall survival when compared with pemetrexed alone (9.3 vs. 5.3 months, *P* = .001) in patients with a PS of 2; however, 4 treatment-related deaths occurred in the carboplatin/pemetrexed arm.[527,531]

Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.[532,533] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.[516,534,535] Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;[510,536-538] non–platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.[539-542] 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 (ie, dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.[543,544] A phase 3 randomized trial reported that an albumin-bound paclitaxel/carboplatin regimen is associated with less neurotoxicity and improved response rate, when compared with standard paclitaxel/carboplatin, in patients with advanced NSCLC.[545] The FDA has approved albumin-bound paclitaxel/carboplatin for patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or RT. Based on the recent trial and the FDA approval, the NCCN Panel recommends an albumin-bound paclitaxel/carboplatin regimen as first-line therapy for patients with advanced NSCLC and good PS (0–1).

Targeted Therapies

Specific targeted therapies are available for the treatment of advanced NSCLC.[119,546,547] Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor. Erlotinib, gefitinib, and afatinib are small molecule inhibitors of EGFR. Crizotinib is a small molecule inhibitor that targets ALK, ROS1, and MET (ie, high-level MET amplification, MET exon 14 skipping mutation). Ceritinib is a small molecule inhibitor that targets ALK and IGF-1 receptor. Alectinib is a small molecule inhibitor that targets ALK and RET. Erlotinib, gefitinib, afatinib, crizotinib, ceritinib, and alectinib are oral TKIs. Other targeted therapies are being developed (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Bevacizumab

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC. The ECOG recommends bevacizumab in combination with paclitaxel/carboplatin for select patients with advanced non-squamous NSCLC based on the results of phase 2 to 3 clinical trials (ECOG 4599).[517] To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: non-squamous NSCLC and no recent 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 non-squamous NSCLC or NSCLC NOS and PS 0 to 1 who are negative for either ALK gene rearrangements or sensitizing EGFR mutations, bevacizumab in combination with chemotherapy is one of the recommended options (see *Sensitizing EGFR Mutation Positive/First-Line Therapy* or *ALK Positive/First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Erlotinib and Gefitinib

In 2004, erlotinib was approved by the FDA for the treatment of patients with locally advanced or metastatic NSCLC after progression on at least one prior chemotherapy regimen. The FDA has approved the use of erlotinib as first-line therapy in patients with sensitizing EGFR mutations.[548] Erlotinib and gefitinib are recommended (category 1) in the NSCLC algorithm as first-line therapy in patients with advanced, recurrent, or metastatic non-squamous NSCLC who have known active sensitizing EGFR mutations regardless of their PS (see *Sensitizing EGFR Mutation Positive* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[76,188,549,550] These recommendations are based on the results of a phase 3 randomized trial (IPASS) in which patients with sensitizing EGFR mutations who received gefitinib had increased PFS (24.9% vs. 6.7%), response rate (71.2% vs. 47.3%), and quality of life with fewer side effects (eg, neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).[188] Updated results from the IPASS study show that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing EGFR

mutation status.[551] However, these results probably occurred because patients who had been assigned to first-line chemotherapy were able to receive TKIs as subsequent therapy if they were found to have sensitizing EGFR mutations. A phase 3 randomized trial (EURTAC) in European patients with metastatic NSCLC and sensitizing EGFR mutations showed increased PFS and response rate for those receiving erlotinib when compared with chemotherapy.[183] For erlotinib, the median PFS was 9.7 months compared with 5.2 months for chemotherapy (HR 0.37, 95% CI, 0.25–0.54; *P* < .0001). Fewer patients receiving erlotinib had severe adverse events or died when compared with those receiving chemotherapy.

TKIs are recommended in patients with metastatic NSCLC and sensitizing EGFR mutations, because quality of life is improved when compared with chemotherapy. Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was recently reapproved by the FDA based on a phase 4 study and is now available in the United States.[118] Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients.[552,553] An analysis of 5 clinical trials in patients, mainly from the Western hemisphere, (n = 223) with advanced NSCLC (stage IIIB or IV) found that those with sensitizing EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.[554] The TORCH trial suggests that EGFR mutation testing should be done in patients with advanced non-squamous NSCLC.[555] Survival was increased in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib first followed by subsequent chemotherapy (11.6 vs. 8.7 months). The OPTIMAL trial found that PFS was increased in patients with sensitizing EGFR mutations who received erlotinib.[186,187] ASCO recommends that patients be tested for EGFR mutations.[556] However, the ESMO Guidelines specify that only patients with non-squamous NSCLC (eg, adenocarcinoma) be assessed for EGFR mutations.[120,526] Patients with pure squamous cell carcinoma are unlikely to have sensitizing EGFR mutations; however, those with adenosquamous carcinoma may have mutations.[122]

An updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.[557] The data showed that erlotinib alone was associated with fewer side effects in patients with sensitizing EGFR mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to interrupt or complete planned chemotherapy and switch to erlotinib, gefitinib, or afatinib therapy in patients found to have sensitizing EGFR mutations during chemotherapy (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[558] For the 2016 update, the NCCN Panel deleted the recommendation to add erlotinib to current chemotherapy based on this study.[557] Erlotinib and gefitinib may also be continued in patients who have progressed if patients do not have multiple systemic symptomatic lesions (see *Continuation of Erlotinib, Gefitinib, or Afatinib After Progression* in this Discussion).

Afatinib

A randomized phase 3 trial showed that afatinib improved PFS when compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who have sensitizing EGFR mutations (11.1 vs. 6.9 months, *P* = .001).[158] The FDA has approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.[157,559] Based on this phase 3 randomized trial and the FDA approval, the NCCN Panel recommends afatinib for first-line therapy (category 1) in patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations (see the NCCN Guidelines for

Non-Small Cell Lung Cancer).[155,158,227] Afatinib may also be continued in patients who have progressed if patients do not have multiple systemic symptomatic lesions (see *Continuation of Erlotinib, Gefitinib, or Afatinib After Progression* in this Discussion).[154] However, afatinib is not recommended as subsequent therapy based on a recent phase 3 randomized trial (see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion).[560]

Osimertinib

As previously mentioned, most patients with sensitizing EGFR mutations and metastatic NSCLC typically progress after about 8 to 16 months of erlotinib, gefitinib, or afatinib therapy.[166] The EGFR T790M mutation is associated with acquired resistance to TKI therapy and has been reported in about 60% of patients with disease progression after initial response to sensitizing EGFR TKI therapy.[134,165-171] Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR sensitizing mutations and T790M mutations. Preliminary data from recent multicenter, single-arm phase 2 clinical trials (AURA/AURA2) report that osimertinib is associated with a response rate of about 61% and disease control rate of about 91% in patients with EGFR T790M mutations who have progressed on sensitizing EGFR TKI therapy; 18% of patients had grade 3 or higher adverse events with one fatal event.[561,562] The FDA has approved osimertinib for patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. Based on recent data and the FDA approval, the NCCN Panel recommends osimertinib as subsequent therapy for patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy (see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion). T790M mutations can be assessed using an FDA-approved test or other validated laboratory test done in a CLIA-approved laboratory.

