

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 7.2017 — June 22, 2017

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Non-Small Cell Lung Cancer

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Clinical Trials: NCCN believes that the best management for any patient with cancer 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 indicated.

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

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2017.



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Updates in Version 7.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 6.2017 include:

[NSCL-20](#)

- **ALK rearrangement discovered prior to first-line chemotherapy:** Alectinib added as a category 1 treatment option and preferred.
- **ALK rearrangement discovered during first-line chemotherapy:** Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by *alectinib* or *crizotinib* or *ceritinib*

[NSCL-21](#)

- **Asymptomatic, Brain and Systemic isolated lesions:** "continue alectinib" added as a treatment option.

[MS-1](#)

- The discussion section was updated based on the recent changes to the Guidelines.

Updates in Version 6.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 5.2017 include:

[NSCL-21](#)

- **Asymptomatic progression; Symptomatic progression - brain or multiple systemic lesions:** Brigatinib added as a treatment option.
- **Footnote "rr" modified:** Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or *brigatinib*.
- **Footnote "tt" added:** Alectinib or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that have progressed on crizotinib.

[MS-1](#)

- The discussion section was updated based on the recent changes to the Guidelines.

Updates in Version 5.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2017 include:

[NSCL-20](#)

- **ALK rearrangement discovered prior to first-line chemotherapy:** Ceritinib added as a category 1 treatment option.
- **ALK rearrangement discovered during first-line chemotherapy:** Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by *crizotinib* or *ceritinib*

[NSCL-21](#)

- **Asymptomatic, Brain and Systemic isolated lesions:** "continue ceritinib" added as a treatment option.
- **Footnote "ss" added:** If not previously given.

[MS-1](#)

- The discussion section was updated based on the recent changes to the Guidelines.



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Non-Small Cell Lung Cancer

Updates in Version 4.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 3.2017 include:

[NSCL-9](#)

- Separate pulmonary nodules; N2, R0 after surgery: Adjuvant treatment recommendation clarified as chemotherapy (category 1) or sequential chemotherapy + RT. Previously noted as sequential chemotherapy (category 1) + RT.

[NSCL-19](#)

- Osimertinib changed from a category 2A to a category 1 recommendation.
- Footnote "nn" modified with this addition: Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.
- Footnote removed: Osimertinib is an option 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.

[NSCL-24](#)

- Atezolizumab changed from a category 2A to a category 1 recommendation. (also applies to NSCL-25)

Updates in Version 3.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 2.2017 include:

[MS-1](#)

- The Discussion section has been updated to reflect the changes in the algorithm.

Updates in Version 2.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 1.2017 include:

[NSCL-17](#)

- Testing results modified: "*PD-L1 positive and EGFR, ALK, ROS1 negative or unknown.*"

[NSCL-24](#)

- Subsequent Therapy; PS 0-2: Atezolizumab added as a treatment option. Reference added: Barlesi F, Park K, Ciardiello F, et al. Primary analysis from OAK, a randomized phase III study comparing atezolizumab with docetaxel in 2L/3L NSCLC [abstract]. ESMO Congress; Copenhagen. ESMO 2016: LBA44. (also applies to NSCL-25)
- Erlotinib removed as a treatment option in subsequent therapy and maintenance therapy.
- Footnote "ww" modified: Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression *levels* $\geq 1\%$, as determined by an FDA-approved test. ~~for PD-L1 with use of pembrolizumab.~~ (also applies to NSCL-25)
- Footnote "aaa" modified: If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, *or atezolizumab*), ~~erlotinib~~, docetaxel (category 2B), pemetrexed (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.

[NSCL-25](#)

- Footnote "bbb" modified: If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, *or atezolizumab*), 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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Updates in Version 1.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2016 include:

[PREV-1](#)

- Link added to the NCCN Guidelines for Smoking Cessation.

[DIAG-2](#) and [DIAG-3](#)

- These pages were revised and adapted from the Fleischner Society Guidelines.

[NSCL-2](#)

- Stage IA: "Consider" added to "pathologic mediastinal lymph node evaluation."
- Stage IB; Brain MRI: category 2B removed and "optional" listed.
- Medically inoperable; N0: Consider adjuvant chemotherapy for high-risk stages IB-IIIA clarified as stages IB-IIB.
- Footnote "j" modified with addition of first sentence: PET/CT performed skull base to knees or whole body. (also applies to NSCL-4, NSCL-7, NSCL-9, NSCL-11 through NSCL-13)
- Footnote "p" modified: 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~~ *unknown lymph node status* (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy. (also applies to NSCL-3)

[NSCL-5](#)

- Surgical reevaluation clarified: including chest CT with or without contrast ± PET/CT.

[NSCL-8](#)

- T1-3, N0-1: Surgery removed, as this is already noted in the Initial Treatment column.
 - ▶ Adjuvant treatment linked back to NSCL-3 for N0-1 and N2.
- T1-2,T3 (other than invasive), N2 nodes positive and T3 (invasion), N2 nodes positive changed to include M0.
 - ▶ Brain MRI and FDG PET/CT removed, as they are already noted on previous page.
 - ▶ Metastatic disease removed, as this is already noted on previous page.
- Footnote "w" is new to the page: "Chest CT with contrast and/or PET/CT to evaluate progression."

[NSCL-10](#)

- Definitive local therapy not possible: "Consider" removed from "palliative chemotherapy ± local palliative therapy" and "Observe" added.
- Footnote "aa" modified: "Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning. *Patients should be evaluated in a multidisciplinary setting (ie, surgery, radiation oncology, medical oncology).*"

[NSCL-13](#)

- Significant revisions for the management of limited metastases. Now covers pages NSCL-13 and NSCL-14.



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Updates in Version 1.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2016 include:

[NSCL-15](#)

- Surveillance title modified: "SURVEILLANCE AFTER COMPLETION OF DEFINITIVE THERAPY"
- Recommendations differentiated based on primary therapy.
 - ▶ *Stage I-II (primary treatment included surgery ± chemotherapy)*
H&P and chest CT ± contrast every 6 mo for 2–3 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
 - ▶ *Stage I-II (primary treatment included RT) or Stage III or Stage IV (oligometastatic with all sites treated with definitive intent)*
H&P and chest CT ± contrast every 3–6 mo for 3 y, then H&P and chest CT ± contrast every 6 mo for 2 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
 - ◊ *Residual or new radiographic abnormalities may require more frequent imaging"*
- Recommendations for stage IV not included.
- "PET/CT or brain MRI is not *routinely* indicated"

[NSCL-16](#)

- Locoregional recurrence post therapy: The following imaging was added to evaluate for disseminated disease: "Chest CT with contrast; Brain MRI with contrast; PET/CT."
- Distant metastasis; Bone metastasis; Recommendations reordered: "If risk of fracture, orthopedic stabilization + palliative external-beam RT."

[NSCL-17](#)

- Testing added for ROS1 and PD-L1.
- Squamous cell carcinoma: "Consider EGFR mutation testing and ALK testing ~~especially~~ in never smokers or small biopsy specimens, or mixed histology."
- Footnote "ff" added: "If repeat biopsy is not feasible, plasma biopsy should be considered."
- Footnote "gg" modified: "The NCCN NSCLC Guidelines Panel strongly ~~endorses~~ *advises* broader molecular profiling..."
- Footnote "kk" added: "PD-L1 expression levels of ≥50% are a positive test for first-line pembrolizumab therapy."
- Footnote removed since the content was added to the algorithm: Consider ROS1 testing; if positive, may treat with crizotinib.

[NSCL-18](#)

- EGFR mutation discovered during first-line chemotherapy: "Interrupt or complete planned chemotherapy, followed by..." changed to "Complete planned chemotherapy, including maintenance therapy, or interrupt, followed by..." (also applies to NSCL-20)

[NSCL-19](#)

- "T790M testing" added with footnote "nn": "If tissue biopsy is not feasible, plasma biopsy should be considered."
- Asymptomatic: "Consider local therapy" added as a treatment option.
- Brain: "Osimertinib" added as a treatment option.
- Asymptomatic, brain lesions, or symptomatic and isolated systemic lesions: progression directed to treatment for multiple lesions.
- Systemic isolated or multiple lesions:
 - ▶ T790M+ added with treatment recommendation of osimertinib.
 - ▶ T790M- added with referral to first-line therapy options for adenocarcinoma, squamous cell carcinoma, or PD-L1 expression positive (≥50%).
- Footnote "pp" modified: "Osimertinib is ~~approved~~ an option for patients..."
- Footnote "qq" added: "For rapid radiologic progression or threatened organ function, alternate therapy should be instituted."



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Updates in Version 1.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2016 include:

[NSCL-21](#)

- Asymptomatic: "Consider local therapy" added as an option.
- Brain and systemic isolated lesions: "continue ALK inhibitor" clarified as "continue crizotinib."
- Symptomatic systemic progression after local therapies and/or switching to ceritinib or alectinib changed to "progression."

[NSCL-22](#)

- New page added for ROS1 rearrangement positive. Crizotinib is noted as a category 2A recommendation.

[NSCL-23](#)

- New page added for PD-L1 expression positive. Pembrolizumab is noted as a category 1 recommendation.

[NSCL-24](#)

- First-line therapy: Doublet chemotherapy and bevacizumab + chemotherapy changed to "Systemic therapy," as specific recommendations are noted on NSCL-F. Associated footnotes moved to NSCL-F.
- Subsequent Therapy; PS 3-4: Erlotinib, afatinib, gefitinib, crizotinib removed as treatment options. Associated footnotes removed.
- Footnote "v" added: "If pembrolizumab not previously given." (also applies to NSCL-25)
- Footnote "xx" added: "If not previously given" (also applies to NSCL-25)

[NSCL-A \(1 of 5\)](#)

- Pathologic Evaluation, bullet 3 modified: "The pathology diagnostic report should include the histologic classification *in resection specimens or small biopsies* 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.~~"
- Pathologic Evaluation, bullet 6 modified: "Limited use of IHC studies in small tissue samples is strongly recommended *in samples that cannot be reliably classified on the basis of routine histology alone*, 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."

[NSCL-A \(3 of 5\)](#)

- ALK; bullet 1: "alectinib" added to third sentence.
- ALK; bullet 2: "translocations" changed to "rearrangements".
- ALK; bullet 3 modified: 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.~~

[NSCL-A \(4 of 5\)](#)

- New sections were added for ROS-1 and PD-L1.

[NSCL-A \(5 of 5\)](#)

- The following references were updated: 6, 7. The following references added: 33–38.

[NSCL-B 1 of 4](#)

- Bullet 6 added: Patients who are active smokers should be provided counseling and smoking cessation support (NCCN Guidelines for Smoking Cessation). While active smokers have a mildly increased incidence of postoperative pulmonary complications, these should not be considered a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely due to smoking status, as surgery provides the predominant opportunity for prolonged survival in patients with early-stage lung cancer."



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Updates in Version 1.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2016 include:

[NSCL-C \(1 of 10\)](#)

- General Principles; bullet 5 modified: "Useful references include the ~~ACR-ASTRO Practice Guidelines for Radiation Oncology Practice Parameters and Technical Standards...~~"
- General Principles; bullet 4 modified with addition of sentence: In a prospective trial of definitive chemo/RT for stage III NSCLC (RTOG 0617), IMRT was associated with a nearly 60% decrease in high-grade radiation pneumonitis and similar survival and tumor control outcomes despite a higher proportion of stage IIIB and larger treatment volumes compared to 3D-CRT; as such, IMRT is preferred over 3D-CRT in this setting.

[NSCL-C \(3 of 10\)](#)

- Node-Negative Early-Stage SABR; bullet 2 modified: "In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well. ~~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, while 54 to 60 Gy in 3 fractions is unsafe and should be avoided. The dose for 5-fraction regimens is being studied prospectively in RTOG 0813. For centrally located tumors (defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura) and even ultra-central tumors (defined as abutting the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe, while 54 to 60 Gy in 3 fractions is unsafe and should be avoided. The maximum tolerated dose for 5-fraction regimens was studied prospectively in RTOG 0813, preliminarily demonstrating no high-grade toxicities at 50 Gy in 5 fractions while final results are pending.~~"

[NSCL-C \(4 of 10\)](#)

- Locally Advanced Stage/Conventionally Fractionated RT; bullet 2 modified: "Dose escalation in RT alone, sequential chemo/RT, or concurrent chemo/RT 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, 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. While optimal RT dose intensification remains a valid question, higher doses of 74 Gy are not currently recommended for routine use.~~"
- Advanced Stage/Palliative RT; last sentence modified: "When higher doses (>30 Gy) are warranted, *technologies to reduce normal tissue irradiation (at least 3D-CRT and including IMRT or proton therapy as appropriate) should be used.*"

[NSCL-C \(7 of 10\)](#)

- "Please note - Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations." (also applies to NSCL-C 8 of 10)

[NSCL-C \(8 of 10\)](#)

- Table 5: Footnote "*" added: "RTOG 0617 data suggest that even lower radiation doses to the heart than previously appreciated may be detrimental to survival after thoracic RT, and more stringent constraints may be appropriate."

[NSCL-C \(9 of 10\)](#)

- The following reference was added: 5, 17.

[NSCL-C \(10 of 10\)](#)

- The following references were added: 52, 53, 55, 89.



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Updates in Version 1.2017 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2016 include:

[NSCL-E](#)

- **Concurrent Chemotherapy/RT Regimens**

- ▶ **Bullet 4 modified:** "Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT (nonsquamous) ± *additional 4 cycles of pemetrexed 500 mg/m²*"
- ▶ **Bullet 5 modified:** "Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT ± *additional 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6*"
- **"Concurrent Chemotherapy/RT Followed by Chemotherapy" removed.**
 - ▶ Cisplatin/etoposide with concurrent RT followed by cisplatin/etoposide removed.

[NSCL-F \(1 of 4\)](#)

- **First-line therapy; bullet 4 modified:** "Response assessment after 4–2 cycles, then every 2–4 cycles *with CT of known sites with or without contrast or when clinically indicated.*"
- **Subsequent therapy; bullets removed for the following agents:** nivolumab, pembrolizumab, docetaxel, pemetrexed, ramucirumab + docetaxel, erlotinib. This information is included in detail in the discussion.
- **Subsequent therapy; bullet added:** "Response assessment with CT of known sites with or without contrast every 6–12 weeks."

[NSCL-F \(2 of 4\)](#)

- **First-line Systemic Therapy Options; Adenocarcinoma, Large cell, NSCLC NOS (PS 0-1);** the following regimens removed: carboplatin/vinorelbine, cisplatin/vinorelbine.
- **First-line Systemic Therapy Options; Adenocarcinoma, Large cell, NSCLC NOS (PS 2);** the following regimens removed: carboplatin/vinorelbine, etoposide, irinotecan, vinorelbine.

[NSCL-F \(3 of 4\)](#)

- **First-line Systemic Therapy Options; Squamous cell carcinoma (PS 0-1);** the following regimens removed: carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, cisplatin/vinorelbine.
- **First-line Systemic Therapy Options; Squamous cell carcinoma (PS 2);** the following regimens removed: carboplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, etoposide, irinotecan, vinorelbine.
- **Footnote added:** "Cisplatin/gemcitabine/necitumumab in the first-line setting and erlotinib or afatinib in the second-line setting are not used at NCCN institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents."

[NSCL-H](#)

- **Emerging Targeted Agents for Patients with Genetic Alterations**
 - ▶ RET rearrangements: vandetanib added as an option.
 - ▶ ROS1 rearrangements were removed, as this information has been added to the algorithm.
 - ▶ Footnotes references updated: 3, 4. Footnote references added: 9, 12.



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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 (<http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>) 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](#)).
- See the [NCCN Guidelines for Smoking Cessation](#).

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

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

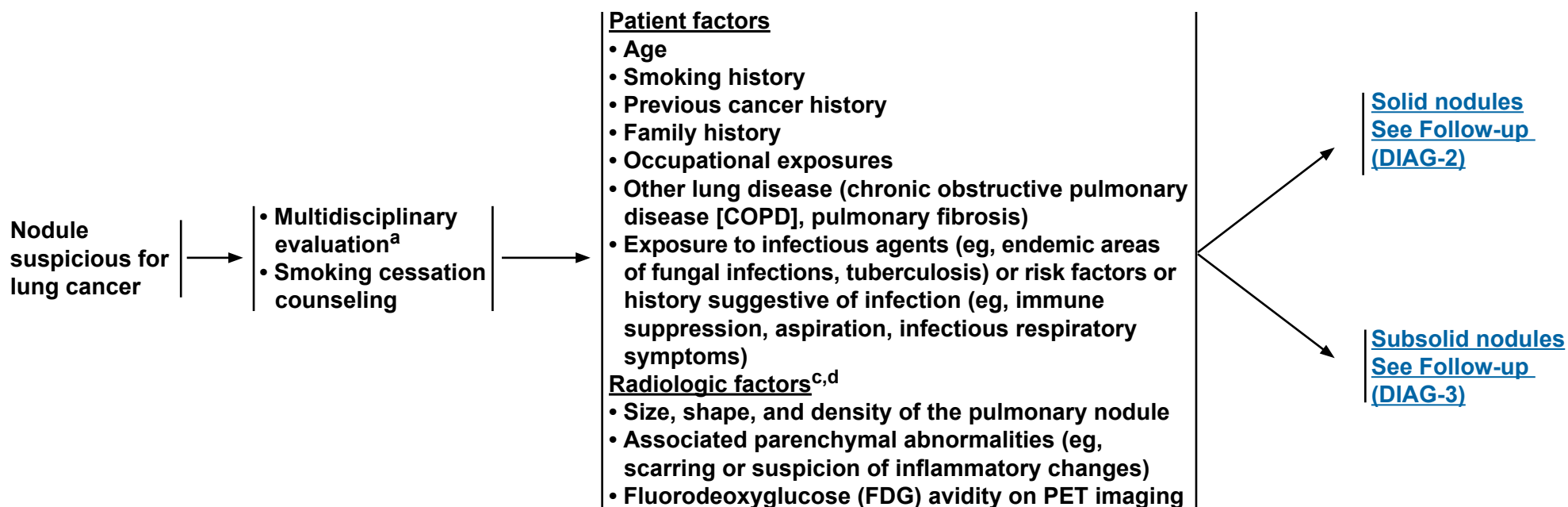


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CLINICAL PRESENTATION

RISK ASSESSMENT^b



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

^bRisk 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 \(DIAG-A 1 of 2\).](#)

^dThe most important radiologic factor is change or stability compared with a previous imaging study.

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



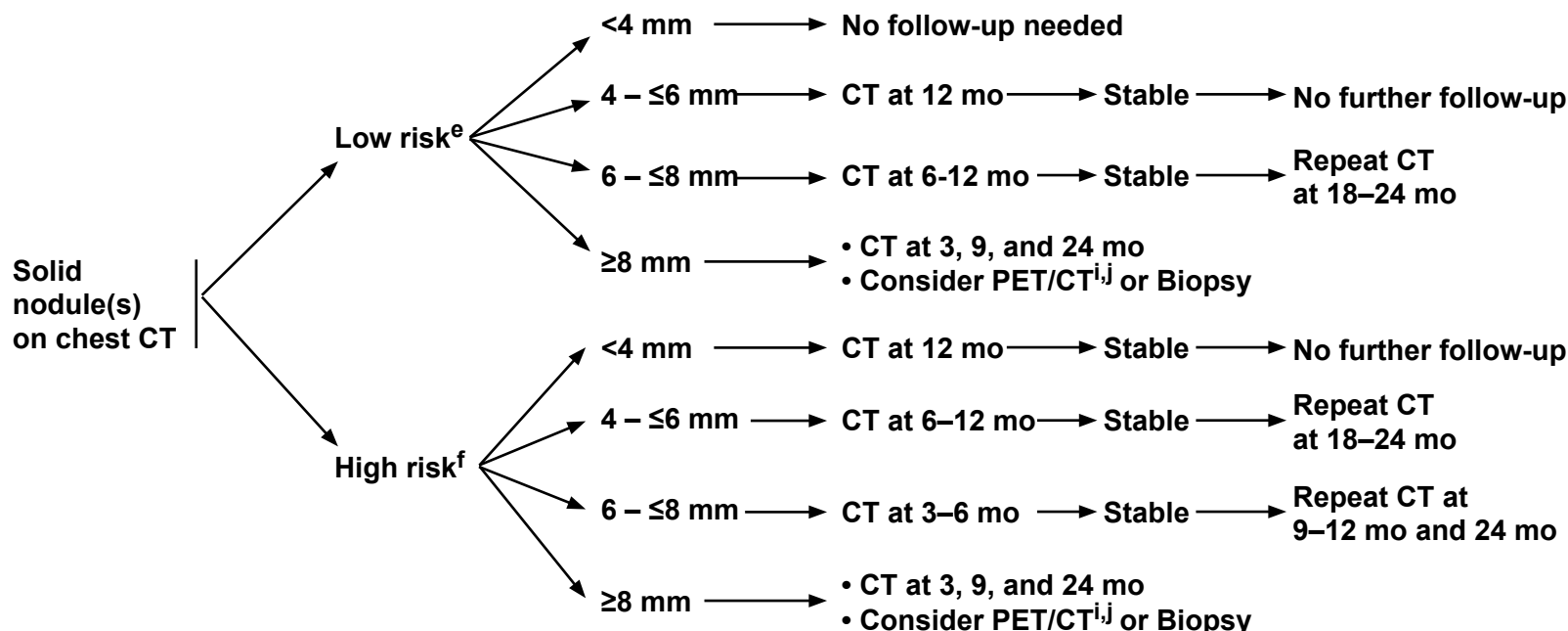
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Non-Small Cell Lung Cancer

- Lung nodules in asymptomatic, high-risk patients detected during lung cancer screening with LDCT, see the [NCCN Guidelines for Lung Cancer Screening](#).
- For incidentally detected lung nodules, see below.

FINDINGS

FOLLOW-UP^{c,d,g,h}



^cSee [Principles of Diagnostic Evaluation \(DIAG-A 1 of 2\)](#).

^dThe most important radiologic factor is change or stability compared with a previous imaging study.

^eLow risk = minimal or absent history of smoking or other known risk factors.

^fHigh risk = history of smoking or other known risk factors. Known risk factors include history of lung cancer in a first-degree relative; exposure to asbestos, radon, or uranium.

^gNon-solid, partially solid, or ground-glass nodules may require longer follow-up to exclude indolent adenocarcinoma.

^hAdapted from Fleischner Society Guidelines: MacMahon H, Austin JH, Gamsu G, et al. Guidelines for management of small pulmonary nodules detected on CT scans: a statement from the Fleischner Society. *Radiology* 2005;237:395-400. © Radiological Society of North America. Fleischner Society Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.

ⁱPET/CT performed skull base to knees or whole body. 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).

^jPatients 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, and interventional pulmonology.

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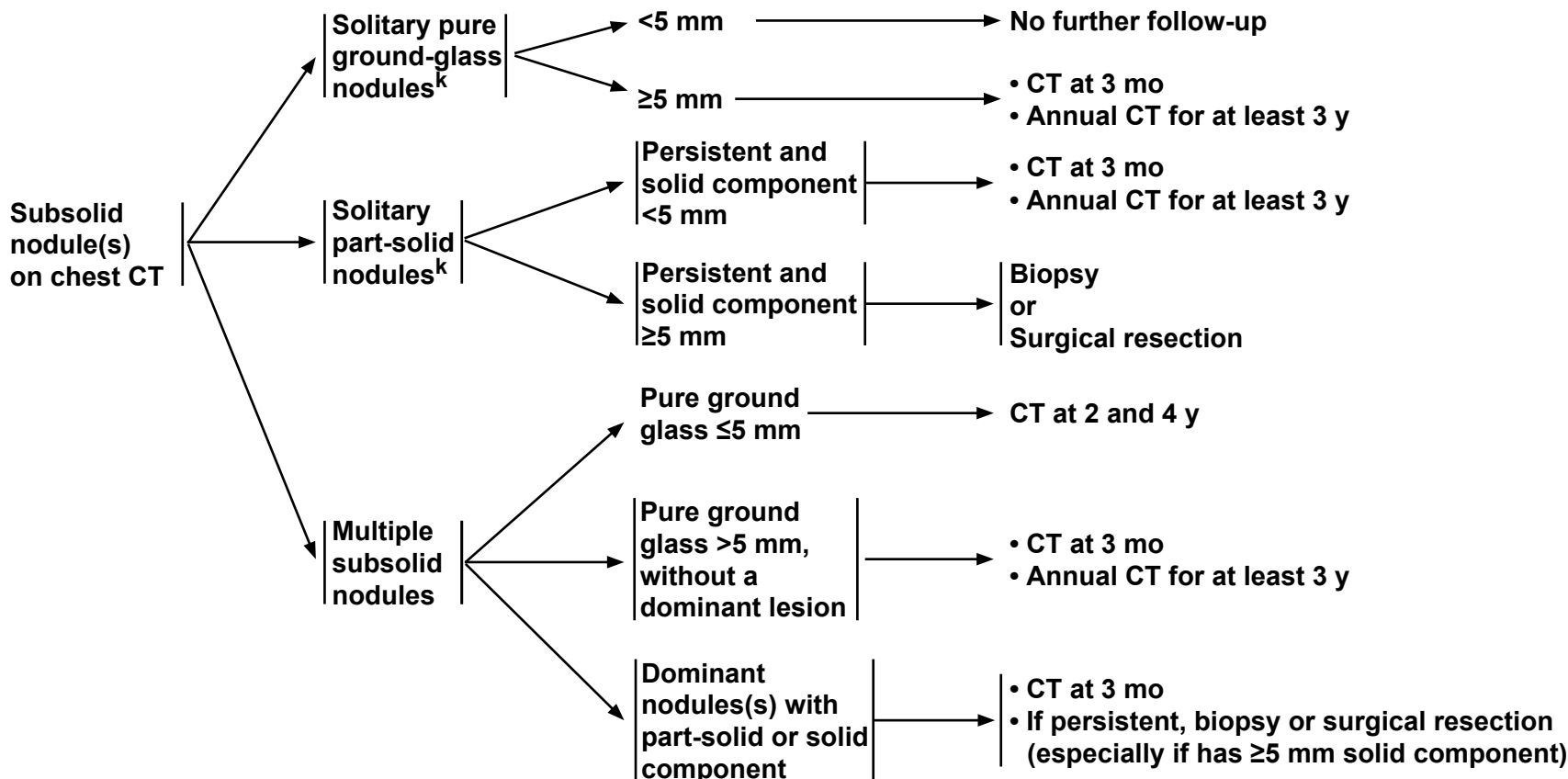
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Non-Small Cell Lung Cancer

- Lung nodules in asymptomatic, high-risk patients detected during lung cancer screening with LDCT, see the [NCCN Guidelines for Lung Cancer Screening](#).
- For incidentally detected lung nodules, see below.

FINDINGS

FOLLOW-UP^{c,d,g}



^cSee [Principles of Diagnostic Evaluation \(DIAG-A 1 of 2\)](#).

^dThe most important radiologic factor is change or stability compared with a previous imaging study.

^gNon-solid, partially solid, or ground-glass nodules may require longer follow-up to exclude indolent adenocarcinoma.

^kNaidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected on CT: A statement from the Fleischner Society.

