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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 4.2015

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Non-Small Cell Lung Cancer

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

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

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

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

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. ©2015.



NCCN Guidelines Version 4.2015 Updates Non-Small Cell Lung Cancer

Updates in Version 4.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 3.2015 include:

[DIAG-2](#)

- The cutoffs for pulmonary nodule and solid non-calcified nodules made consistent with the values in the NCCN Guidelines for Lung Cancer Screening.

[NSCL-C \(6 of 9\)](#)

- Table 3 Maximum Dose Constraints for SABR: Dosing for rib in 5 fractions changed to NS (not specified).

[NSCL-F \(1 of 3\)](#)

- First-line therapy, last bullet added: Response assessment after 1-2 cycles, then every 2-4 cycles.

[MS-1](#)

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

Updates in Version 3.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 2.2015 include:

[NSCL-19](#) and [NSCL-20](#)

- The recommendation for ramucirumab + docetaxel changed from a category 2B to a category 2A.

Updates in Version 2.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 1.2015 include:

[NSCL-2](#)

- Stage IIIA (T3, N1) added to the page.

[NSCL-7](#)

- Separate pulmonary nodules changed to include N1. (also applies to NSCL-9).

[NSCL-8](#)

- T1-2, T3 (≥7 cm), N2 nodes positive changed to T1-2, T3 (other than invasive), N2 nodes positive.

[NSCL-12](#)

- Stage IIIB modified: (T4 ~~extension~~, N2–3)



NCCN Guidelines Version 4.2015 Updates

Non-Small Cell Lung Cancer

Updates in Version 1.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2014 include:

DIAG-1

- Footnote “d” added: “The most important radiologic factor is change or stability compared with a previous imaging study.” (also applies to DIAG-2)

DIAG-A 1 of 2

- Bullet 4, sub-bullet 1, third entry modified: “Image-guided transthoracic needle *core biopsy (preferred) or fine-needle aspiration.*”
- Bullet 4, sub-bullet 2, second entry added: “Endoscopic ultrasound (EUS)–guided biopsy.”

DIAG-A 2 of 2

- Bullet 1, sub-bullet 1, then sub-bullet 5, sentence added to second entry: “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.”
- Bullet 1, sub-bullet 1, then sub-bullet 7 added: “Tumor viability at proposed biopsy site from PET imaging.”
- Bullet 1, sub-bullet 2, second sentence modified: “Multidisciplinary evaluation *should also include* ~~may also benefit from involvement of a pulmonologist or thoracic surgeon with expertise~~ ~~experience~~ in advanced bronchoscopic techniques for diagnosis.”; ~~depending on local expertise.~~
- Bullet 1, sub-bullet 3, then sub-bullet 2 modified: “Patients with peripheral (outer one-third) nodules *may benefit from* ~~should have~~ navigational bronchoscopy, radial EBUS, or TTNA.”
- Bullet 1, sub-bullet 3, then sub-bullet 3 modified: “Patients with suspected nodal disease should be biopsied by EBUS, *EUS*, navigational bronchoscopy, or mediastinoscopy.”
- Bullet 1, sub-bullet 3, then sub-bullet 3, first entry modified: “Esophageal ultrasound (EUS)–guided biopsy provides additional access to stations 2L, 4L, 5, 7, 8, and 9 lymph nodes if these are clinically suspicious.”
- Bullet 1, sub-bullet 3, then sub-bullet 4 added: “EUS also provides reliable access to the left adrenal gland.”
- Bullet 1, sub-bullet 3, then sub-bullet 6 modified: “Patients suspected of having a solitary site of metastatic disease should ~~preferably have~~ tissue confirmation of that site if feasible.”

NSCL-1

- Initial evaluation, footnote “b” added: “Enhanced frailty or geriatric assessments may predict complications better following treatment modalities, particularly surgery. A preferred frailty assessment system has not been established.”

NSCL-2

- Footnote “l” added: “Interventional radiology ablation is an option for selected patients.” (also applies to NSCL-15)
- Footnote “m” added: “After surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.”

NSCL-13

- Footnote “aa” added: “Aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease.”

NSCL-14

- Bullet 1: “low-dose” added as a qualifier to annual non-contrast-enhanced chest CT scans starting at year 3.
- Footnote “ff” added: “Patients treated with chemotherapy ± RT who have residual abnormalities may require more frequent imaging.”
- Footnote “gg” added: “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.”



NCCN Guidelines Version 4.2015 Updates

Non-Small Cell Lung Cancer

Updates in Version 1.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2014 include:

NSCL-16

- Footnote “hh” added: “The NCCN NSCLC Guidelines Panel strongly endorses broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. [See Emerging Targeted Agents for Patients with Genetic Alterations \(NSCL-H\).](#)”
- Testing results added for squamous cell carcinoma with links to treatment recommendations.
- Testing results modified: “*Both* sensitizing EGFR mutation and ALK are negative or unknown.”

NSCL-17

- For progressive disease with multiple symptomatic systemic lesions, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- If there is second disease progression after subsequent therapy, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- Footnote “pp” modified: “Prior to changing therapy, a biopsy ~~on progression~~ is reasonable to determine mechanism of acquired resistance.”; ~~because proportion of patients will transform to SCLC at progression.~~

NSCL-18

- Crizotinib changed from a category 2A recommendation to a category 1 recommendation for patients with an ALK rearrangement discovered prior to first-line chemotherapy.
- For progressive disease with multiple symptomatic systemic lesions, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- If there is second disease progression after subsequent therapy, recommendation is for treatment with first-line therapy options as per NSCL-19 or NSCL-20.
- Footnote “ll” added: For performance status 0-4.
- Footnote removed: See third-line therapy (NSCL-21) for progressive disease with multiple symptomatic systemic lesions after treatment with crizotinib, ceritinib, and/or platinum doublet ± bevacizumab.

NSCL-19

- First-line therapy: the combination regimen cetuximab/vinorelbine/cisplatin was deleted. (also applies to NSCL-20)
- Maintenance therapy:
 - ▶ Continuation maintenance with cetuximab removed as a treatment option. (also applies to NSCL-20)
- Subsequent therapy: Ramucirumab + docetaxel added as a treatment option with a category 2B designation. (also applies to NSCL-20)
- Footnote “yy” added: “Chemotherapy preferred in this setting. Grassino M, Martelli O, Broggini M, et al. Erlotinib versus docetaxel as second line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. Lancet Oncol 2013; 14:981-988.” (also applies to NSCL-20)
- Footnote “zz” added: “Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a ‘poor’ classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. Lancet Oncol 2014; 15:713-21.” (also applies to NSCL-20)

NSCL-19

- Footnote “bbb” added: Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation. (also applies to NSCL-20)
- Footnote “ccc” added: If not already given, options for PS 0-2 include erlotinib, docetaxel (category 2B), pemetrexed (category 2B) or gemcitabine (category 2B), options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.



NCCN Guidelines Version 4.2015 Updates

Non-Small Cell Lung Cancer

Updates in Version 1.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2014 include:

[NSCL-20](#)

- Footnote “ddd” added: If not already given, options for PS 0-2 include erlotinib, docetaxel (category 2B), or gemcitabine (category 2B), options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

[NSCL-21](#)

- This page deleted and incorporated into pages NSCL-19 and NSCL-20.

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

• Pathologic Evaluation

- ▶ Bullet 3, first sentence modified: The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung. ~~with squamous morphology, neuroendocrine differentiation, and other variant carcinomas.~~
- ▶ Bullet 4, last sentence modified: Mutational testing (eg, epidermal growth factor receptor [EGFR]) ~~should be performed in this setting is strongly recommended in all NSCLC favor adenocarcinomas.~~
- ▶ Bullet 5 modified: ~~Although Formalin-fixed paraffin-embedded tumor may be used is acceptable for most molecular analyses., acquisition of fresh cryopreserved tumor tissue for advanced molecular studies should be considered.~~
- ▶ Bullet 6, last sentence modified: 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 \(2 of 4\)](#)

• Immunohistochemical Staining

- ▶ Bullet 3, sub-bullet 4 modified: 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.
- ▶ Bullet 5, sub-bullet 1, then sub-bullet 2 modified: Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, *claudin-4* and TTF-1 (negative in mesothelioma).

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

• Molecular Diagnostic Studies in Lung Cancer

- ▶ Bullet 1, sub-bullet 2 modified: “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 TKIs.”
- ▶ Bullet 1, sub-bullet 4 modified: “*Overlapping EGFR and KRAS mutations are mutually exclusive occur in <1% of patients with lung cancer.*”
- ▶ Bullet 1, sub-bullet 5, last sentence added: “*KRAS testing may identify patients who may not benefit from further molecular diagnostic testing.*”
- ▶ Bullet 2, sub-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. ~~A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of *ALK*-rearranged anaplastic large cell lymphomas (ALCL), is applicable for the diagnosis of *ALK*-rearranged lung adenocarcinomas. The IHC tests used to diagnose *ALK*-rearranged ALCLs in clinical laboratories worldwide are inadequate for the detection of most *ALK*-rearranged lung cancer.^{32,33} This inadequacy is because of the lower level of *ALK* expression in *ALK*-rearranged NSCLCs compared with *ALK*-rearranged ALCLs. A molecular diagnostic test that uses FISH was recently approved by the FDA to determine which patients have *ALK*-positive lung cancer. 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.~~



NCCN Guidelines Version 4.2015 Updates

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Updates in Version 1.2015 of the NCCN Guidelines for Non-Small Cell Lung Cancer from Version 4.2014 include:

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

- Resection, Bullet 5 modified: “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.”

[NSCL-C \(3 of 9\)](#)

- Locally advanced stage/conventionally fractionated RT
 - ▶ Bullet 2, sentence 4 modified: “*While* doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected, ~~The final results from preliminary results from~~ RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy ~~are pending, but preliminarily, found that~~ 74 Gy does not improve overall survival, *and therefore is not currently a standard dose.*”

[NSCL-C \(4 of 9\)](#)

Advanced Stage/Palliative RT

- Third sentence added: “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.” Reference 75 also added.

[NSCL-C \(6 of 9\)](#)

- Table 3 Maximum Dose Constraints for SABR: doses modified.

[NSCL-D](#)

- Reference “e” added: Kreuter 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.

[NSCL-F \(1 of 3\)](#)

- First-line therapy
 - ▶ Bullet removed: “Cetuximab + vinorelbine/cisplatin is an option for patients with performance status 0-1 (category 2B).”
 - ▶ Bullet removed: “Single-agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.”
 - ▶ Bullets 3 and 4: “select” removed before “patients.”
 - ▶ Bullet 7, second sentence added: “Single-agent therapy may be appropriate in select patients.”