Crizotinib

Crizotinib is approved by the FDA for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. The approval is based on a phase 2 trial that showed dramatic response rates (>80%) to crizotinib in patients who had previously progressed.[204,205] Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough. A recent phase 3 trial compared first-line crizotinib versus chemotherapy in patients with ALK rearrangements; patients receiving crizotinib had improved PFS, quality of life, and response rates when compared with those receiving chemotherapy.[202] The NCCN Panel recommends first-line therapy with crizotinib (category 1) based on this phase 3 trial and the FDA approval; the panel also feels that crizotinib is appropriate for patients with PS 0 to 4. Crizotinib may also be continued for patients with ALK rearrangements who have progressed if patients do not have multiple systemic symptomatic lesions.[203]

Ceritinib

Ceritinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The approval is based on a recent expanded phase 1 study showing overall response rates of 56% to ceritinib in patients who had previously received crizotinib.[217] Some patients with CNS lesions responded to ceritinib. Based on the study and the FDA approval, the NCCN Panel recommends ceritinib as subsequent therapy for patients with ALK-positive NSCLC who have progressed after crizotinib; patients who do not tolerant crizotinib may be switched to ceritinib or alectinib.

Alectinib

Alectinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The approval is based on a recent phase 2 study showing overall response rates of 50% to alectinib in patients who had previously received crizotinib.[117] For CNS disease, the control rate was 83% (95% CI, 74% to 91%), and the median duration of response was 10.3 months (95% CI, 7.6 to 11.2 mo). Of patients with baseline CNS metastases, 10 (43%) had a complete CNS response to alectinib. Based on this study and the FDA approval, the NCCN Panel recommends alectinib as subsequent therapy for patients with ALK-positive NSCLC who have progressed after crizotinib; patients who do not tolerant crizotinib may be switched to alectinib or ceritinib.

Cetuximab

Cetuximab is a monoclonal antibody that targets EGFR. A large phase 3 randomized trial (FLEX) assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC (most patients had stage IV disease).[563] Adding cetuximab slightly increased overall survival (11.3 vs. 10.1 months, $P = .04$). Patients receiving cetuximab had increased grade 4 events versus control (62% vs. 52%, $P < .01$); cetuximab was also associated with grade 2 acne-like rash.

The cetuximab/cisplatin/vinorelbine regimen was recently removed from the NCCN Guidelines. The benefits of this cetuximab-based regimen are very slight, it is a difficult regimen to administer, and patients have poorer tolerance for this regimen when compared with other regimens; for example, almost 40% of patients have grade 4 neutropenia.[473] Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. The cetuximab/cisplatin/vinorelbine regimen is generally not used in the United States because of concerns about toxicity.[473,487,563] Some oncologists feel that although the FLEX trial results were statistically significant they were not clinically significant.[473]

Nivolumab

The NCCN Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic non-squamous NSCLC who have progressed on or after first-line chemotherapy based on data from a phase 3 randomized trial (CheckMate-057) and recent FDA approval.[564] For the 2016 update, the NCCN Panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy.[564,565] Human immune-checkpoint--inhibitor antibodies inhibit the programmed death (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.[564,566,567] Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy. Pseudoprogression has been reported; therefore, traditional RESIST criteria may not be applicable.[568]

For the 2016 update, the NCCN Panel revised the recommendation for nivolumab to category 1 (from category 2A) based on the published data from CheckMate-057 and the recent FDA approval of nivolumab for patients with metastatic non-squamous NSCLC. For patients receiving nivolumab, median overall survival was 12.2 months compared with 9.4 months for docetaxel (HR, 0.73; 95% CI, 0.59–0.89; $P = .002$).[564] The median duration of response was 17.2 months with nivolumab compared with 5.6 months for docetaxel. At 18 months, the overall survival rate was 39% (95% CI, 34%–45%) with nivolumab compared with 23% (95% CI, 19%–28%) with docetaxel. Fewer grade 3 to 5 adverse events were reported for nivolumab (10%) when compared with docetaxel (54%) in the CheckMate-057 trial. Although many

patients with metastatic non-squamous NSCLC benefit from nivolumab, those whose tumors have PD-L1 staining of 1% to 10% or more have overall survival of 17 to 19 months compared with 8 to 9 months for docetaxel. However, the NCCN Panel does not recommend testing for PD-L1, because many patients with metastatic NSCLC benefit from nivolumab. For patients who did not have PD-L1 expression, there was no difference in overall survival for nivolumab versus docetaxel; however, nivolumab was associated with a longer duration of response and fewer side effects. To help clinicians determine which patients with non-squamous NSCLC may benefit most from treatment with nivolumab, the FDA has approved a complementary diagnostic biomarker test to assess for PD-L1 protein expression.[569] Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.[570] Current or former smoking status correlated with the response rate to immune checkpoint inhibitors.[564] Recent data suggest that mismatch repair deficiency is associated with response to immune checkpoint inhibitors.[571]

The NCCN Panel also recommends (category 1) nivolumab as subsequent therapy for patients with metastatic squamous cell NSCLC who have progressed on or after first-line chemotherapy based on data from a phase 3 randomized trial (CheckMate-017), the recent FDA approval, and results of a phase 2 trial.[565,572] In the CheckMate-017 trial, the median overall survival was 9.2 months with nivolumab compared with 6.0 months for docetaxel.[565] Patients had a response rate of 20% with nivolumab compared with 9% for docetaxel (P = .008). PD-L1 expression was not associated with response to nivolumab in patients with squamous cell NSCLC. There were fewer grade 3 to 4 adverse events with nivolumab (7%) when compared with docetaxel (55%). No patients died in the nivolumab arm versus 3 deaths in the docetaxel arm. Immune-related adverse events, such as pneumonitis, may occur with nivolumab.[567,572-576] High-dose corticosteroids should be administered based on the severity of the reaction for patients with immune-mediated adverse events. Nivolumab should be discontinued for patients with severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

Pembrolizumab

For the 2016 update, the NCCN Panel added a recommendation for pembrolizumab (category 2A) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression based on the KEYNOTE-001 trial and recent FDA approval.[577] In addition, the NCCN Panel recommends immune checkpoint inhibitors, such as pembrolizumab and nivolumab, as preferred agents for subsequent therapy. As previously mentioned, human immune-checkpoint--inhibitor antibodies inhibit the programmed death (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.[566,567]

A recent phase I trial (KEYNOTE-001) assessed the safety and efficacy of pembrolizumab for patients with metastatic NSCLC.[577] Among all patients, the response rate was 19%, the median duration of response was 12.5 months, PFS was 3.7 months, and median overall survival was 12.0 months. Patients with a PD-L1 expression score of at least 50% had a response rate of 45%, PFS of 6.3 months, and overall survival was not reached. Current or former smoking status also correlated with the response rate.[577,578] Less than 10% of patients had serious grade 3 or more toxicity. Similar to nivolumab, immune-mediated adverse events may also occur with pembrolizumab.[573,579] For patients with immune-mediated adverse events, high-dose corticosteroids should be administered based on the severity of the reaction. Pembrolizumab should also be discontinued for patients with

severe or life-threatening pneumonitis and should be withheld or discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information). The FDA has approved pembrolizumab as subsequent therapy for patients with metastatic NSCLC whose disease has progressed after platinum-based chemotherapy if their tumors express PD-L1. The FDA has approved a companion diagnostic biomarker test for assessing PD-L1 expression and determining which patients are eligible for pembrolizumab therapy.