Radiology 2013;266:304-317. Guidelines do not direct whether or not contrast is necessary or if an LDCT is appropriate. LDCT is preferred unless there is a reason for contrast enhancement for better diagnostic resolution.

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Non-Small Cell Lung Cancer

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

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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 transthoracic needle aspiration (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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Non-Small Cell Lung Cancer

PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

CLINICAL STAGE

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](#))

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 IIB^f (T1-3, N3) mediastinal CT positive
Contralateral (lymph nodes ≥1 cm) or
palpable supraclavicular lymph nodes

[See Pretreatment Evaluation \(NSCL-11\)](#)

Stage IIB^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 \(NSCL-A\)](#).

^bEnhanced frailty or geriatric assessments may predict complications better following treatment modalities, particularly surgery. A preferred frailty assessment system has not been established.

^cTemel 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.

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

^eT3, N0 related to size or satellite nodules.

^fFor 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.

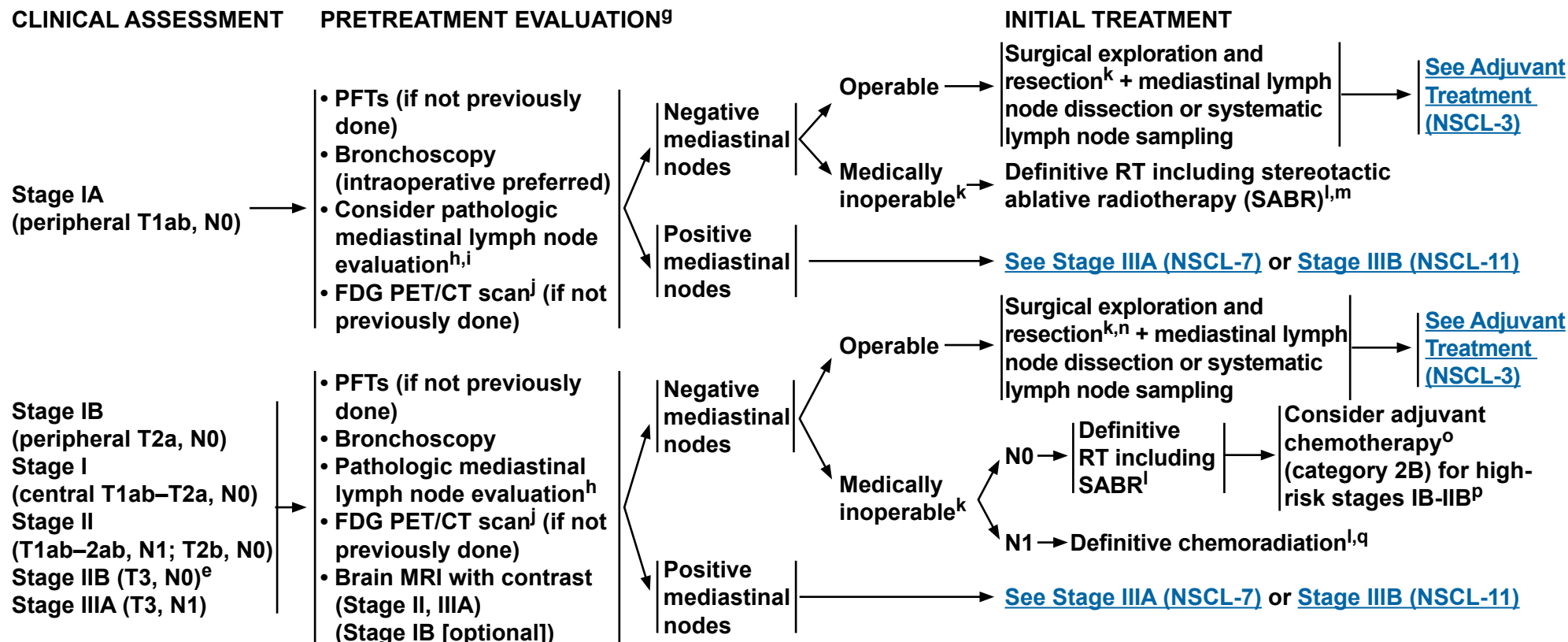
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Non-Small Cell Lung Cancer


^eT3, N0 related to size or satellite nodules.

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

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

ⁱSolid 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.

^jPET/CT performed skull base to knees or whole body. 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 \(NSCL-C\).](#)
^mInterventional radiology ablation is an option for selected patients.

ⁿAfter 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 \(NSCL-D\).](#)
^pExamples 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 unknown lymph node status (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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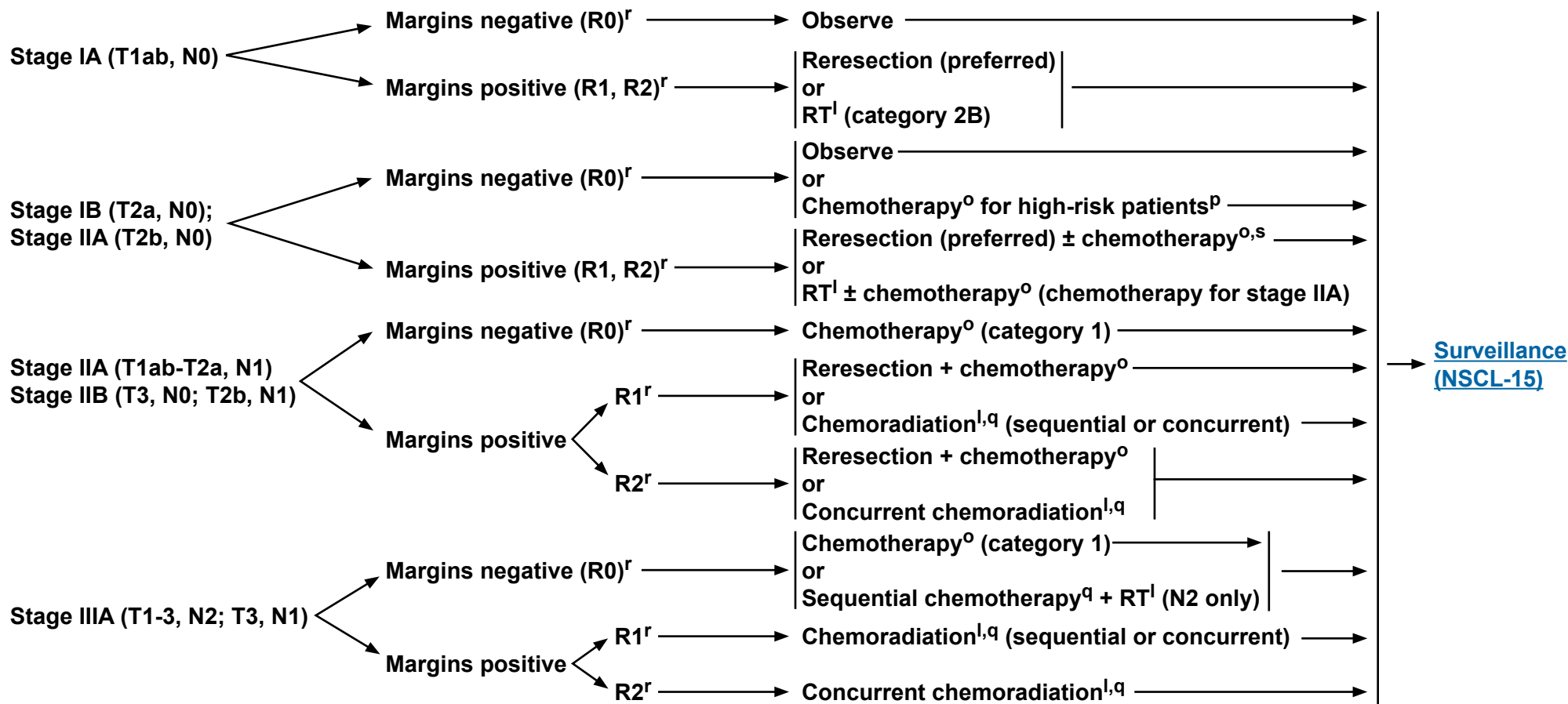
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Non-Small Cell Lung Cancer

FINDINGS AT SURGERY


^lSee Principles of Radiation Therapy (NSCL-C).

^oSee Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

^pExamples 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 unknown lymph node status (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

^qSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

^rR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

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

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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

CLINICAL EVALUATION

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

- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation^h
- Brain MRI with contrast
- MRI with contrast of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels
- FDG PET/CT scan^j (if not previously done)

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

Chest wall → [See Treatment \(NSCL-6\)](#)

Proximal airway
or mediastinum → [See Treatment \(NSCL-6\)](#)

Unresectable disease → [See Treatment \(NSCL-6\)](#)

Metastatic disease → [See Treatment for Metastasis
limited sites \(NSCL-13\) or
distant disease \(NSCL-16\)](#)

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

^jPET/CT performed skull base to knees or whole body. 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.

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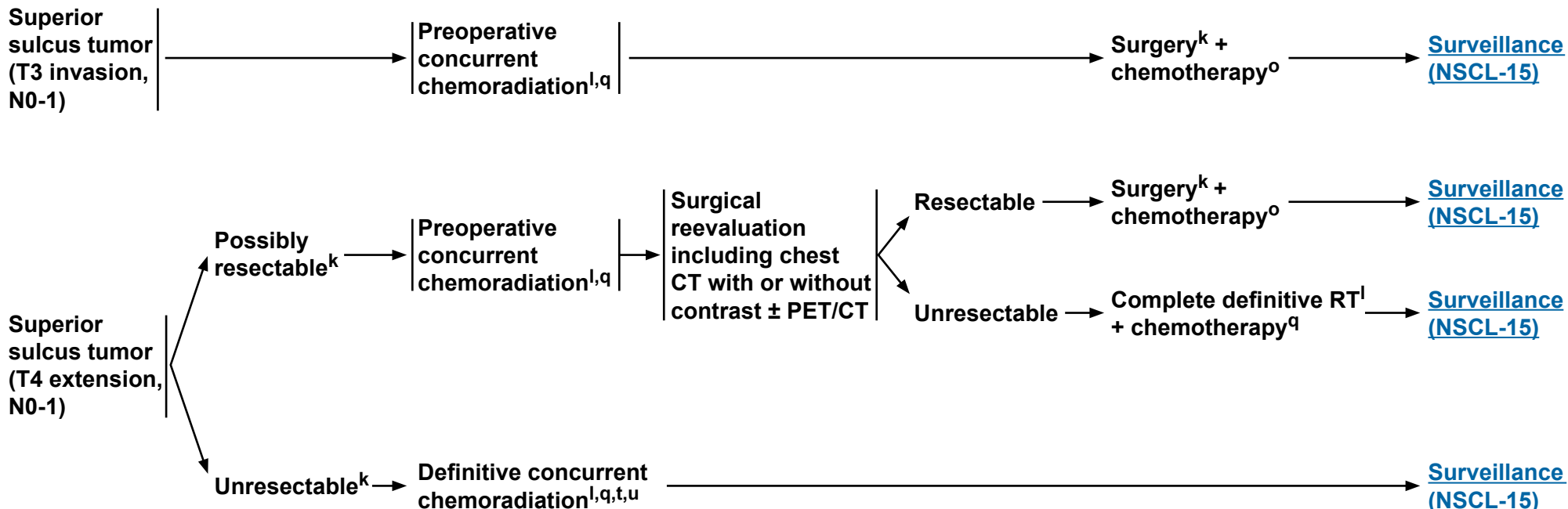
Non-Small Cell Lung Cancer

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CLINICAL PRESENTATION

INITIAL TREATMENT

ADJUVANT TREATMENT



^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 \(NSCL-E\).](#)

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

^uIf full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

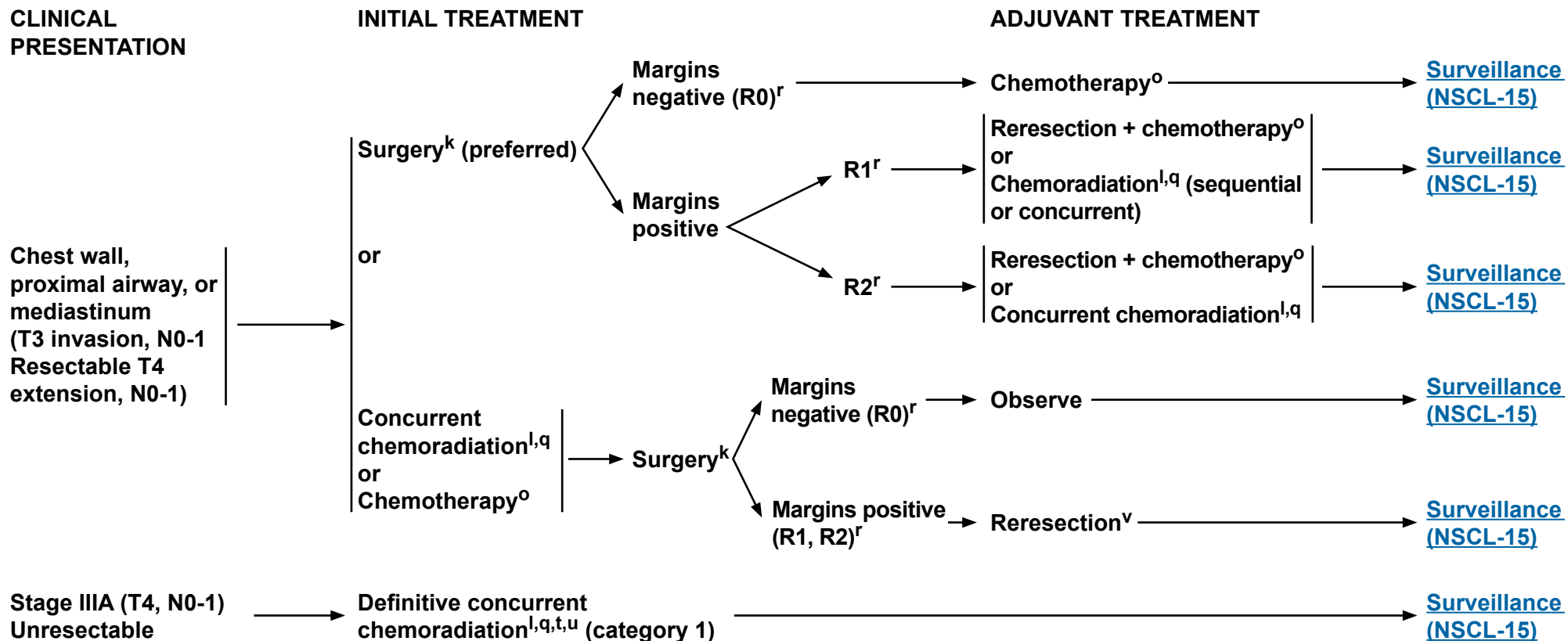
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Non-Small Cell Lung Cancer


^kSee Principles of Surgical Therapy (NSCL-B).

^lSee Principles of Radiation Therapy (NSCL-C).

^oSee Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

^qSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

^rR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

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

^uIf full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

^vConsider RT boost if chemoradiation is given as initial treatment.

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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY

Stage IIIA
(T1-3, N2)

- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation^h
- FDG PET/CT scan^j (if not previously done)
- Brain MRI with contrast

N2, N3 nodes negative → [See Treatment T 1-3, N0-1 \(NSCL-8\)](#)

N2 nodes positive, M0 → [See Treatment \(NSCL-8\)](#)

N3 nodes positive, M0 → [See Stage IIIB \(NSCL-11\)](#)

Metastatic disease → [See Treatment for Metastasis limited sites \(NSCL-13\) or distant disease \(NSCL-16\)](#)

Separate pulmonary
nodule(s)
(Stage IIB, IIIA, IV)

- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation^h
- Brain MRI with contrast
- FDG PET/CT scan^j (if not previously done)

Separate pulmonary
nodule(s), same lobe
(T3, N0-1) or ipsilateral
non-primary lobe (T4, N0-1) → [See Treatment \(NSCL-9\)](#)

Stage IV (N0, M1a):
Contralateral lung
(solitary nodule) → [See Treatment \(NSCL-9\)](#)

Extrathoracic
metastatic disease → [See Treatment for Metastasis limited sites \(NSCL-13\) or distant disease \(NSCL-16\)](#)

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

^jPET/CT performed skull base to knees or whole body. 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.

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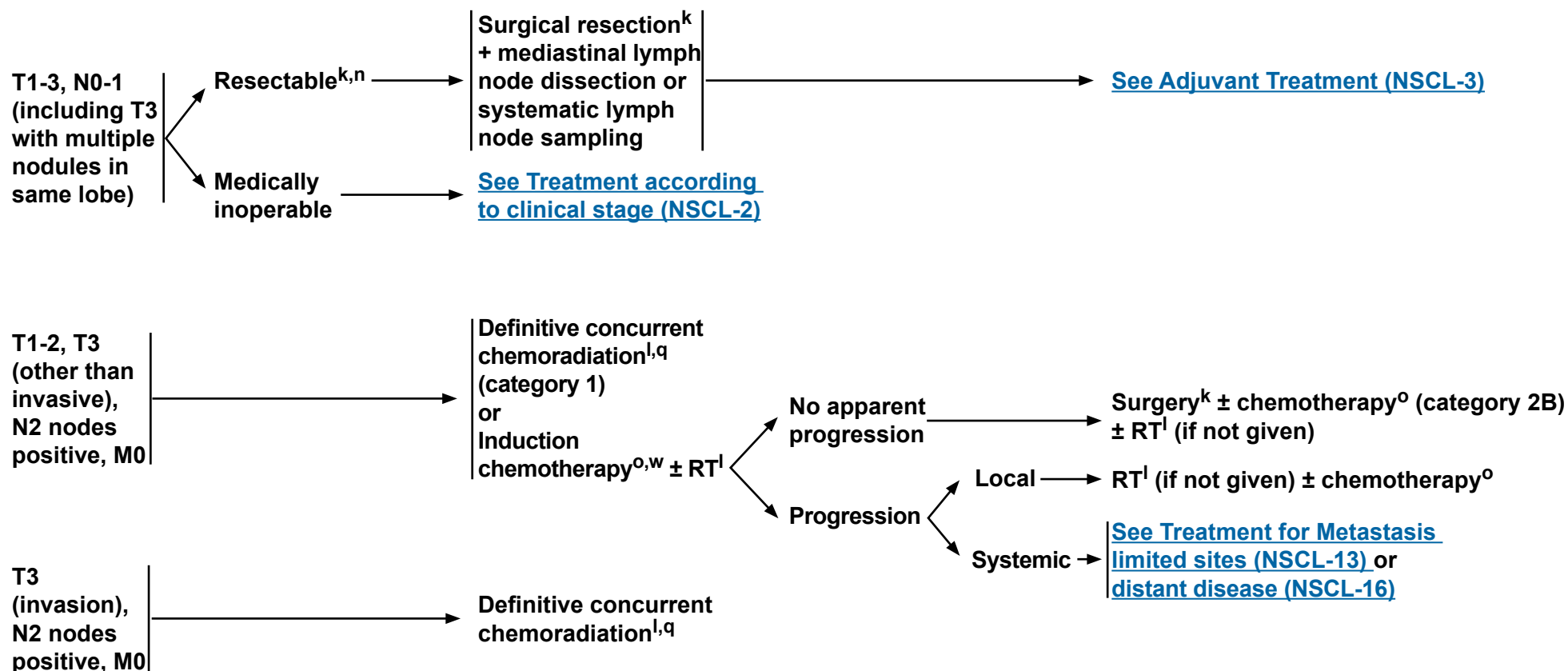
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Non-Small Cell Lung Cancer

MEDIASTINAL BIOPSY FINDINGS



^k[See Principles of Surgical Therapy \(NSCL-B\).](#)

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

ⁿAfter 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 \(NSCL-D\).](#)

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

^wChest CT with contrast and/or PET/CT to evaluate progression.

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Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

Separate pulmonary nodule(s), same lobe (T3, N0-1), or ipsilateral non-primary lobe (T4, N0-1)

Surgery^k

N0-1

Margins negative (R0)^r

N2

Margins positive

R1^r

R2^r

ADJUVANT TREATMENT

Chemotherapy^o

Chemotherapy^o (category 1) or Sequential chemotherapy^o + RT^l

Chemoradiation^{l,o,q} (sequential or concurrent)

Concurrent chemoradiation^{l,q}

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

[Surveillance \(NSCL-15\)](#)

Stage IV (N0, M1a): Contralateral lung (solitary nodule)

Treat as two primary lung tumors if both curable

[See Evaluation \(NSCL-1\)](#)

Suspected multiple lung cancers (based on the presence of biopsy-proven synchronous lesions or history of lung cancer)^{x,y}

• Chest CT with contrast
• FDG PET/CT scan (if not previously done)^j
• Brain MRI with contrast

Disease outside of chest

No disease outside of chest

[See Systemic Therapy for Metastatic Disease \(NSCL-17\)](#)

Pathologic mediastinal lymph node evaluation^h

N0-1

N2-3

[See Initial Treatment \(NSCL-10\)](#)

[See Systemic Therapy for Metastatic Disease \(NSCL-17\)](#)

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

^jPET/CT performed skull base to knees or whole body. 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 \(NSCL-C\)](#).

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

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

^rR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^xLesions 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.

^yFor 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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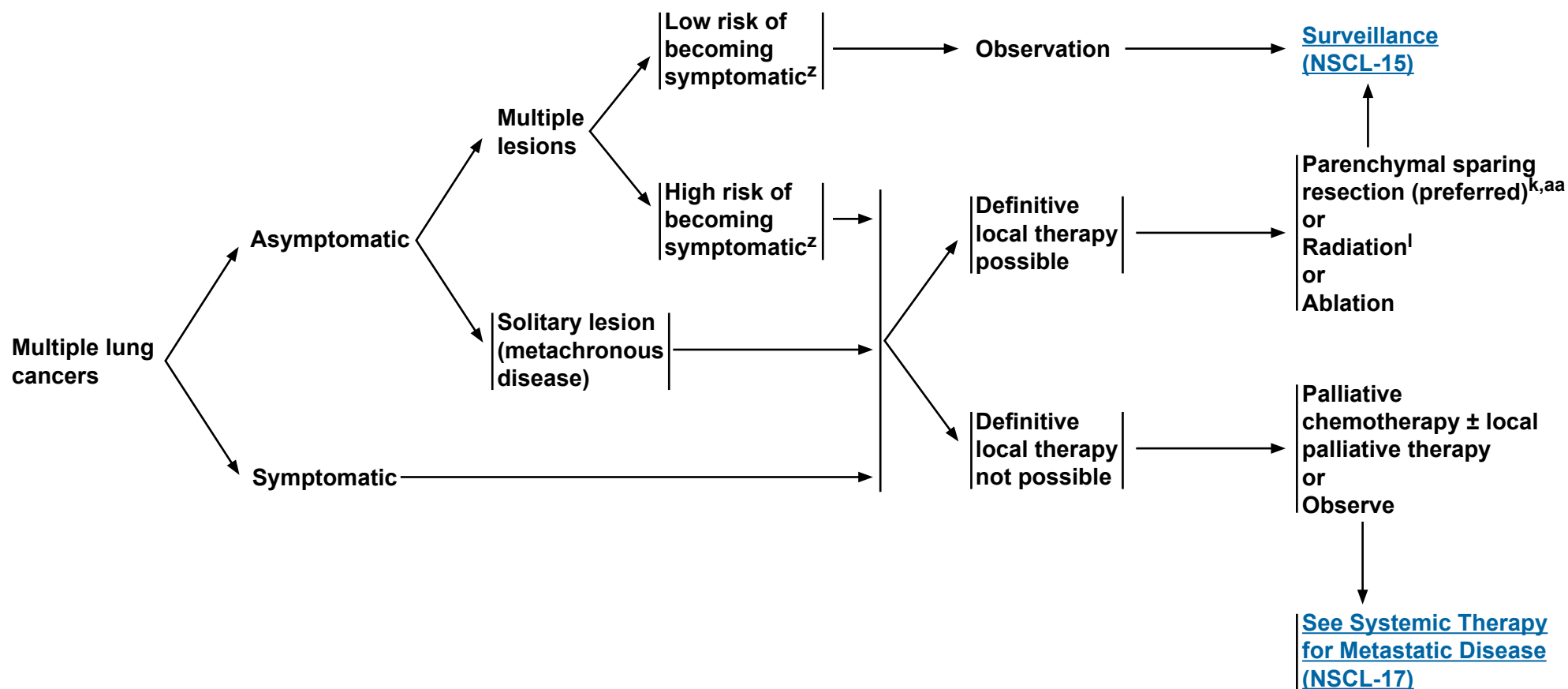


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Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

INITIAL TREATMENT



^kSee Principles of Surgical Therapy (NSCL-B).

^lSee Principles of Radiation Therapy (NSCL-C).

^zLesions 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.

^{aa}Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning. Patients should be evaluated in a multidisciplinary setting (ie, surgery, radiation oncology, medical oncology).