[NSCL-F \(2 of 3\)](#)

- Maintenance therapy: Bullet removed: “Continuation of cetuximab after 4-6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).”
- “Second-line therapy” changed to “Subsequent therapy.”
- Subsequent therapy: Sub-bullet 3 added: “Ramucirumab + docetaxel improves survival when compared to docetaxel alone.”
- Subsequent therapy: Sub-bullets 5 and 6: “select” removed before “patients.”

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

- Ramucirumab added to systemic therapy options with reference. Cetuximab deleted as a recommendation.

[NSCL-H](#)

- “Emerging” added to the title of the table.
- Category changes for the following regimens:
 - ▶ HER2 mutations: trastuzumab and afatinib changed from a category 2A to a category 2B recommendation.
 - ▶ RET rearrangements: cabozantinib changed from a category 2A to a category 2B recommendation.
- BRAF mutation clarified as BRAF V600E mutation and footnote added: Non-V600E mutations have variable kinase activity and response to these agents.



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Non-Small Cell Lung Cancer

LUNG CANCER PREVENTION AND SCREENING

- Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85% to 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products, and other tobacco control measures.
- Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life, and reduced survival.
- Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk for lung cancer from second-hand smoke exposure associated with living with a smoker (<http://www.ncbi.nlm.nih.gov/books/NBK44324/>). Every person should be informed of the health consequences, addictive nature, and mortal threat posed by tobacco consumption and exposure to tobacco smoke, and effective legislative, executive, administrative, or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke (www.who.int/tobacco/framework/final_text/en/).
- Further complicating this problem, the delivery system of lung carcinogens also contains the highly addictive substance, nicotine. Reduction of lung cancer mortality will require widespread implementation of Agency for Healthcare Research and Quality (AHRQ) Guidelines (www.ahrq.gov/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the [NCCN Guidelines for Lung Cancer Screening](#)).

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

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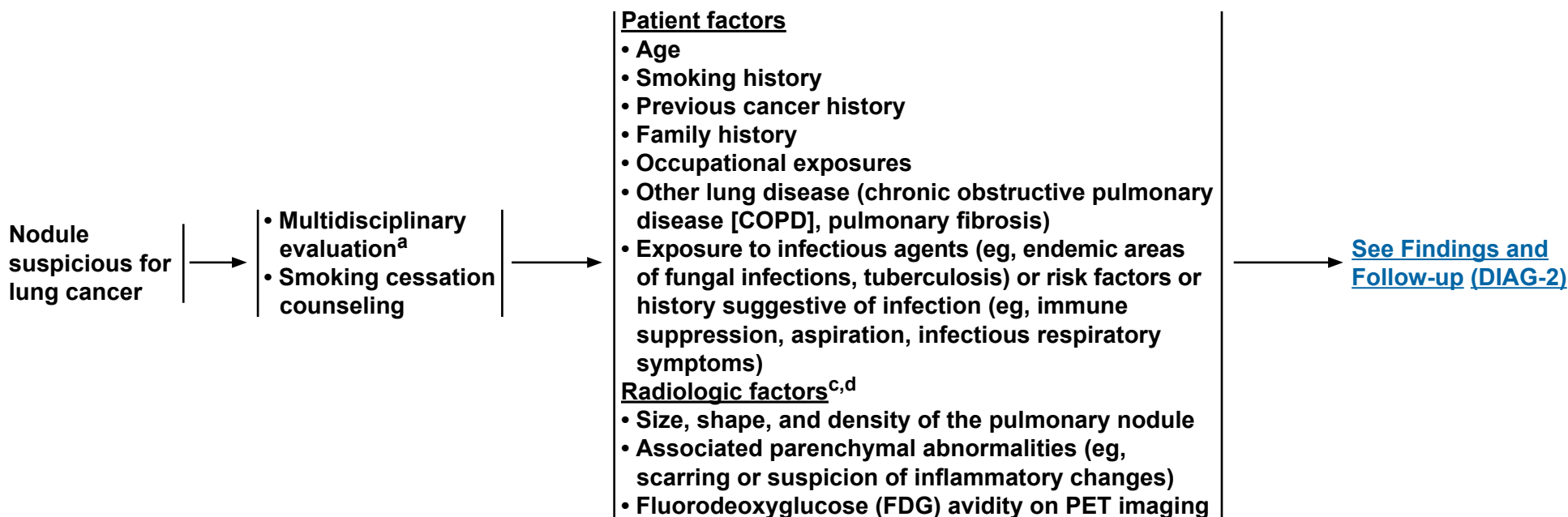


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CLINICAL PRESENTATION

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.

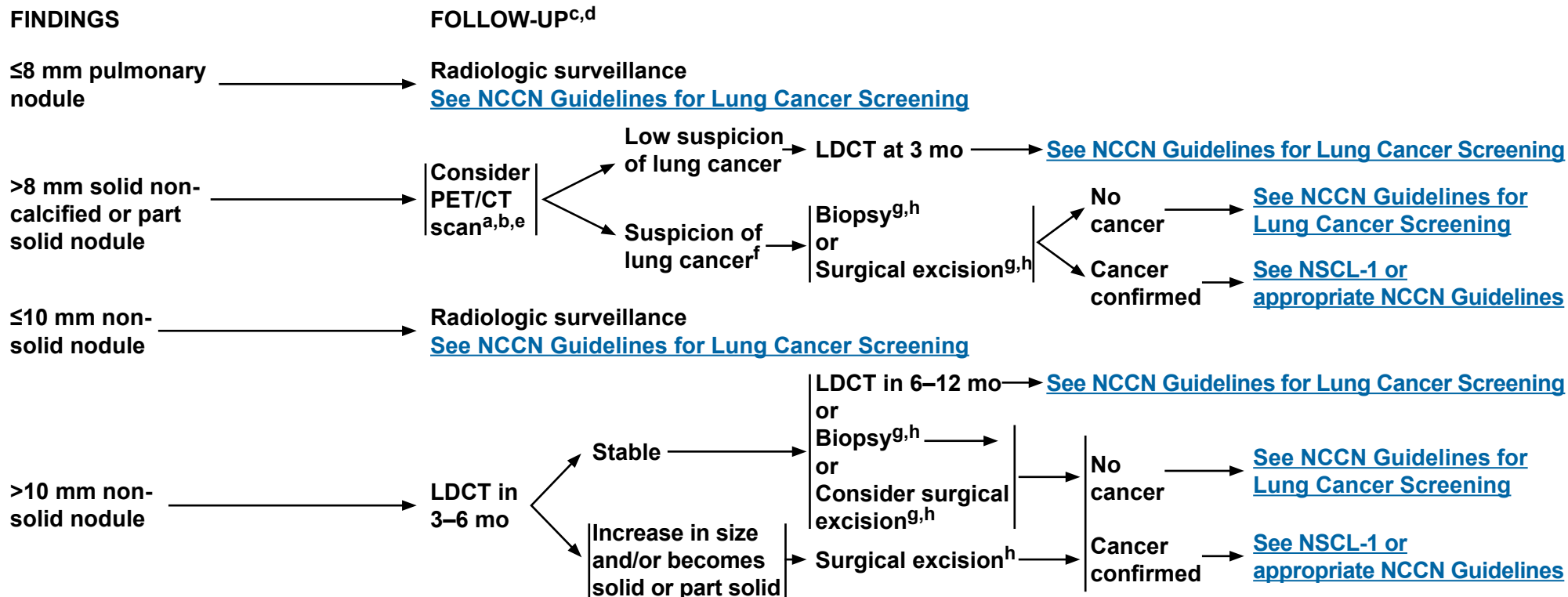
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^c[See Principles of Diagnostic Evaluation \(DIAG-A 1 of 2\).](#)

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

^eA 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).

^fPatients with a suspicion of lung cancer after PET/CT require histologic confirmation before any nonsurgical therapy.

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

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

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

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

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

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



PRINCIPLES OF DIAGNOSTIC EVALUATION

- **The preferred diagnostic strategy for an individual patient depends on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (such as pulmonary pathology and/or other significant comorbidities), and local experience and expertise.**
 - ▶ **Factors to be considered in choosing the optimal diagnostic step include:**
 - ◊ **Anticipated diagnostic yield (sensitivity)**
 - ◊ **Diagnostic accuracy including specificity and particularly the reliability of a negative diagnostic study (ie, true negative)**
 - ◊ **Adequate volume of tissue specimen for diagnosis and molecular testing**
 - ◊ **Invasiveness and risk of procedure**
 - ◊ **Efficiency of evaluation**
 - **Access and timeliness of procedure**
 - **Concomitant staging is beneficial, because it avoids additional biopsies or procedures. It is preferable to biopsy the pathology that would confer the highest stage (ie, to biopsy a suspected metastasis or mediastinal lymph node rather than the pulmonary lesion). Therefore, PET imaging is frequently best performed before a diagnostic biopsy site is chosen in cases of high clinical suspicion for aggressive, advanced stage tumors.**
 - ◊ **Technologies and expertise available**
 - ◊ **Tumor viability at proposed biopsy site from PET imaging.**
 - ▶ **Decisions about the optimal diagnostic steps for suspected stage I to III lung cancer should be made by thoracic radiologists, interventional radiologists, and board-certified thoracic surgeons who devote a significant portion of their practice to thoracic oncology. Multidisciplinary evaluation should also include a pulmonologist or thoracic surgeon with expertise in advanced bronchoscopic techniques for diagnosis.**
 - ▶ **The least invasive biopsy with the highest yield is preferred as the first diagnostic study.**
 - ◊ **Patients with central masses and suspected endobronchial involvement should undergo bronchoscopy.**
 - ◊ **Patients with peripheral (outer one-third) nodules may benefit from navigational bronchoscopy, radial EBUS, or TTNA.**
 - ◊ **Patients with suspected nodal disease should be biopsied by EBUS, EUS, navigational bronchoscopy, or mediastinoscopy.**
 - **Esophageal ultrasound–guided biopsy provides additional access to stations 2L, 4L, 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, 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 metastasis 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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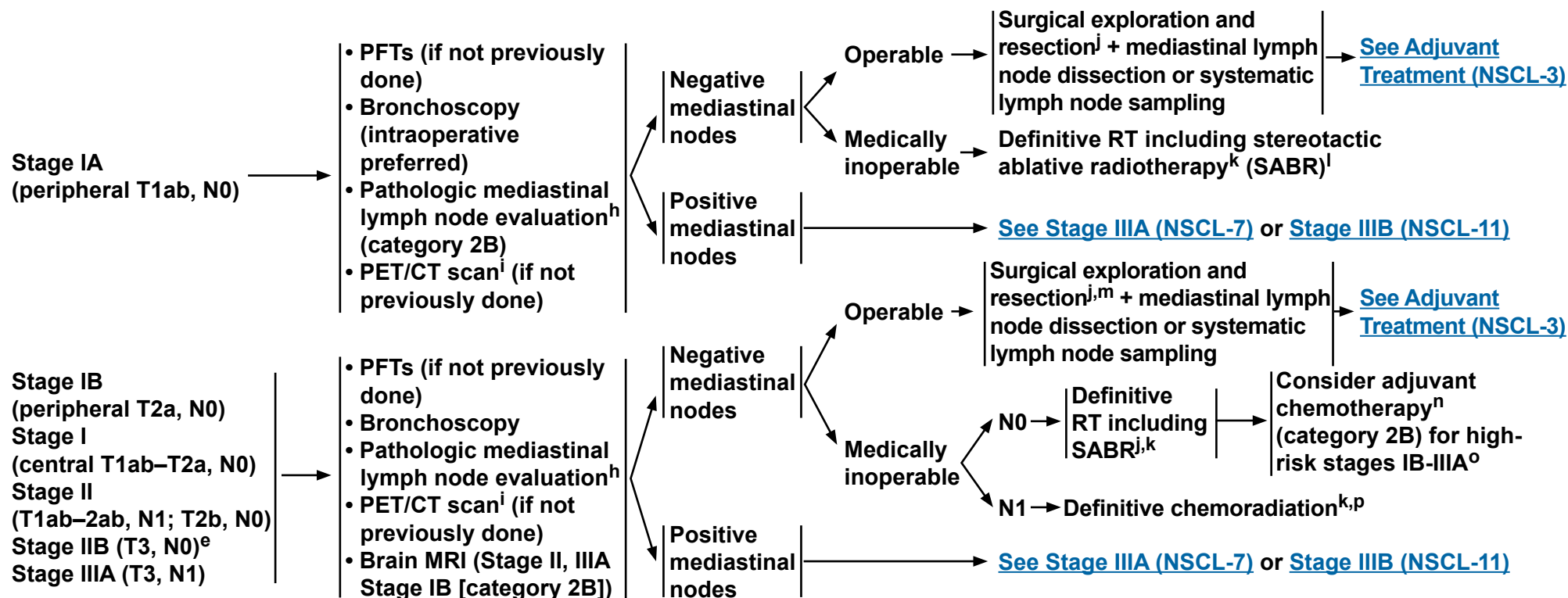
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION^g