Ramucirumab

A recent phase 3 randomized trial (REVEL) assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed.[580] The median overall survival was slightly increased with ramucirumab/docetaxel versus docetaxel alone (10.5 vs. 9.1 mo; HR, 0.86, 95% CI, 0.75-0.98; *P*<.023). Ramucirumab in combination with docetaxel is approved by the FDA for patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. The NCCN Panel added ramucirumab/docetaxel (category 2A) as an option for subsequent therapy for metastatic NSCLC that has progressed after first-line chemotherapy based on the phase 3 randomized trial and the FDA approval. Some panel members feel that the data are statistically significant but not clinically relevant. More than 70% of patients had grade 3 or higher adverse events in both groups (79% for ramucirumab/docetaxel versus 71% for docetaxel alone). Adverse events of special concern with ramucirumab/docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, impaired wound healing, and poorly controlled hypertension. There were 16 deaths from grade 3 or worse pulmonary hemorrhage and other adverse events in the REVEL trial: 8 in the ramucirumab/docetaxel arm and 8 in the docetaxel alone arm.

Maintenance Therapy

Maintenance therapy refers to systemic therapy that may be given for patients with advanced NSCLC after 4 to 6 cycles of first-line chemotherapy.[581] However, patients are only candidates for maintenance therapy if they have responded to their previous treatment (ie, tumor response) or have stable disease and their tumors have not progressed. *Continuation maintenance* therapy refers to the use of at least one of the agents that was given in the first-line regimen. *Switch maintenance* (category 2B) therapy refers to the initiation of a different agent that was not included as part of the first-line regimen. Selection of appropriate maintenance therapy depends on several factors (eg, histologic type, presence of mutations or gene rearrangements, PS). Maintenance therapy is an option in the NCCN Guidelines for select patients with tumor response or stable disease and is not considered the standard of care for all patients (eg, not recommended for PS 3–4, those with progression); close observation (category 2A) is also a valid treatment option (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[582]

Continuation Maintenance Therapy

For continuation maintenance therapy, select agents (which were initially given in combination with conventional chemotherapy) may be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. Single-agent bevacizumab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab) in patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations.[517,583,584] Single-agent pemetrexed (category 1) may also be given as

continuation maintenance therapy in patients with non-squamous NSCLC (who are negative for ALK rearrangements or sensitizing EGFR mutations).[583,585] A recent phase 3 randomized trial (PARAMOUNT) found that continuation maintenance therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 vs. 2.8 months).[585] Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).[586] Based on the recent trial and the FDA approval, the NCCN Panel recommends single-agent pemetrexed as continuation maintenance therapy (category 1) in patients with non-squamous NSCLC but without ALK rearrangements or sensitizing EGFR mutations. Continuation maintenance therapy with cetuximab was recently removed from the NCCN Guidelines, because the first-line regimen of cetuximab/cisplatin/vinorelbine was removed (see *Cetuximab* in this Discussion).

Continuation maintenance therapy using bevacizumab/pemetrexed is also an option in patients with non-squamous NSCLC but without ALK rearrangements or sensitizing EGFR mutations; this is a category 2A recommendation. Data from the recent POINTBREAK study showed a very slight improvement in PFS (6 vs. 5.6 months) when comparing bevacizumab/pemetrexed versus bevacizumab alone as maintenance therapy; the initial regimens were either bevacizumab/carboplatin/pemetrexed or bevacizumab/carboplatin/paclitaxel.[522] It is important to note that the pemetrexed-based arm was associated with less toxicity (eg, less neurotoxicity, less neutropenia, less hair loss) than the paclitaxel-based arm. When using bevacizumab/pemetrexed versus bevacizumab alone as maintenance therapy, data from the recent AVAPERL study showed a 3.7-month increase in PFS (7.4 vs. 3.7 months); the initial regimen was bevacizumab/cisplatin/pemetrexed.[587,588]

A phase 3 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 single-agent 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).[589,590] Another phase 3 randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.[591] The data showed a slight difference in PFS but no difference in overall survival. The NCCN Guidelines recommend using gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients without ALK rearrangements or sensitizing EGFR mutations.

Use of continuation maintenance therapy depends on several factors such as whether the patient had minimal toxicity during treatment. A drug vacation may be more appropriate for some patients.[520] Some clinicians feel that continuation maintenance therapy is only appropriate for select patients, because it has not been shown to improve overall survival or quality of life, although it has been shown to improve PFS.[520,592] In addition, maintenance therapy has not been shown to be superior to subsequent therapy, which is initiated at disease progression. Data from a phase 3 randomized trial suggest that conventional cytotoxic agents should not be continued beyond 4 to 6 cycles of therapy; however, many patients assigned to a longer duration of therapy did not receive the planned number of cycles (see *Maintenance Therapy* in this Discussion).[592,593]

Switch Maintenance Therapy

Issues have been raised about switch maintenance therapy, including the design of the trials, modest survival benefits, quality of life, and toxicity.[520,594] Therefore, switch maintenance therapy is a category 2B

recommendation in the NCCN Guidelines. Two phase 3 randomized trials have shown a benefit in PFS and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4–6 cycles) in patients with no apparent disease progression.[595,596] Switch maintenance therapy with pemetrexed is recommended (category 2B) in patients with non-squamous cell carcinoma who are negative for ALK rearrangements or sensitizing EGFR mutations.[596] The FDA has approved maintenance therapy with pemetrexed.[597] Likewise, switch maintenance therapy with erlotinib is recommended (category 2B) in patients with non-squamous NSCLC but without ALK rearrangements or sensitizing EGFR mutations.[590,595] For the 2016 update, the NCCN Panel deleted the recommendation for switch maintenance therapy with erlotinib in patients with squamous cell NSCLC, because overall survival and quality of life were not improved.[589,598] Both erlotinib and pemetrexed have a category 2B recommendation for switch maintenance therapy in patients with non-squamous NSCLC. The FDA has approved maintenance therapy with erlotinib.[599] A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.[600] Switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines for patients with squamous cell carcinoma, because many patients in the delayed chemotherapy arm did not receive docetaxel.

Clinical Evaluation

As previously described, low-dose CT screening is now recommended for asymptomatic select patients who are at high risk for lung cancer (see the NCCN Guidelines for Non-Small Cell Lung Cancer and for Lung Cancer Screening, available at NCCN.org). Low-dose CT screening may find lung nodules that are suspicious for cancer; the workup and evaluation of these lung nodules is described in the NSCLC algorithm (see *Diagnostic Evaluation of Lung Nodules* in this Discussion and see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

After patients are confirmed to have NSCLC based on a pathologic diagnosis, a clinical evaluation needs to be done (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with symptoms, the clinical stage is initially determined from disease history (ie, cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests (see *Evaluation* and *Clinical Stage* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The NCCN Panel also recommends that smoking cessation advice, counseling, and pharmacotherapy be provided to patients.[28,601-603] After the clinical stage is determined, 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. Note that for some patients, diagnosis, staging, and surgical resection are done during the same operative procedure. A multidisciplinary evaluation should be done before treatment.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. FDG PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease); however, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer (see *Mediastinoscopy* and *Other Imaging Studies* in this Discussion).[604-607] 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 to T3 lesions even if the FDG PET/CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive FDG PET/CT scan. In patients with solid tumors less than 1 cm or for nonsolid tumors (ie, GGOs) less than 3 cm, pathologic mediastinal lymph node evaluation is not required if the nodes are FDG-PET/CT negative.[608] In patients with peripheral T2a, central T1ab, or T2 lesions with negative FDG PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy and/or EUS-FNA and EBUS-TBNA are recommended (see *Other Imaging Studies* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer).