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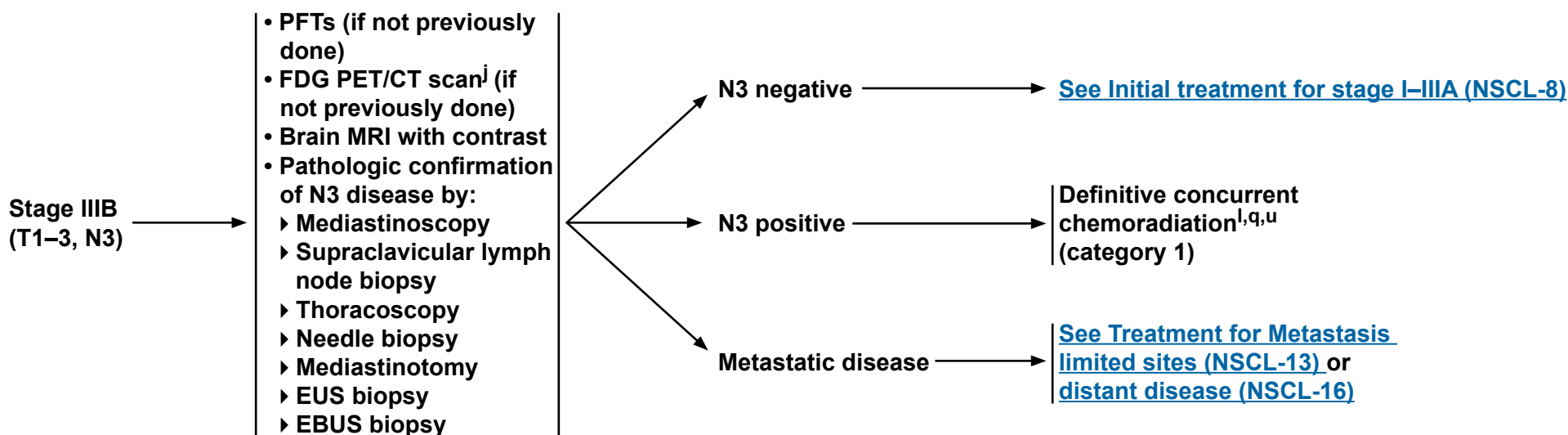
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



^jPET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan 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 \(NSCL-E\).](#)

^uIf full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

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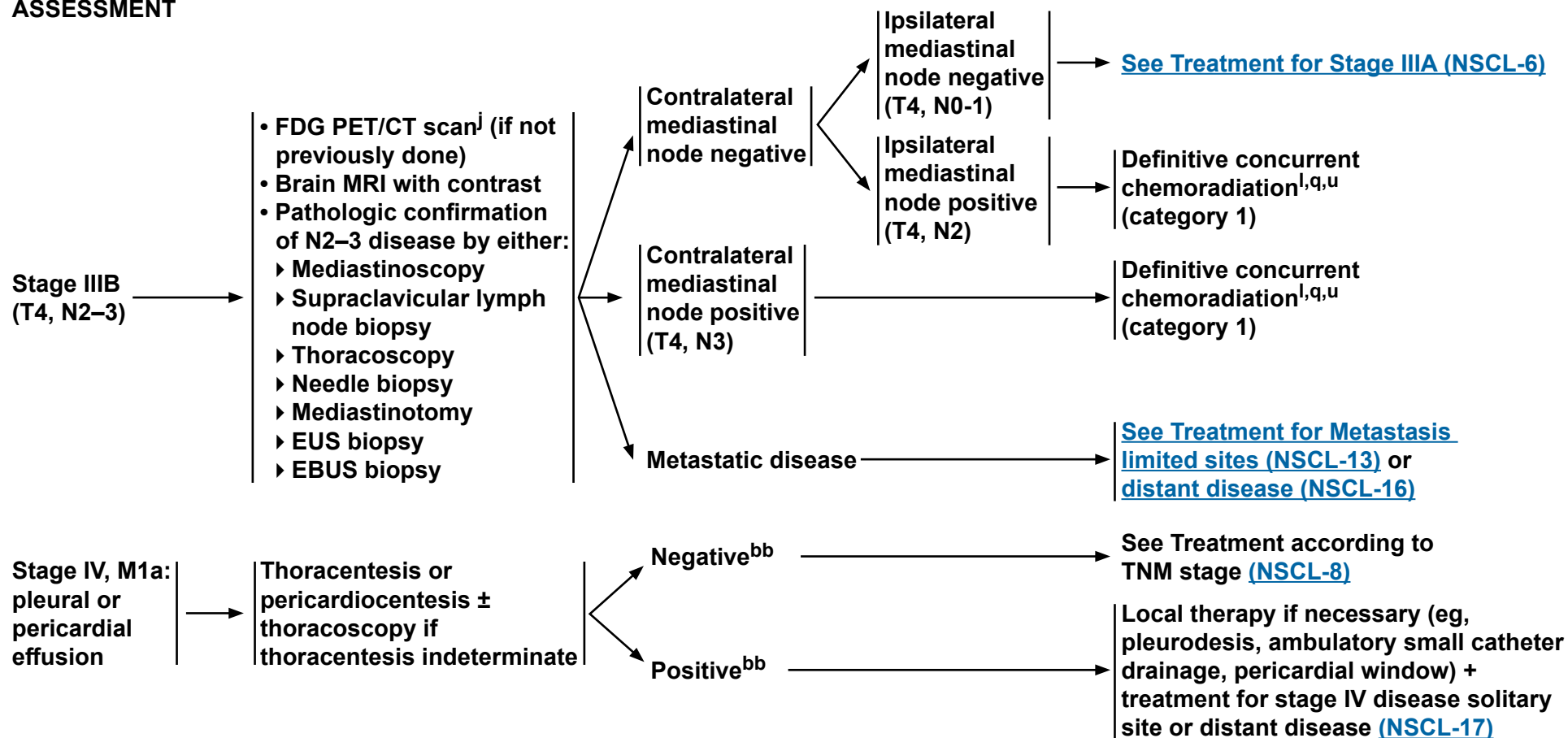
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



^jPET/CT performed skull base to knees or whole body. 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 \(NSCL-E\).](#)

^uIf full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

^{bb}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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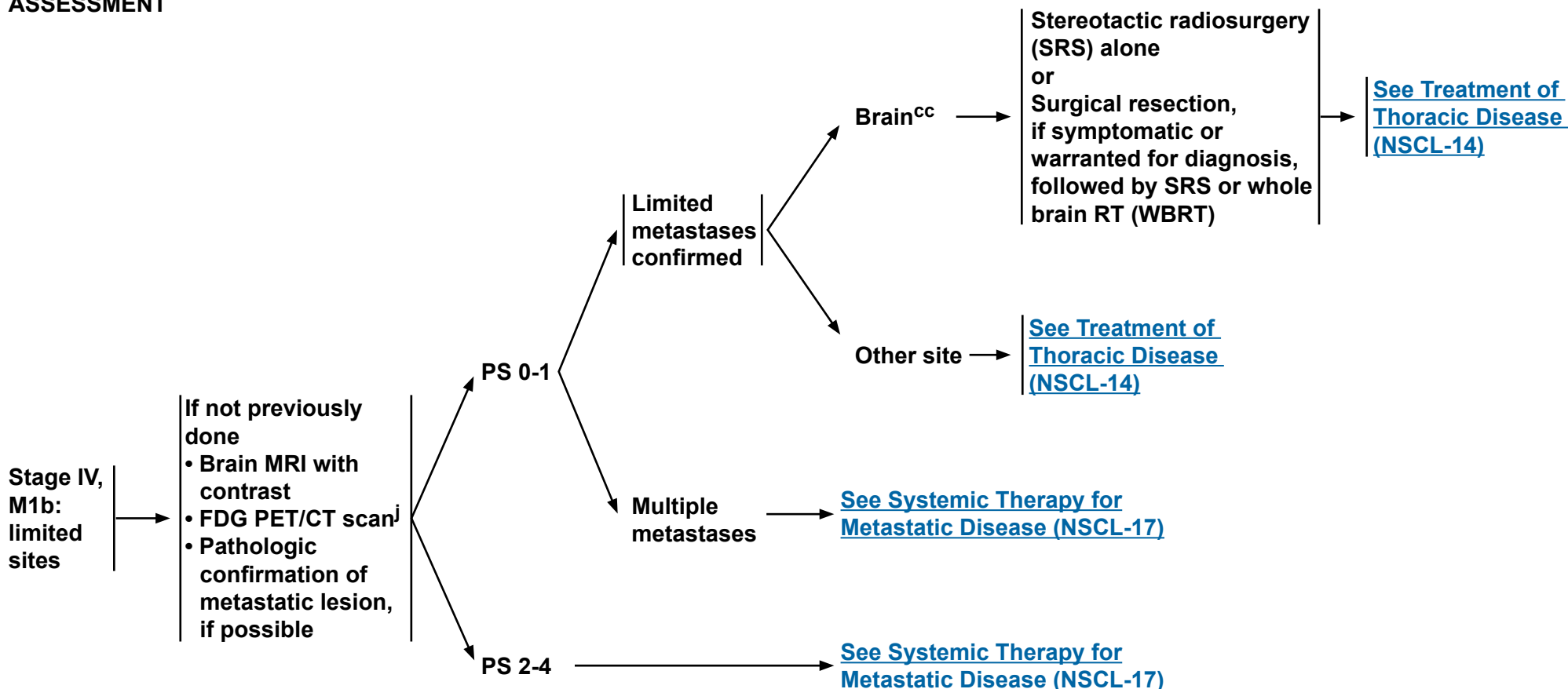
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CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT^{cc}



^jPET/CT performed skull base to knees or whole body. Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation.

^{cc}[See NCCN Guidelines for Central Nervous System Cancers.](#)

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

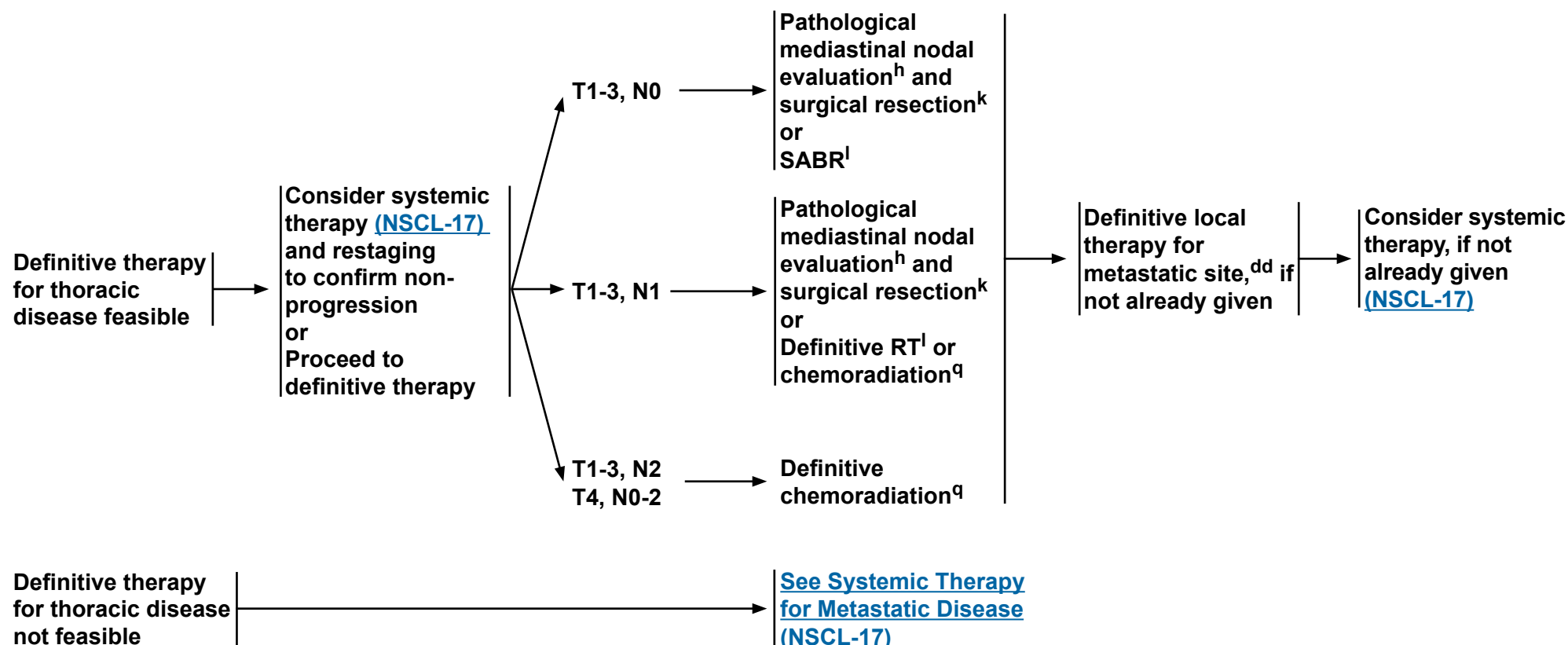
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Non-Small Cell Lung Cancer

TREATMENT OF THORACIC DISEASE



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

^k[See Principles of Surgical Therapy \(NSCL-B\).](#)

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

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

^{dd}Typically, RT (including SABR) or surgical resection.

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

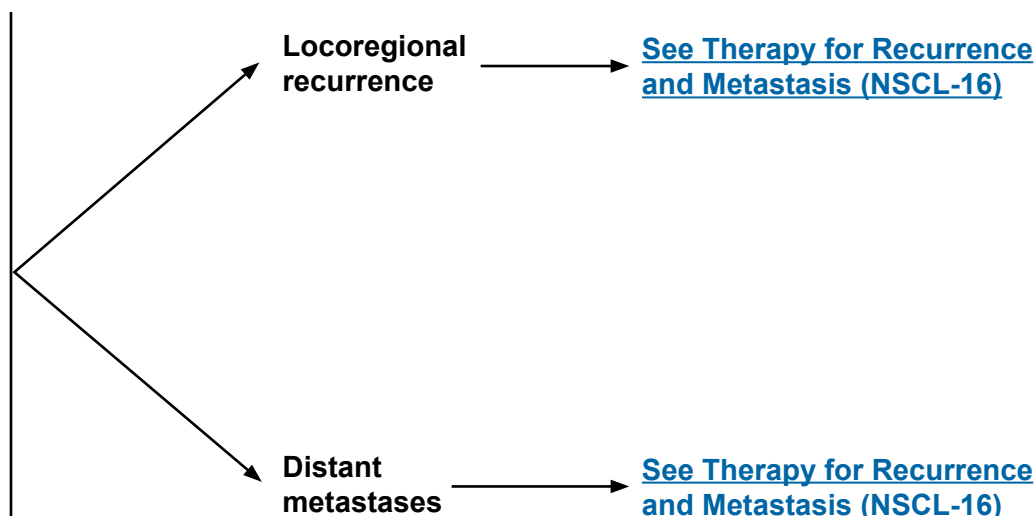
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SURVEILLANCE AFTER COMPLETION OF DEFINITIVE THERAPY

No evidence of clinical/radiographic disease

- Stage I–II (primary treatment included surgery ± chemotherapy)
 - H&P and chest CT ± contrast every 6 mo for 2–3 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
- Stage I–II (primary treatment included RT) or Stage III or Stage IV (oligometastatic with all sites treated with definitive intent)
 - H&P and chest CT ± contrast every 3–6 mo for 3 y, then H&P and chest CT ± contrast every 6 mo for 2 y, then H&P and a low-dose non-contrast-enhanced chest CT annually
 - ◊ Residual or new radiographic abnormalities may require more frequent imaging
- Smoking cessation advice, counseling, and pharmacotherapy
- PET/CT^{ee} or brain MRI is not routinely indicated
- [See Cancer Survivorship Care \(NSCL-G\)](#)



^{ee}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.

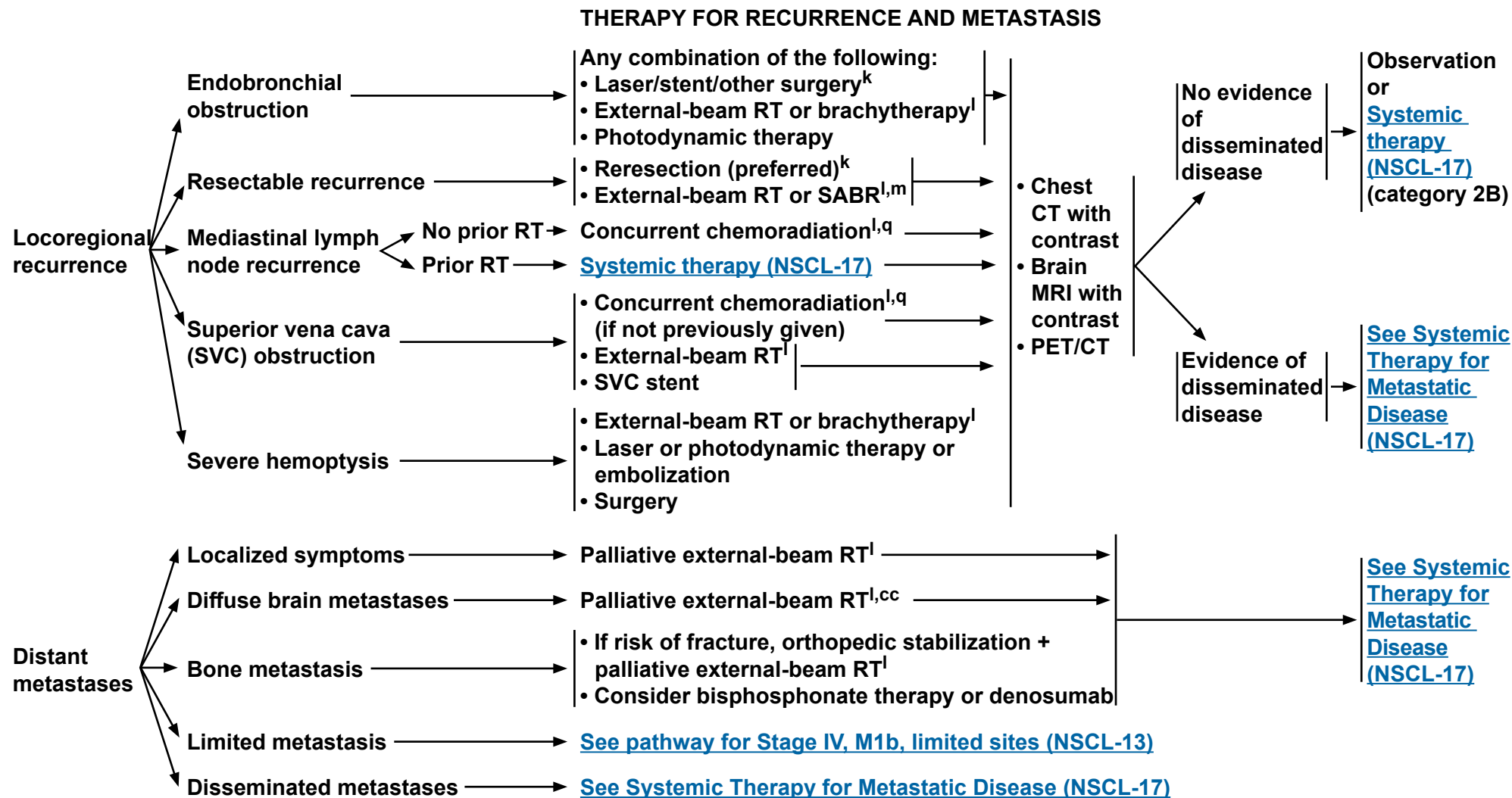
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Non-Small Cell Lung Cancer


^kSee Principles of Surgical Therapy (NSCL-B).

^lSee Principles of Radiation Therapy (NSCL-C).

^mInterventional radiology ablation is an option for selected patients.

^qSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

^{cc}See NCCN Guidelines for Central Nervous System Cancers.

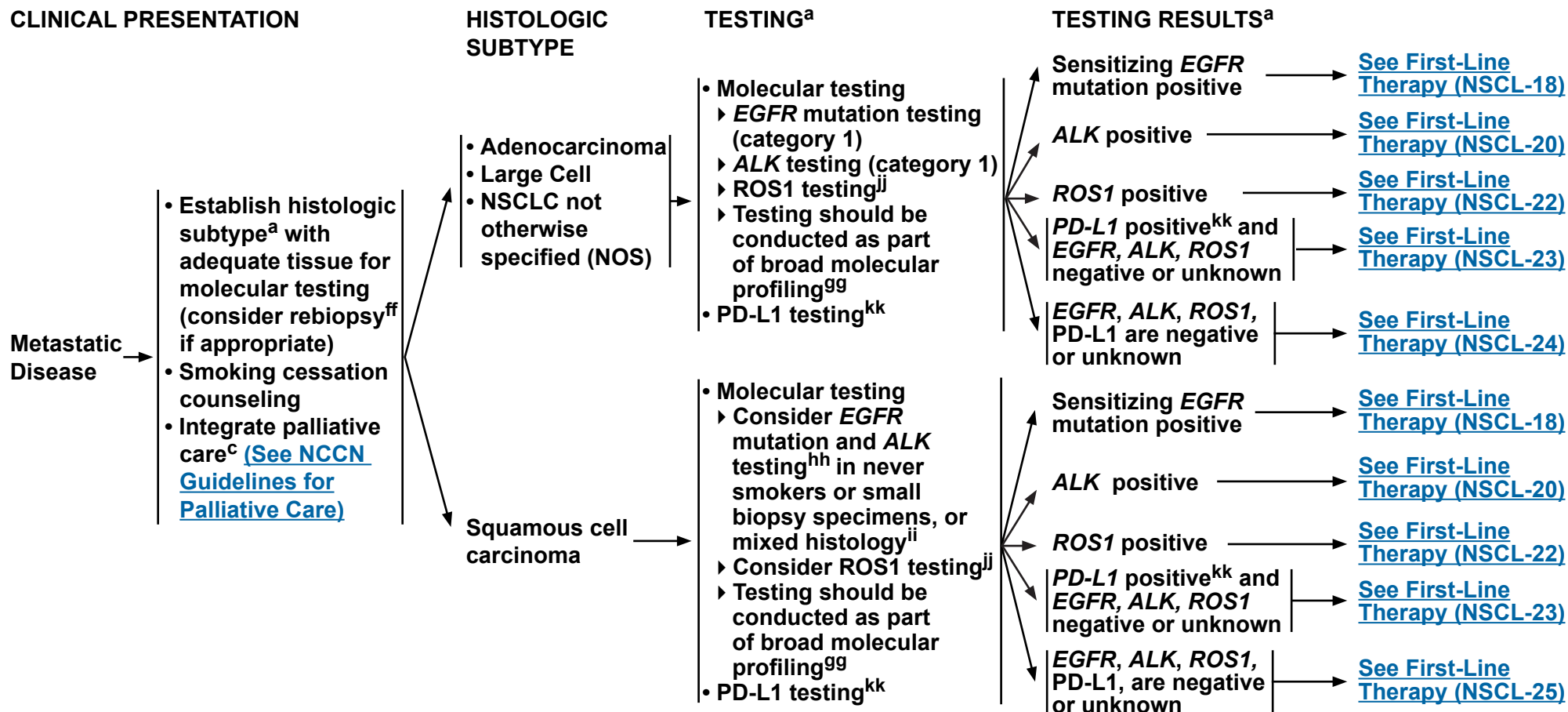
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Non-Small Cell Lung Cancer


^a[See Principles of Pathologic Review \(NSCL-A\).](#)
^cTemel 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.

^{ff}If repeat biopsy is not feasible, plasma biopsy should be considered.

^{gg}The NCCN NSCLC Guidelines Panel strongly advises 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 \(NSCL-H\).](#)
^{hh}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, Bharmia G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIC). *Curr Protoc Hum Genet* 2008;chapter 10:unit 10.11.

ⁱⁱPaik 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.

^{jj}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.

^{kk}PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

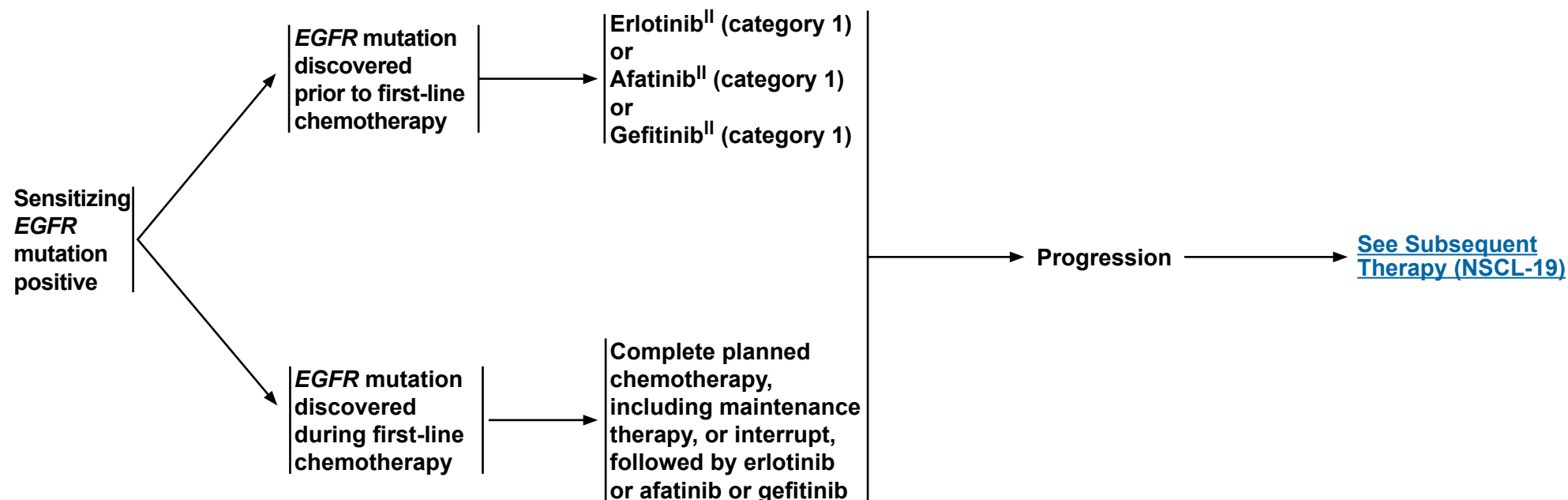
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SENSITIZING EGFR MUTATION POSITIVE^a

FIRST-LINE THERAPY



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

^{||}For performance status 0-4.

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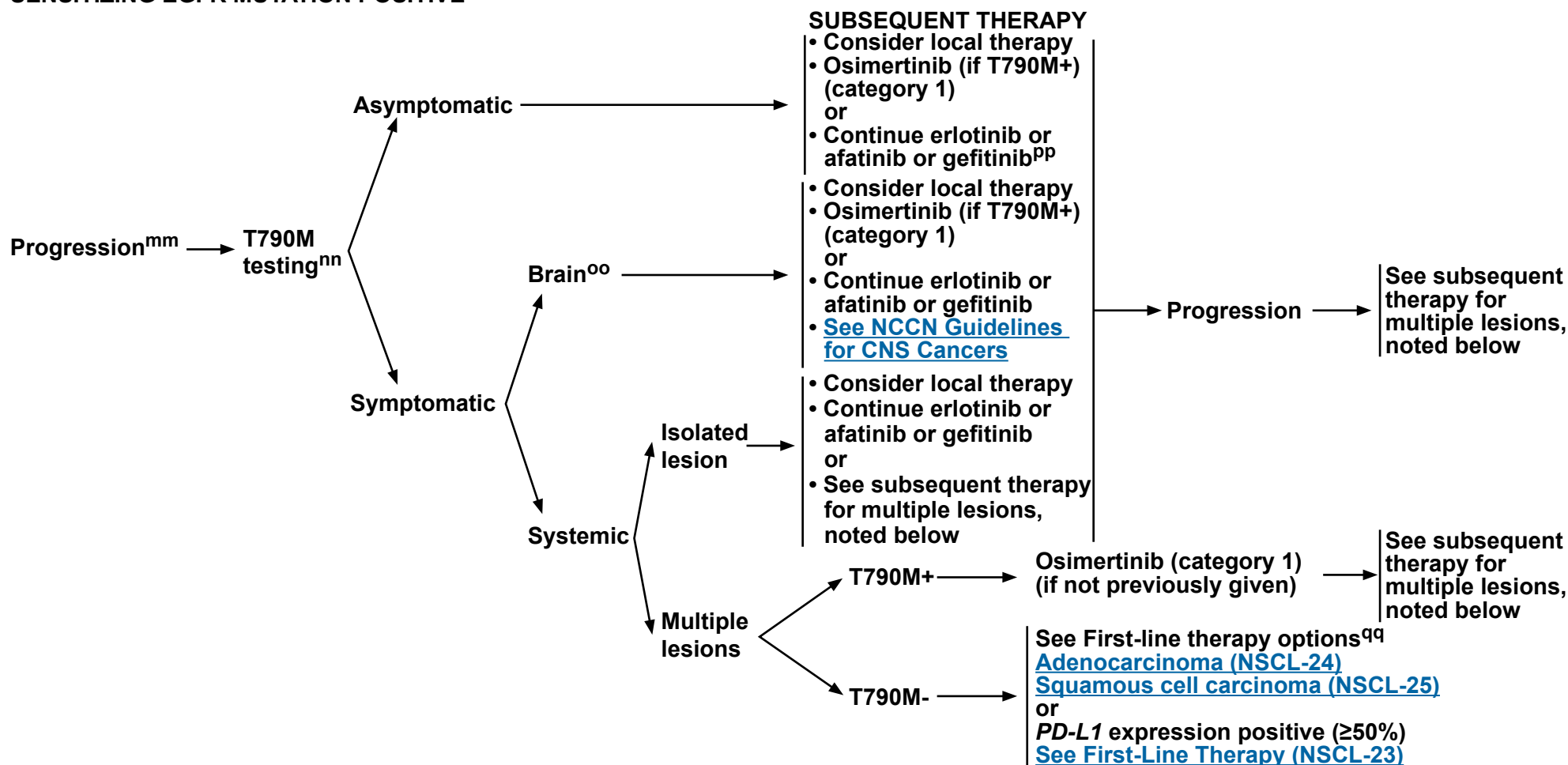
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Non-Small Cell Lung Cancer

SENSITIZING EGFR MUTATION POSITIVE^a


^a[See Principles of Pathologic Review \(NSCL-A\).](#)
^{mm}Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

ⁿⁿIf tissue biopsy is not feasible, plasma biopsy should be considered. Consider reflex to tissue-based testing, if plasma test is negative for the T790M mutation.