INITIAL TREATMENT

^eT3, N0 related to size or satellite nodules.^gTesting is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.^hMethods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.ⁱPositive 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.^jSee Principles of Surgical Therapy (NSCL-B).^kSee Principles of Radiation Therapy (NSCL-C).^lInterventional radiology ablation is an option for selected patients.^mAfter surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.ⁿSee Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).^oExamples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.^pSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

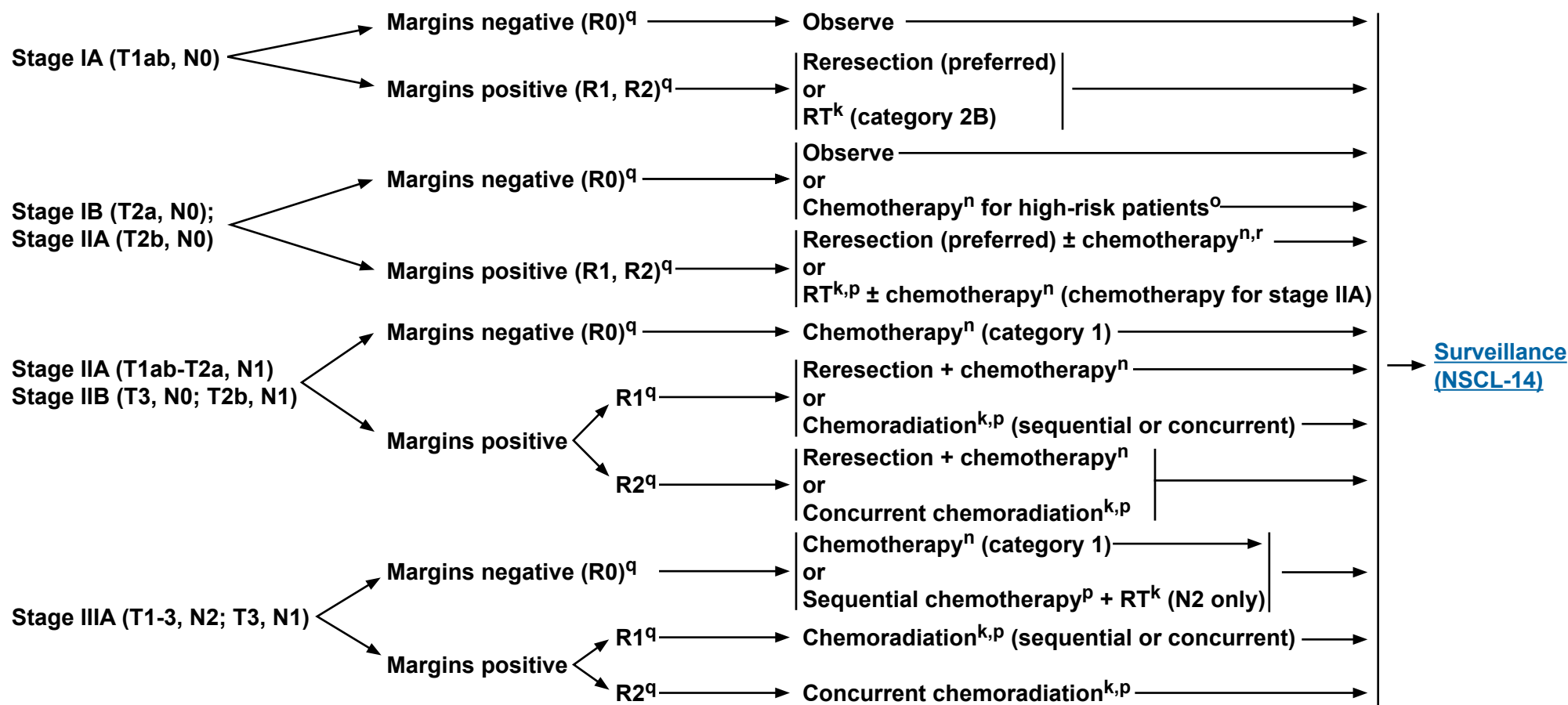


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Non-Small Cell Lung Cancer

FINDINGS AT SURGERY

ADJUVANT TREATMENT



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

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

^oExamples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

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

^qR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^rIncreasing 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
- MRI of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels
- PET/CT scanⁱ (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 \(NSCL-15\)](#)

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

ⁱPositive 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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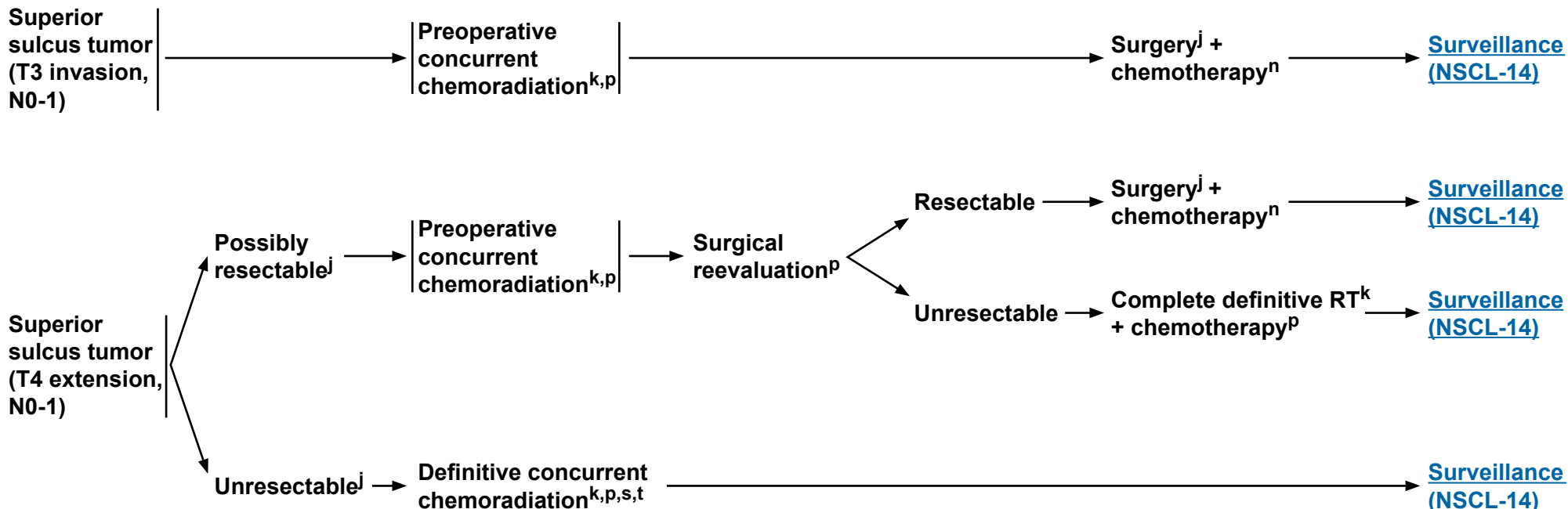
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Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