Dillemans et al have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT.[609] 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% vs. 71%) than using the chest CT scan alone for identifying N2 disease. When using CT scans, node positivity is based on the size of the lymph nodes. Therefore, the CT scan will miss small metastases that do not result in node enlargement. To address this issue, Arita et al specifically examined lung cancer metastases to normal size mediastinal lymph nodes in 90 patients and found an incidence of 16% (14/90) false-negative chest CT scans with histologic identification of occult N2 or N3 disease.[610]

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I to 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.[605] PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN Panel reviewed the diagnostic performance of CT and PET scans. 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.[604,611,612] However, FDG PET/CT is even more sensitive and is recommended by NCCN.[613-615]

The NCCN Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.[616] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.[617] 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.[618] Chin et al found that PET, when used to stage the mediastinal nodes, was 78% sensitive and 81% specific with a negative predictive value of 89%.[619] Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[620] The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% vs. 65%). FDG PET/CT has been shown to be useful in restaging patients after adjuvant therapy.[621,622]

When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.[613] However, positive FDG PET/CT scan findings for distant disease need pathologic or other radiologic confirmation (eg, MRI of bone). If the FDG PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.[604,623] Transesophageal EUS-FNA and 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.[624-627] 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.[628] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[629,630] However, in patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[625,630-632] Note that EBUS is also known as endosonography.

The routine use of bone scans (to exclude bone metastases) is not recommended. Brain MRI (with contrast), to rule out asymptomatic brain metastases, is recommended for patients with stage II, III, and IV disease to rule out metastatic disease if aggressive combined-modality therapy is being considered.[633] Patients with stage IB NSCLC are less likely to have brain metastases; therefore, brain MRI is only a category 2B recommendation in this setting. If brain MRI cannot be done, then CT of the head with contrast is an option. Note that PET scans are not recommended for assessing the presence of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).

Initial Therapy

Before treatment, 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 Guidelines for Non-Small Cell Lung Cancer). *Principles of Radiation Therapy* recommends doses for RT (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In addition, the NCCN Guidelines also recommend regimens for chemotherapy and chemoradiation (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy*, *Chemotherapy Regimens Used with Radiation Therapy*, and *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Stage I, Stage II, and Stage IIIA 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 lymph node dissection. Definitive RT, particularly SABR, is recommended for patients with early-stage NSCLC who are medically inoperable or refuse surgery, and can be considered as an alternative to surgery in patients at high risk of complications (see *Stereotactic Ablative Radiotherapy* in this Discussion and see *Initial Treatment* for Stage I and II in the NCCN Guidelines for Non-Small Cell Lung Cancer).[233,250,253,319,325,634] 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 (ie, inclusion of systematic mediastinal lymph node dissection) must be modified accordingly. Therefore, the NCCN Guidelines include 2 different tracks for T1–3, N2 disease (ie, stage IIIA 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 (with contrast) and FDG PET/CT scan (if not previously done) are recommended to rule out metastatic 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 is recommended. For the subsets of stage IIB (T3, N0) and stage IIIA (T4, N0–1) tumors, treatment options are organized according to the location of the tumor such as the superior sulcus, chest wall, proximal airway, or mediastinum.[241] For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

For patients with resectable tumors (T3 invasion, N0–1) in the superior sulcus, the NCCN Panel recommends preoperative concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see *Initial Treatment for Superior Sulcus Tumors* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.[241,341,343,635-638] The overall 5-year survival rate is approximately 40%.[343] Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T4 extension, N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.[504,639]

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 unresectable T4, N0–1 tumors without pleural effusion, definitive concurrent chemoradiation (category 1) is recommended.[259,469] If full-dose chemotherapy was not given initially as concurrent treatment, then an additional 2 cycles of full-dose chemotherapy can be administered (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[259,344,469,504]

Multimodality therapy is recommended for most patients with stage III NSCLC.[501] 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 *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with negative mediastinal biopsy findings are candidates for surgery. For those patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the operation. Those individuals who are medically inoperable should be treated according to the clinical stage (see the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients with (T1–2 or T3) N2 node-positive disease, a brain MRI (with contrast) and FDG PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the NCCN Panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[318,470] Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread (see the NCCN Guidelines for Non-Small Cell Lung Cancer).

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; however, systemic therapy is recommended. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery (see *Multiple Lung Cancers* in this Discussion).[640] Patients with separate pulmonary nodule(s) in the same lobe (T3, N0-1) or ipsilateral non-primary lobe (T4, N0-1) without other systemic metastases are potentially curable by surgery; 5-year survival

rates are about 30%.[641] Intrapulmonary metastases were downstaged in the TNM staging (ie, AJCC 7th edition).[105,641,642] For those with N2 nodes after surgery, concurrent chemoradiation is recommended for those with positive margins and a R2 resection; either sequential or concurrent chemoradiation is recommended after an R1 resection. Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential chemoradiation is reasonable in frailer patients.[643] For those with N2 nodes and negative margins, sequential chemotherapy (category 1) with RT is recommended. Chemotherapy alone is recommended for those with N0-1 nodes (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with synchronous solitary nodules (contralateral lung), the NCCN Panel recommends treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[644]

Multiple Lung Cancers

Patients with a history of lung cancer or those with biopsy-proven synchronous lesions may be suspected of having multiple lung cancers (see *Clinical Presentation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[645,646] It is important to determine whether the multiple lung cancers are metastases or separate lung primaries (synchronous or metachronous), because most multiple lung tumors are metastases.[57,241,647,648] Therefore, it is essential to determine the histology of the lung tumor (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Infection and other benign diseases also need to be ruled out (eg, inflammatory granulomas).[649,650] Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.[650-653] The Martini and Melamed criteria are often used to diagnose multiple lung cancers as follows: 1) the histologies are different; 2) the histologies are the same but there is no lymph node involvement and no extrathoracic metastases.[653]

Treatment of multiple lung cancers depends on status of the lymph nodes (eg, N0–1) and on whether the lung cancers are asymptomatic, symptomatic, or at high risk of becoming symptomatic (see *Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[647,654-656] In patients eligible for definitive local therapy, parenchymal-sparing resection is preferred (see the *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[646,647] VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.[657] Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on low-dose CT scans; some of these nodules can be followed with imaging, whereas others need to be biopsied or excised (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).[658]

Stage IIIB Disease

Stage IIIB tumors comprise 2 groups, including: 1) T1–3, N3 tumors; and 2) T4, N2–3 tumors, which are unresectable and include contralateral mediastinal nodes (T4, N3). Surgical resection is not recommended in patients with T1–3, N3 disease. However, in patients with suspected N3 disease, the NCCN Guidelines recommend pathologic confirmation of nodal status (see *Pretreatment Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[659,660] In addition, FDG PET/CT scans (if not previously done) and brain MRI (with contrast) 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 Guidelines for Non-Small Cell Lung Cancer). If N3 disease is confirmed, definitive concurrent chemoradiation (category 1) is recommended followed by 2

cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.[259,469,504,661,662] For metastatic disease that is confirmed by FDG PET/CT scan and brain MRI (with contrast), treatment is described in the NCCN Guidelines.