^{oo}Consider pulse erlotinib for carcinomatosis meningitis.

^{pp}For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

^{qq}Afatinib + cetuximab may be considered in patients with disease progression on EGFR TKI therapy.

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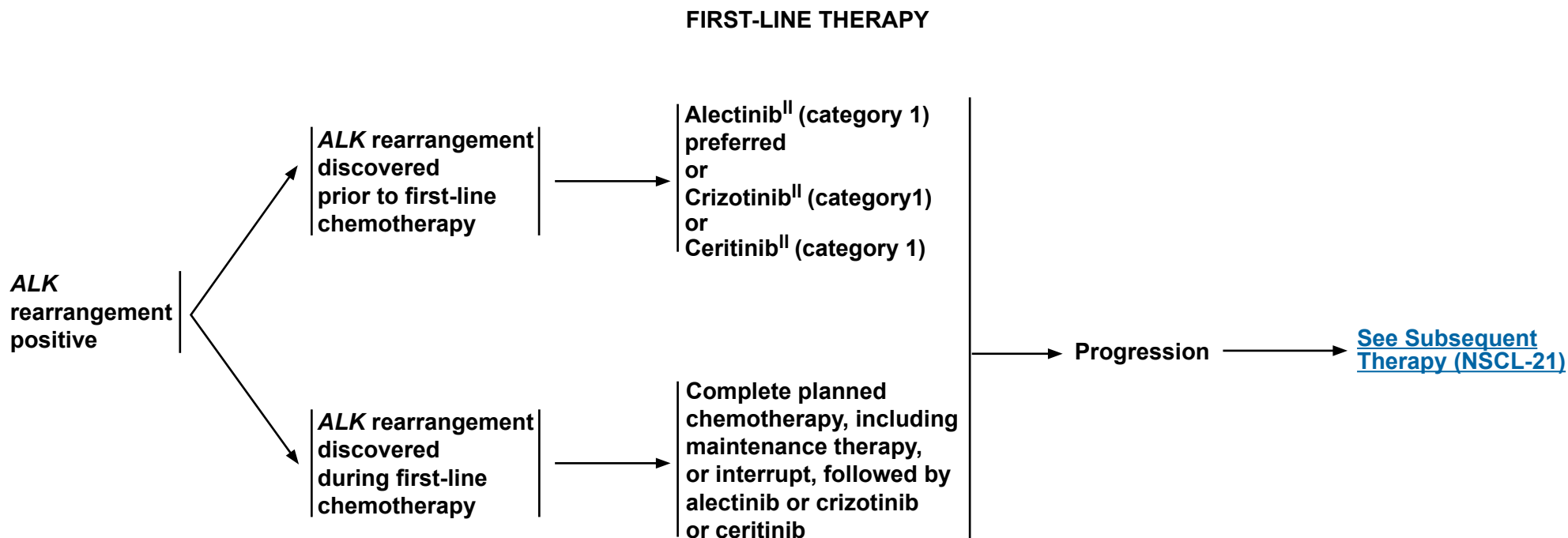
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Non-Small Cell Lung Cancer

ALK REARRANGEMENT POSITIVE^a



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

^{||}For performance status 0-4.

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

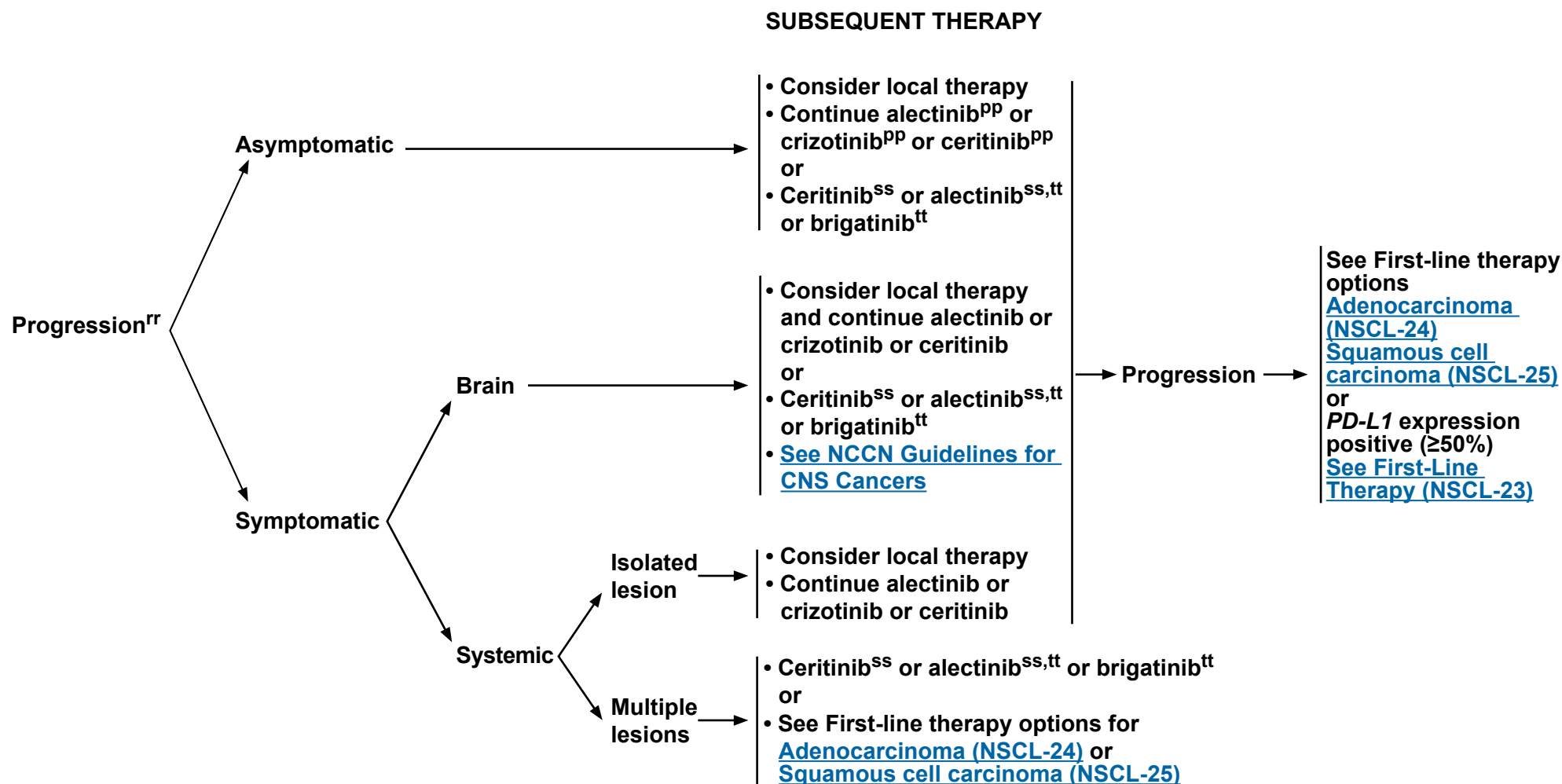
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Non-Small Cell Lung Cancer

ALK REARRANGEMENT POSITIVE^a



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

^{pp}For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.

^{rr}Patients who are intolerant to crizotinib may be switched to ceritinib, alectinib, or brigatinib.

^{ss}If not previously given.

^{tt}Alectinib or brigatinib are treatment options for patients with ALK-positive metastatic NSCLC that have progressed on crizotinib.

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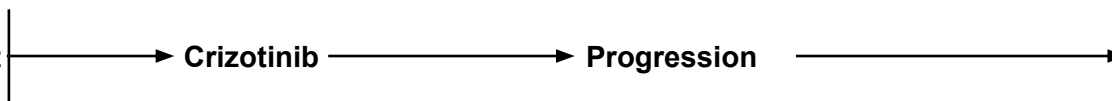
Non-Small Cell Lung Cancer

ROS1 REARRANGEMENT POSITIVE^a

FIRST-LINE THERAPY

SUBSEQUENT THERAPY

ROS1
rearrangement
positive



See First-line therapy options
[Adenocarcinoma \(NSCL-24\)](#)
[Squamous cell carcinoma \(NSCL-25\)](#)
or
PD-L1 expression positive (≥50%)
[See First-Line Therapy \(NSCL-23\)](#)

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

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PD-L1 EXPRESSION POSITIVE^a

FIRST-LINE THERAPY

SUBSEQUENT THERAPY



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

^{uu}Reck M, Rodríguez-Abreu D, Robinson AG, et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. *N Engl J Med* 2016;375:1823-1833.

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

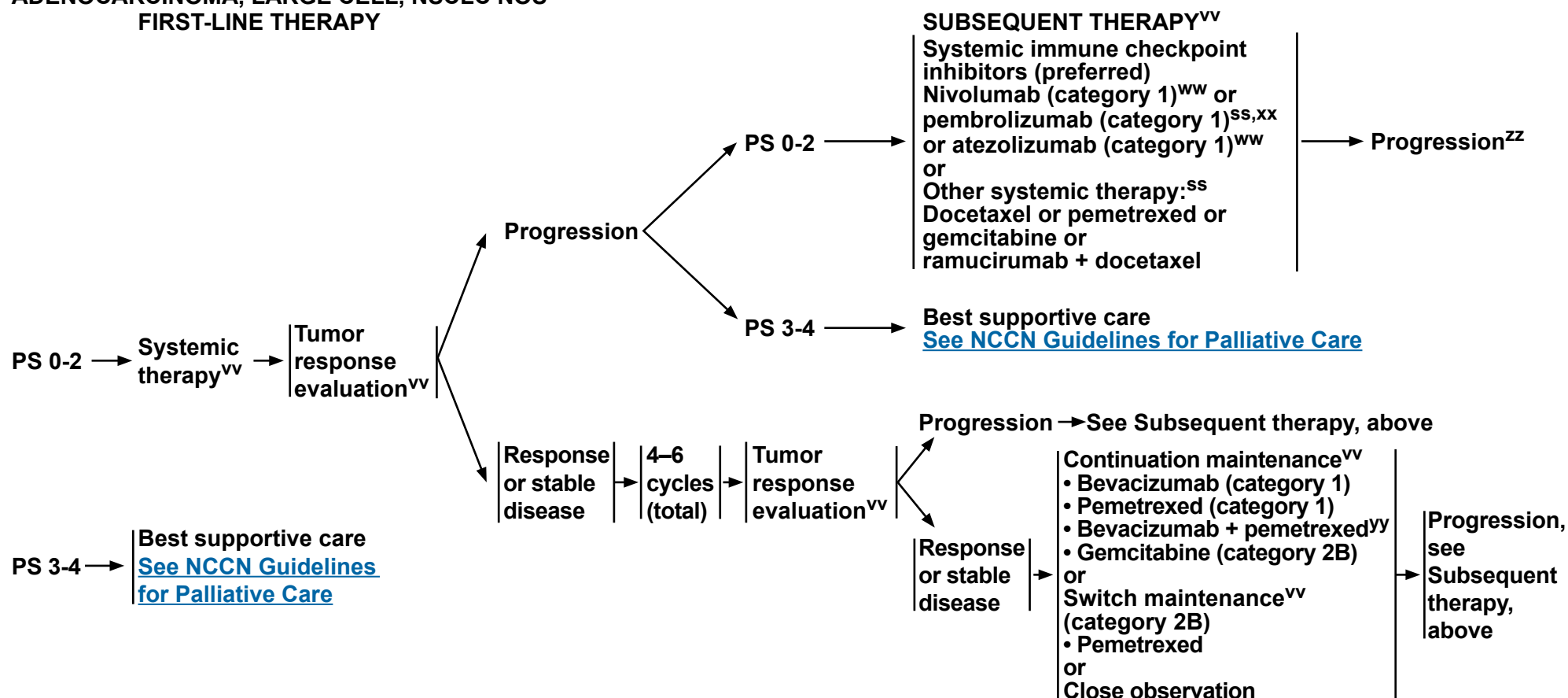
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Non-Small Cell Lung Cancer

ADENOCARCINOMA, LARGE CELL, NSCLC NOS FIRST-LINE THERAPY


^{ss}If not previously given.

^{vv}[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)
^{ww}If pembrolizumab not previously given.

^{xx}Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

^{yy}If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

^{zz}If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), docetaxel (category 2B), pemetrexed (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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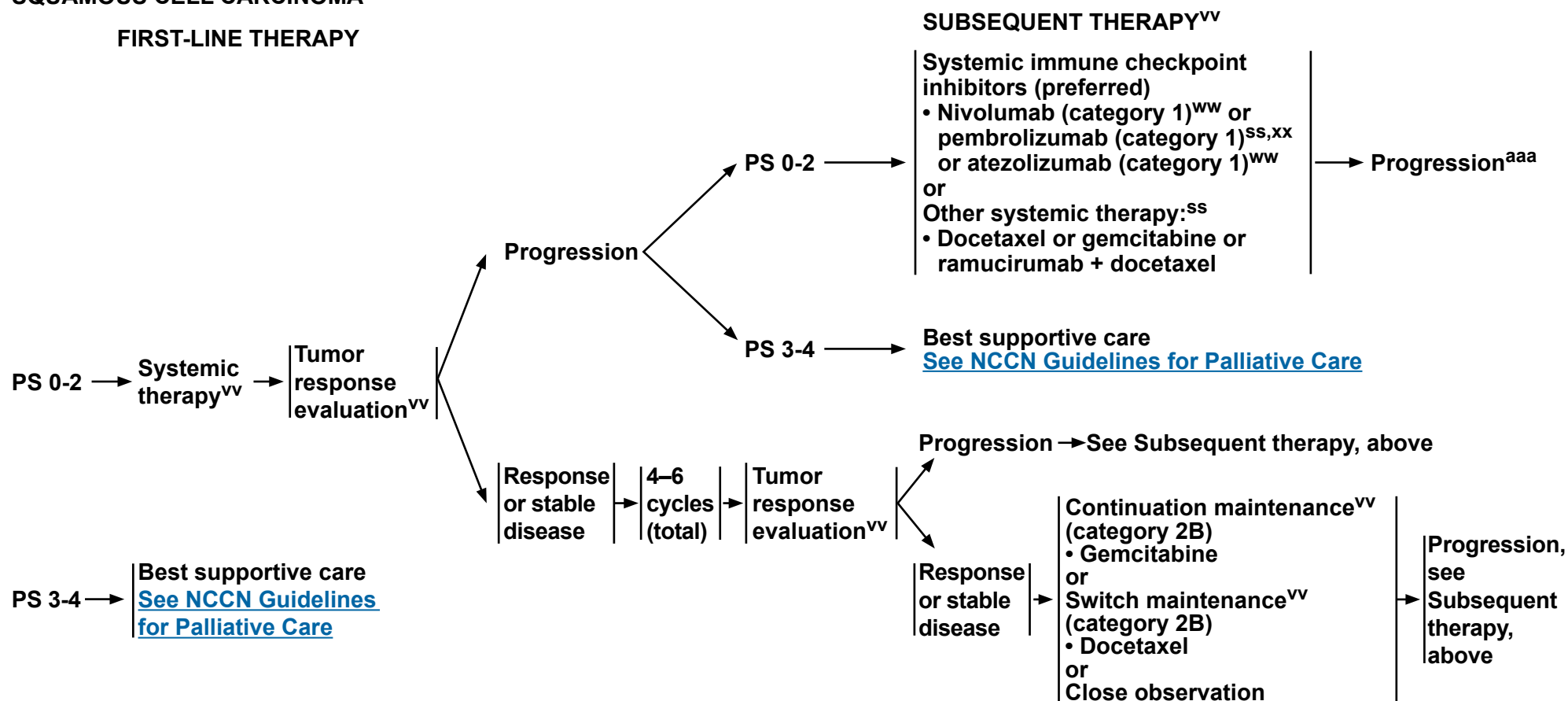


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Non-Small Cell Lung Cancer

SQUAMOUS CELL CARCINOMA

FIRST-LINE THERAPY


^{ss}If not previously given.

^{vv}[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)
^{ww}If pembrolizumab not previously given.

^{xx}Pembrolizumab is approved for patients with NSCLC tumors with PD-L1 expression levels ≥1%, as determined by an FDA-approved test.

^{aaa}If not already given, options for PS 0-2 include (nivolumab, pembrolizumab, or atezolizumab), 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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NCCN Guidelines Version 7.2017

Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (1 of 5)

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 in resection specimens or small biopsies as described by the WHO for carcinomas of the lung. 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 in samples that cannot be reliably classified on the basis of routine histology alone, 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 Classification⁸

- 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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NCCN Guidelines Version 7.2017

Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 5)

Immunohistochemical Staining

- **Judicious use of IHC 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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Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (3 of 5)

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, ceritinib, and alectinib 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* rearrangements and *EGFR* mutations are mutually exclusive.^{27, 29-31}
- ▶ The current standard method for detecting *ALK* NSCLC is fluorescence in situ hybridization (FISH). 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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Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 5)

Molecular Diagnostic Studies in Lung Cancer.

• **ROS-1**

- ▶ Although ROS1 is a distinct receptor tyrosine kinase, ROS1 has a high degree of homology with ALK (approximately 50% within the kinase domain and 75% within the ATP-binding site).³³
- ▶ The majority of patients with ROS1-positive NSCLC respond to the first-generation ALK inhibitor crizotinib; however, certain other ALK inhibitors such as alectinib do not appear to have activity against ROS1-positive NSCLC.³⁴
- ▶ ROS1 rearrangements occur in 1%–2% of patients with NSCLC.³⁴ Similar to testing for ALK rearrangements, testing for ROS1 is also done using FISH.³⁵

• **PD-L1**

- ▶ Immune checkpoint inhibitors target programmed death receptor 1 (PD-1) or its ligand, programmed death ligand 1 (PD-L1).³⁶
- ▶ PD-1 is expressed by T-cells and regulates the activation of T-cells in peripheral tissues. PD-1 has two ligands, PD-L1 (also known as B7-H1 or CD274) and PD-L2 (B7-DC or CD273). These ligands are expressed on a wide range of immune effector cells, antigen-presenting cells, and tumor cells. PD-1 activation by ligand binding with PD-L1 on the tumor cells produces a number of intracellular effects that result in T-cell inactivity and reduced proliferation.
- ▶ The therapeutic focus in NSCLC has been to interrupt the interaction of PD-1 and its ligand PD-L1 between tumor cells and immune effectors cells using monoclonal antibodies against PD-L1 or PD-1.³⁷
- ▶ Anti-PD-L1 IHC may be a biomarker used to select patients with NSCLC more likely to respond to immune checkpoint inhibitors, but the development of a variety of therapeutics, each with a different anti-PD-L1 IHC assay, has raised concerns among both pathologists and oncologists.^{37,38}
- ▶ The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.³⁷ PD-L1 expression levels of ≥50% are a positive test result for first-line pembrolizumab therapy.

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



PRINCIPLES OF PATHOLOGIC REVIEW (5 of 5) - References

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Non-Small Cell Lung Cancer

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).
- Patients who are active smokers should be provided counseling and smoking cessation support ([NCCN Guidelines for Smoking Cessation](#)). While active smokers have a mildly increased incidence of postoperative pulmonary complications, these should not be considered a prohibitive risk for surgery. Surgeons should not deny surgery to patients solely due to smoking status, as surgery provides the predominant opportunity for prolonged survival in patients with early-stage lung cancer.

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 \geq the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
 - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
 - Peripheral nodule¹ ≤ 2 cm with at least one of the following:
 - ◊ Pure AIS histology
 - ◊ Nodule has $\geq 50\%$ 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](#))

¹Peripheral 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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Non-Small Cell Lung Cancer

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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Non-Small Cell Lung Cancer

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.

- Would consider surgery in patients with one N2 lymph node station involved by a lymph node smaller than 3 cm: (90.5%)
- 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%)
- Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%)
- Uses pathologic evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%)
- 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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Non-Small Cell Lung Cancer

PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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

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Non-Small Cell Lung Cancer

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/Daily-Practice/Reimbursement/Model-Policies/Model-Policies/>). Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.²⁻⁴ In a prospective trial of definitive chemo/RT for stage III NSCLC (RTOG 0617), IMRT was associated with a nearly 60% decrease in high-grade radiation pneumonitis and similar survival and tumor control outcomes despite a higher proportion of stage IIIB and larger treatment volumes compared to 3D-CRT;⁵ as such, IMRT is preferred over 3D-CRT in this setting.
- 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 Practice Parameters and Technical Standards (<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.⁶⁻¹¹
- 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.¹²⁻¹³
- 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.¹⁴ 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.¹⁵⁻¹⁷
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC* in this section).

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Non-Small Cell Lung Cancer

PRINCIPLES OF RADIATION THERAPY (2 of 10)

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II (node positive) and stage III is concurrent chemotherapy/RT.¹⁸⁻²⁰ 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.^{21,22} Accelerated RT regimens may be beneficial, particularly if concurrent chemotherapy would not be tolerated (ie, in a sequential or RT-only approach).^{23,24}
- RT has a role before or after surgery.
 - ▶ Preoperative concurrent chemotherapy/RT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)²⁵ and is recommended for resectable superior sulcus tumors.^{26,27}
 - ▶ Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.^{28,29} The optimal timing of RT in trimodality therapy (preoperative with chemotherapy or postoperative) is not established and is controversial.^{30,31}
 - ▶ The determination of resectability in trimodality therapy should be made prior to initiation of all treatment. Upfront 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.^{32,33} 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 patients³⁴⁻³⁶ and is recommended for positive resection margins.³⁷
 - ▶ 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.³⁸

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.^{39,40}
- 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.^{41,42} Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.^{43–47}

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.⁴⁸ In the United States, only regimens of ≤ 5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.^{48,49} For centrally located tumors (defined variably as within 2 cm of the proximal bronchial tree and/or abutting mediastinal pleura) and even ultra-central tumors (defined as abutting the proximal bronchial tree), 4 to 10 fraction risk-adapted SABR regimens appear to be effective and safe,^{50–53} while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.⁵⁴ The maximum tolerated dose for 5-fraction regimens was studied prospectively in RTOG 0813, preliminary results demonstrate no high-grade toxicities at 50 Gy in 5 fractions.⁵⁵
- 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.^{54,56}
- 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.^{57,58} 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.⁵⁹⁻⁶³ Two randomized trials found improved survival for IFI versus ENI, possibly because it enabled dose escalation.⁶⁴ IFI is reasonable in order to optimize definitive dosing to the tumor.⁶⁵
- 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.⁶⁶ Dose escalation in RT alone,⁶⁷ sequential chemo/RT,⁶⁸ or concurrent chemo/RT⁶⁹ is associated with better survival in non-randomized comparisons. While optimal RT dose intensification remains a valid question, higher doses of 74 Gy are not currently recommended for routine use.⁷⁰⁻⁷⁴ A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,⁷⁵ 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.⁷⁶ Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,⁷⁷⁻⁸⁰ 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.⁸¹ 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.^{32,33,82} 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.⁸³

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,⁸⁴⁻⁸⁷ 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.^{88,89} When higher doses (>30 Gy) are warranted, technologies to reduce normal tissue irradiation (at least 3D-CRT and including IMRT or proton therapy as appropriate) should be used.

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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,⁹⁰ 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.⁹¹ Given the potential for rapid progression of NSCLC,^{92,93} 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 the 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.⁶⁰
- 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 76.⁹⁴
- 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	ICRU	International Commission on Radiation Units and Measurements
2D-RT	2-Dimensional RT	IFI	Involved Field Irradiation
3D-CRT	3-Dimensional Conformal RT	IGRT	Image-Guided RT
4D-CT	4-Dimensional Computed Tomography	IMRT	Intensity-Modulated RT
AAPM	American Association of Physicists in Medicine	ITV*	Internal Target Volume
ABC	Active Breathing Control	OAR	Organ at Risk
ACR	American College of Radiology	OBI	On-Board Imaging
ASTRO	American Society for Radiation Oncology	PORT	Postoperative RT
BED	Biologically Effective Dose	PTV*	Planning Target Volume
CBCT	Cone-Beam CT	QUANTEC	Quantitative Analysis of Normal Tissue Effects in the Clinic
CTV*	Clinical Target Volume	RTOG	Radiation Therapy Oncology Group now part of NRG Oncology
ENI	Elective Nodal Irradiation	SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
GTV*	Gross Tumor Volume	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

Please note - Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

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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](#)

Please note: Tables 2–5 provide doses and constraints used commonly or in past clinical trials as useful references rather than specific recommendations.

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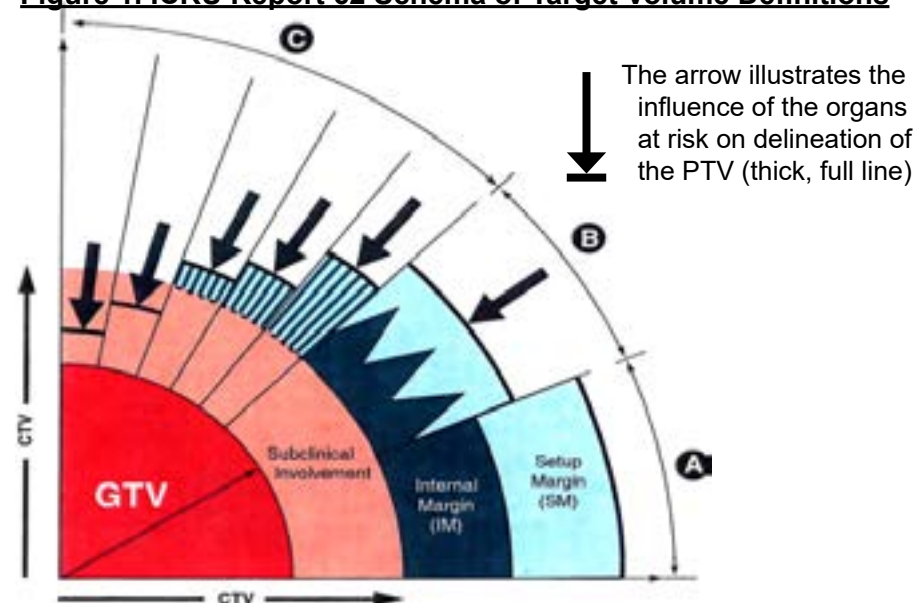
Table 5. Normal Tissue Dose-Volume Constraints for Conventionally Fractionated RT

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.