INITIAL TREATMENT

ADJUVANT TREATMENT



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

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

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

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

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

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

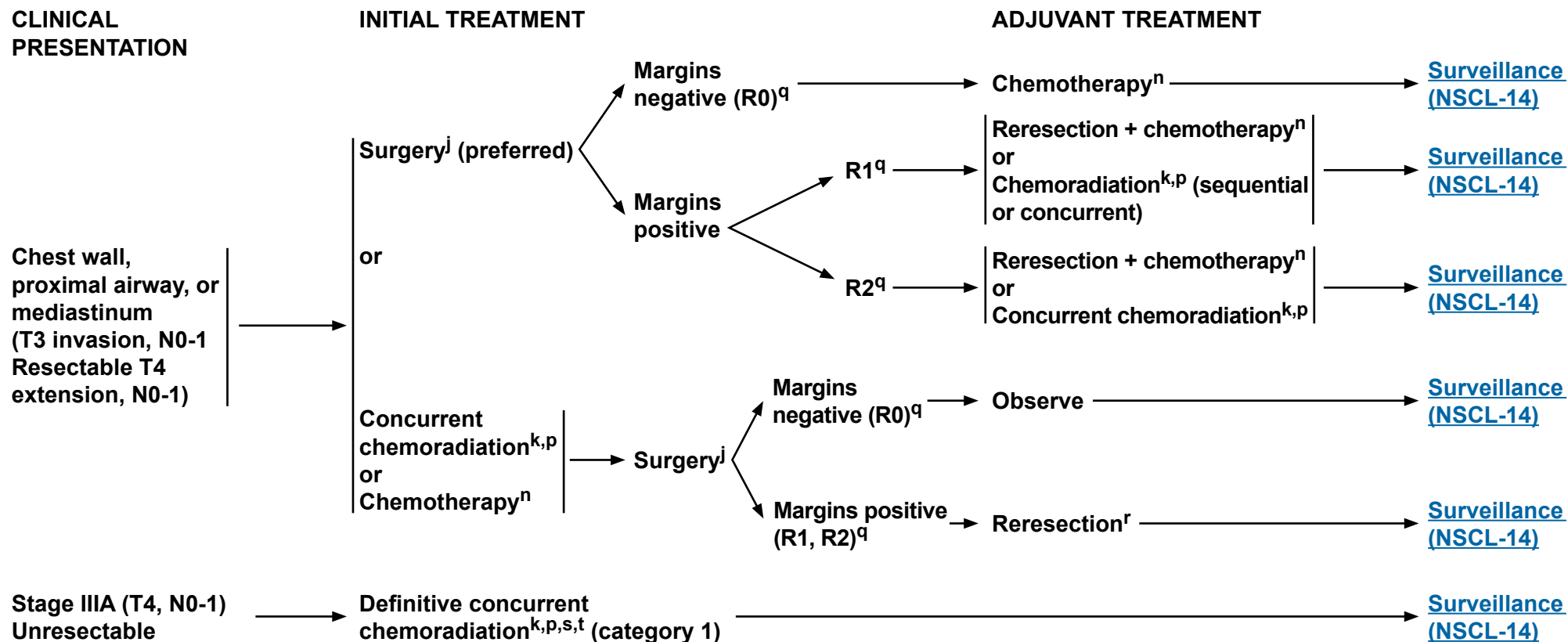
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Non-Small Cell Lung Cancer


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

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

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

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

^qR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

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

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

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

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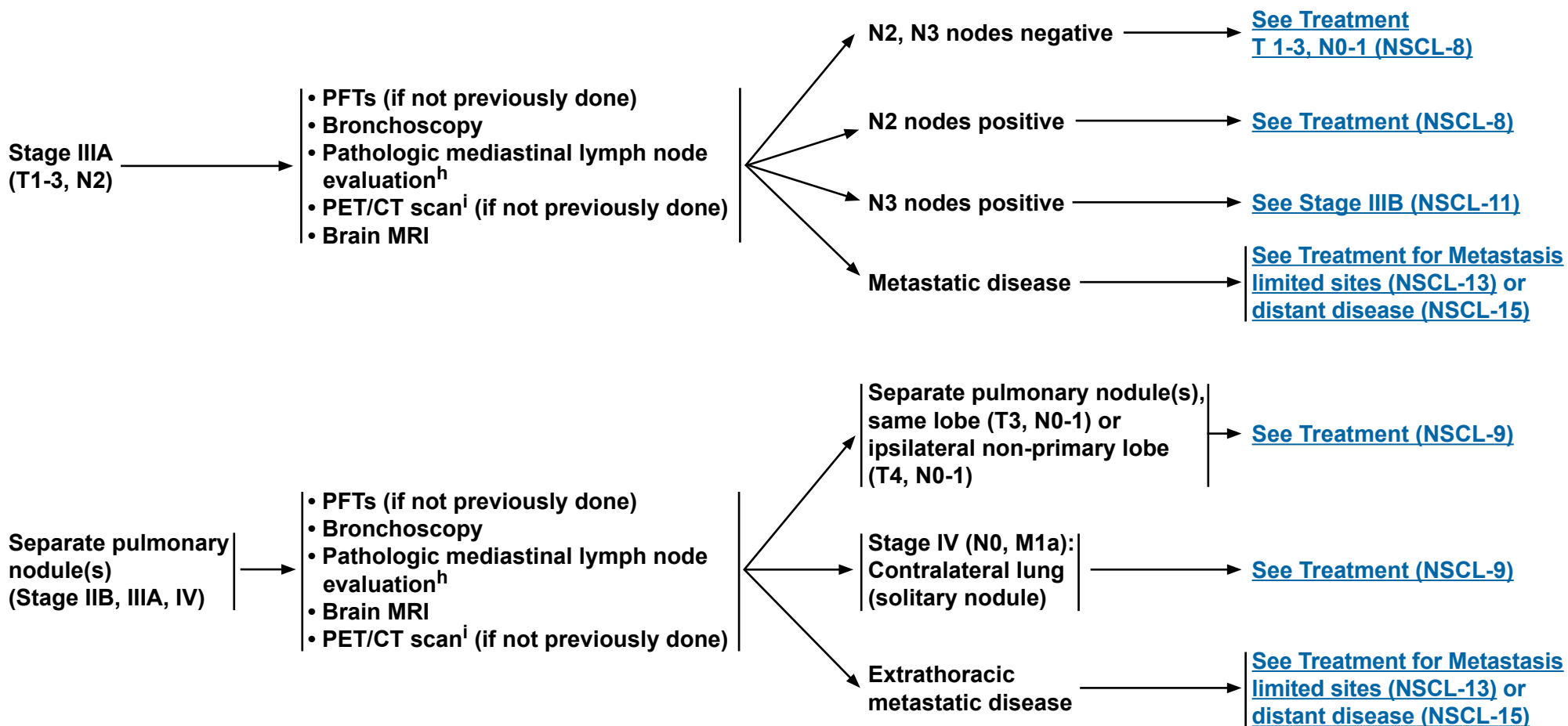
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY



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

ⁱPositive 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.

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

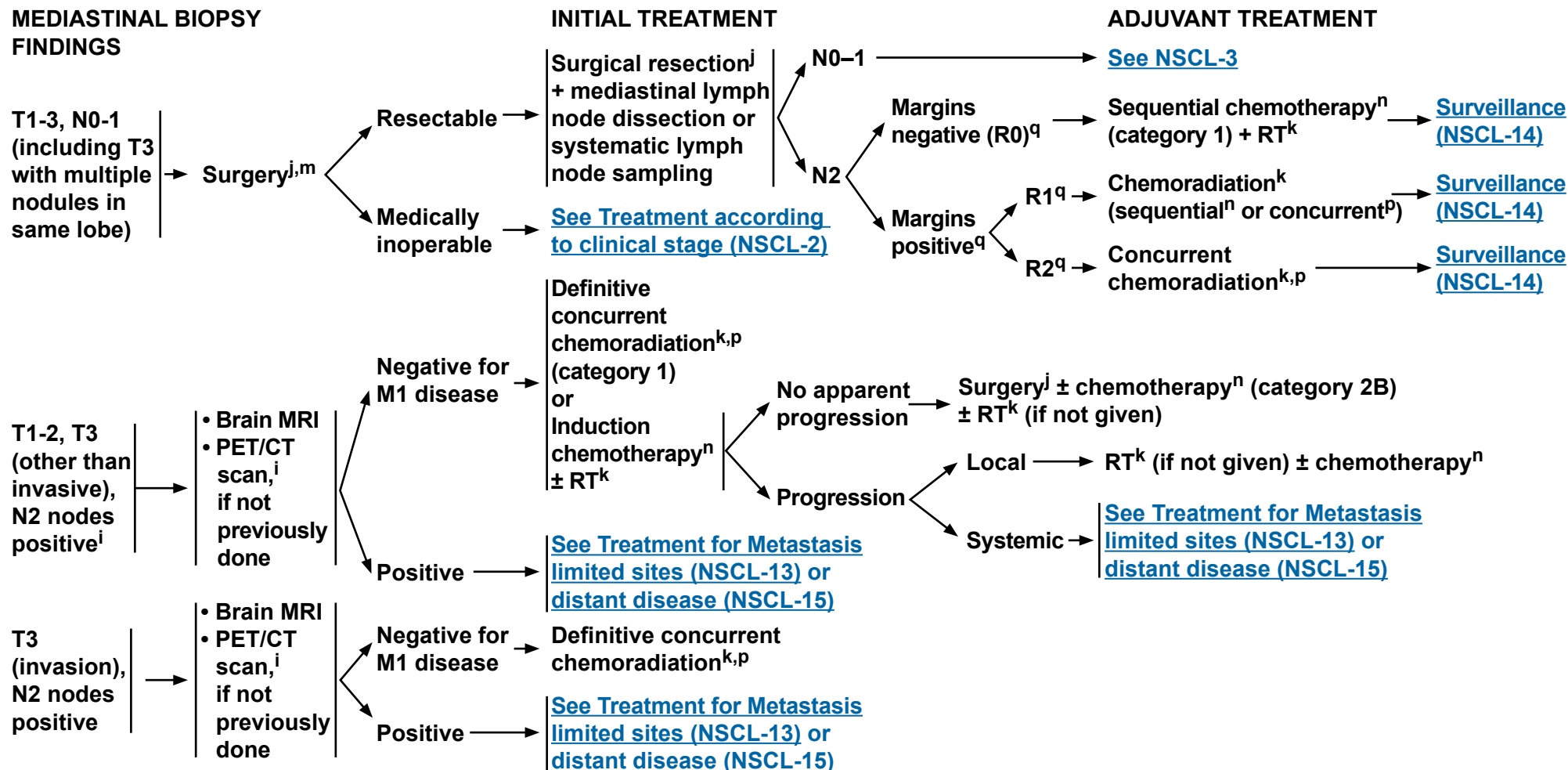
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Non-Small Cell Lung Cancer

MEDIASTINAL BIOPSY FINDINGS



ⁱPositive 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.

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

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

^mAfter surgical evaluation, patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

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

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

^qR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

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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^j

N0-1

Margins negative (R0)^q

N2

Margins positive^q

R1^q

R2^q

ADJUVANT TREATMENT

Chemotherapyⁿ

Sequential chemotherapyⁿ (category 1) + RT^k

Chemoradiation^k (sequentialⁿ or concurrent^p)

Concurrent chemoradiation^{k,p}

[Surveillance \(NSCL-14\)](#)

[Surveillance \(NSCL-14\)](#)

[Surveillance \(NSCL-14\)](#)

[Surveillance \(NSCL-14\)](#)

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)^{v,w}

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

Disease outside of chest

No disease outside of chest

[See Systemic Therapy for Metastatic Disease \(NSCL-16\)](#)

Pathologic mediastinal lymph node evaluation^h

N0-1

N2-3

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

[See Systemic Therapy for Metastatic Disease \(NSCL-16\)](#)

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

ⁱPositive 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.

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

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

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

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

^qR0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

^vLesions 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.