For patients with T4, N2–3 disease (stage IIIB), surgical resection is not generally recommended. The initial workup includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0–1) disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If either the contralateral or ipsilateral mediastinal node is positive, definitive concurrent chemoradiation therapy is recommended (category 1) followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not given concurrently with RT as initial treatment (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[259,469,504,661-663]

Stage IV Disease

In general, systemic therapy is recommended for patients with metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[558] This section focuses on patients with limited metastatic disease; management of widespread distant metastases is described in another section (see *Treatment of Recurrences and Distant Metastases* in this Discussion and *Systemic Therapy for Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Pleural or pericardial effusion is a criterion for stage IV, M1a disease. T4 with pleural effusion is classified as stage IV, M1a (see Table 3 in *Staging* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[105] Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (eg, obstructive pneumonia), an exudate or sanguinous effusion is considered malignant regardless of the results of cytologic examination. If the pleural effusion is considered negative, recommended treatment is based on the confirmed T and N stage (see the NCCN Guidelines for Non-Small Cell Lung Cancer). However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.[664] In patients with effusions that are positive for malignancy, the tumor is treated as M1a with local therapy (ie, ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[665]

Management of patients with distant metastasis in limited sites (ie, stage IV, M1b) depends on the location of the metastases—a few nodules in the brain or adrenal gland—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, FDG PET/CT scan, and brain MRI (with contrast). The increased sensitivity of FDG PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. However, positive FDG PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If the FDG PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Patients with limited oligometastatic disease (eg, single brain or adrenal metastasis) and otherwise limited disease in the chest may benefit from aggressive local therapy to both the primary chest and metastatic sites.[666,667] Aggressive local therapy may comprise surgery or definitive RT including SABR to each site, and may be preceded or

followed by chemotherapy. Recent data suggest that erlotinib combined with SABR or SRS may also be useful.[429]

Metastases to the adrenal gland 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. Local therapy (category 2B) of the adrenal lesion has produced some long-term survivors when an adrenal metastasis has been found and the lung lesion has been curable (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[668-671] Some NCCN Panel Members feel that local therapy for adrenal metastases is only advisable if the synchronous lung disease is stage I or possibly stage II (ie, resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Post-surgical treatment options for patients with stage IA tumors (T1ab, N0) and with positive surgical margins (R1, R2) include re-resection (preferred) or 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. Adjuvant chemotherapy is a category 2A recommendation for patients with high-risk features (including poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling [Nx]) (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[493,672] If the surgical margins are positive in patients with T2ab, N0 tumors, options include: 1) re-resection (preferred) with (or without) chemotherapy; or 2) RT with (or without) chemotherapy (chemotherapy is recommended for stage IIA).[308,493]

The NCCN Panel recommends chemotherapy (category 1) for patients with negative surgical margins and stage II disease, including 1) T1ab–2a, N1; 2) T2b, N1; or 3) T3, N0 disease.[489,673] If surgical margins are positive in these patients, options after an R1 resection include: 1) re-resection and chemotherapy; or 2) chemoradiation (either sequential or concurrent). Options after an R2 resection include: 1) re-resection and chemotherapy; or 2) concurrent chemoradiation. Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential is reasonable in frailer patients.[643]

Adjuvant chemotherapy can also be used in patients with stage III NSCLC who have had surgery (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with T1-3, N2 or T3, N1 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation; either sequential or concurrent chemoradiation is recommended for an R1 resection, whereas concurrent chemoradiation is recommended for an R2 resection (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with negative margins may be treated with either 1) chemotherapy (category 1); or 2) sequential chemotherapy plus RT (for N2 only).[489]

For stage IIIA superior sulcus tumors (T4 extension, N0–1) that convert to a resectable status (ie, become resectable) after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If the lesion remains unresectable after preoperative concurrent chemoradiation, the full course of definitive chemo/RT should be completed, followed by chemotherapy as an adjuvant

treatment if full doses were not given with concurrent therapy. Among patients with chest wall lesions with T3 invasion–T4 extension, N0–1 disease, those who 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 1) sequential or concurrent chemoradiation; or 2) re-resection with chemotherapy. As previously mentioned, most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential is reasonable in frailer patients.[643] 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) with no apparent disease progression after initial treatment, recommended treatment includes surgery with (or without) RT (if not given preoperatively) and/or with (or without) chemotherapy (category 2B for chemotherapy) (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Alternatively, if the disease progresses, patients may be treated with either 1) local therapy using RT (if not given previously) with (or without) chemotherapy; or 2) systemic treatment. In patients with separate pulmonary nodules in the same lobe (T3, N0-1) or ipsilateral non-primary lobe (T4, N0-1), surgery is recommended. In patients with N2 disease, if the margins are negative, sequential chemotherapy (category 1) with radiation is recommended. If the resection margins are positive in patients with N2 disease, concurrent chemoradiation is recommended for an R2 resection, whereas either concurrent or sequential chemoradiation is recommended for an R1 resection. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.

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 (see the NCCN Guidelines for Non-Small Cell Lung Cancer). 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 neoadjuvant and adjuvant chemotherapy for NSCLC,[457-459] the NCCN Panel has included cisplatin combined with docetaxel, etoposide, gemcitabine, or vinorelbine for adjuvant chemotherapy for all histologies in the NCCN Guidelines; other options include cisplatin combined with pemetrexed for non-squamous NSCLC (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[494,510,513] For the 2016 update, the NCCN Panel deleted vinblastine since this agent is rarely used. For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel is an option.[494,674] A phase 3 randomized trial in elderly patients (70–89 years) 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 (10.3 vs. 6.2 months).[675] A number of phase 2 studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.[676-678]

Three phase 3 trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[464,679-681] The S9900 trial (a SWOG study)—one of the largest randomized trials examining preoperative chemotherapy in early-stage NSCLC—assessed surgery alone compared with surgery plus preoperative paclitaxel/carboplatin in patients with stage IB/IIA and stage IIB/IIIA NSCLC (excluding superior sulcus tumors). PFS and overall survival were improved with preoperative chemotherapy.[680,681] All

3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase 3 studies had a 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

After complete resection of clinical early-stage NSCLC, postoperative RT has been found to be detrimental in the context of pathological N0 or N1 stage disease in a meta-analysis of small randomized trials using older techniques and dosing regimens and a population-based analysis of data from SEER.[682] However, there was an apparent survival benefit of postoperative RT in patients with N2 nodal stage diagnosed surgically.[338] The analysis of the ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.[308] A recent review of the National Cancer Data Base concluded that postoperative RT and chemotherapy provided a survival advantage for patients with completely resected N2 disease when compared with chemotherapy alone.[683] A recent meta-analysis also concluded that postoperative RT improves survival for patients with N2 disease.[684] Postoperative adjuvant sequential chemotherapy with RT is recommended for patients with T1–3, N2 disease and negative margins (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients mainly with stage III disease.[673] In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemo/RT. Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide.

The ACR Appropriateness Criteria® provide specific recommendations for postoperative adjuvant therapy.[685,686] Either concurrent or sequential chemoradiation may be used for postoperative adjuvant therapy, depending on the type of resection and the setting (eg, N2 disease) (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Concurrent chemo/RT is recommended for R2 resections, whereas either sequential or concurrent chemo/RT is recommended for R1 resections. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.[643] Cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel are chemoradiation regimens recommended by the NCCN Panel for all histologies (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[503] Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with non-squamous NSCLC. Chemoradiation regimens cited in the NCCN Guidelines may also be used for stage II to III disease.[309,310,469,470,504,507,508]

Surveillance

The surveillance guidelines for patients with no clinical or radiographic evidence of disease are as follows (see *Surveillance* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A chest CT scan with (or without) contrast is recommended every 6 to 12 months postoperatively for 2 years;[687-692] a low-dose non–contrast-enhanced chest CT is recommended annually thereafter. However, patients treated with chemotherapy with (or without) RT who have residual abnormalities may require more frequent imaging. FDG PET/CT or brain MRI are not recommended for routine surveillance in patients without symptoms. But, PET may be useful for assessing CT scans that appear to show malignant neoplasms but may be radiation fibrosis, atelectasis, or other benign conditions. It is important to note that areas previously treated

with RT may remain FDG avid for up to 2 years; therefore, histologic confirmation of apparent "recurrent" disease is needed.[693]

Recent data show that low-dose CT screening of select current and former smokers at high risk for lung cancer (ie, ≥30 pack-years of smoking) decreased the mortality from lung cancer.[51] Information about smoking cessation (eg, advice, counseling, therapy) should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients.