**RTOG 0617 data suggest that even lower radiation doses to the heart than previously appreciated may be detrimental to survival after thoracic RT, and more stringent constraints may be appropriate.

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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Non-Small Cell Lung Cancer

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 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

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

^bArriagada R, Bergman B, Dunant A, et al. The International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small cell lung cancer. N Engl J Med 2004;350:351-360.

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

^dPérol 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.

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

^fKreuter M, Vansteenkiste J, Fishcer JR, et al. Randomized phase 2 trial on refinement of early-stage NSCLC adjuvant chemotherapy with cisplatin and pemetrexed versus cisplatin and vinorelbine: the TREAT study. Ann Oncol 2013;24:986-992.

^gStrauss GM, Herndon III JE, Maddaus MA, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-5051.

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Non-Small Cell Lung Cancer

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,e} (nonsquamous)^{*,**} ± additional 4 cycles of pemetrexed 500 mg/m²^{**}
- Paclitaxel 45–50 mg/m² weekly; carboplatin AUC 2, concurrent thoracic RT^{f,*,**} ± additional 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6^{**}

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^g

*Regimens can be used as neoadjuvant/preoperative/induction chemoradiotherapy.

**Regimens can be used as adjuvant or definitive concurrent chemotherapy/RT.

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

^bCurran WJ Jr, Paulus R, Langer CJ, et al. Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer: randomized phase III trial RTOG 9410. J Natl Cancer Inst. 2011;103:1452-1460.

^cGovindan R, Bogart J, Stinchcombe T, et al. Randomized phase II study of pemetrexed, carboplatin, and thoracic radiation with or without cetuximab in patients with locally advanced unresectable non-small-cell lung cancer: Cancer and Leukemia Group B trial 30407. J Clin Oncol 2011;29:3120-3125.

^dChoy 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

^eSenan S, Brade A, Wang LH, et al. PROCLAIM: randomized phase III trial of pemetrexed-cisplatin or etoposide-cisplatin plus thoracic radiation therapy followed by consolidation chemotherapy in locally advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2016;34:953-962.

^fBradley 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.

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

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Non-Small Cell Lung Cancer

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 (\approx 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 2 cycles, then every 2–4 cycles with CT of known sites of disease with or without contrast or when clinically indicated.

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

- Response assessment with CT of known sites of disease with or without contrast every 6–12 weeks.

[See First-line Systemic Therapy Options for
Adenocarcinoma, Large cell, NSCLC NOS on NSCL-F \(2 of 4\)](#)

[See First-line Systemic Therapy Options for
Squamous Cell Carcinoma on NSCL-F \(3 of 4\)](#)

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Non-Small Cell Lung Cancer

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
- Cisplatin/docetaxel (category 1)⁵
- Cisplatin/etoposide (category 1)¹¹
- Cisplatin/gemcitabine (category 1)^{9,12}
- Cisplatin/paclitaxel (category 1)¹³
- Cisplatin/pemetrexed (category 1)¹²
- Gemcitabine/docetaxel (category 1)¹⁴
- Gemcitabine/vinorelbine (category 1)¹⁵

Adenocarcinoma, Large Cell, NSCLC NOS (PS 2)

- Albumin-bound paclitaxel¹⁶
- Carboplatin/albumin-bound paclitaxel^{17,18}
- Carboplatin/docetaxel⁵
- Carboplatin/etoposide^{6,7}
- Carboplatin/gemcitabine⁸
- Carboplatin/paclitaxel⁹
- Carboplatin/pemetrexed¹⁰
- Docetaxel^{19,20}
- Gemcitabine²¹⁻²³
- Gemcitabine/docetaxel¹⁴
- Gemcitabine/vinorelbine¹⁵
- Paclitaxel²⁴⁻²⁶
- Pemetrexed²⁷

[†]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.

*Bevacizumab should be given until progression.

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

***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.

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Non-Small Cell Lung Cancer

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/gemcitabine (category 1)⁸
- Carboplatin/paclitaxel (category 1)⁹
- Cisplatin/docetaxel (category 1)⁵
- Cisplatin/etoposide (category 1)¹¹
- Cisplatin/gemcitabine (category 1)^{9,12}
- Cisplatin/paclitaxel (category 1)¹³
- Gemcitabine/docetaxel (category 1)¹⁴
- Gemcitabine/vinorelbine (category 1)¹⁵

Squamous Cell Carcinoma (PS 2)

- Albumin-bound paclitaxel¹⁶
- Carboplatin/albumin-bound paclitaxel^{17,18}
- Carboplatin/docetaxel⁵
- Carboplatin/etoposide^{6,7}
- Carboplatin/gemcitabine⁸
- Carboplatin/paclitaxel⁹
- Docetaxel^{19,20}
- Gemcitabine²¹⁻²³
- Gemcitabine/docetaxel¹⁴
- Gemcitabine/vinorelbine¹⁵
- Paclitaxel²⁴⁻²⁶

[†]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.

^{††}Cisplatin/gemcitabine/necitumumab in the first-line setting and erlotinib or afatinib in the second-line setting are not used at NCCN institutions for these indications related to the efficacy and safety of these agents compared to the efficacy and safety of other available agents.

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Non-Small Cell Lung Cancer

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

- ¹Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med* 2006;355:2542-2550.
- ²Patel JD, Socinski MA, Garon EB, et al. Pointbreak: a randomized phase III study of pemetrexed plus carboplatin and bevacizumab followed by maintenance pemetrexed and bevacizumab versus paclitaxel plus carboplatin and bevacizumab followed by maintenance bevacizumab in patients with stage IIIB or IV nonsquamous non-small cell lung cancer. *J Clin Oncol* 2013;31:4349-4357.
- ³Barlesi F, Scherpereel A, Rittmeyer A, et al. Randomized phase III trial of maintenance bevacizumab with or without pemetrexed after first-line induction with bevacizumab, cisplatin, and pemetrexed in advanced nonsquamous non-small cell lung cancer: AVAPERL. *J Clin Oncol* 2013;31:3004-3011.
- ⁴Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based paclitaxel plus carboplatin as first-line therapy in patients with advanced non-small cell lung cancer: final results of a phase III trial. *J Clin Oncol* 2012;30:2055-2062.
- ⁵Fossella F, Periera JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol* 2003;21(16):3016-3024.
- ⁶Klastersky J, Sculier JP, Lacroix H, et al. A randomized study comparing cisplatin or carboplatin with etoposide in patients with advanced non-small cell lung cancer: European Organization for Research and Treatment of Cancer Protocol 07861. *J Clin Oncol* 1990;8:1556-1562.
- ⁷Frasci G, Comella P, Panza N, et al. Carboplatin-oral etoposide personalized dosing in elderly non-small cell lung cancer patients. Gruppo Oncologico Cooperativo Sud-Italia. *Eur J Cancer* 1998;34:1710-1714.
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- ¹¹Cardenal F, Lopez-Cabrerizo MP, Anton A, et al. Randomized phase III study of gemcitabine-cisplatin versus etoposide-cisplatin in the treatment of locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 1999;17:12-18.
- ¹²Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543-3551.
- ¹³Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small cell lung cancer. *N Engl J Med* 2002;346:92-98.
- ¹⁴Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. *Ann Oncol* 2005;16:602-610.
- ¹⁵Tan EH, Szczesna A, Krzakowski M, et al. Randomized study of vinorelbine--gemcitabine versus vinorelbine--carboplatin in patients with advanced non-small cell lung cancer. *Lung Cancer* 2005;49:233-240.
- ¹⁶Green M, Manikhas G, Orlov S, et al. Abraxane®, a novel Cremophor®-free, albumin-bound particle form of paclitaxel for the treatment of advanced non-small-cell lung cancer. *Ann Oncol* 2006;17:1263-1268.
- ¹⁷Rizvi N, Riely G, Azzoli C, et al. Phase I/II Trial of Weekly Intravenous 130-nm Albumin-Bound Paclitaxel As Initial Chemotherapy in Patients With Stage IV Non-Small-Cell Lung Cancer. *J Clin Oncol* 2008;26:639-643.
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- ²¹Zatloukal P, Kanitz E, Magyar P, et al. Gemcitabine in locally advanced and metastatic non-small cell lung cancer: the Central European phase II study. *Lung Cancer* 1998;22:243-250.
- ²²Sederholm C, Hillerdal G, Lamberg K, et al. Phase III trial of gemcitabine plus carboplatin versus single agent gemcitabine in the treatment of locally advanced or metastatic non-small cell lung cancer: the Swedish Lung Cancer Study group. *J Clin Oncol* 2005;23:8380-8288.
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NCCN Guidelines Version 7.2017

Non-Small Cell Lung Cancer

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](#)

¹ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention:

<http://www.cancer.org/healthy/eathealthygetactive/acsguidelinesonnutritionphysicalactivityforcancerprevention/index?sitearea=PED>.

²Memorial Sloan Kettering Cancer Center Screening Guidelines: <https://www.mskcc.org/cancer-care/risk-assessment-screening/screening-guidelines>.

³American Cancer Society Guidelines for Early Detection of Cancer:

<http://www.cancer.org/healthy/findcancerearly/cancerscreeningguidelines/american-cancer-society-guidelines-for-the-early-detection-of-cancer?sitearea=PED>.

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Non-Small Cell Lung Cancer

EMERGING TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
<i>BRAF</i> V600E mutation* *Non-V600E mutations have variable kinase activity and response to these agents.	vemurafenib^{1,2} dabrafenib^{2,3} dabrafenib + trametinib⁴
High-level <i>MET</i> amplification or <i>MET</i> exon 14 skipping mutation	crizotinib⁵⁻⁹
<i>RET</i> rearrangements	cabozantinib^{10,11} vandetanib¹²
<i>HER2</i> mutations	trastuzumab¹³ (category 2B) afatinib¹⁴ (category 2B)

¹Hyman DM, Puzanov I, Subbiah V, et al. Vemurafenib in multiple nonmelanoma cancers with BRAF V600 mutations. *N Engl J Med* 2015;373:726-736.

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⁴Planchard D, Besse B, Groen HJ, et al. Dabrafenib plus trametinib in patients with previously treated BRAF(V600E)-mutant metastatic non-small cell lung cancer: an open-label, multicentre phase 2 trial. *Lancet Oncol* 2016;17:984-993.

⁵Ou SH, Kwak EL, Siwak-Tapp C, et al. Activity of crizotinib (PF02341066), a dual mesenchymal-epithelial transition (MET) and anaplastic lymphoma kinase (ALK) inhibitor, in a non-small cell lung cancer patient with de novo MET amplification. *J Thorac Oncol* 2011;6:942-946.

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⁷Frampton GM, Ali SM, Rosenzweig M, et al. Activation of MET via diverse exon 14 splicing alterations occurs in multiple tumor types and confers clinical sensitivity to MET inhibitors. *Cancer Discov* 2015;5:850-859.

⁸Paik PK, Drilon A, Fan PD, et al. Response to MET inhibitors in patients with stage IV lung adenocarcinomas harboring MET mutations causing exon 14 skipping. *Cancer Discov* 2015;5:842-849.

⁹Awad MM, Oxnard GR, Jackman DM, et al. MET exon 14 mutations in non-small-cell lung cancer are associated with advanced age and stage-dependent MET genomic amplification and cMET overexpression. *J Clin Oncol* 2016;34:721-730.

¹⁰Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013; 3:630-635.

¹¹Drilon AE, Sima CS, Somwar R, et al. Phase II study of cabozantinib for patients with advanced RET-rearranged lung cancers. *J Clin Oncol* 2015;33: Abstract 8007.

¹²Lee S-H, Lee J-K, Ahn M-J, et al. A phase II study of vandetanib in patients with non-small cell lung cancer harboring RET rearrangement [abstract]. *J Clin Oncol* 2016;34: Abstract 9013.

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¹⁴Mazieres J, Peters S, Lepage B, et al. Lung cancer that harbors an HER2 mutation: epidemiologic characteristics and therapeutic perspectives. *J Clin Oncol* 2013;31:1997-2003.

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NCCN Guidelines Version 7.2017 Staging Non-Small Cell Lung Cancer

Table 1. Definitions for T, N, M*

T	Primary Tumor	N	Regional Lymph Nodes	M	Distant Metastasis
TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy	NX	Regional lymph nodes cannot be assessed	MX	Distant metastasis cannot be assessed
T0	No evidence of primary tumor	N0	No regional lymph node metastasis	M0	No distant metastasis
Tis	Carcinoma in situ	N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension	M1	Distant metastasis
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus) ^a	N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)	M1a	Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion ^c
	T1a Tumor ≤2 cm in greatest dimension	N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)	M1b	Distant metastasis
	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				

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

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

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

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



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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

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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.

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Overview

Lung cancer is the leading cause of cancer death in the United States.¹ In 2017, an estimated 222,500 new cases (116,990 in men and 105,510 in women) of lung and bronchial cancer will be diagnosed, and 155,870 deaths (84,590 in men and 71,280 in women) are estimated to occur because of the disease.² Only 18% of all patients with lung cancer are alive 5 years or more after diagnosis.³ However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, and advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), targeted therapies, and immunotherapies.⁴⁻⁷ 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.⁸

The NCCN Guidelines® for Non-Small Cell Lung Cancer (NSCLC) are updated at least once a year by the NCCN Panel (eg, there were 6 updates from May 2016 to May 2017). These NCCN Guidelines® were first published in 1996.⁹ 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 July 1, 2015 and July 1, 2016 using the following search term: non-small cell lung cancer. 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 176 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.^{1,10-14} Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).^{13,15} 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).^{11,15-18}

Other possible risk factors for lung cancer include disease history (eg, COPD), cancer history, family history of lung cancer, and exposure to



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other carcinogens (see the NCCN Guidelines for Lung Cancer Screening, available at [NCCN.org](#)).^{19,20} 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.²¹⁻²³ 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.²⁴ 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,²⁵ 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.²⁵ In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.²⁶

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.¹² 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.¹² Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.²⁷ Those

who live with someone who smokes have an increased risk for lung cancer.¹⁶ Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer (see the NCCN Guidelines for Smoking Cessation, available at [NCCN.org](#)).²⁸⁻³¹ The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).³² It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.³³ Some surgeons will not operate on a current smoker, because active smoking may increase postoperative pulmonary complications.³⁴ However, active smoking should not be used to exclude patients with early-stage lung cancer from surgical treatment that will prolong survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful.³⁵ The American Cancer Society (ACS) has a *Guide to Quitting 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.^{36,37} A study suggests that cytidine is more efficacious than nicotine replacement therapy, although more side effects were reported with cytidine such as nausea, vomiting, and sleep disorders.³⁸ Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.³⁹⁻⁴¹ The effectiveness of varenicline for preventing relapse has not been clearly established.⁴² 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.⁴³⁻⁴⁶ Other side effects with



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varenicline include nausea, abnormal dreams, insomnia, and headache.^{41,47,48} Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.⁴⁹ However, in spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.⁴⁹

Lung Cancer Screening

Lung cancer is the leading cause of cancer death worldwide in men, and late diagnosis is a major obstacle to improving lung cancer outcomes.^{1,50,51} 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.⁵² 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%.⁵³ 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.^{52,54} The NCCN, ACS, U.S. Preventive Services Task Force (USPSTF), 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](#)).⁵⁵⁻⁵⁸

Low-dose CT screening and follow-up are 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](#)).^{59,60} NSCLC accounts for more than 80% 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.³ 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), which has been adopted by the WHO.⁵⁹⁻⁶¹ 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.⁶²

Diagnostic Evaluation

Incidental Lung Nodules

Lung cancer screening is recommended for early diagnosis in asymptomatic patients at high risk. Risk assessment is used to determine which individuals are at high risk for lung cancer and thus are candidates for screening with low-dose CT.⁶³ Clinicians are referred to the NCCN Guidelines for Lung Cancer Screening for risk assessment criteria to determine which patients are eligible for screening and for how to evaluate and follow up on low-dose CT screening findings.⁶⁴ The



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NCCN Guidelines for Lung Cancer Screening were recently revised to harmonize with the LungRADs system developed by the American College of Radiology with the goal of decreasing the false-positive low-dose CT screening results reported in the NLST.⁶⁵

The diagnostic algorithm for pulmonary nodules in the NCCN Guidelines for NSCLC incorporates information from the NCCN Guidelines for Lung Cancer Screening. For the 2017 update (Version 1), the NCCN Panel revised the diagnostic algorithm to focus on incidental solid and subsolid lung nodules detected on chest CT (see the NCCN Guidelines for NSCLC).⁶⁶⁻⁶⁹ Note that the Fleischner Society Guidelines do not specify whether a CT with contrast is necessary for follow-up or whether a low-dose CT is sufficient. Low-dose CT is preferred unless contrast enhancement is needed for better diagnostic resolution.

Solid and subsolid nodules are the 2 main types of pulmonary nodules that may be seen on chest CT scans. The Fleischner Society has recommendations for patients with solid and subsolid nodules.^{66,67} 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.^{67,70-72} 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.^{61,67,70,71,73-75} 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.^{73,76,77} 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 the NCCN Guidelines for Lung Cancer Screening, available at [NCCN.org](#)).^{64,66,67}

All findings and factors for a patient 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 the NCCN Guidelines for Lung Cancer Screening, available at [NCCN.org](#)). 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.⁵³ However, the revised cutoff values for suspicious nodules recommended by the American College of Radiology and incorporated into the LungRADs system have been reported to decrease the false-positive rate from low-dose CT.⁷⁸⁻⁸⁰

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 NSCLC). 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.⁸¹ PET/CT 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 NSCLC). 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 NSCLC). 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 NSCLC). 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 NSCLC).⁸² Data show that targeted therapy is potentially very effective in patients with specific gene mutations or rearrangements (see *EGFR Mutations*, *ALK Gene Rearrangements*, and *ROS1 Rearrangements* in this Discussion).^{6,83-88} Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, sputum, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.^{81,89} Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC;^{90,91} however, diagnosis may be more difficult when using small biopsies and cytology.⁷⁴ 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).^{92,93}

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.^{59,60,94} In 2011, the classification for lung adenocarcinoma was revised by an international panel, which has been adopted by the WHO (see *Adenocarcinoma* in this Discussion).⁵⁹⁻⁶¹ The revised classification recommends immunohistochemical (IHC) and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).⁹⁵



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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.⁶¹ 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, ROS1 rearrangements, and programmed death (PD-1) receptor expression levels. The panel also advises testing for other genetic alterations to identify rare driver mutations for which effective therapy may be available such as BRAF V600E. The terms—*AIS*, *MIA*, and *large cell carcinoma*—should not be used for small samples because of challenges with cytology specimens.⁶¹

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. IHC staining is described in the NSCLC algorithm (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). However, limited use of IHC in small tissue samples is recommended to

conserve tumor tissue for molecular studies, especially in patients with advanced disease.^{91,96} The NCCN Panel recommends 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.^{61,97} Squamous cell carcinomas are often TTF-1 negative and p63 positive, whereas adenocarcinomas are usually TTF-1 positive.⁶¹ These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.^{61,97} Other markers (eg, p40, Napsin A) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.^{98,99}

An appropriate panel of IHC 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.⁹⁷ However, TTF-1 is positive in tumors from patients with thyroid cancer.¹⁰⁰ 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.

Malignant pleural mesothelioma is a rare disease; IHC is valuable for distinguishing between malignant mesothelioma and lung



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adenocarcinoma.^{101,102} 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.¹⁰³ Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin antibody),¹⁰⁴ HMBW-1, and cytokeratin 5/6.^{101,102} 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).^{101,102,105}

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC.^{81,97,106} 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.^{107,108} 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.¹⁰⁹ Data suggest that microRNA expression can be used to distinguish SCLC from NSCLC.¹¹⁰

Staging

A new edition of the AJCC Cancer Staging Manual (8th edition) was published in late 2016 and will be effective for all cancer cases

recorded on or after January 1, 2018.¹¹¹ The NCCN Guidelines will use the AJCC (7th edition) staging system for lung cancer until January 1, 2018.¹¹² 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 NSCLC). 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).¹¹³⁻¹¹⁵ and was adopted by the AJCC.^{116,117} 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).¹¹²

From 2007 to 2013, the overall 5-year relative survival rate for lung cancer was 18.1% in the United States.³ 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 55.6% for localized, 28.9% for regional, 4.5% for distant, and 7.5% for unstaged.³ 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.¹¹⁸ 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%.¹¹⁹ Of patients with stage I



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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]), ROS1 gene rearrangements, sensitizing EGFR mutations, and PD-1 ligand (PD-L1) (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). Emerging biomarkers include HER2 (also known as ERBB2) and BRAF V600E mutations, RET gene rearrangements, and high-level MET amplifications or MET exon 14 skipping mutations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for NSCLC). The presence of EGFR exon 19 deletions or exon 21 L858R mutations is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy (ie, erlotinib, gefitinib, afatinib); therefore, these mutations are referred to as *sensitizing* EGFR mutations (see *EGFR Mutations* in this Discussion).^{120,121} 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.¹²² ALK fusion oncogenes (ie, ALK gene rearrangements) and ROS1 rearrangements are predictive biomarkers that have been identified in a small subset of patients with NSCLC; both predict for

benefit from crizotinib (see *ALK Gene Rearrangements* and *ROS1 Gene Rearrangements* in this Discussion and *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). For the 2017 update (Version 1), the NCCN Panel added a new section on *ROS1 Gene Rearrangements* to the pathology recommendations (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). Other gene rearrangements (ie, gene fusions) have recently been identified (such as RET) that are susceptible to targeted therapies (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for NSCLC).¹²³⁻¹²⁸

Testing for ALK gene rearrangements and EGFR mutations is recommended (category 1 for both) in the NSCLC algorithm for patients with non-squamous 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, and crizotinib (see *Targeted Therapies* in this Discussion and the NCCN Guidelines for NSCLC).¹²⁹⁻¹³³ Testing for ROS1 rearrangements (category 2A) is also recommended in the NCCN Guidelines. Although rare, patients with ALK rearrangements or EGFR mutations can have mixed squamous cell histology.^{134,135} Therefore, testing for ALK rearrangements, ROS1 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, ROS1, and ALK genetic alterations do not usually overlap.^{123,136,137}

Patients with NSCLC may have other genetic alterations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for NSCLC).^{83,138,139} Mutation screening assays for detecting multiple biomarkers simultaneously (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) have been developed that can



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detect more than 50 point mutations, including EGFR.^{140,141} However, these multiplex polymerase chain reaction (PCR) systems do not detect gene rearrangements, because they are not point mutations. ROS1 and ALK gene rearrangements can be detected using fluorescence in situ hybridization (FISH) (see *ALK Gene Rearrangements* and *ROS1 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.¹⁴²⁻¹⁴⁹ 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 BRAF V600E mutations, RET gene rearrangements, high-level MET amplification or MET exon 14 skipping mutation, and HER2 (also known as ERBB2).^{123,124,126,128,150-161} 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 NSCLC).^{147,162} Thus, the NCCN Panel strongly advises 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.¹³² Several online resources are available that describe NSCLC driver events such

as DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment)¹⁶³ and *My Cancer Genome*.^{140,164} 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).¹⁶⁵ KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.^{120,166,167} EGFR, KRAS, ROS1, and ALK genetic alterations do not usually overlap.^{136,137,168} Sensitizing EGFR TKI therapy is not effective in patients with KRAS mutations, ALK gene rearrangements, or ROS1 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).¹⁶⁹ 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.¹³⁰ Afatinib is an oral TKI that inhibits the entire ErbB/HER family of receptors including EGFR and HER2.^{170,171} The FDA has approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.^{172,173}



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These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.¹⁷⁴ Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).¹⁷⁵ Primary resistance to TKI therapy is associated with KRAS mutations and ALK or ROS1 gene rearrangements. Patients with exon 20 insertion mutations are also resistant to TKIs.¹⁷⁶⁻¹⁷⁹ EGFR T790M is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease progression after initial response to erlotinib, gefitinib, or afatinib.^{146,180-186} Most patients with sensitizing EGFR mutations become resistant to erlotinib, gefitinib, or afatinib after about 9 to 13 months of EGFR TKI therapy.^{181,187-189} However, studies suggest T790M may also occur in patients who have not previously received EGFR TKI therapy, although this is a rare event.¹⁹⁰ Osimertinib is recommended (category 1) as second-line and beyond (subsequent) therapy for patients with EGFR T790M who have progressed on sensitizing EGFR TKI therapy such as, erlotinib, gefitinib, afatinib (see *Osimertinib* in this Discussion).^{189,191} Acquired resistance may also 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 NSCLC).¹⁹²⁻¹⁹⁴

DNA mutational analysis is the preferred method to assess for EGFR status.¹⁹⁵⁻¹⁹⁷ Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells.¹⁹⁸ 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.^{174,196,199-201} Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) can detect more than 50 point mutations, including EGFR.¹⁴¹ NGS can also be used to detect EGFR mutations.¹⁴⁸

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.¹⁶⁹ Retrospective studies have shown an objective response rate of approximately 80% with a median progression-free survival (PFS) of 13 months to single-agent EGFR TKI therapy in patients with a bronchioloalveolar variant of adenocarcinoma and a sensitizing EGFR mutation.¹²⁰ 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.¹²¹ 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.¹³⁴ Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.¹³⁴

Data show 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.^{173,187,202-205} 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.^{173,187,188} Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.^{187,206} A phase 4 trial showed that gefitinib is safe and effective in patients with sensitizing EGFR mutations.¹³⁰ Based on these data and the FDA approvals, erlotinib and gefitinib are recommended (category 1) as first-line systemic therapy in patients with



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sensitizing EGFR mutations.^{130,187} 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.²⁰⁶ 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.¹⁷³ However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.¹⁷³ 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.²⁰⁷

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.⁸⁸ 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.¹³⁹ In these selected populations, estimates are that about 30% of patients will have ALK rearrangements.^{139,208} 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.¹³⁵ 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.

Rapid prescreening with IHC to assess for ALK rearrangements can be done; if positive, FISH analysis can confirm ALK positivity.^{133,137,209-216} 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.²¹⁷⁻²¹⁹

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) or ROS1 rearrangements.^{123,220-226} Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements, including those with brain metastases.^{88,222,227-229} Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).^{228,230,231} However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.²²⁴ Patients whose disease responds to crizotinib may have rapid improvement in symptoms (eg, cough, dyspnea, pain); median time to progression on crizotinib is about 7 months to 1 year.^{232,233}

Randomized phase 3 trials have compared crizotinib with standard second-line (ie, subsequent) chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014).^{6,222,234} 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).²²² Based on this trial, crizotinib is recommended (category 1) for first-line therapy in patients with ALK-positive NSCLC (see the NCCN Guidelines for NSCLC). 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



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patients with ALK-positive NSCLC who had progressed after first-line chemotherapy.²²³ 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, second-generation ALK inhibitors include ceritinib, alectinib, and brigatinib; others are in development.^{129,235-247} Ceritinib is an orally active TKI of ALK, which also inhibits the insulin-like growth factor-1 (IGF-1) receptor but not MET. An expanded phase 1 trial showed that ceritinib was very active in 122 patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements.²⁴⁰ 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 approved by the FDA for patients with ALK-positive metastatic NSCLC who progress on or are intolerant to crizotinib.²⁴⁸ 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 FDA approval.^{240,248} For the 2017 update (Version 5), the panel also recommends ceritinib as first-line treatment (category 1) for ALK-positive metastatic NSCLC based on a recent phase 3 randomized trial (see *Ceritinib* in this Discussion).