^wFor 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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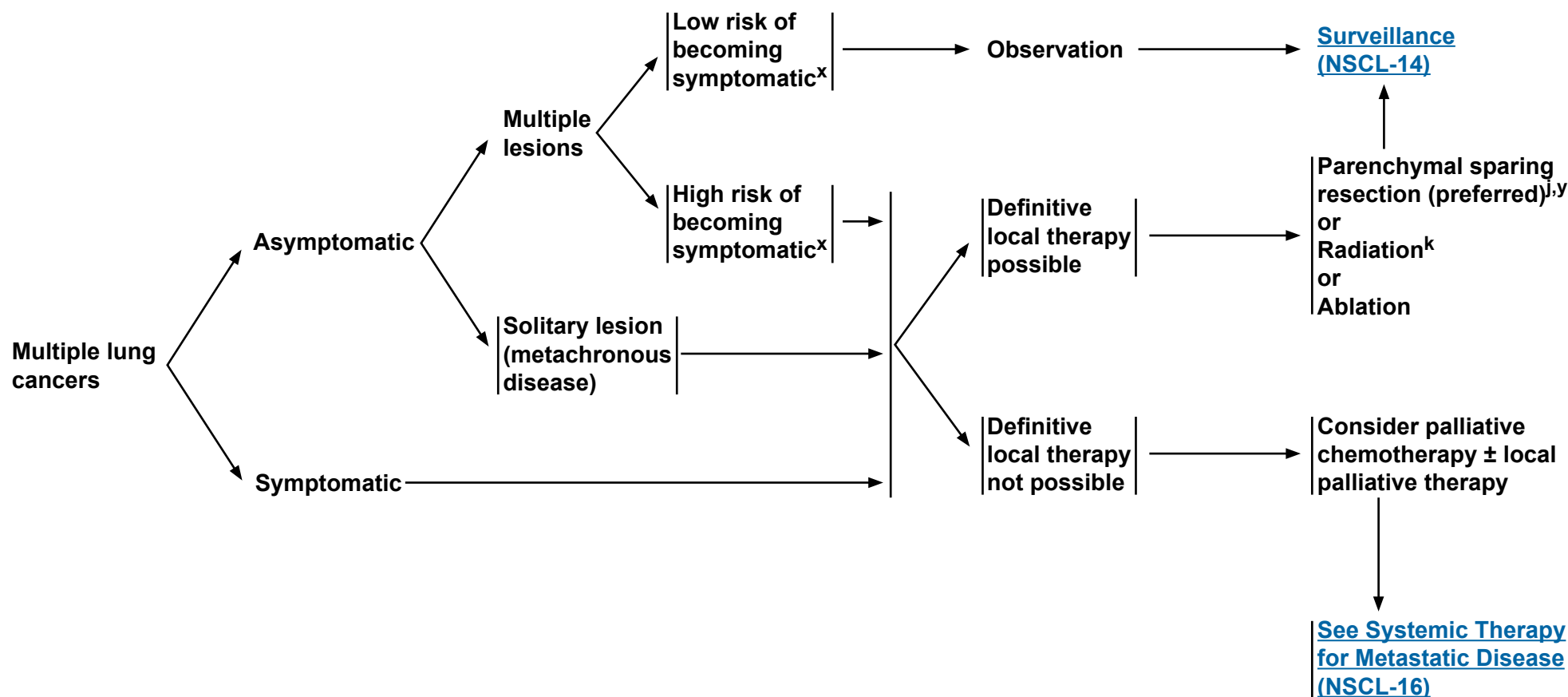


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Non-Small Cell Lung Cancer

CLINICAL PRESENTATION

INITIAL TREATMENT



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

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

^xLesions 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.

^yLung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning.

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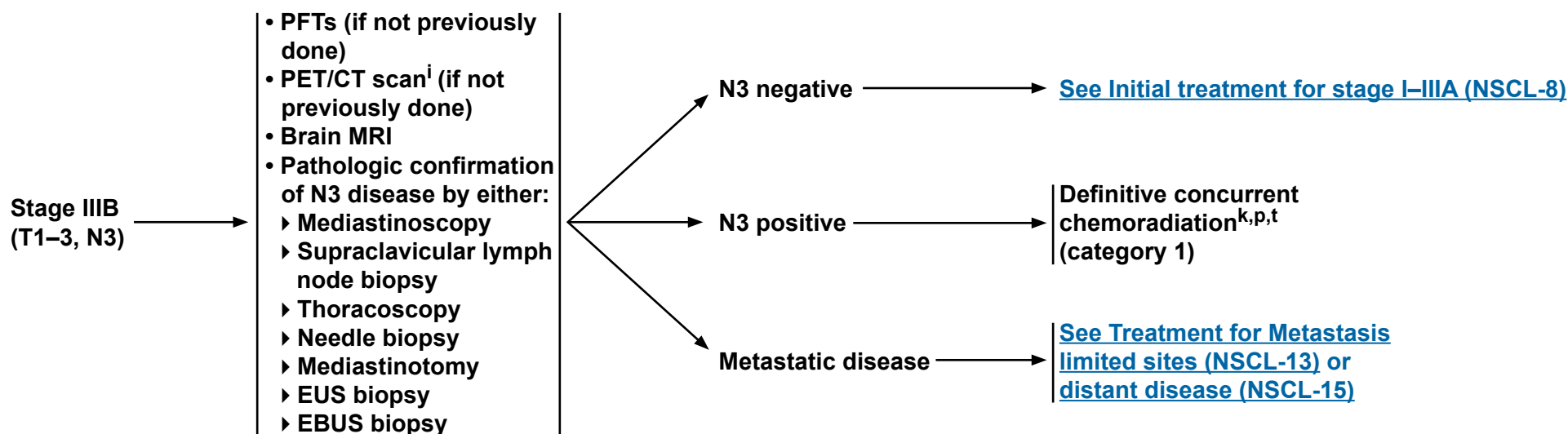
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



ⁱPositive 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.

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

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

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

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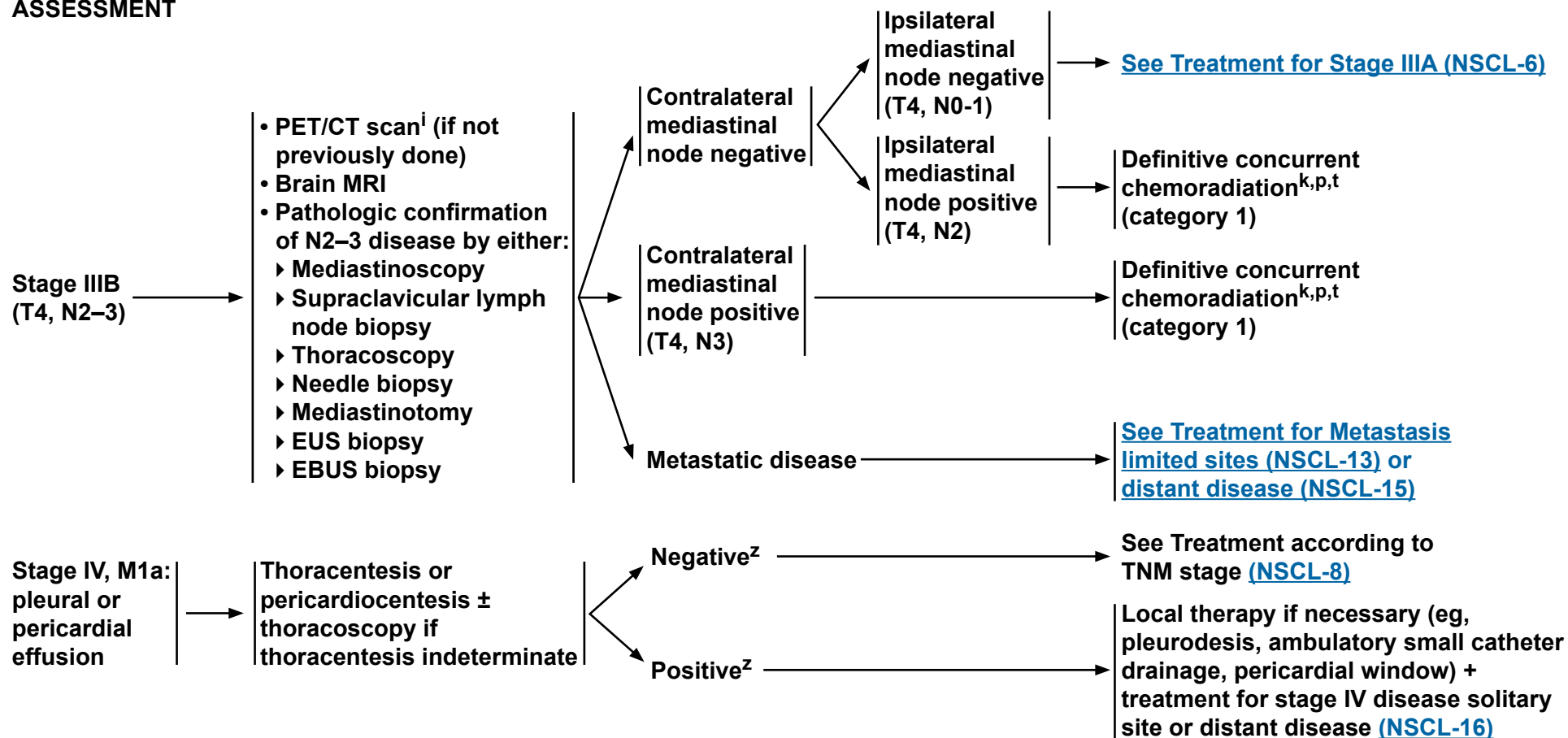
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



ⁱPositive 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 Radiation Therapy \(NSCL-C\).](#)