The NCCN Guidelines include information about the long-term follow-up care of NSCLC survivors (see *Cancer Survivorship Care* in the NCCN Guidelines for Non-Small Cell Lung Cancer). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening. A recent analysis suggests that patients who survive lung cancer have a high symptom burden 1 year after diagnosis and therefore need management after treatment.[694]

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[7] For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in patients who are severely compromised, and may improve the quality of life.[695] After the treatment for the locoregional recurrence, observation or systemic therapy (category 2B for systemic therapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic therapy is recommended. The type of systemic therapy depends on the histologic type, whether any genetic alterations are present, and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Management of distant metastases (eg, localized symptoms; bone, limited, diffuse brain, or disseminated metastases) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Palliation of symptoms can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bone metastasis.[316,696,697]

Of note, recurrent and metastatic disease have historically been regarded as incurable. However, selected limited locoregional recurrences may be treated with curative intent therapy (surgery or RT with [or without] chemotherapy) (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Similarly, patients with limited-site oligometastatic disease may benefit from aggressive local therapies to the metastatic and primary sites, with clinical data suggesting the possibility of long-term survival (see *Initial Treatment for Stage IV, M1b: Limited Sites* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[403,404,407,698-702] In addition, emerging clinical data suggest the feasibility of definitive reirradiation of local recurrences within prior RT fields using highly conformal techniques, although this should be limited to highly selected cases in specialty centers with appropriate expertise because of the potential for severe toxicity with high cumulative radiation doses to critical structures.[313,414-416,703-706]

Denosumab or intravenous bisphosphonate therapy can be considered in patients with bone metastasis.[119,707-710] In patients with NSCLC who have bone metastases, data suggest that denosumab increases

median overall survival when compared with zoledronic acid (9.5 vs. 8 months).[711] Denosumab and bisphosphonate therapy can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. The FDA has approved the use of zoledronic acid and denosumab in patients with bone metastases from solid tumors.[712,713]

For patients with recurrent and metastatic disease, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see *Metastatic Disease*: *Histologic Subtype* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[513] In addition, testing for genetic alterations (ie, driver events) is now recommended in select patients with NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic alterations. The number of available targeted agents is increasing. Several targeted agents have category 1 recommendations for first-line therapy based on larger trials such as erlotinib, gefitinib, afatinib, and crizotinib.[558]

Additional targeted therapies for patients with other genetic alterations are also recommended, although there is less evidence for these agents (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The following targeted agents are recommended (category 2A) for patients with specific genetic alterations: crizotinib (for ROS1 rearrangements and for high-level MET amplification or MET exon 14 skipping mutation), dabrafenib (with or without trametinib) and vemurafenib (for BRAF V600E mutations), and cabozantinib (for RET rearrangements).[73,78,112-114,135,138,139,143,146,147,156,158,549,714-723] For the 2016 update, the NCCN Panel added a recommendation for a dabrafenib/trametinib regimen for patients with BRAF V600E mutations based on data from a recent phase II study.[717] In addition, the recommendation for cabozantinib for RET rearrangements was revised to category 2A (from category 2B) based on data from another phase II study.[716] Trastuzumab and afatinib (both for HER2 mutations) are category 2B recommendations, because response rates are lower and treatment is less effective when these agents are used for patients with the indicated genetic alterations.[147,719] Other targeted therapies (such as ceritinib, alectinib) are recommended or being developed as subsequent therapies for patients who become resistant to first-line targeted therapies.

EGFR mutation testing (category 1) is recommended in patients with non-squamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC NOS, because erlotinib, gefitinib, and afatinib (category 1 for all) are recommended for patients who are positive for sensitizing EGFR mutations (see *EGFR Mutation Positive*/*First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[76,154,185,188,724] Testing for ALK rearrangements (category 1) is also recommended in patients with non-squamous NSCLC, because crizotinib is recommended for patients who are positive for ALK rearrangements.[121,725] Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification (see *Emerging Targeted Agents for Patients with Genetic Alternations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[112,114,146,726] Ceritinib and alectinib are recommended for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib.[217] The NCCN Panel recommends that EGFR mutation testing be done as part of broad molecular profiling (eg, multiplex mutation screening assays or NGS). Testing for ALK gene rearrangements can be done with FISH or with NGS if the platform is validated and can identify gene fusions.[135-137]

As previously mentioned, recent recommendations from an international panel suggest that general histologic categories be avoided (eg, NSCLC), because more effective treatment can be selected when the histology is known.[57] Patients with pure squamous cell carcinoma do not seem to have ALK rearrangements or sensitizing EGFR mutations; therefore, routine testing is not recommended in these patients.[122,727-729] However, testing for ALK rearrangements or EGFR mutations can be considered in patients with squamous cell carcinomas who never smoked and those whose histology was determined using small biopsy specimens or mixed histology specimens.[122] Treatment recommendations and eligibility criteria for patients with non-squamous NSCLC (or NSCLC NOS) who are negative for ALK rearrangements or sensitizing EGFR mutations are described in the NCCN Guidelines. Treatment recommendations and eligibility criteria for patients with squamous cell carcinoma are also described in the NCCN Guidelines. These recommendations are briefly summarized in the following paragraphs. Data supporting these recommendations are described in the following section (see *Trial Data* in this Discussion).

In general, 2-drug regimens (ie, doublet chemotherapy) are recommended over single agents (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer); however, targeted therapy is sometimes added to the 2-drug regimen (eg, the addition of bevacizumab to carboplatin/paclitaxel). Single-agent targeted therapy may also be recommended for patients with ALK rearrangements, sensitizing EGFR mutations, or other driver mutations (see *Emerging Targeted Agents for Patients With Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Doublet chemotherapy regimens, such as cisplatin/pemetrexed, are recommended (category 1) for patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations if eligibility criteria are met (ie, they do not have squamous cell carcinoma); these regimens are also recommended in patients who have not had testing for mutations or rearrangements.[513] Bevacizumab/chemotherapy is another option for patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations if eligibility criteria are met.[730] 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.[731] Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on histology, PS, and other factors (see *Trial Data* in this Discussion, *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer, and the NCCN Drugs & Biologics Compendium [NCCN Compendium®]).[558,732] A phase 3 randomized trial in elderly patients (70–89 years) 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 (10.3 vs. 6.2 months).[675] Systemic therapy for elderly patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.[733]

Cisplatin/gemcitabine (category 1) is an option for patients with squamous cell carcinoma.[513] Carboplatin/paclitaxel, cisplatin/vinorelbine (category 1 for both), and other regimens listed in the NSCLC algorithm may also be used (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer and the NCCN Compendium®). As previously indicated, regimens containing pemetrexed or bevacizumab are not recommended for squamous cell carcinoma. Currently, there are fewer treatment options for patients with

squamous cell carcinoma when compared with non-squamous NSCLC. Research is ongoing to find newer options.[5,73,137,734,735]