Alectinib is another oral TKI of ALK, which also inhibits RET but not MET or ROS1. Two phase 2 trials in patients with ALK rearrangements showed that alectinib was very active in those who had progressed on crizotinib.^{129,249} In the larger trial (138 patients) by Ou et al, patients on alectinib had a response rate of 50% (95% CI, 41%–59%), and median duration of response of 11.2 months (95% CI, 9.6 months to not reached).¹²⁹ For central nervous system (CNS) disease, the control rate

was 83% (95% CI, 74%–91%), and the median duration of response was 10.3 months (95% CI, 7.6–11.2 months). Of 84 patients with baseline CNS metastases, 23 (27%) had a complete CNS response to alectinib. Of 23 patients with baseline CNS metastases and no previous brain RT, 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. One death due to intestinal perforation may have been related to alectinib.

The other phase 2 trial—in 87 patients with ALK-positive NSCLC who had progressed on crizotinib—reported that 48% of patients had an objective response to alectinib.²⁴⁹ Of 16 patients with baseline CNS metastases, 4 (25%) achieved a complete response in the CNS; 11 of these patients had previously received RT.²⁴⁹ One treatment-related death occurred due to hemorrhage. Based on these studies, alectinib was approved by the FDA for patients with ALK-positive metastatic NSCLC who progress on or are intolerant to crizotinib.²⁵⁰ 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 these 2 trials and FDA approval.^{129,249,250} For the 2017 update (Version 7), the panel now recommends alectinib as first-line treatment (category 1) for ALK-positive metastatic NSCLC based on a recent phase 3 randomized trial (see *Alectinib* in this Discussion). Panel members also voted that alectinib (category 1) is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for ALK gene rearrangements.

Brigatinib is an oral TKI ALK inhibitor that 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 data from a phase 2 trial (ALTA) assessing 2 different doses of



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brigatinib: 90 mg (arm A) or 180 mg (arm B) every day.^{235,247} The overall response rates were 45% (97% CI, 34%–56%) and 54% (97% CI, 43%–65%) in arms A and B, respectively. Many patients had brain metastases (71% and 67%, respectively). The intracranial overall response rates were 42% (11/26) and 67% (12/18), respectively in patients with measurable brain metastases. The median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached), respectively. Grade 3 or higher adverse events included hypertension (6% and 6%, respectively) and pneumonia (3% and 5%, respectively). For the 2017 update (Version 6), the NCCN Panel recommends brigatinib (category 2A) as subsequent therapy for patients with ALK-positive NSCLC who have progressed after crizotinib based on this trial and the FDA approval.^{235,247} Patients who do not tolerate crizotinib may be switched to alectinib or ceritinib (if not previously given), or brigatinib.

ALK or ROS1 rearrangements and sensitizing EGFR mutations are generally mutually exclusive.^{137,251,252} Thus, erlotinib, gefitinib, and afatinib are not recommended as subsequent therapy in patients with ALK or ROS1 rearrangements who relapse on crizotinib (see *ALK Positive: Subsequent Therapy* in the NCCN Guidelines for NSCLC).^{138,139} 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 alectinib or ceritinib (if not previously given), or brigatinib (see *Ceritinib*, *Alectinib*, and *Brigatinib* in this Discussion and the NCCN Guidelines for NSCLC).^{129,228,247,253,254} Continuing alectinib, crizotinib, or ceritinib may also be appropriate for patients who progress on alectinib, crizotinib, or ceritinib, respectively.²⁵⁵

ROS1 Rearrangements

Although ROS1 is a distinct receptor tyrosine kinase, it is very similar to ALK and members of the insulin receptor family (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).^{124,256} It is estimated that ROS1 gene rearrangements occur in about 1% to 2% of patients with NSCLC; they occur more frequently in younger women with adenocarcinoma who are never smokers and in those who are negative for EGFR mutations, KRAS mutations, and ALK gene rearrangements (also known as triple negative).^{124,126,168} Crizotinib is very effective for patients with ROS1 rearrangements with response rates of about 70% including complete responses.¹²⁴ In 50 patients, crizotinib yielded a response rate of 66% (95% CI, 51%–79%); the median duration of response was 18 months.²⁵⁷ The FDA has approved crizotinib for patients with ROS1 rearrangements.²⁵⁷

For the 2017 update (Version 1), the NCCN Panel moved the recommendation for ROS1 testing into the main algorithm (and deleted the footnote recommending ROS1 testing), added a new algorithm for ROS1, and added a new section on ROS1 to the molecular diagnostic studies section based on data showing the efficacy of crizotinib for patients with ROS1 rearrangements and on the recent FDA approval (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).^{123,124,257} Similar to testing for ALK rearrangements, testing for ROS1 is also done using FISH.^{126,209,258–260} NGS can also be used to assess whether ROS1 rearrangements are present, if the platform has been appropriately designed and validated to detect ROS1 rearrangements.¹²⁴ Because a companion diagnostic test has not been approved for ROS1, clinicians should use an appropriately validated test to detect ROS1.²⁵⁷ Alectinib and ceritinib are not recommended in patients with ROS1 rearrangements whose disease becomes resistant to crizotinib.¹²⁴ Studies are ongoing regarding new agents for patients



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with ROS1 rearrangements whose disease becomes resistant to crizotinib.^{236,261-263}

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.^{86,120,147,162,167} KRAS mutation prevalence is associated with cigarette smoking.²⁶⁴ Patients with KRAS mutations appear to have a shorter survival than patients with wild-type KRAS; therefore, KRAS mutations are prognostic biomarkers.^{165,167,265} KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.^{86,120,166} KRAS mutations do not generally overlap with EGFR mutations, ALK rearrangements, or ROS1 rearrangements.^{136,137,266} Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.^{132,166} Targeted therapy is not currently available for patients with KRAS mutations, although immune checkpoint inhibitors appear to be effective; MEK inhibitors are in clinical trials.^{162,239,267,268}

PD-L1 Expression Levels

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells (see *Immunotherapies* in this Discussion).²⁶⁹⁻²⁷¹ Nivolumab and pembrolizumab inhibit PD-1 receptors.^{272,273} Atezolizumab inhibits PD-L1.²⁷⁴ For the 2017 update (Version 1), the NCCN Panel recommends (category 2A) IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements.²⁷⁵ Although it is not an optimal biomarker, PD-L1 expression is currently the best available

biomarker to assess whether patients are candidates for pembrolizumab.^{276,277} Testing for PD-L1 is not required for prescribing nivolumab or atezolizumab for subsequent therapy. PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses.²⁷⁶ Unique anti-PD-L1 IHC assays are being developed for each one of the different immune checkpoint inhibitors currently in clinical trials.^{276,278} The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.²⁷⁸

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.²⁷⁹ 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.²⁷⁹⁻²⁸³ Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.²⁸⁴⁻²⁸⁶



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The *Principles of Surgical Therapy* are described in the NSCLC algorithm and are summarized here (see the NCCN Guidelines for NSCLC). 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 NSCLC).²⁸⁷ 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.^{279,288,289} 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 NSCLC).²⁹⁰⁻²⁹⁴ Resection (including wedge resection) is preferred over ablation.^{279,289} Wide wedge resection may improve outcomes.²⁹⁵ Patients with medically inoperable disease may be candidates for SABR, also known as stereotactic body RT (SBRT).²⁹⁶ If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended (see *Stereotactic Ablative Radiotherapy* in this Discussion).²⁹⁷⁻²⁹⁹

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.^{300,301} 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.³⁰⁰ 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.³⁰² 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 NSCLC): 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.



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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 NSCLC) 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.^{303,304} Randomized controlled trials suggest that surgery does not increase survival in these patients.^{305,306} However, one of these trials (EORTC) only enrolled patients with unresectable disease.³⁰⁶ 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.³⁰⁷ 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.^{308,309} In patients with N2 disease, 50% of the NCCN Member Institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.³¹⁰ 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.³⁰⁹ 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 whose disease responds to induction chemotherapy (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).^{303,311} However, it is controversial whether

pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.^{305,311-317} Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.^{311,318}

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 NSCLC).^{319,320} Published studies suggest that thorascopic lobectomy has several advantages over standard thoracotomy.³²¹⁻³²⁵ Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.^{326,327} Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.³²⁸⁻³³² Thorascopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.³³³⁻³³⁶

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.³³⁷⁻³⁴¹ Thorascopic lobectomy has also been shown to improve discharge independence in older populations and patients at high risk.^{342,343} Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.^{344,345} 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



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thoracic surgery are not compromised (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).³⁴⁶⁻³⁴⁹ Robotic VATS seems to be more expensive with longer operating times than conventional VATS.^{350,351}

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.³⁵²⁻³⁵⁷ 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 NSCLC).

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.^{299,358-365} 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.³⁶⁶⁻³⁷⁰ 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).^{296,299,365,371} Interventional radiology ablation is an option for selected patients who are medically inoperable.^{279,372,373} 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).^{297,374} 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 NSCLC).³⁷⁵ Definitive chemoradiation is recommended for patients with stage II to III disease who are not appropriate surgical candidates.³⁷⁶ 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).³⁷⁷⁻³⁸⁰

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.^{365,381-383} 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



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NSCLC). 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.^{381,384} 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 NSCLC).

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 NSCLC). 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 NSCLC).^{354,385} 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 NSCLC).^{303,305,316,386}

For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some oncologists prefer chemotherapy alone rather than chemoradiotherapy for the preoperative treatment;³⁰⁹ RT should generally be given postoperatively if not given preoperatively. The NCCN Panel recommends a preoperative RT dose of 45 to 54 Gy based on a recent study.³⁰⁸ NCCN Member Institutions are evenly split in their use of neoadjuvant chemotherapy versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.³⁰³ 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,³⁰⁵ 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.³⁸⁷⁻³⁸⁹ 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 NSCLC).^{353,355,362,387-390} 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 NSCLC), more conservative constraints should be used for postoperative RT. For the 2017 update (Version 1), the NCCN Panel noted that the doses and constraints provided in the tables are useful reference doses that have been commonly used or are from previous clinical trials rather than specific prescriptive recommendations.

For definitive RT, the commonly prescribed dose is 60 to 70 Gy in 2 Gy fractions over 6 to 7 weeks.^{391,392} The use of higher RT doses is discussed in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).³⁹³⁻³⁹⁸ Doses more than 74 Gy are not currently recommended for routine use.³⁹⁹ 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.^{398,400-402} Although optimal RT dose intensification remains a valid question, at higher RT doses, normal tissue constraints become even more important.⁴⁰¹ Although the RT dose to the heart was decreased in the RTOG 0617 trial, survival was decreased; thus, more stringent constraints may be appropriate.

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 NSCLC);^{403,404} the ACR Practice Parameters and Technical Standards are also a helpful reference.^{366,405,406} 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*).⁴⁰⁷ These constraints are mainly empirical and have for the most part not been validated rigorously.⁴⁰⁸⁻⁴¹⁵ However, the QUANTEC review provides the most comprehensive estimates from clinical data of dose-response relationships for normal tissue complications.⁴¹⁶⁻⁴²⁰ 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.⁴²¹ 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 NSCLC).^{369,422-426} 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 NSCLC).⁴²⁷

Stereotactic Ablative Radiotherapy

SABR (also known as SBRT) uses short courses of very conformal and dose-intensive RT precisely delivered to limited-size targets.⁴²⁸⁻⁴³⁰ 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.^{299,431-434} 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%.²⁹⁶ 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.^{279,296,373,375,426,433,435-440} Substantially higher survival has been observed in patients with potentially operable disease who are treated with SABR; survival is comparable in population-based



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comparisons to surgical outcomes, but locoregional recurrences are more frequent.^{375,432,441-446} It has not been shown 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.⁴⁴⁷ If possible, biopsy should confirm NSCLC before use of SABR.⁴⁴⁸

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 NSCLC).^{279,434,436,449,450} A combined analysis of 2 randomized trials (that did not complete accrual) assessed SABR compared with lobectomy in operable patients.⁴⁴⁹ The analysis does not alter the fact that surgical resection is recommended and typically used for operable patients, but it helps to confirm the indication of SABR for patients with 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.^{428,434,451-457} 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.^{458,459} This careful follow-up is particularly relevant, because selected patients with localized recurrences after SABR may benefit from surgery or re-treatment with SABR.⁴⁶⁰⁻⁴⁶⁴

SABR fractionation regimens and a limited subset of historically used maximum dose constraints are provided in the NSCLC algorithm (see Tables 2 and 3 in the *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).^{431,433,440,465-474} These dose constraints are point of

reference doses and are not intended to be prescriptive; they are used commonly or have been used in clinical trials. 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. For centrally located tumors—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—regimens of 54 to 60 Gy in 3 fractions are not safe and should be avoided; 4 to 10 fraction SABR regimens appear to be effective and safe (see *Principles of Radiation Therapy* in the NCCN Guidelines for NSCLC).^{297,475-477} Preliminary results (RTOG 0813) suggest that 5-fraction regimens are safe.⁴⁷⁸

SRS or SABR for limited oligometastases to the brain or other body sites, respectively, may be useful for patients with good PS and thoracic disease that can be treated with definitive therapy (see *Stage IV, M1b: Limited Sites* in the NCCN Guidelines for NSCLC).^{287,434,479,480} Local therapy combined with targeted therapy is a category 2A recommendation for patients with ALK or ROS1 rearrangements or sensitizing EGFR mutations.^{481,482} 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.^{483,484} 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.^{279,299,373}



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Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.^{8,485} For the 2017 update (Version 1), the NCCN Panel revised the recommendations for treatment of limited brain metastases by decreasing recommendations for whole brain RT. Options for treatment of limited brain metastases now include 1) SRS alone; and 2) surgical resection for selected patients followed by SRS or whole brain RT; selected patients include those with symptomatic metastases or whose tumor tissue is needed for diagnosis (see the NCCN Guidelines for NSCLC).^{454,485-493} Treatment of limited brain metastases in patients with NSCLC differs from that recommended in the NCCN Guidelines for Central Nervous System Cancers, because patients with NSCLC and brain metastases often have long-term survival; therefore, the potential neurocognitive issues that may occur with whole brain RT are a concern. Clinicians are not using whole brain RT as often in patients with limited brain metastases, which is reflected in the revised recommendations in the 2017 update (Version 1).⁴⁸⁶

A recent randomized trial assessed cognitive function in 213 patients with 1 to 3 brain metastases who received SRS alone versus SRS with whole brain RT; most patients had lung cancer.⁴⁸⁶ At 3 months after SRS alone, patients had less cognitive deterioration (40/63 patients [63.5%]) than those receiving SRS plus whole brain RT (44/48 patients [91.7%]; difference, -28.2%; 90% CI, -41.9% to -14.4%; $P < .001$). Decisions about whether to recommend SRS alone or brain surgery followed by whole brain RT or SRS for limited brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.^{487,494-496} Treatment should be individualized for patients with recurrent or progressive brain lesions.⁴⁹⁷

For multiple metastases (eg, >3), whole brain RT is recommended; SRS may be preferred for patients who have good PS and low systemic tumor burden (see the NCCN Guidelines for Central Nervous System Cancers, available at [NCCN.org](#)).⁴⁹⁸⁻⁵⁰¹ Whole brain RT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.⁵⁰²⁻⁵⁰⁴ However, control of brain metastases confers improved neurocognitive function.^{505,506} For limited metastases, randomized trials have found that the addition of whole brain RT to SRS decreases intracranial recurrence but does not improve survival and may increase the risk of cognitive decline.^{506,507} Thus, SRS or whole brain RT alone is recommended for patients with limited volume metastases.⁴⁹⁸ Some have suggested that resection followed by SRS to the cavity (instead of resection followed by whole brain RT) will decrease the risk of neurocognitive problems.^{508,509} A study suggests that using IMRT to avoid the hippocampus may help decrease memory impairment after whole brain RT.⁵¹⁰ A recent phase 3 randomized trial assessed optimal supportive care (including dexamethasone) with whole brain RT versus optimal supportive care alone in patients with NSCLC and brain metastases who were not eligible for brain surgery or SRS.⁵¹¹ Overall survival was similar between the groups (HR, 1.06; 95% CI, 0.90–1.26). Overall quality of life, use of dexamethasone, and reported adverse events were also similar between the arms.

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 NSCLC). In patients with



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completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.⁵¹²⁻⁵¹⁴ Some studies suggest 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).^{303,515-521} A randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.⁵²² 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.^{279,523} Concurrent chemoradiation is superior to sequential chemoradiation for patients with unresectable stage III disease.⁵²⁴⁻⁵²⁷

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.⁵²⁸⁻⁵³³ Data show that early palliative care combined with standard care improved 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.⁵³⁴ Patients should receive treatment for debilitating symptoms.^{8,535,536} A study also suggests that social support, such as being married, is as effective as chemotherapy.⁵³⁷ Surgery is rarely recommended for patients with stage IV disease. However, surgical resection of limited brain metastases may improve survival in selected patients with stage IV disease and is recommended for select patients in the NCCN Guidelines (see the NCCN Guidelines for NSCLC, available at NCCN.org).⁵³⁸ Definitive local therapy with surgical resection or RT is recommended for limited metastases located in sites other than the brain if definitive thoracic therapy is feasible (see *Stage IV, M1b: Limited Sites* in the NCCN Guidelines for NSCLC).^{287,434} 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 NSCLC). 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.⁵¹² 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 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 reported 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.⁵³⁹ 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.⁵¹³ 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.⁵⁴⁰ 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.⁵¹⁴ 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.⁵¹⁴

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;⁵⁴¹ however, most clinicians in the United States prefer to use regimens with less toxicity.^{542,543}

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).⁵⁴⁴ A subgroup analysis found that cisplatin/vinorelbine also increased survival.⁵⁴¹ 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.^{282,545}

The CALGB 9633 trial assessed paclitaxel/carboplatin in patients with T2, N0, M0, stage IB lung cancer.⁵⁴⁶⁻⁵⁴⁸ 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 a subset analysis showed a benefit for tumors 4 cm or more), although 3-year survival was significant (80% vs. 73%, $P = .02$).^{547,548} 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 NSCLC).⁵⁴⁹ However, it is important to note that the CALGB trial was underpowered for patients with stage 1B disease.⁵⁵⁰

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 systemic 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.⁵²⁰ 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;



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response rate and quality of life were similar in both arms.⁵²²

Postoperative chemotherapy (with or without RT or resection) is recommended and typically used for early-stage disease in the NCCN Guidelines.²⁷⁹

Several trials suggest that neoadjuvant therapy is beneficial in patients with N2 disease.^{303,309,519} Other trials suggest that neoadjuvant therapy is beneficial in patients with earlier stage disease.^{516,517,521} 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.⁵²¹

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).⁵¹⁶ 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; the HR suggests that overall survival in the neoadjuvant chemotherapy arm is similar to the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92; $P = .0001$).⁵¹⁵ These results are similar to those reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; $P = .02$).⁵¹⁶ The benefit from neoadjuvant chemotherapy is similar to that attained with postoperative chemotherapy.^{516,522,544}

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 NSCLC]). All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used when treating stage III disease. The ongoing debate centers on which modalities to use and in what sequence.⁵⁵¹⁻⁵⁵⁵ For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.^{551,552,554,555} Concurrent chemoradiation is superior to sequential chemoradiation.⁵²⁴⁻⁵²⁷ 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 anticipated response to therapy but also on how well the patient is anticipated to tolerate therapy. Frail patients may not be able to tolerate concurrent chemoradiation.^{280,556}

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 NSCLC).^{400,524,526,557-561} For non-squamous NSCLC, additional concurrent chemoradiation regimens may be used including carboplatin/pemetrexed and cisplatin/pemetrexed.⁵⁶²⁻⁵⁶⁴ A weekly paclitaxel/carboplatin regimen is another chemoradiation option.⁴⁰⁰ The different options for neoadjuvant/preoperative/induction, definitive, and adjuvant chemotherapy/RT are described in detail in the algorithm. Recently, the NCCN Panel removed the *preferred* designation for the cisplatin/etoposide and cisplatin/vinblastine regimens based on data from a phase 3 randomized trial and a recent retrospective assessment of the Veterans Administration data.^{557,561,565}

Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.⁵³⁰⁻⁵³² However, chemotherapy is only recommended for patients with stage IV NSCLC and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression. Recommended agents 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 NSCLC). To clarify use of systemic therapy, the NCCN Guidelines list all of the combination systemic therapy regimens and single agents that are recommended for patients with metastatic NSCLC depending on histology and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).

For the 2017 update (Version 1), these lists of systemic therapy regimens were revised by deleting options that are less effective, more toxic, and/or infrequently used in the United States based on each panel member's experience and data generated by surveying the NCCN Panel (see the NCCN Evidence Blocks™ for NSCLC, available at [NCCN.org](#)). For patients with non-squamous NSCLC and NSCLC NOS, panel members deleted carboplatin/vinorelbine, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine. For patients with squamous cell NSCLC, panel members deleted carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine. Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents.^{549,566-569} 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.^{570,571} Gemcitabine/cisplatin is recommended for patients with either squamous cell carcinoma or non-squamous NSCLC.⁵⁶⁹⁻⁵⁷² These regimens are recommended based on phase 3 randomized trials (eg, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).^{569,573}

For the 2017 update (Version 1), the NCCN Panel voted unanimously to delete the necitumumab/cisplatin/gemcitabine regimen from the NCCN Guidelines for patients with metastatic squamous cell NSCLC. This decision reflects the fact that the NCCN Panel feels the addition of necitumumab to the regimen is not beneficial 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 [95% CI, 8.9–11.1]).⁵⁷⁴ 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 it has been suggested that adding necitumumab to cisplatin/gemcitabine adds value and is cost effective, the NCCN Panel does not agree.⁵⁷⁵

Many oncologists use pemetrexed-based regimens for adenocarcinomas (if patients are not candidates for targeted therapy or immunotherapy), because taxane-based regimens are associated with more toxicity (eg, neurotoxicity).^{569,576} There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.⁵⁷⁷ 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.⁵⁷⁸ However, the POINTBREAK trial showed that both regimens are similar in regard to overall survival rates;



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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.⁵⁷⁹ However, another retrospective cohort study reported increased survival in older patients.⁵⁸⁰ A combined analysis of the ECOG 4599 and POINTBREAK trials found a 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.⁵⁸¹

For patients with advanced NSCLC who have a PS of 2 (ie, poor PS), platinum-based combinations and a few single-agent chemotherapy agents are recommended in the NCCN Guidelines; cisplatin-based regimens are not recommended in this setting.⁵⁸² For non-squamous NSCLC or NSCLC NOS, single-agent chemotherapy includes gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.⁵⁸³⁻⁵⁸⁵ However, patients with a PS of 2 are often just treated with single-agent chemotherapy because of concerns about toxicity.⁵⁸⁶ Results from a 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.^{583,587} For the 2017 update (Version 1), the NCCN Panel deleted etoposide, irinotecan, and vinorelbine from the list of recommended single-agent chemotherapy for patients with all histologies because these agents are rarely used in the United States.

Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.^{588,589} The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy

for their patients.^{572,590,591} Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;^{566,592-594} non-platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.⁵⁹⁵⁻⁵⁹⁸ 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.^{599,600} 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.⁶⁰¹ 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 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.^{131,602,603} Afatinib, alectinib, brigatinib, ceritinib, crizotinib, erlotinib, gefitinib, and osimertinib are oral TKIs. Bevacizumab and ramucirumab are recombinant monoclonal antibodies that inhibit vascular endothelial growth factor (VEGF) receptors. Cetuximab is a monoclonal antibody that targets EGFR.



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Erlotinib, gefitinib, and afatinib inhibit EGFR; osimertinib inhibits both EGFR sensitizing mutations and T790M. Crizotinib inhibits ALK, ROS1, and MET (ie, high-level MET amplification, MET exon 14 skipping mutation). Ceritinib inhibits ALK and IGF-1 receptor. Alectinib inhibits ALK and RET. Brigatinib inhibits various ALK rearrangements and other targets.⁶⁰⁴ Other targeted therapies are being developed (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for NSCLC).

VEGF Receptor Inhibitors

Bevacizumab

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC.⁶⁰⁵ 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).⁵⁷³ 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. Bevacizumab in combination with chemotherapy (ie, carboplatin/paclitaxel, carboplatin/pemetrexed, cisplatin/pemetrexed) is one of the recommended options for patients with a PS 0 to 1 and non-squamous NSCLC or NSCLC NOS and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression (see *Sensitizing EGFR Mutation Positive/First-Line Therapy* or *ALK Positive/First-Line Therapy* in the NCCN Guidelines for NSCLC). Bevacizumab is not recommended for patients with squamous cell NSCLC.

Ramucirumab

A phase 3 randomized trial (REVEL) assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed.⁶⁰⁶ The median overall survival was reported to be slightly increased with ramucirumab/docetaxel versus docetaxel alone (10.5 vs. 9.1 months; 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.⁶⁰⁷ 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.^{606,607} 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 vs. 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.

Oral TKIs

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.⁶⁰⁸ The FDA has also approved the use of erlotinib as first-line therapy in patients with sensitizing EGFR mutations.⁶⁰⁹ Erlotinib and gefitinib are recommended (category 1) in the NSCLC algorithm as first-line therapy in patients with advanced,



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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 NSCLC).^{86,188,610,611}

These recommendations are based on 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 showed that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing EGFR mutation status.⁶¹² 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.¹⁸⁷ 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 reapproved by the FDA based on a phase 4 study and is now available in the United States.^{130,613} Erlotinib and gefitinib are orally active TKIs that are very well tolerated by most patients.^{614,615} 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.⁶¹⁶ The TORCH trial suggested that EGFR mutation testing should be done in patients with advanced non-squamous NSCLC.⁶¹⁷ 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 reported that PFS was increased in patients with sensitizing EGFR mutations who received erlotinib.^{204,205} ASCO recommends that patients be tested for EGFR mutations.⁶¹⁸ However, the ESMO Guidelines specify that only patients with non-squamous NSCLC (eg, adenocarcinoma) be assessed for EGFR mutations.^{132,582} Patients with pure squamous cell carcinoma are unlikely to have sensitizing EGFR mutations; however, those with adenosquamous carcinoma may have mutations.¹³⁴

An updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.⁶¹⁹ 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 NSCLC).⁶²⁰ The NCCN Guidelines do not recommend adding erlotinib, gefitinib, or afatinib to current chemotherapy based on this CALGB study.⁶¹⁹ Erlotinib, gefitinib, or afatinib may be continued in patients who have progressed if patients do not have multiple systemic symptomatic



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lesions (see *Continuation of Erlotinib, Gefitinib, or Afatinib After Progression* in this Discussion).

A recent phase 3 trial (WJOG 5108L) assessed gefitinib versus erlotinib for patients with advanced lung cancer who had been previously treated with chemotherapy; most patients (72%) were positive for EGFR mutations.⁶²¹ The median PFS for gefitinib versus erlotinib was 8.3 and 10.0 months, respectively, in patients positive for EGFR mutations (HR, 1.093; 95% CI, 0.879–1.358; $P = .424$). The main grade 3 or 4 toxicities included rash (gefitinib: 2.2% vs. erlotinib: 18.1%) and increases in alanine aminotransferase (ALT)/aspartate aminotransferase (AST) levels (gefitinib: 6.1%/13.0% vs. erlotinib: 2.2%/3.3%).