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

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

^zWhile 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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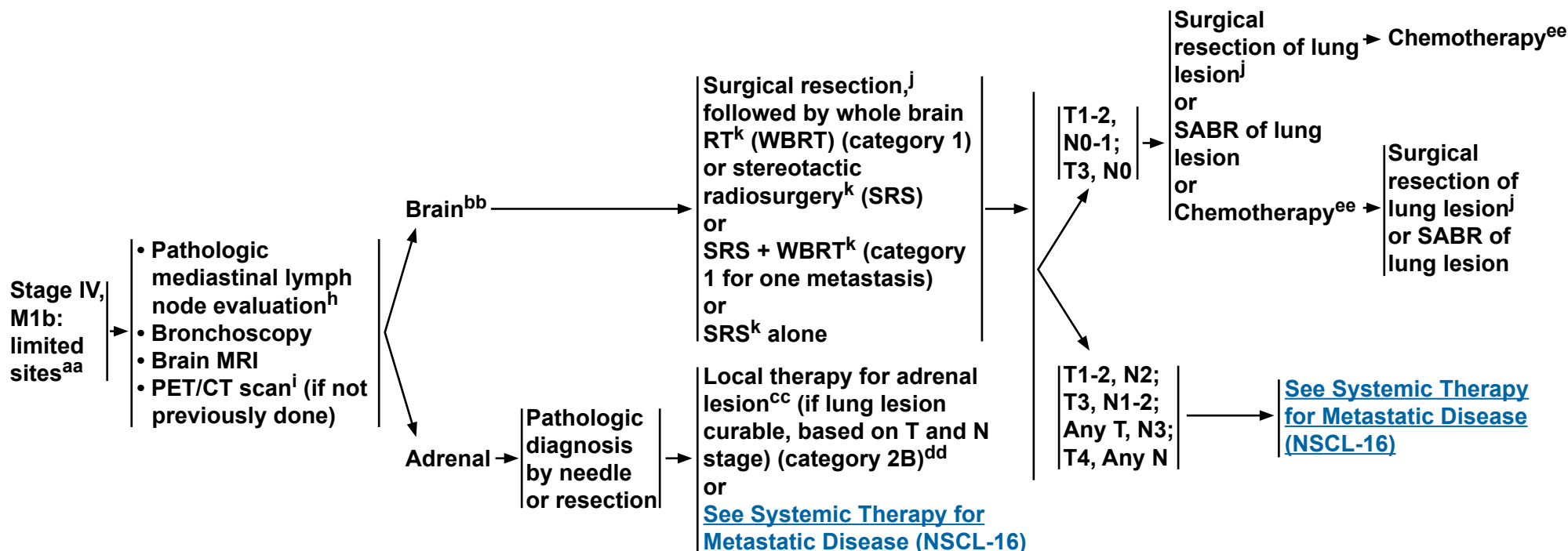
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Non-Small Cell Lung Cancer

CLINICAL ASSESSMENT

PRETREATMENT EVALUATION

INITIAL TREATMENT



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

ⁱPositive 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.

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

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

^{aa}Aggressive local therapy may be appropriate for selected patients with limited-site oligometastatic disease.

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

^{cc}May include adrenalectomy or RT (including SABR).

^{dd}Patients with N2 disease have a poor prognosis and systemic therapy should be considered.

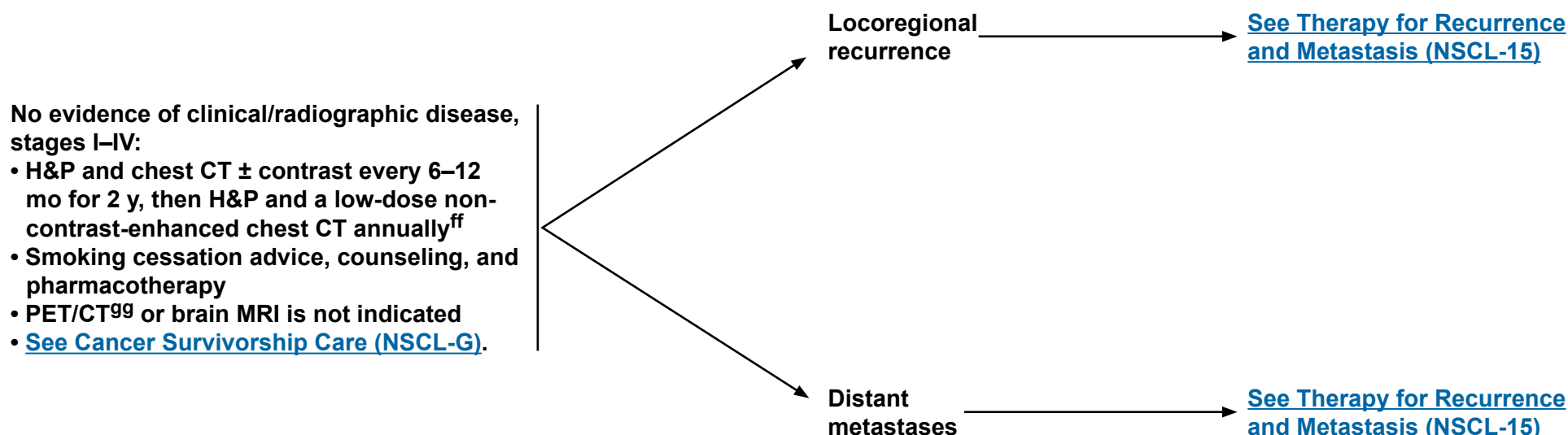
^{ee}[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)

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SURVEILLANCE



^{ff}Patients treated with chemotherapy ± RT who have residual abnormalities may require more frequent imaging.

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

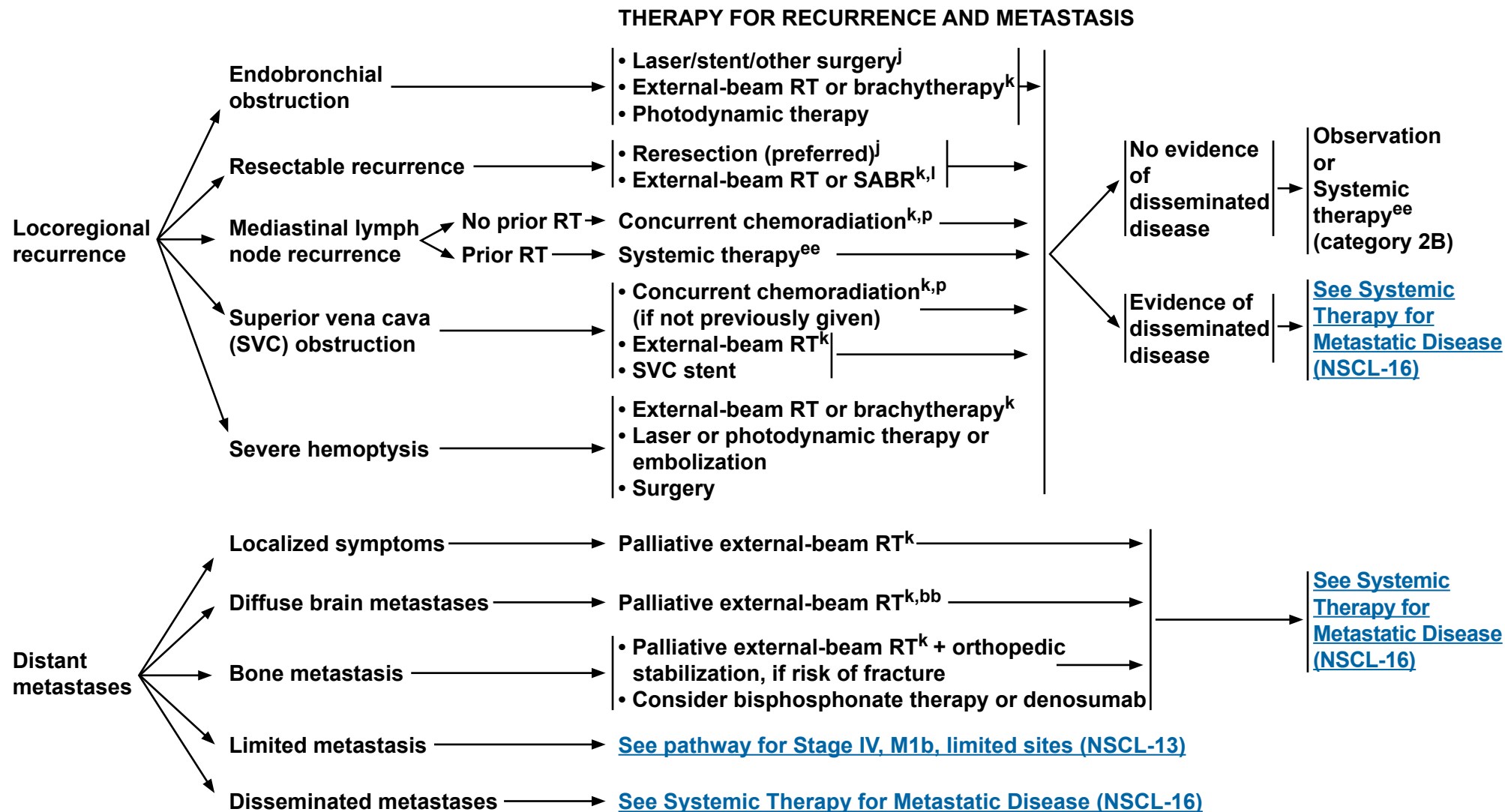
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Non-Small Cell Lung Cancer

^jSee Principles of Surgical Therapy (NSCL-B).^kSee Principles of Radiation Therapy (NSCL-C).^lInterventional radiology ablation is an option for selected patients.^pSee Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).^{bb}See NCCN Guidelines for Central Nervous System Cancers.^{ee}See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).**Note:** All recommendations are category 2A unless otherwise indicated.**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



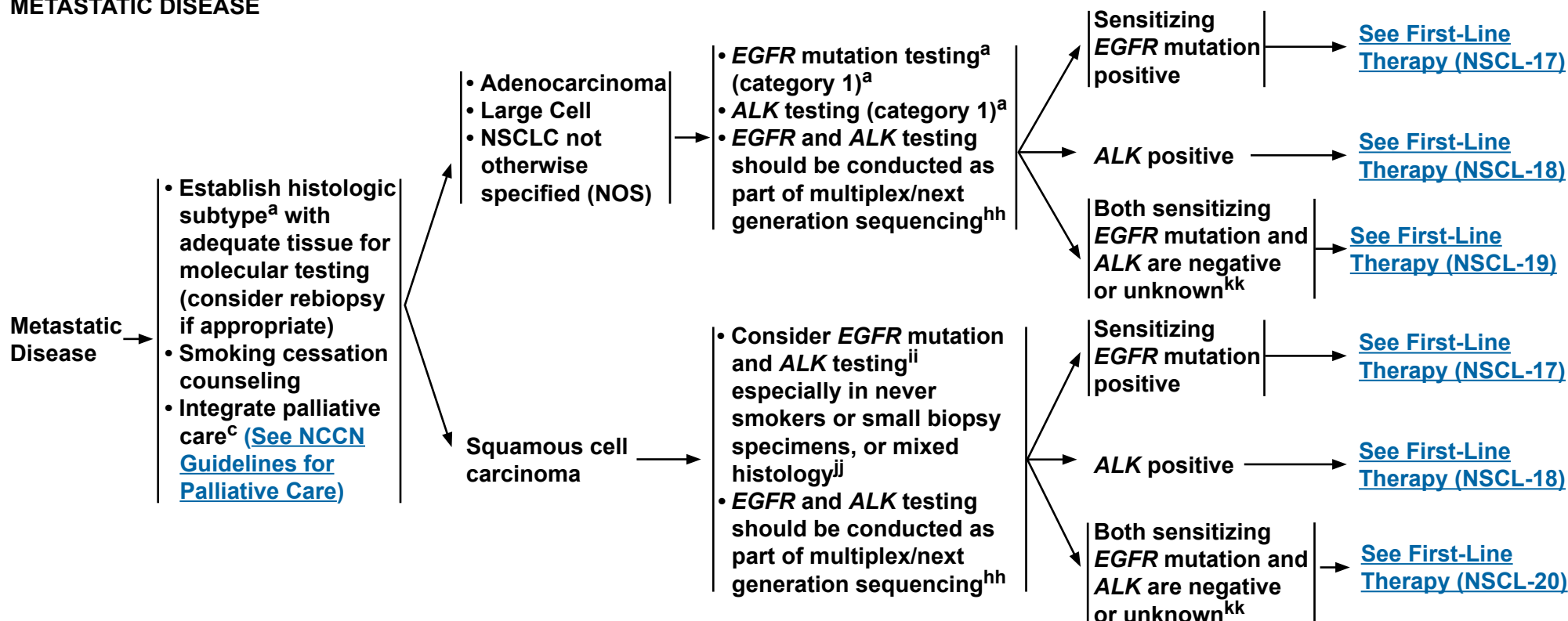
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Non-Small Cell Lung Cancer