Trial Data

In a phase 2/3 trial (ECOG 4599), 878 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel/carboplatin; or 2) paclitaxel/carboplatin alone.[517,736] Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin showed an improved median survival (12.3 vs. 10.3 months, $P = .003$) when compared to patients receiving paclitaxel/carboplatin alone.[517] The overall 1-year and 2-year survival was 51% vs. 44% and 23% vs. 15%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.[517] However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel/carboplatin (grade 4 neutropenia: 25.5% vs. 16.8%, grade 5 hemoptysis: 1.2% vs. 0% and grade 3 hypertension: 6.8% vs. 0.5%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (15 patients) than with paclitaxel/carboplatin (2 patients) ($P = .001$). A recent analysis of ECOG 4599 found that patients with adenocarcinoma histology receiving bevacizumab/paclitaxel/carboplatin had improved survival compared with chemotherapy alone (14.2 vs. 10.3 months).[730] However, a trial (AVAiL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.[737,738]

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin/gemcitabine compared with cisplatin/pemetrexed.[513] Patients with either adenocarcinoma or large cell carcinoma (ie, non-squamous NSCLC) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 vs. 10.9 months). Patients with squamous cell carcinoma had improved survival with the cisplatin/gemcitabine regimen (10.8 vs. 9.4 months). When compared with the cisplatin/gemcitabine regimen, the cisplatin/pemetrexed regimen had significantly lower rates of grade 3 or 4 neutropenia, anemia, and thrombocytopenia ($P \leq .001$); febrile neutropenia ($P = .002$); and alopecia ($P < .001$). Treatment-related deaths were similar for both regimens (cisplatin/pemetrexed, 9 patients [1.0%]; cisplatin/gemcitabine, 6 patients [0.7%]). A recent analysis of three phase 3 trials confirmed that pemetrexed improves survival for patients with non-squamous NSCLC in first-line, subsequent, and maintenance therapy.[739]

Data show that platinum-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Cisplatin or carboplatin have been proven effective in combination with many of the following agents: docetaxel, etoposide, gemcitabine, paclitaxel (and albumin-bound paclitaxel), pemetrexed, and vinorelbine (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[494,510-513,536,537,545] Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.[539-542,740]

Number of Cycles of First-Line Systemic Therapy

Patients receiving first-line systemic therapy for advanced disease should be evaluated for tumor response with a CT scan. Approximately 25% of patients show disease progression after the initial cycle of chemotherapy; subsequent therapy is recommended for these patients (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with responsive or stable disease can continue to receive a total of 4 to

6 cycles of systemic therapy.[474,593,741] Currently, the NCCN Guidelines do not recommend continuing chemotherapy beyond 4 to 6 cycles.

Recent data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;[585] tumors can shrink between 4 to 6 cycles of chemotherapy. However, patients may not be able to tolerate more than 4 cycles of chemotherapy, and most of the maintenance trials used only 4 cycles of chemotherapy.[520] A meta-analysis suggests that continuing the initial regimen beyond 4 to 6 cycles is associated with increased PFS; however, patients have more adverse events.[742] A phase 3 randomized trial suggested that continuing chemotherapy beyond 4 to 6 cycles is not beneficial; however, many patients assigned to longer duration of therapy did not receive the planned number of cycles.[592,593] In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.[593]

Many patients with adenocarcinoma now receive pemetrexed-based regimens and not taxane-based regimens. Pemetrexed-based regimens are less toxic than taxane-based regimens. Thus, data suggesting that more than 6 cycles of first-line chemotherapy are not appropriate may only apply to taxane-based regimens.[520] Studies report that 60% of patients were able to receive 6 cycles of pemetrexed-based chemotherapy (and had a low incidence of toxicity), whereas only 42% were able to receive more than 5 cycles of taxane-based chemotherapy and often stopped therapy because of neurotoxicity.[583,593]

Maintenance Therapy

In patients with advanced NSCLC, maintenance therapy is another option for those with responsive or stable disease after first-line systemic therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations, continuation maintenance therapy includes bevacizumab (category 1), pemetrexed (category 1), bevacizumab/pemetrexed, or gemcitabine (category 2B) (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[517,522,563,585,587,589,590] Switch maintenance therapy for these patients includes pemetrexed or erlotinib (both are category 2B).[589,590,595,596] A phase 3 randomized trial (n = 663) assessed the effect of best supportive care with (or without) switch maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but had not progressed.[596] In patients with non-squamous NSCLC, overall survival was increased with pemetrexed when compared with placebo (15.5 vs. 10.3 months, P = .002). Close observation is another option. Maintenance therapy is discussed in greater detail earlier in this Discussion (see *Combined Modality Therapy: Maintenance Therapy*).

For patients with squamous cell carcinoma, gemcitabine (category 2B) is recommended as continuation maintenance therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[590,595] Switch maintenance therapy for these patients includes docetaxel (category 2B). Close observation is a category 2A option. As previously mentioned, a phase 3 randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Continuation maintenance therapy with single-agent 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).[589,590] However, the benefits of maintenance therapy were very slight; therefore, the recommendation is only category 2B for maintenance therapy with gemcitabine. A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until

progression.[600] However, switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines, because many patients in the delayed chemotherapy arm did not receive docetaxel.[743]

Continuation of Erlotinib, Gefitinib, or Afatinib After Progression

Previously, erlotinib was commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib was recently re-approved by the FDA based on a phase 4 study and is now available in the United States.[118] Patients may continue to derive benefit from erlotinib, gefitinib, or afatinib after disease progression; discontinuation of these TKIs leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).[744] 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.[745] Data support the continued use of erlotinib, gefitinib, or afatinib in patients with lung adenocarcinoma with sensitizing *EGFR* mutations after development of acquired resistance.[746] The NCCN Panel recommends continuing erlotinib, gefitinib, or afatinib in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see *Sensitizing EGFR Mutation Positive*: *Subsequent Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[720,747,748] In most cases, erlotinib, gefitinib, or afatinib is continued for these patients; however, additional therapy may be added or substituted (eg, whole brain RT, local therapy, systemic therapy).

Accumulating data suggest how cancers become resistant to EGFR inhibitors.[749] The most common known mechanism is the acquisition of the T790M mutation (which is a secondary mutation in EGFR), that renders the kinase resistant to erlotinib, gefitinib, or afatinib.[750,751] Amplification of the MET oncogene is another validated resistance mechanism. To overcome resistance, EGFR must still be inhibited. In the case of MET amplification, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely et al show that when cancers start to progress, which were once sensitive to EGFR inhibitors, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer.[744,752] Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.[746]

Second-Line and Beyond (Subsequent) Systemic Therapy

The phrase *subsequent* therapy was recently substituted for the terms *second-line, third-line, and beyond* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents. Subsequent systemic therapy regimens for patients who have disease progression during or after first-line therapy are described in the NSCLC algorithm and depend on the specific genetic alteration, the histologic subtype, and whether the patient has symptoms (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[753-762]

For the 2016 update, the NCCN Panel decided that immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are preferred agents for subsequent therapy in patients with metastatic NSCLC based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Nivolumab* and *Pembrolizumab* in this Discussion).[564,565] Human immune-checkpoint--inhibitor antibodies inhibit the programmed death (PD-1) receptor, which improves antitumor immunity; PD-1 receptors are

expressed on activated cytotoxic T-cells.[564,566,567] For 2016, NCCN Panel revised the recommendation for nivolumab to category 1 (from category 2A) based on the published data from a phase 3 randomized trial (CheckMate-057) and the recent FDA approval of nivolumab for patients with metastatic non-squamous NSCLC.[564] For 2016, the NCCN Panel also added a recommendation for pembrolizumab (category 2A) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression based on the KEYNOTE-001 trial and recent FDA approval.[577]

For 2016, the NCCN Panel recommends osimertinib as subsequent therapy for patients with metastatic EGFR T790M mutation-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy based on recent data and on the FDA approval (see *Osimertinib* in this Discussion). Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR sensitizing mutations and T790M mutations. Preliminary data from recent phase 2 trials (AURA/AURA2) report that osimertinib is associated with a response rate of about 61% and disease control rate of about 91% in patients who have progressed on sensitizing EGFR TKI therapy; 18% of patients had grade 3 or higher adverse events with one fatal event.[561,562] The FDA has approved osimertinib for patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. Most patients with sensitizing EGFR mutations and metastatic NSCLC typically progress after about 8 to 16 months of erlotinib or gefitinib therapy.[166] The EGFR T790M mutation is associated with acquired resistance to TKI therapy and has been reported in about 60% of patients with disease progression after initial response to sensitizing EGFR TKI therapy.[134,165-171] T790M mutations can be assessed using an FDA-approved test or other validated laboratory test done in a CLIA-approved laboratory.