Afatinib

A randomized phase 3 trial reported that first-line therapy with afatinib improved PFS when compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who have sensitizing EGFR mutations (11.1 vs. 6.9 months, $P = .001$).¹⁷³ The FDA has approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.^{172,622} 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 NSCLC).^{170,173,254} 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).¹⁶⁹ 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).⁶²³

A recent phase 2B trial assessed afatinib compared with gefitinib for first-line therapy in patients with metastatic adenocarcinoma and sensitizing EGFR mutations.⁶²⁴ The PFS was essentially the same in patients receiving afatinib when compared with those receiving gefitinib (median PFS, 11.0 months [95% CI, 10.6–12.9] with afatinib vs. 10.9 months [9.1–11.5] with gefitinib; HR, 0.73 [95% CI, 0.57–0.95]; $P = .017$). These slight PFS differences are not clinically relevant and the NCCN Guidelines do not state that one EGFR TKI is more efficacious than another (see the NCCN Evidence Blocks for NSCLC, available at [NCCN.org](#)).⁶²¹ Overall survival data are not yet available. Patients receiving afatinib had more serious treatment-related side effects when compared with those receiving gefitinib (11% [17/160] for afatinib vs. 4% [7/159] for gefitinib). One patient receiving gefitinib died from treatment-related hepatic and renal failure; other deaths were not considered to be related to treatment (9% vs. 6% [15/160 vs. 10/159]). More patients receiving afatinib had diarrhea (13% vs. 1%), whereas more patients receiving gefitinib had elevations in liver enzyme levels (0% vs. 9%). For the 2017 update (Version 1), the NCCN Panel revised the afatinib evidence block for efficacy to highly effective (ie, the highest rating of 5), so the value is now the same as that for erlotinib and gefitinib (see the NCCN Evidence Blocks for NSCLC, available at [NCCN.org](#)). However, afatinib is rated as slightly less safe than erlotinib or gefitinib (ie, a rating of 3 for afatinib versus 4 for erlotinib and gefitinib).

Osimertinib

As previously mentioned, most patients with sensitizing EGFR mutations and metastatic NSCLC typically progress after about 9 to 13 months of erlotinib, gefitinib, or afatinib therapy.^{181,187-189} EGFR T790M is a mutation associated with acquired resistance to EGFR TKI therapy and has been reported in about 60% of patients with disease



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progression after initial response to sensitizing EGFR TKI therapy.^{146,180-186} Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR sensitizing mutations and T790M.

A recent phase 3 randomized trial assessed osimertinib versus platinum-pemetrexed chemotherapy in patients with EGFR T790M positive metastatic NSCLC. Data show that osimertinib increased PFS when compared with chemotherapy (10.1 vs. 4.4 months; HR, 0.30; 95% CI, 0.23–0.41; $P < .001$).¹⁸⁹ PFS was also increased in patients with CNS metastases who received osimertinib (8.5 vs. 4.2 months; HR, 0.32; 95% CI, 0.21–0.49). In addition, the objective response rate was improved with osimertinib (71%; 95% CI, 65%–76%) when compared with chemotherapy (31%; 95% CI, 24%–40%) (odds ratio for objective response, 5.39; 95% CI, 3.47–8.48; $P < .001$). The disease control rate is about 93% with osimertinib (95% CI, 90%–96%) and about 74% with chemotherapy (95% CI, 66%–81%). Patients receiving osimertinib had fewer grade 3 or higher adverse events when compared with those receiving chemotherapy (23% vs. 47% [63/279 vs. 64/136]); however, there were 4 fatal events with osimertinib (respiratory failure [2], pneumonitis, ischemic stroke) and one with chemotherapy (hypovolemic shock).

Data from a multicenter, single-arm phase 2 clinical trial indicate that osimertinib is associated with a response rate of about 61% (78/127; 95% CI, 52–70), PFS of 9.6 months (95% CI, 8.3 to not reached), and disease control rate of about 95% (121/127; 95% CI, 90–98) in patients with EGFR T790M who have progressed on sensitizing EGFR TKI therapy; 13% (33/253) of patients had drug-related grade 3 or higher adverse events with one fatal event from pneumonia possibly related to treatment.^{191,625,626} In patients without EGFR T790M, the response rate was 21% (13/61; 95% CI, 12–34) and the PFS was 2.8 months (95% CI, 2.1–4.3).¹⁹¹

The FDA has approved osimertinib for patients with metastatic EGFR T790M-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR TKI therapy. Based on the data and FDA approval, the NCCN Panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic EGFR T790M-positive NSCLC who have progressed on erlotinib, gefitinib, or afatinib therapy (see *Second-Line and Beyond (Subsequent) Systemic Therapy* in this Discussion). For the 2017 update (Version 4), the NCCN Panel revised the recommendation to category 1 (from category 2A) for osimertinib in patients with EGFR T790M-positive metastatic NSCLC based on the recent phase 3 randomized trial.¹⁸⁹ T790M can be assessed using an FDA-approved test or other validated laboratory test done in a CLIA-approved laboratory. Recent data suggest that plasma genotyping (also known as liquid biopsy or plasma biopsy) may be considered instead of tissue biopsy to detect whether patients have T790M; however, if the plasma biopsy is negative, then tissue biopsy is recommended if feasible.^{627,628} For the 2017 update (Version 4), the NCCN Panel now also recommends osimertinib (category 1) for patients with T790M who have progression with symptomatic brain metastases based on data showing an improvement.^{189,629-632}

Crizotinib

Crizotinib is an oral TKI ALK inhibitor that is approved by the FDA for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement.²²⁰ The approval is based on a phase 2 trial that showed dramatic response rates (>80%) to crizotinib in patients who had previously progressed.^{224,225} Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough. A 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.²²² 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.²²³ Patients who do not tolerate crizotinib may be switched to alectinib or ceritinib (if not previously given), or brigatinib. For the 2017 update (Version 7), panel members voted that alectinib (category 1) is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for ALK gene rearrangements (see *Alectinib* in this Discussion).

Crizotinib is also very effective for patients with ROS1 rearrangements with response rates of about 70% including complete responses (see *ROS1 Rearrangements* in this Discussion).^{124,257} For the 2017 update (Version 1), the NCCN Panel moved the recommendation for ROS1 testing into the main algorithm (and deleted the footnote recommending ROS1 testing), added a new algorithm for ROS1, and added a new section on ROS1 to the molecular diagnostic studies section based on data showing the efficacy of crizotinib for patients with ROS1 rearrangements and on the recent FDA approval (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC).^{123,124,257} Alectinib and ceritinib are not recommended in patients with ROS1 rearrangements whose disease become resistant to crizotinib.

Ceritinib

Ceritinib is an oral TKI ALK inhibitor that is approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.²⁴⁸ The approval is based on an expanded phase 1 study (ASCEND-1) showing overall response rates of 56% to ceritinib in patients (92/163) who had previously received crizotinib; the

median duration of response was 8.3 months (6.8–9.7).^{240,633} Common grade 3 to 4 adverse events included increased alanine aminotransferase (73 [30%] patients) and increased aspartate aminotransferase (25 [10%]).⁶³³ 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 tolerate crizotinib may be switched to alectinib or ceritinib (if not previously given), or brigatinib. A phase 2 trial (ASCEND-2) assessed ceritinib in patients who had previously received at least 2 or more treatments, had progressed on crizotinib, and had brain metastases.⁶³⁴ The overall response rate was 38%; the duration of response was 9.7 months (95% CI, 7.1–11.1 months).⁶³⁴ The intracranial overall response rate was 45.0% (95% CI, 23.1%–68.5%).

A recent phase 3 trial assessed ceritinib versus platinum-based chemotherapy as first-line therapy for patients with ALK-positive metastatic NSCLC.⁶³⁵ The data show that PFS was improved when using ceritinib when compared with platinum-based chemotherapy; the median PFS was 16.6 months (95% CI, 12.6–27.2) for ceritinib and 8.1 months (CI, 5.8–11.1) for chemotherapy (hazard ratio 0.55 [95% CI, 0.42–0.73]; $P<.00001$). For ceritinib, common adverse events included diarrhea (85% [160/189] of patients), nausea (69% [130/189]), vomiting (66% [125/189]), and an increase in alanine aminotransferase (60% [114/189]). For chemotherapy, common adverse events included nausea (55% [97/175 patients]), vomiting (36% [63/175]), and anemia (35% [62/175]). For the 2017 update (Version 5), the NCCN Panel recommends (category 1) ceritinib as first-line therapy for patients with ALK-positive metastatic NSCLC based on this phase 3 trial. For the 2017 update (Version 7), panel members voted that alectinib (category 1) is the preferred agent for first-line therapy for patients with metastatic

NSCLC who are positive for ALK gene rearrangements (see *Alectinib* in this Discussion).

Alectinib

Alectinib is an oral TKI ALK inhibitor that is approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib.²⁵⁰ The approval is based on two phase 2 trials showing overall response rates of 48% to 50% to alectinib in patients who had previously received crizotinib.^{129,249} In the larger trial by Ou et al, the control rate for CNS disease was 83% (95% CI, 74%–91%), and the median duration of response was 10.3 months (95% CI, 7.6–11.2 months).¹²⁹ Of 84 patients with baseline CNS metastases, 23 (27%) had a complete CNS response. Of 23 patients with baseline CNS metastases and without previous brain RT, 10 (43%) had a complete CNS response to alectinib. Based on these trials 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 tolerate crizotinib may be switched to alectinib or ceritinib (if not previously given), or brigatinib.

For the 2017 update (Version 7), the NCCN Panel now recommends alectinib as first-line therapy (category 1) for patients with ALK-positive metastatic NSCLC based on a recent phase 3 randomized trial (ALEX).⁶³⁶ Panel members also voted that alectinib is the preferred agent for first-line therapy for patients with metastatic NSCLC who are positive for ALK gene rearrangements. The phase 3 trial assessed first-line therapy with alectinib versus crizotinib in 303 patients with ALK-positive advanced NSCLC including those with asymptomatic CNS disease.⁶³⁶ Disease progression or death occurred in fewer patients receiving alectinib (41% [62/152]; median follow-up of 18.6 months) when compared with crizotinib (68% [102/151]; median follow-up of 17.6 months). The hazard ratio was 0.47 (95% CI, 0.34 to 0.65); $P < .001$) for

disease progression or death. PFS was significantly increased with alectinib (68.4% [95% CI, 61.0 to 75.9] versus crizotinib (48.7% [95% CI, 40.4 to 56.9]. The median PFS was not reached for alectinib (95% CI, 17.7 months to not estimable) when compared with crizotinib at 11.1 months (95% CI, 9.1 to 13.1). Fewer patients receiving alectinib had CNS progression (12% [18/152] versus crizotinib (45% [68/151])). Response rates were 83% (126/152) in the alectinib group versus 75% (114/151) in the crizotinib group ($P = .09$). Patients receiving alectinib had fewer grade 3 to 5 adverse events when compared with crizotinib (41% [63/152] vs. 50% [75/151], respectively) even though patients received alectinib for longer duration than crizotinib (median, 17.9 vs. 10.7 months). There were also fewer deaths in the alectinib arm (3.3% [5/152]) versus the crizotinib arm (4.6% [7/151]); 2 treatment-related deaths were reported in the crizotinib arm and none in the alectinib arm.

Brigatinib

Brigatinib is an oral TKI ALK inhibitor that 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 data from a phase 2 trial (ALTA) assessing 2 different doses of brigatinib: 90 mg (arm A) or 180 mg (arm B) every day.^{235,247} The overall response rates were 45% (97% CI, 34%–56%) and 54% (97% CI, 43%–65%) in arms A and B, respectively. Many patients had brain metastases (71% and 67%, respectively). The intracranial overall response rates were 42% (11/26) and 67% (12/18), respectively in patients with measurable brain metastases. The median PFS was 9.2 months (95% CI, 7.4–15.6) and 12.9 months (95% CI, 11.1–not reached), respectively. Grade 3 or higher adverse events included hypertension (6% and 6%, respectively) and pneumonia (3% and 5%, respectively). For the 2017 update (Version 6), the NCCN Panel recommends brigatinib (category 2A) as subsequent therapy for



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patients with ALK-positive NSCLC who have progressed after crizotinib based on this trial and the FDA approval.^{235,247}

EGFR Inhibitor

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.⁶³⁷ Adding cetuximab was reported to slightly increase overall survival (11.3 vs. 10.1 months, HR for death, 0.87 [95% CI, 0.762–0.996]; $P=.044$). 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.⁵²⁸

Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. Cisplatin/vinorelbine with (or without) cetuximab is generally not used in the United States because of concerns about toxicity.^{528,542,637} Some oncologists feel that although the FLEX trial results were reported to be statistically significant they were not clinically significant.⁵²⁸ For the 2017 update (Version 1), the NCCN Panel deleted the cisplatin/vinorelbine and carboplatin/vinorelbine regimens from the list of recommended systemic therapy regimens for metastatic NSCLC with all histologies.

Immunotherapies

Human immune-checkpoint–inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.²⁶⁹⁻²⁷¹ Nivolumab and pembrolizumab inhibit PD-1 receptors.^{272,273} Atezolizumab inhibits PD-L1.²⁷⁴ Immune checkpoint inhibitors are associated with a delay in benefit when compared with targeted therapy or cytotoxic chemotherapy. Nivolumab, pembrolizumab, and atezolizumab 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). Pseudoprogression has been reported; therefore, traditional RECIST criteria may not be applicable.⁶³⁸

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 FDA approval.^{269,639} The NCCN Panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy based on improved overall survival rates, longer duration of response, and fewer adverse events when compared with cytotoxic chemotherapy.^{269,272,640,641}

The category 1 recommendation for nivolumab is based on the published data from CheckMate-057 and 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; $P = .002$).²⁶⁹ 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



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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. 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.⁶⁴² Testing for PD-L1 is not required for prescribing nivolumab but may provide useful information.²⁷⁸ Current or former smoking status correlated with the response rate to immune checkpoint inhibitors.²⁶⁹ Recent data suggest that mismatch repair deficiency is associated with response to immune checkpoint inhibitors.⁶⁴³

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.^{272,644} In the CheckMate-017 trial, the median overall survival was 9.2 months with nivolumab compared with 6.0 months for docetaxel.²⁷² 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.^{271,644-650} Intravenous 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 2017 updates (Versions 1 and 2), the NCCN Panel recommends pembrolizumab (category 1) as first-line therapy for patients with PD-L1 expression levels of 50% or more and with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements based on a recent phase 3 randomized trial (Keynote-024) comparing pembrolizumab versus platinum-based chemotherapy; the FDA recently approved pembrolizumab for first-line therapy based on this trial.²⁷³ At 6 months, the rate of overall survival was 80.2% in the pembrolizumab group versus 72.4% in the chemotherapy group (HR for death, 0.60; 95% CI, 0.41–0.89; $P = .005$). Responses were higher in the pembrolizumab group than in the chemotherapy group (44.8% vs. 27.8%).²⁷³ There were fewer severe treatment-related adverse events (grades 3-5) in patients receiving pembrolizumab compared with those receiving chemotherapy (26.6% vs. 53.3%).

For the 2017 update (Version 1), the NCCN Panel recommends (category 2A) IHC testing for PD-L1 expression before first-line treatment in patients with metastatic NSCLC with negative or unknown tests results for EGFR mutations, ALK rearrangements, and ROS1 rearrangements.²⁷⁵ Although it is not an optimal biomarker, PD-L1 expression is currently the best available biomarker to assess whether



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patients are candidates for pembrolizumab.^{276,277} PD-L1 expression is continuously variable and dynamic; thus, a cutoff value for a positive result is artificial. Patients with PD-L1 expression levels just below and just above 50% will probably have similar responses.²⁷⁶ Unique anti-PD-L1 IHC assays are being developed for each one of the different immune checkpoint inhibitors currently in clinical trials.^{276,278} The definition of a positive PD-L1 test result varies depending on which biomarker assay is used.²⁷⁸

Ideally, PD-L1 expression levels are assessed in patients with negative or unknown test results for EGFR mutations, ALK rearrangements, or ROS1 rearrangements. Every effort needs to be made to establish the genetic alteration status. However, if the risk of biopsy is high and genetic alteration testing is not feasible and therefore technically unknown, then it is appropriate to test for PD-L1 expression levels. Of note, there are blood assays to evaluate for EGFR mutations and ALK rearrangements although they are less sensitive than tissue assays.

The NCCN Panel also recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression based on the randomized phase 2/3 trial (KEYNOTE-010), the phase 1 KEYNOTE-001 trial, and FDA approval.^{641,651,652} In addition, the NCCN Panel recommends immune checkpoint inhibitors as preferred agents for subsequent therapy. As previously mentioned, human immune-checkpoint-inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.^{270,271} Pembrolizumab inhibits the PD-1 receptor.²⁷³

A randomized phase 2/3 trial (KEYNOTE-010) assessed pembrolizumab in patients with previously treated advanced non-squamous and squamous NSCLC who were PD-L1 positive (\geq

1%); most patients were current or former smokers.⁶⁴¹ There were 3 arms in this trial: pembrolizumab at 2 mg/kg, pembrolizumab at 10 mg/kg, and docetaxel at 75 mg/m² every 3 weeks. The median overall survival was 10.4 months for the lower dose of pembrolizumab, 12.7 months for the higher dose, and 8.5 months for docetaxel. Overall survival was significantly longer for both doses of pembrolizumab when compared with docetaxel (pembrolizumab 2 mg/kg: HR, 0.71; 95% CI, 0.58–0.88; $P=$.0008) (pembrolizumab 10 mg/kg: HR, 0.61; CI, 0.49–0.75; $P<$.0001). For those patients with at least 50% PD-L1 expression in tumor cells, overall survival was also significantly longer at either dose of pembrolizumab when compared with docetaxel (pembrolizumab 2 mg/kg: 14.9 vs. 8.2 months; HR, 0.54; 95% CI, 0.38–0.77; $P=$.0002) (pembrolizumab 10 mg/kg: 17.3 vs. 8.2 months; HR, 0.50; CI, 0.36–0.70; $P<$.0001). When compared with docetaxel, there were fewer grade 3 to 5 treatment-related adverse events at either dose of pembrolizumab (pembrolizumab 2 mg/kg: 13% [43/339] of patients, pembrolizumab 10 mg/kg: 16% [55/343], and docetaxel: 35% [109/309]). A total of 6 treatment-related deaths occurred in patients receiving pembrolizumab (3 at each dose) and 5 treatment-related deaths occurred in the docetaxel arm.

A phase I trial (KEYNOTE-001) assessed the safety and efficacy of pembrolizumab for patients with metastatic NSCLC.⁶⁵¹ 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.^{651,653} Less than 10% of patients had serious grade 3 or more toxicity.



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Similar to nivolumab and atezolizumab, immune-mediated adverse events may also occur with pembrolizumab.^{645,647,654} For patients with immune-mediated adverse events, intravenous 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-L1.⁶⁵² The FDA has approved a companion diagnostic biomarker test for assessing PD-L1 expression and determining which patients are eligible for pembrolizumab therapy. Other immunotherapeutic agents are being investigated.^{274,640,655,656}

Atezolizumab

For the 2017 update (Version 4), the NCCN Panel revised the recommendation to category 1 for atezolizumab as subsequent therapy for patients with metastatic non-squamous or squamous cell NSCLC based on a recent phase 3 trial;⁶⁵⁷ previously this was a category 2A recommendation based on data from a phase 3 randomized trial, data from a phase 2 trial, and recent FDA approval.^{274,658} Testing for PD-L1 expression levels is not required for prescribing atezolizumab but may provide useful information. Human immune-checkpoint-inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.^{270,271} Atezolizumab inhibits PD-L1.²⁷⁴

A phase 3 randomized trial (OAK) assessed atezolizumab versus docetaxel alone in patients with metastatic NSCLC who had progressed during or after systemic therapy.^{657,658} Most patients were current or former smokers and had received platinum-based

chemotherapy; few patients (10%) had EGFR mutations and ALK rearrangements were not reported.^{657,658} Data show that patients with non-squamous NSCLC who received atezolizumab had improved overall survival when compared with those receiving docetaxel (15.6 vs. 11.2 months; HR, 0.73 [0.6–0.89]; $P = .0015$). Overall survival was only slightly improved in patients with squamous cell NSCLC receiving atezolizumab versus docetaxel (8.9 vs. 7.7 months; HR, 0.73 [0.54–0.98]; $P = .038$); however, there were fewer patients in the squamous group when compared with the nonsquamous group (222 vs. 628). There were fewer treatment-related severe adverse events (grades 3-4) for atezolizumab versus docetaxel (15% vs. 43% [90/609 vs. 247/578]).

Similar to nivolumab and pembrolizumab, immune-mediated adverse events may also occur with atezolizumab.⁶⁵⁷ For patients with immune-mediated adverse events, intravenous high-dose corticosteroids should be administered based on the severity of the reaction. Atezolizumab should also be permanently discontinued for patients with severe or life-threatening pneumonitis and should be discontinued for other severe or life-threatening immune-mediated adverse events when indicated (see prescribing information).

For the 2017 update (Version 4), the NCCN Panel revised the atezolizumab evidence block for efficacy to a rating of 4 (very effective); previously the rating was 3 (moderately effective) (see the NCCN Evidence Blocks for NSCLC, available at [NCCN.org](#)).

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.⁶⁵⁹ However, patients are only candidates for maintenance therapy if their tumors 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 recommended 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 NSCLC).⁶⁶⁰

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 based on 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 and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression.^{573,661,662} Single-agent pemetrexed (category 1) may also be given as continuation maintenance therapy in patients with non-squamous NSCLC and negative or unknown test results.^{661,663} A 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).⁶⁶³ Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).⁶⁶⁴ Based on the trial and the FDA approval, the NCCN Panel

recommends single-agent pemetrexed as continuation maintenance therapy (category 1) in patients with non-squamous NSCLC and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression.

Continuation maintenance therapy using bevacizumab/pemetrexed is also an option in patients with non-squamous NSCLC and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression; this is a category 2A recommendation. Data from the recent POINTBREAK study reported 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.⁵⁷⁸ 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 AVAPERL study showed a 3.7-month increase in PFS (7.4 vs. 3.7 months); the initial regimen was bevacizumab/cisplatin/pemetrexed.^{665,666}

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 was reported to increase PFS to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).^{667,668} Another phase 3 randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.⁶⁶⁹ The data showed a slight difference in PFS but no difference in overall survival. The NCCN Guidelines recommend



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using gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients without ALK or ROS1 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.⁵⁷⁶ 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.^{576,670} 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).^{670,671}

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.^{576,672} Therefore, switch maintenance therapy is a category 2B recommendation in the NCCN Guidelines; for squamous cell NSCLC, all maintenance therapy is a category 2B recommendation. Two phase 3 randomized trials reported a benefit in PFS and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4–6 cycles) in patients with non-squamous NSCLC and no apparent disease progression.^{673,674} Switch maintenance therapy with pemetrexed is recommended (category 2B) in patients with non-squamous cell carcinoma and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression.⁶⁷⁴ The FDA has approved maintenance therapy with pemetrexed.⁶⁷⁵

Likewise, switch maintenance therapy with erlotinib is recommended (category 2B) in patients with non-squamous NSCLC with negative or unknown test results.^{668,673} Recently, 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.^{667,676} 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.⁶⁷⁷ A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.⁶⁷⁸ 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 recommended for asymptomatic select patients who are at high risk for lung cancer (see the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org). For the 2017 update (Version 1), the NCCN Panel added a new algorithm for incidental lung nodules that are detected on CT scans; the workup and evaluation of these incidental lung nodules is described in the NSCLC algorithm (see *Diagnostic Evaluation of Lung Nodules* in this Discussion and the NCCN Guidelines for NSCLC).

After patients are confirmed to have NSCLC based on a pathologic diagnosis, a clinical evaluation needs to be done (see the NCCN Guidelines for NSCLC). 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



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NSCLC). The NCCN Panel also recommends that smoking cessation advice, counseling, and pharmacotherapy be provided to patients.^{29,679-681} 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, to determine whether the N1, N2, or N3 nodes are positive for cancer, which is a key determinant 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).⁶⁸²⁻⁶⁸⁵ 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.⁶⁸⁶ Mediastinal evaluation can be considered in patients with clinical stage 1A disease (T1ab, N0). 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 NSCLC).

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.⁶⁸⁷ 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.⁶⁸⁸

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.⁶⁸³ PET



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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.^{682,689,690} However, FDG PET/CT is even more sensitive and is recommended by NCCN.^{691–693} PET/CT is typically done from the skull base to the knees; whole body PET/CT may also be done.

The NCCN Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.⁶⁹⁴ Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.⁶⁹⁵ 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.⁶⁹⁶ 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%.⁶⁹⁷ Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.⁶⁹⁸ 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.^{699,700}

When patients with early-stage disease are accurately staged using FDG PET/CT, inappropriate surgery is avoided.⁶⁹¹ 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.^{682,701} 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.^{702–705} 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.⁷⁰⁶ In patients with positive nodes on CT or PET, EBUS-TBNA can be used to clarify the results.^{707,708} However, in patients with negative findings on EBUS-TBNA, conventional mediastinoscopy can be done to confirm the results.^{703,708–710} 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.⁷¹¹ Patients with stage IB NSCLC are less likely to have brain metastases; therefore, brain MRI is optional in this setting and can be considered for select patients at high risk (eg, tumors greater than 5 cm, central location). 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 whether brain metastases are present (see the NCCN Guidelines for Central Nervous System Cancers, available at NCCN.org).

Initial Therapy

As previously mentioned, accurate pathologic assessment and staging are essential before treatment for NSCLC, because management varies depending on the stage, histology, presence of genetic alterations, and PS. 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 NSCLC).

Principles of Radiation Therapy recommends doses for RT (see the NCCN Guidelines for NSCLC). 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 NSCLC). Targeted therapy is recommended for patients with metastatic NSCLC and positive test results for ALK or ROS1 rearrangements, or sensitizing EGFR mutations.

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; RT 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 NSCLC).^{279,296,299,365,371,712} 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.²⁸⁷ For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).

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 NSCLC). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.^{287,388,390,713-716} The overall 5-year survival rate is approximately 40%.³⁹⁰ Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical re-evaluation (including CT ± PET/CT). For patients with unresectable tumors (T4 extension, N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended. Two additional cycles of full-dose chemotherapy can be given if full-dose chemotherapy was not given concurrently with RT.^{560,717}

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.^{305,524} If full-dose chemotherapy was not given as concurrent treatment, then an additional 2 cycles of full-dose



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chemotherapy can be administered (see *Adjuvant Treatment* in the NCCN Guidelines for NSCLC).^{305,391,524,560}

Multimodality therapy is recommended for most patients with stage III NSCLC.⁵⁵⁶ 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 NSCLC). 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 NSCLC). For patients with (T1–3) 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 NSCLC).^{364,525} Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread (see the NCCN Guidelines for NSCLC).