SYSTEMIC THERAPY FOR METASTATIC DISEASE

HISTOLOGIC SUBTYPE

TESTING RESULTS



^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.

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

ⁱⁱIn 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, Bharmra G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). *Curr Protoc Hum Genet* 2008;chapter 10:unit 10.11.

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

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

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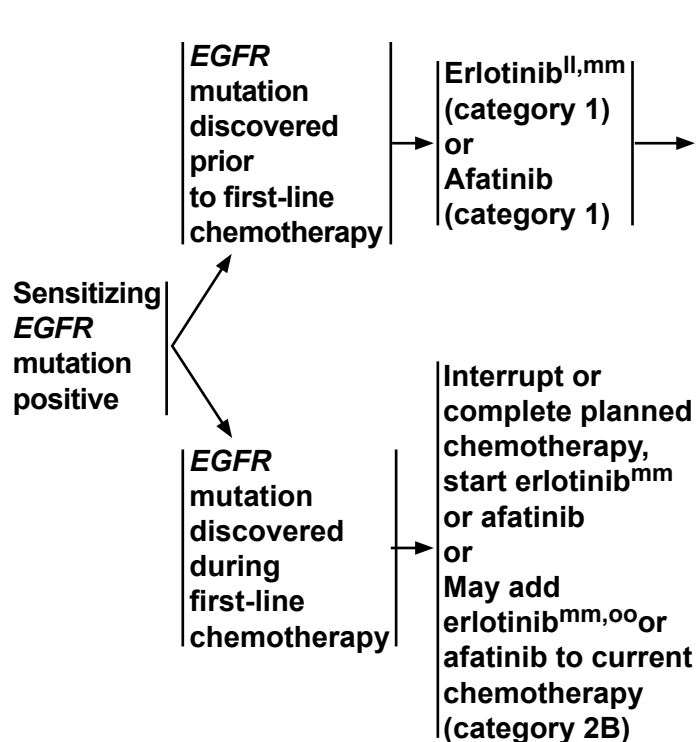


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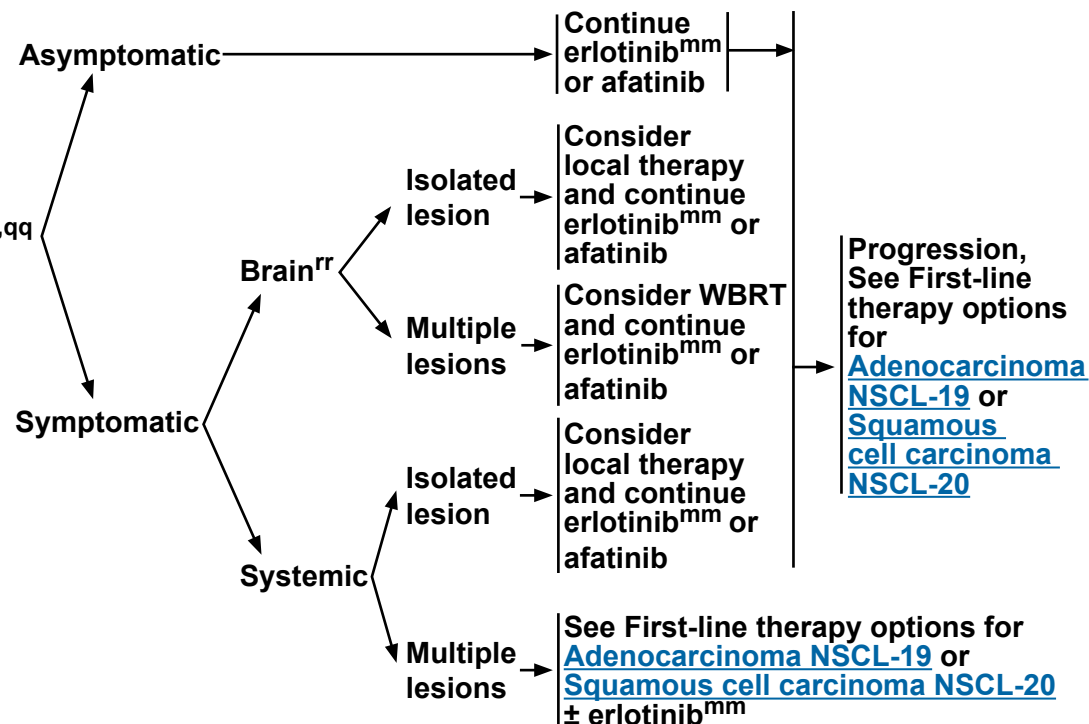
Non-Small Cell Lung Cancer

SENSITIZING EGFR MUTATION POSITIVE^a

FIRST-LINE THERAPY^{ee}



SUBSEQUENT THERAPY^{ee,ss}



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

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

^{ll}For performance status 0-4.

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

^{oo}Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who are never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol* 2012;30:2063-2069.

^{pp}Prior to changing therapy, a biopsy is reasonable to determine mechanism of acquired resistance.

^{qq}Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

^{rr}Consider pulse erlotinib for carcinomatosis meningitis.

^{ss}Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. *Lancet Oncol* 2012;13:528-38.

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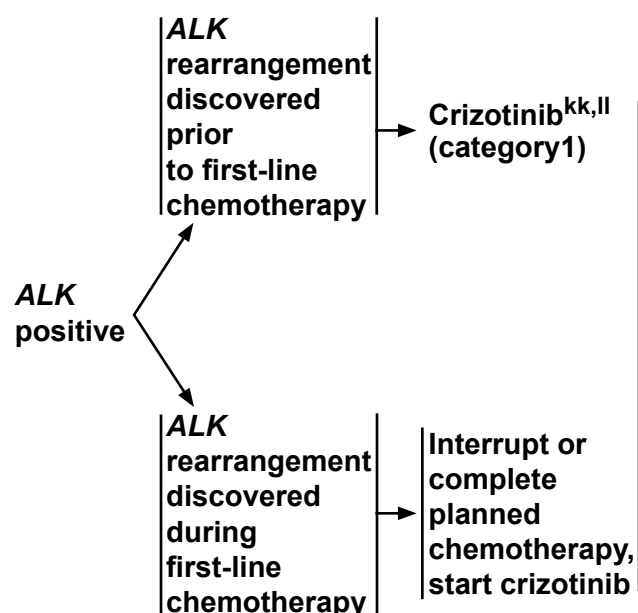


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Non-Small Cell Lung Cancer

ALK POSITIVE^a

FIRST-LINE THERAPY^{ee}



SUBSEQUENT THERAPY^{ee}

Asymptomatic

Symptomatic

Brain

Systemic

Isolated lesion

Multiple lesions

Isolated lesion

Multiple lesions

Continue crizotinib^{uu} or switch to ceritinib

Consider local therapy and continue ALK inhibitor

Consider WBRT and continue ALK inhibitor

Consider local therapy and continue ALK inhibitor

Ceritinib or See First-line therapy options for [Adenocarcinoma NSCL-19](#) or [Squamous cell carcinoma NSCL-20](#)

Symptomatic systemic progression after local therapies and/or after switching to ceritinib. See First-line therapy options for [Adenocarcinoma NSCL-19](#) or [Squamous cell carcinoma NSCL-20](#)
^aSee [Principles of Pathologic Review \(NSCL-A\)](#).

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

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

^{ll}For performance status 0-4.

^{tt}Patients who are intolerant to crizotinib may be switched to ceritinib.

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

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

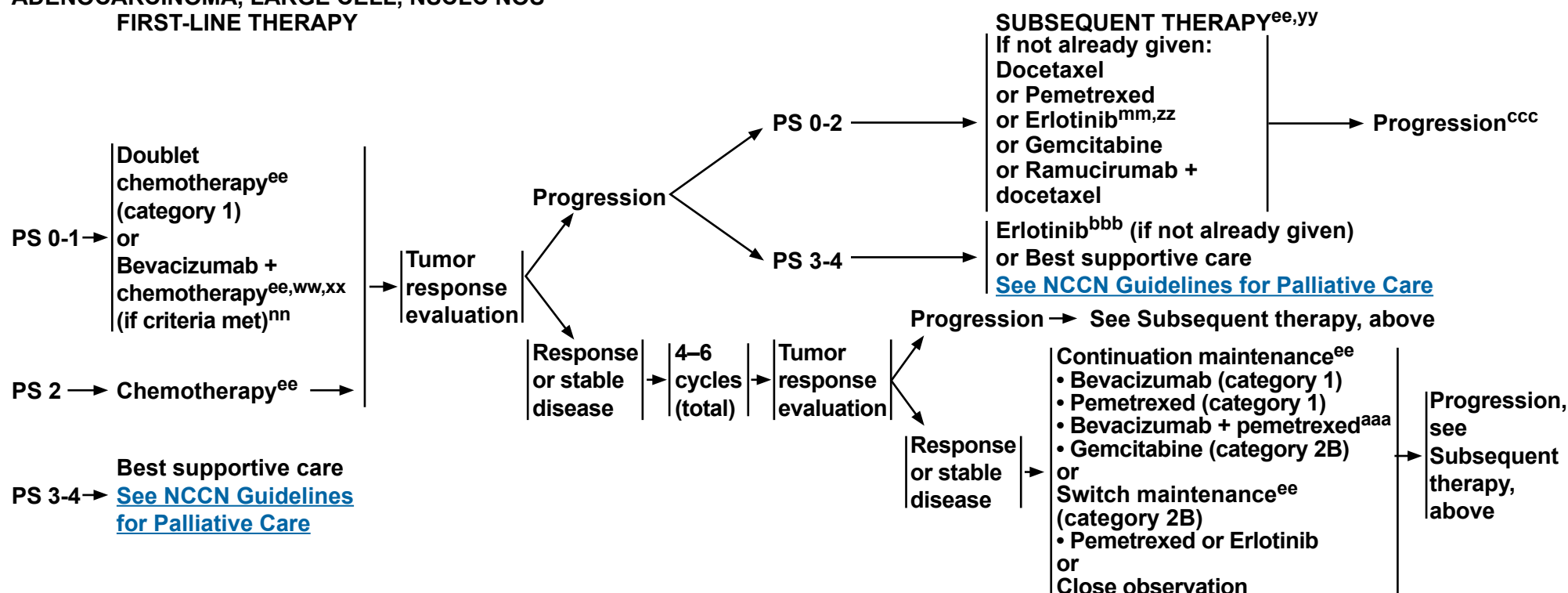
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



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Non-Small Cell Lung Cancer

ADENOCARCINOMA, LARGE CELL, NSCLC NOS^{vv} FIRST-LINE THERAPY


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

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

ⁿⁿCriteria 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.