For patients with sensitizing EGFR mutations who progress during or after first-line targeted therapy, recommended therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) switching to osimertinib; 2) continuing erlotinib, afatinib, or gefitinib with (or without) local therapy; or 3) switching to subsequent therapy using a first-line systemic therapy regimen for either non-squamous or squamous cell NSCLC (such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively). Recent data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving EGFR TKI therapy and chemotherapy.[763] Patients with T790M-positive and T790M-negative tumors had a similar response rate (32% vs. 25%; P = .341). For the 2016 update, the NCCN Panel added a recommendation (category 2A) to consider an afatinib/cetuximab regimen for patients who have progressed after receiving EGFR TKIs and chemotherapy based on these data. For 2016, a footnote that stating that afatinib had some efficacy in patients who progressed after EGFR therapy was deleted from the NCCN Guidelines based on a phase 2b/3 trial (LUX-Lung 1).[720] Median overall survival was not better in the afatinib group (10.8 months [95% CI, 10.0–12.0]) when compared with the placebo group (12.0 months [95% CI, 10.2–14.3]) (HR, 1.08; 95% CI, 0.86–1.35; P = .74). In the afatinib group, 2 deaths occurred possibly related to treatment.

For patients with ALK rearrangements who progress during or after first-line targeted therapy, recommended therapy also depends on whether the progression is asymptomatic or symptomatic and includes: 1) continuing ALK inhibitors with (or without) local therapy; 2) switching to ceritinib or alectinib; or 3) switching to a first-line systemic therapy regimen for either non-squamous or squamous cell NSCLC. After further progression on subsequent targeted therapy, first-line combination chemotherapy options for non-squamous NSCLC or

squamous cell carcinoma are recommended for patients with PS of 0 to 1 such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively.[119,764] Other chemotherapy options are also recommended for patients with PS 2 (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Most patients with NSCLC do not have ALK rearrangements or sensitizing EGFR mutations. For patients with all histologic subtypes but without ALK rearrangements or sensitizing EGFR mutations with PS of 0 to 2 who have disease progression during or after first-line therapy, recommended subsequent systemic therapy options include nivolumab (category 1), pembrolizumab, docetaxel with (or without) ramucirumab, or gemcitabine if not already given. The NCCN Panel recently added nivolumab and pembrolizumab as preferred options for subsequent therapy for all histologic subtypes based on improved survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy (see *Nivolumab* and *Pembrolizumab* in this Discussion).[564,565] Panel members also recently added ramucirumab/docetaxel as an additional option for all histologic subtypes for subsequent therapy based on a recent phase 3 randomized trial.[580] The median overall survival was slightly increased with ramucirumab/docetaxel versus docetaxel alone (10.5 vs. 9.1 months, respectively). Contraindications for ramucirumab/docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, and poorly controlled hypertension.

For patients with advanced non-squamous NSCLC but without ALK rearrangements or sensitizing EGFR mutations with PS of 0 to 2 who have disease progression during or after first-line therapy, recommended subsequent systemic therapy options include erlotinib, gefitinib, or pemetrexed in addition to the agents mentioned in the previous paragraph (ie, nivolumab, docetaxel with or without ramucirumab, or gemcitabine) if these agents have not already been given.[754,765,766] Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.[759,760] However, ifosfamide was deleted by the NCCN Panel for the 2016 update, since it is rarely used. When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[761,767] Pemetrexed is recommended in patients with non-squamous NSCLC.[596] Docetaxel is recommended for patients with wild-type EGFR tumors based on 2 randomized trials comparing erlotinib versus docetaxel.[768,769] Proteomic testing can be used to determine whether erlotinib should be used in patients with unknown EGFR status.[770] Erlotinib is superior to best supportive care with significantly improved survival and delayed time to symptom deterioration in patients with non-squamous NSCLC.[762] In patients with PS of 3 to 4 who have sensitizing EGFR mutations, erlotinib, afatinib, or gefitinib are recommended options for subsequent therapy for progressive disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[7,480,481] Patients often have a limited response to subsequent chemotherapy other than immune checkpoint inhibitors, although it may serve a useful palliative role.[771]

For the 2016 update, panel members revised the recommendation to *preferred* for nivolumab as subsequent therapy for patients with squamous cell NSCLC. The NCCN Panel also decided to delete erlotinib as an option for subsequent therapy for patients with squamous cell NSCLC for the 2016 update based on a recent study comparing afatinib with erlotinib; this study was statistically significant but not clinically significant.[560] Overall survival was slightly better in the afatinib group than in the erlotinib group (median overall survival, 7.9 months [95% CI, 7.2–8.7] vs. 6.8 months [5.9–7.8]; HR, 0.81 [95% CI, 0.69–

0.95], *P* = .0077); however, almost 60% of patients in each arm had grade 3 or higher adverse events. In contrast, the median overall survival was 9.2 months with nivolumab compared with 6.0 months for docetaxel for patients with squamous cell NSCLC.[565] In addition, only 7% of patients receiving nivolumab had grade 3 or higher adverse events.

If patients with either ALK fusions or sensitizing EGFR mutations progress with symptomatic systemic multiple lesions after therapy with crizotinib, erlotinib, gefitinib, or afatinib and/or after ceritinib, alectinib, or osimertinib, then first-line doublet chemotherapy options are recommended for either non-squamous NSCLC or squamous cell carcinoma.[517] Erlotinib, gefitinib, or afatinib may be continued in patients with sensitizing EGFR mutations who have progressed after first-line therapy.[154,720,747,748] For the 2016 update, the NCCN Panel now recommends afatinib/cetuximab for patients with sensitizing EGFR mutations who have progressed after EGFR TKI therapy and chemotherapy.[763] Ceritinib or alectinib may also be continued in patients with ALK-positive NSCLC who have progressed after first-line therapy with crizotinib or are intolerant to crizotinib.[117,217]

In a randomized 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-line or subsequent chemotherapy.[762] Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (HR, 0.70; *P* < .001). PFS was 2.2 months for the erlotinib group versus 1.8 months for placebo (HR, 0.61; *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-line or subsequent systemic therapy. A randomized phase 3 trial in 829 patients found that oral topotecan was not inferior to docetaxel as subsequent therapy for patients with advanced NSCLC.[772]

Nivolumab, pembrolizumab, erlotinib (non-squamous only), docetaxel with or without ramucirumab (category 2B for both), gemcitabine (category 2B), or pemetrexed (non-squamous only) (category 2B) are recommended for subsequent therapy after second disease progression in patients with advanced NSCLC and PS 0–2 if these agents have not already been given.[754,765,766,769]

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