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).⁷¹⁸ 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%.⁷¹⁹ 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.⁷²⁰ 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 NSCLC). 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 NSCLC).⁷²¹

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 NSCLC).^{722,723} 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.^{61,287,724,725} Therefore, it is essential to determine the histology of the lung tumor (see *Principles of Pathologic Review* in the NCCN Guidelines for NSCLC). Infection and other benign diseases also need to be ruled out (eg, inflammatory granulomas).^{726,727} Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.⁷²⁷⁻⁷³⁰ The Martini and Melamed criteria are often used to diagnose multiple lung cancers as follows: 1) the histologies are different; or 2) the histologies are the same but there is no lymph node involvement and no extrathoracic metastases.⁷³⁰



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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 or low risk of becoming symptomatic (see *Initial Treatment* in the NCCN Guidelines for NSCLC).^{724,731-733} Patients should be evaluated in a multidisciplinary setting (eg, surgeons, radiation oncologists, medical oncologists). In patients eligible for definitive local therapy, parenchymal-sparing resection is preferred (see the *Principles of Surgical Therapy* in the NCCN Guidelines for NSCLC).^{723,724} VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.⁷³⁴ Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on CT scans; some of these nodules can be followed with imaging, whereas others need to be biopsied or excised (see the *Diagnostic Evaluation of Incidental Lung Nodules* in this Discussion and the NCCN Guidelines for Lung Cancer Screening, available at NCCN.org).⁷³⁵

Stage IIIB Disease

Stage IIIB tumors comprise 2 unresectable groups, including: 1) T1–3, N3 tumors; and 2) T4, N2–3 tumors, which 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 NSCLC).^{736,737} 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 imaging tests are negative, then treatment options for the appropriate nodal status should be followed (see the NCCN Guidelines for NSCLC). If N3 disease is confirmed, definitive concurrent chemoradiation (category 1) is recommended; 2 additional cycles of full-dose chemotherapy can be given if full-dose chemotherapy was not given concurrently with RT.^{305,524,560,738,739} For

metastatic disease that is confirmed by FDG PET/CT scan and brain MRI (with contrast), treatment is described in the NCCN Guidelines for limited or metastatic disease.

For patients with T4, N2–3 disease (stage IIIB), surgical resection is not 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 NSCLC). 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 NSCLC).^{305,524,560,738-740}

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 NSCLC).⁶²⁰ In addition, palliative treatment, including RT, may be needed during the disease course to treat localized symptoms, diffuse brain metastases, or bone metastases (see *Therapy for Recurrence and Metastases* in the NCCN Guidelines for NSCLC). 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 NSCLC). 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 NSCLC).¹¹⁷ 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 for malignancy (M0), recommended treatment is based on the confirmed T and N stage (see the NCCN Guidelines for NSCLC). However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.⁷⁴¹ 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 NSCLC).⁷⁴²

Management of patients with distant metastasis in limited sites (ie, stage IV, M1b) and good PS depends on the location and number of the metastases; the diagnosis 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 futile 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, brain metastases) and otherwise limited disease in the chest may benefit from aggressive local therapy to both the primary chest and metastatic sites.^{743,744} For the 2017 update (Version 1), the NCCN Panel revised the recommendations for treatment of limited brain metastases by decreasing recommendations for whole brain RT (see *Whole Brain RT*

and *Stereotactic Radiosurgery* in this Discussion text). Clinicians are not using whole brain RT as often in patients with limited brain metastases because of concerns about neurocognitive problems.⁴⁸⁶ Aggressive local therapy may comprise surgery and/or definitive RT including SRS and SABR, and may be preceded or followed by chemotherapy. After progression on TKIs, patients with EGFR mutations may be able to continue with their current TKIs; local therapy can be considered to treat their limited metastases (eg, SRS to brain metastases or other sites, SABR for thoracic disease).^{745,746}

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 NSCLC).⁷⁴⁷⁻⁷⁵⁰ 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-T2ab, N0 tumors and with negative surgical margins (R0). Adjuvant chemotherapy is a category 2A recommendation for patients with T2ab, N0 tumors and negative surgical margins who have



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high-risk features (including poorly differentiated tumors, vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and unknown lymph node sampling [Nx]) (see *Adjuvant Treatment* in the NCCN Guidelines for NSCLC).^{548,751} 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).^{354,548}

The NCCN Panel recommends chemotherapy (category 1) for patients with negative surgical margins and stage II disease, including 1) T1ab–T2a, N1; 2) T2b, N1; or 3) T3, N0 disease.^{544,752} 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.⁷²⁰

Adjuvant chemotherapy can also be used in patients with stage III NSCLC who have had surgery (see the NCCN Guidelines for NSCLC). 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 NSCLC). Patients with negative margins may be treated with either 1) chemotherapy (category 1); or 2) sequential chemotherapy plus RT (for N2 only).⁵⁴⁴

For stage IIIA superior sulcus tumors (T4 extension, N0–1) that become resectable after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN Guidelines for NSCLC). Surgical reevaluation (including imaging) is done to determine whether the tumor is resectable after treatment. If the lesion remains unresectable after preoperative concurrent chemoradiation, the full course of definitive chemo/RT should be completed; an additional 2 cycles of chemotherapy as an adjuvant treatment can be given 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.⁷²⁰ 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 NSCLC). 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 therapy. 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 NSCLC). 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,⁵¹²⁻⁵¹⁴ the NCCN Panel recommends 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 NSCLC).^{549,566,569} For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel is an option.^{549,753} A number of phase 2 studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.⁷⁵⁴⁻⁷⁵⁶

Three phase 3 trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.^{519,757-759} 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.^{758,759} 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 for 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.⁷⁶⁰ However, there was an apparent survival benefit of postoperative RT in patients with N2 nodal stage diagnosed surgically.³⁸⁵ The analysis of the ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.³⁵⁴ 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.⁷⁶¹ A recent meta-analysis also concluded that postoperative RT improves survival for patients with N2 disease.⁷⁶² 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 NSCLC). A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients mainly with stage III disease.⁷⁵² In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemo/RT.



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Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide.

The ACR Appropriateness Criteria® provide specific recommendations for postoperative adjuvant therapy.^{763,764} 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 NSCLC).

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.⁷²⁰

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 NSCLC).⁵⁵⁹ Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with non-squamous NSCLC.^{562,765,766} When chemoradiation is recommended in the NCCN Guidelines, these regimens may be used for stage II to III disease.^{355,356,524,525,560,563,564}

A recent phase 3 trial (PROCLAIM) assessed concurrent thoracic RT with cisplatin/pemetrexed versus cisplatin/etoposide followed by consolidation chemotherapy in patients with unresectable stage III non-squamous NSCLC.⁵⁵⁷ Both regimens were equivalent in terms of survival, but the cisplatin/pemetrexed regimen was associated with less neutropenia (24.4% vs. 44.5%; $P < .001$) and fewer grade 3 to 4 adverse events (64.0% vs. 76.8%; $P = .001$). For the 2017 update (Version 1), the NCCN Panel deleted the cisplatin/etoposide consolidation regimen based on the PROCLAIM trial. In addition, the NCCN Panel clarified that the cisplatin/pemetrexed and

carboplatin/paclitaxel regimens may be followed by consolidation chemotherapy alone.

Surveillance

Because recurrence is common after treatment for NSCLC, surveillance with H&P and chest CT (with or without contrast) is recommended in the NCCN Guidelines. Data from randomized phase 3 trials are not available to clarify surveillance recommendations; therefore, the most appropriate schedules are controversial.⁷⁶⁷⁻⁷⁷¹ For the 2017 update (Version 1), the surveillance guidelines were revised by polling the NCCN Panel regarding their practice patterns. Details regarding the specific surveillance schedules for patients with no clinical or radiographic evidence of disease after completion of definitive therapy are outlined in the algorithm based on stage (see *Surveillance* in the NCCN Guidelines for NSCLC). A chest CT scan with (or without) contrast and an H&P are recommended for the initial surveillance schedules (2–5 years) followed by an annual low-dose non-contrast-enhanced CT and an H&P.^{769,770,772-775} Patients treated with chemotherapy with (or without) RT who have residual abnormalities may require more frequent imaging.

Data show that low-dose CT screening decreased the mortality from lung cancer;⁵³ low-dose CT may be beneficial for identifying recurrences. FDG PET/CT or brain MRI is not routinely 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.⁷⁷⁶ Information about smoking cessation (eg, advice, counseling, therapy) should be



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provided for patients undergoing surveillance to improve their quality of life.

The NCCN Guidelines include information about the long-term follow-up care of NSCLC survivors (see *Cancer Survivorship Care* in the NCCN Guidelines for NSCLC). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening. An analysis suggests that patients who survive lung cancer have a high symptom burden 1 year after diagnosis and therefore need management after treatment.⁷⁷⁷

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 NSCLC).⁸ 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.⁷⁷⁸

After treatment for the locoregional recurrence, observation or systemic therapy (category 2B for systemic therapy) is recommended if disseminated disease is not evident. However, systemic therapy is recommended for disseminated disease. The type of systemic therapy depends on the histologic type, whether genetic alterations are present that can be treated with targeted therapy, and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC). For the 2017 update (Version 1), the NCCN Panel recommends response assessment after 2 cycles of systemic therapy then after every 2 to 4 cycles of therapy or when clinically indicated;

assessment is done using CT with (or without contrast) of known sites of disease.

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 NSCLC). Palliation of symptoms throughout the disease course can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bone metastasis (bisphosphonate or denosumab therapy can be considered).^{362,779,780} For patients at risk of fracture in weight-bearing bone, orthopedic stabilization and palliative RT are recommended.

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 NSCLC). Similarly, patients with limited-site oligometastatic disease and good PS 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 NSCLC).^{451,452,455,781-785} 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.^{359,462-464,786-789}

Denosumab or intravenous bisphosphonate therapy can be considered in patients with bone metastasis.^{131,790-793} In patients with NSCLC who have bone metastases, data suggest that denosumab increases



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median overall survival when compared with zoledronic acid (9.5 vs. 8 months).^{790,794} 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.^{795,796}

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 NSCLC).⁵⁶⁹ In addition, testing for genetic alterations (ie, driver events) is recommended in 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.⁶²⁰

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 NSCLC). The following targeted agents are recommended (category 2A) for patients with specific genetic alterations: crizotinib (for high-level MET amplification or MET exon 14 skipping mutation); dabrafenib (with or without trametinib) and vemurafenib (for BRAF V600E mutations); and cabozantinib and vandetanib (for RET rearrangements).^{83,88,124-126,147,150-153,157,160,161,171,173,221,610,797-809} The dabrafenib/trametinib regimen is recommended for patients with BRAF V600E mutations based on data from a recent phase II study; patients

had a response rate of 63% (36/57).^{150,803} Grade 3 to 4 adverse events included neutropenia (9%), hyponatremia (7%), and anemia (5%). For the 2017 update (Version 1), the NCCN Panel added a recommendation for vandetanib (category 2A) based on preliminary data from a phase 2 study in 18 patients.⁷⁹⁸ Partial remission (17%) was reported in 3 patients; stable disease (44%) was reported in another 8 patients. Six (33%) patients died within 3 months of enrollment of the study due to rapid tumor progression. The recommendation for cabozantinib for RET rearrangements is based on data from a phase II study.^{125,802} 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.^{161,805} Targeted therapies—such as ceritinib, alectinib, brigatinib, osimertinib—are recommended as subsequent therapies for patients whose disease becomes resistant to first-line targeted therapies; other targeted therapies are being investigated for resistance.²³⁶

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 NSCLC).^{86,169,188,203,810} Testing for ALK rearrangements (category 1) is also recommended in patients with non-squamous NSCLC, because crizotinib is recommended (category 1) for patients who are positive for ALK rearrangements.^{133,811} Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification.^{124,126,160,812} For the 2017 update (Version 1), the NCCN Panel added a recommendation for testing for ROS1 rearrangements (category 2A). Testing for ROS1 has typically been



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done using FISH; however, a validated NGS platform that can detect this gene fusion may also be used.²⁵⁹ 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.¹⁴⁷⁻¹⁴⁹ For the 2017 update (Version 1), the NCCN Panel also added a recommendation for upfront PD-L1 expression testing before first-line therapy in patients with metastatic NSCLC to assess whether patients are candidates for immune checkpoint inhibitors (see *Pembrolizumab* in this Discussion).

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.⁶¹ Patients with pure squamous cell carcinoma do not seem to have ALK rearrangements, ROS1 rearrangements, or sensitizing EGFR mutations; therefore, routine testing is not recommended in these patients.^{134,813-815} However, testing for ALK rearrangements, ROS1 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.¹³⁴ Treatment recommendations and eligibility criteria for patients with non-squamous NSCLC (or NSCLC NOS) who are negative or unknown for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression 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 NSCLC); however, targeted therapy is sometimes added to the 2-drug regimen (eg, the addition of bevacizumab to carboplatin/paclitaxel). Single-agent targeted therapy is recommended for patients with ALK or ROS1 rearrangements, sensitizing EGFR mutations, or other driver mutations (see *Emerging Targeted Agents for Patients With Genetic Alterations* in the NCCN Guidelines for NSCLC). Pembrolizumab is now recommended as first-line therapy for patients with PD-L1 expression of 50% or more.

Doublet chemotherapy regimens, such as cisplatin/pemetrexed, are recommended (category 1) for patients with non-squamous NSCLC who are negative or unknown for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression (also known as wild-type) (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC, the NCCN Drugs & Biologics Compendium [NCCN Compendium®] for NSCLC, and the NCCN Evidence Blocks™ for NSCLC).⁵⁶⁹ For the 2017 update (Version 1), the NCCN Panel revised the lists of recommended doublet and single-agent systemic therapy regimens for patients with non-squamous NSCLC or NSCLC NOS who are negative or unknown for mutations, rearrangements, or PD-L1 expression by deleting regimens that are rarely used in the United States. Deleted regimens include carboplatin/vinorelbine, cisplatin/vinorelbine, etoposide, irinotecan, and vinorelbine.

Bevacizumab/chemotherapy is another option for patients with non-squamous NSCLC who are negative or unknown for mutations, rearrangements, or PD-L1 expression if eligibility criteria are met.⁸¹⁶ 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.⁸¹⁷ For the 2017 update (Version 1), the NCCN Panel deleted the bevacizumab/cisplatin/pemetrexed regimen because it is rarely used. 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 NSCLC, the NCCN Compendium® for NSCLC, and the NCCN Evidence Blocks™ for NSCLC).^{620,818} 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).⁸¹⁹ Systemic therapy for elderly patients with advanced NSCLC needs to be carefully selected to avoid adverse reactions.⁸²⁰

Cisplatin/gemcitabine (category 1) is a recommended doublet option for patients with squamous cell carcinoma.⁵⁶⁹ Carboplatin/paclitaxel, carboplatin/gemcitabine (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 NSCLC, the NCCN Compendium® for NSCLC, and the NCCN Evidence Blocks™ for NSCLC). For the 2017 update (Version 1), the NCCN Panel revised the lists of recommended doublet systemic therapy regimens for patients with squamous cell NSCLC who are negative or unknown for mutations, rearrangements, or PD-L1 expression by deleting regimens that are rarely used. Deleted regimens include carboplatin/etoposide, carboplatin/vinorelbine, cisplatin/vinorelbine, cisplatin/gemcitabine/necitumumab, etoposide, irinotecan, and vinorelbine. 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.^{6,83,149,821,822}

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.^{573,823} 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.⁵⁷³ 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.⁵⁷³ 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).⁸¹⁶ However, a trial (AVAIL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.^{824,825}

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.⁵⁶⁹ 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.⁸²⁶

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 NSCLC).^{549,566-569,592,593,601} Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.^{595-598,827}

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 NSCLC). Patients with responsive or

stable disease can continue to receive a total of 4 to 6 cycles of systemic therapy.^{529,671,828} 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;⁶⁶³ 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.⁵⁷⁶ 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.⁸²⁹ 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.^{670,671} In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.⁶⁷¹

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.⁵⁷⁶ 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.^{661,671}

Maintenance Therapy

For patients with non-squamous NSCLC and negative or unknown test results for ALK or ROS1 rearrangements, sensitizing EGFR mutations, or PD-L1 expression, maintenance therapy is another option for those



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with responsive or stable disease after first-line systemic therapy (see the NCCN Guidelines for NSCLC). Continuation maintenance therapy includes bevacizumab (category 1), pemetrexed (category 1), bevacizumab/pemetrexed, or gemcitabine (category 2B) (see the NCCN Guidelines for NSCLC).^{573,578,637,663,665,667,668} Switch maintenance therapy for these patients includes pemetrexed (category 2B).^{667,668,673,674}

For the 2017 update (Version 2), the NCCN Panel deleted the recommendation for erlotinib as switch maintenance therapy (and as subsequent therapy) for patients with non-squamous NSCLC and PS 0-2 but without EGFR mutations based on preliminary results from a randomized trial (IUNO) and revised indication by the FDA. The data showed that overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo. 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.⁶⁷⁴ 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 NSCLC).^{668,673} 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).^{667,668} 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.⁶⁷⁸ 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.⁸³⁰

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 re-approved by the FDA based on a phase 4 study and is now available in the United States.¹³⁰ 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).⁸³¹ 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.⁸³²

After development of acquired resistance in patients with lung adenocarcinoma and sensitizing *EGFR* mutations, erlotinib, gefitinib, or afatinib may be continued, but osimertinib is also an option for select patients; local therapy should be considered (eg, SRS to brain metastases or other sites, SABR for thoracic disease).^{481,745,746,833} The NCCN Panel recommends continuing erlotinib, gefitinib, or afatinib and



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considering local therapy 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 NSCLC).^{806,834,835} For the 2017 update (Version 1), the NCCN Panel revised the recommendations for patients with sensitizing *EGFR* mutations who have progressed on erlotinib, gefitinib, or afatinib. Osimertinib is now recommended (category 1) for patients with symptomatic brain metastases.¹⁸⁹ Another option is to continue use of erlotinib, gefitinib, or afatinib for these patients; however, additional therapy may be added or substituted (eg, local therapy, systemic therapy). First-line systemic therapy options are recommended for patients with multiple symptomatic lesions who are negative for T790M; osimertinib is recommended (category 1) for patients positive for T790M.

Accumulating data suggest how cancers become resistant to EGFR inhibitors.⁸³⁶ The most common known mechanism is the acquisition of T790M (which is a secondary mutation in EGFR), that renders the kinase resistant to erlotinib, gefitinib, or afatinib.^{837,838} Therefore, if patients are T790M positive, osimertinib is recommended (category 1) and erlotinib, gefitinib, or afatinib are discontinued. 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.^{831,839} Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.⁸³³

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 NSCLC).⁸⁴⁰⁻⁸⁴⁹ For the 2017 update (Version 1), the NCCN Panel recommends response assessment of known sites of disease with CT (with contrast) every 6 to 12 weeks in patients receiving subsequent therapy. Note that traditional RECIST response criteria (1.1) are used to assess response for most types of systemic therapy but different response criteria may be useful for assessing response in patients receiving immunotherapy.⁸⁵⁰⁻⁸⁵²

The NCCN Panel recommends immune checkpoint inhibitors, as 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*, *Pembrolizumab*, and *Atezolizumab* in this Discussion).^{269,272,658} Human immune-checkpoint-inhibitor antibodies inhibit the PD-1 receptor or PD-L1, which improves antitumor immunity; PD-1 receptors are expressed on activated cytotoxic T-cells.²⁶⁹⁻²⁷¹ The NCCN Panel recommends nivolumab (category 1) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC based on a phase 3 randomized trial (CheckMate-057) and FDA approval.²⁶⁹ The NCCN Panel recommends pembrolizumab (category 1) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC and PD-L1 expression based on a recent phase 2/3 randomized trial (KEYNOTE-010) trial, KEYNOTE-001

trial, and FDA approval.^{641,651} The NCCN Panel also recommends atezolizumab (category 1) as subsequent therapy for patients with metastatic non-squamous or squamous NSCLC based on a phase 3 randomized trial (OAK), data from a phase 2 trial (POPLAR), and recent FDA approval.^{274,657,658}

The NCCN Panel recommends osimertinib (category 1) as subsequent therapy for patients with metastatic EGFR T790M-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).^{189,191} Osimertinib (AZD9291) is an oral TKI that inhibits both EGFR-sensitizing mutations and T790M. Data from a recent phase 3 trial report that osimertinib is associated with a response rate of about 71% and disease control rate of about 93% (95% CI, 90%–96%) in patients who have progressed on sensitizing EGFR TKI therapy; 23% of patients had drug-related grade 3 or higher adverse events with 4 fatal events.^{189,191,625,626} The FDA has approved osimertinib for patients with metastatic EGFR T790M-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 9 to 13 months of erlotinib or gefitinib therapy.¹⁸⁷⁻¹⁸⁹ EGFR T790M 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.^{146,180-186} T790M 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) continuing erlotinib, afatinib, or gefitinib with (or without) local

therapy; 2) osimertinib; or 3) a first-line systemic therapy regimen for either non-squamous or squamous cell NSCLC (such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively). For the 2017 update (Version 4), the NCCN Panel now also recommends osimertinib (category 1) for patients with T790M who have brain metastases.^{189,629-631} Data suggest that an afatinib/cetuximab regimen may be useful for patients who have progressed after receiving EGFR TKI therapy and chemotherapy.⁸⁵³ Patients with T790M-positive and T790M-negative tumors had a similar response rate to an afatinib/cetuximab regimen (32% vs. 25%; $P = .341$). The NCCN Panel recommends (category 2A) considering an afatinib/cetuximab regimen for patients who have progressed after receiving EGFR TKIs and chemotherapy based on these data.

Among patients with sensitizing EGFR mutations, no improvement in overall survival has been noted in the phase 3 trials assessing pembrolizumab, nivolumab, or atezolizumab compared to docetaxel, but there were not enough patients with these mutations to determine whether there were statistically significant differences (see next paragraph).^{269,641,658,854} Immunotherapy was not worse than chemotherapy and was better tolerated. In the phase 3 trials for pembrolizumab, nivolumab, or atezolizumab versus docetaxel as subsequent therapy for patients with metastatic NSCLC, subset analyses were done in patients with EGFR mutations to determine the best subsequent therapy.^{269,641,658} The HRs for overall survival do not favor docetaxel over nivolumab (HR, 1.18; CI, 0.69–2.0), pembrolizumab (HR, 0.88; CI, 0.45–1.7), or atezolizumab (HR, 1.24; CI, 0.7–2.2); the CIs for the HRs are wide probably because there were so few patients with EGFR mutations. The HRs for PFS do favor docetaxel for patients with EGFR mutations when compared with either pembrolizumab (HR, 1.79; CI, 0.94–3.42) or nivolumab (HR, 1.46; CI,



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0.90–2.37). But again, the CIs are wide. The evidence is weak for recommending docetaxel, pembrolizumab, nivolumab, or atezolizumab as subsequent therapy for patients with EGFR mutations. Recent data suggest that patients with EGFR mutations or ALK rearrangements have a low response rate to PD-1 or PD-L1 inhibitors when compared with patients without these genetic alterations (response rate, 3.6% vs. 23%, respectively).⁸⁵⁴

For patients with ALK rearrangements who progress during or after first-line targeted therapy, recommended subsequent therapy also depends on whether the progression is asymptomatic or symptomatic and includes: 1) continuing alectinib, crizotinib, or ceritinib with (or without) local therapy; 2) ceritinib (if not previously given); 3) alectinib (if not previously given); 4) brigatinib; or 5) 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 (both are category 1), respectively.^{131,855} Other chemotherapy options are also recommended for patients with PS 2, such as docetaxel (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for NSCLC).

Most patients with NSCLC do not have ALK rearrangements, ROS1 rearrangements, or sensitizing EGFR mutations. For patients with all histologic subtypes and PS of 0 to 2 but without these genetic alterations who have disease progression during or after first-line therapy, recommended subsequent systemic therapy options include nivolumab (category 1), pembrolizumab (category 1), atezolizumab (category 1), docetaxel with (or without) ramucirumab, or gemcitabine if not already given; pemetrexed is recommended for patients with

non-squamous NSCLC. For the 2017 update (Version 4), the NCCN Panel revised the recommendation for atezolizumab to category 1 (from category 2A) as subsequent therapy. The NCCN Panel recommends immune checkpoint inhibitors—nivolumab, pembrolizumab, and atezolizumab—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, Pembrolizumab, and Atezolizumab* in this Discussion).^{269,272,658}

For the 2017 update (Version 2), the NCCN Panel deleted the recommendation for erlotinib as subsequent therapy (and as switch maintenance therapy) for patients with non-squamous NSCLC and PS 0-2 but without EGFR mutations based on preliminary results from a randomized trial (IUNO) and revised indication by the FDA. The data showed that overall survival and PFS were not improved in patients receiving erlotinib when compared with placebo.

Ramucirumab/docetaxel is an option for all histologic subtypes for subsequent therapy based on a phase 3 randomized trial.⁶⁰⁶ 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.

Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.^{846,847} When compared with docetaxel, pemetrexed has similar median survival but less toxicity.^{848,856} Pemetrexed is recommended in patients with non-squamous NSCLC.⁶⁷⁴ Docetaxel is recommended for patients with wild-type EGFR tumors based on 2 randomized trials comparing



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erlotinib versus docetaxel.^{857,858} In patients with PS of 3 to 4, best supportive care is recommended (see the NCCN Guidelines for NSCLC).^{8,535,536} Patients often have a limited response to subsequent chemotherapy other than immune checkpoint inhibitors, although it may serve a useful palliative role.⁸⁵⁹

Recently, the NCCN Panel deleted erlotinib as an option for subsequent therapy for patients with squamous cell NSCLC based on a study comparing afatinib with erlotinib; this study was statistically significant but not clinically significant.⁶²³ 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.²⁷² In addition, only 7% of patients receiving nivolumab had grade 3 or higher adverse events. Erlotinib and afatinib are not recommended as second-line therapy for squamous cell carcinoma based on a phase 3 randomized trial showing low response rates and because they are less efficacious and safe compared to other available options.⁶²³

If patients with either ALK fusions or sensitizing EGFR mutations progress with symptomatic systemic multiple lesions after therapy with alectinib, crizotinib, ceritinib, erlotinib, gefitinib, or afatinib and/or after ceritinib, alectinib, brigatinib, or osimertinib, then first-line doublet chemotherapy options are recommended for either non-squamous NSCLC or squamous cell carcinoma.⁵⁷³ Erlotinib, gefitinib, or afatinib may be continued in patients with sensitizing EGFR mutations who have progressed after first-line therapy, depending on the type of progression.^{169,806,834,835} Osimertinib is recommended for patients with T790M whose disease becomes resistant to erlotinib, afatinib, or

gefitinib.¹⁹¹ Afatinib/cetuximab may be considered for patients with sensitizing EGFR mutations who have progressed after EGFR TKI therapy and chemotherapy.⁸⁵³ Ceritinib, alectinib, or brigatinib are recommended in patients with ALK-positive NSCLC who have progressed after first-line therapy with crizotinib or for patients who are intolerant to crizotinib.^{129,240,247} Subsequent therapy is recommended after second disease progression in patients with advanced NSCLC and PS 0–2 if these agents have not already been given: 1) immune checkpoint inhibitors including nivolumab, pembrolizumab, and atezolizumab (all are category 2A); 2) docetaxel with or without ramucirumab (category 2B for both); 3) gemcitabine (category 2B); or 4) pemetrexed (non-squamous only) (category 2B).^{841,858,860,861}



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