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

^{ww}Bevacizumab should be given until progression.

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

^{yy}Chemotherapy preferred in this setting. Grassino M, Martelli O, Brogini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. *Lancet Oncol* 2013; 14:981-988.

^{zz}Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a “poor” classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. *Lancet Oncol* 2014; 15:713-21.

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

^{bbb}Erlotinib may be considered for PS 3 and 4 patients with sensitizing EGFR mutations.

^{ccc}If not already given, options for PS 0-2 include erlotinib, docetaxel (category 2B), pemetrexed (category 2B) or gemcitabine (category 2B), options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

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

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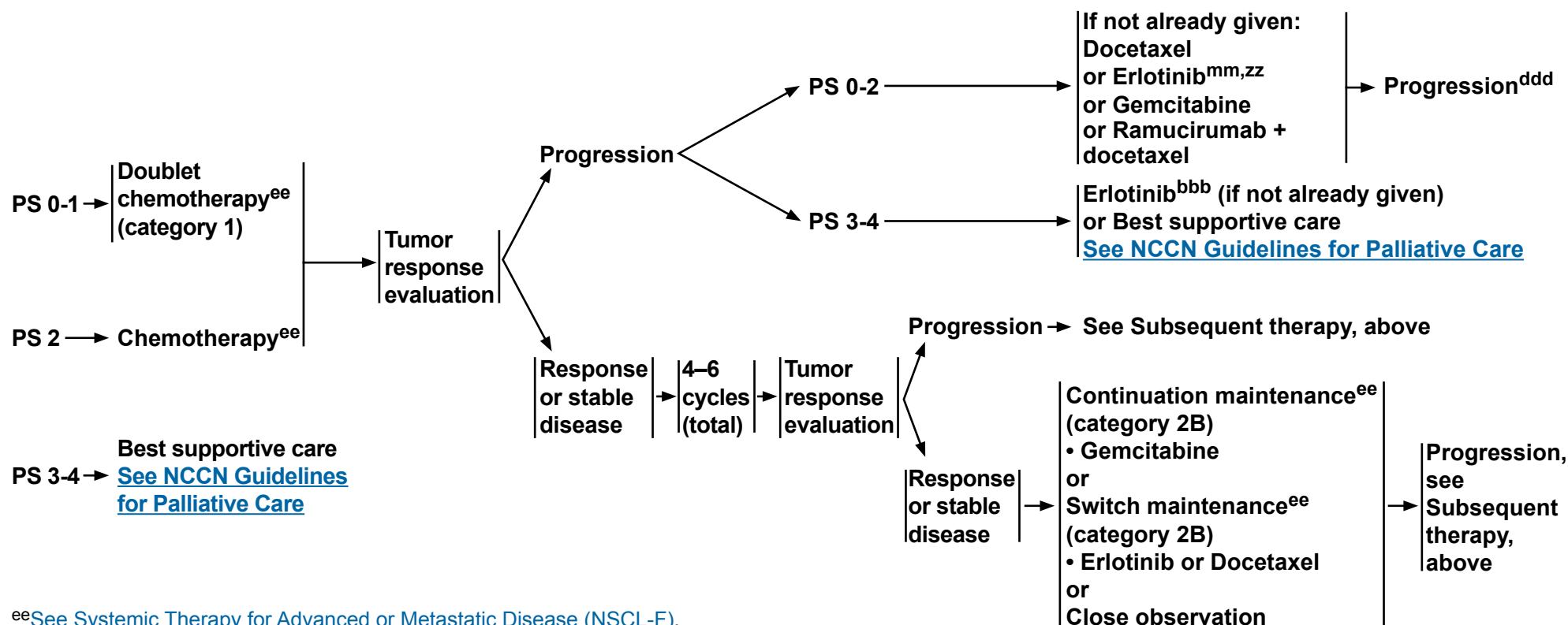


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Non-Small Cell Lung Cancer

SQUAMOUS CELL CARCINOMA^{vv}

FIRST-LINE THERAPY



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

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

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

^{yy}Chemotherapy preferred in this setting. Grassino M, Martelli O, Brogini M, et al. Erlotinib versus docetaxel as second line treatment of patients with advanced NSCLC and wild type EGFR tumors (TAILOR): a randomized trial. *Lancet Oncol* 2013; 14:981-988.

^{zz}Recommend proteomic testing for patients with NSCLC and wild-type EGFR or with unknown EGFR status. A patient with a “poor” classification should not be offered erlotinib in the second-line setting. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker stratified, randomised phase 3 trial. *Lancet Oncol* 2014; 15:713-21.

^{bbb}Erlotinib may be considered for PS 3 and 4 patients with sensitizing EGFR mutations.

^{ddd}If not already given, options for PS 0-2 include erlotinib, docetaxel (category 2B), or gemcitabine (category 2B), options for PS 3-4 include erlotinib or best supportive care. Options for further progression are best supportive care or clinical trial.

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PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Pathologic Evaluation

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

Adenocarcinoma 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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Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (2 of 4)

Immunohistochemical Staining

- 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
 - 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) is made by using a panel of markers, including 2 with known immunopositivity in mesothelioma (but negative in adenocarcinoma) and 2 with known positivity in adenocarcinoma (but negative in mesothelioma).¹¹
 - ◊ Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma).^{14,15}
 - ◊ Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, claudin-4 and TTF-1 (negative in mesothelioma).^{8,11}

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

Molecular Diagnostic Studies in Lung Cancer.

• *EGFR* and *KRAS*

- ▶ *EGFR* is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of *EGFR*-activating mutations represents a critical biological determinant for proper therapy selection in patients with lung cancer.
- ▶ There is a significant association between *EGFR* mutations—especially exon 19 deletion and exon 21 (L858R, L861), exon 18 (G719X, G719), and exon 20 (S768I) mutations—and sensitivity to *EGFR* TKIs.¹⁶⁻¹⁹
- ▶ The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.^{20,21}
- ▶ Overlapping *EGFR* and *KRAS* mutations occur in <1% of patients with lung cancer.²²
- ▶ *KRAS* mutations are associated with intrinsic *EGFR* TKI resistance, and *KRAS* gene sequencing could be useful for the selection of patients as candidates for *EGFR* TKI therapy.²³ *KRAS* testing may identify patients who may not benefit from further molecular diagnostic testing.
- ▶ The prevalence of *EGFR* mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher *EGFR* mutation frequency in non-smokers, women, and non-mucinous cancers. *KRAS* mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.²⁴ The most common *EGFR* mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations are more common in non-mucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.
- ▶ Primary resistance to *EGFR* TKI therapy is associated with *KRAS* mutation. Acquired resistance is associated with second-site mutations within the *EGFR* kinase domain (such as T790M), amplification of alternative kinases (such as *MET*), histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).

• *ALK*

- ▶ Anaplastic lymphoma kinase (*ALK*) gene rearrangements represent the fusion between *ALK* and various partner genes, including echinoderm microtubule-associated protein-like 4 (*EML4*).²⁵ *ALK* fusions have been identified in a subset of patients with NSCLC and represent a unique subset of NSCLC patients for whom *ALK* inhibitors may represent a very effective therapeutic strategy.²⁶ Crizotinib and ceritinib are oral *ALK* inhibitors that are approved by the FDA for patients with metastatic NSCLC who have the *ALK* gene rearrangement (ie, *ALK* positive).
- ▶ *ALK* NSCLC occurs most commonly in a unique subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor *EGFR* mutations.^{27,28} However, for the most part, *ALK* translocations and *EGFR* mutations are mutually exclusive.^{27, 29-31}
- ▶ The current standard method for detecting *ALK* NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. The appropriate antibody and detection method for *ALK* protein expression can be used for rapid prescreening of *ALK*-rearranged lung adenocarcinomas and selection of cases that will subsequently be confirmed by FISH testing.³²

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Non-Small Cell Lung Cancer

PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

- ¹Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.
- ²Fossella FV, Putnam JB, Komaki R, eds. Lung Cancer. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.
- ³Schrump DS, Carter D, Kelsey CR, et al. Non-small cell lung cancer. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, et al., eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology. Philadelphia: Lippincott Williams & Wilkins; 2011.
- ⁴Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol 2007;2:423-429.
- ⁵Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005;23:5900-5909.
- ⁶Travis WD. Pathology and genetics of tumours of the lung, pleura, thymus and heart Lyon: IARC Press; 2004.
- ⁷Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-1068.
- ⁸Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol 2011;6:244-285.
- ⁹Rekhtman N, Ang DC, Sima CS, et al. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. Mod Pathol 2011;24:1348-1359.
- ¹⁰Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. Am J Surg Pathol 2011;35:15-25.
- ¹¹Husain AN, Colby T, Ordonez N, et al. Guidelines for Pathologic Diagnosis of Malignant Mesothelioma: 2012 Update of the Consensus Statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med 2012 Aug 28. [Epub ahead of print]
- ¹²Jagirdar J. Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. Arch Pathol Lab Med 2008;132:384-396.
- ¹³Goldstein NS, Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001;116:319-325.
- ¹⁴Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-380.
- ¹⁵Chirieac LR, Pinkus GS, Pinkus JL, et al. The immunohistochemical characterization of sarcomatoid malignant mesothelioma of the pleura. Am J Cancer Res 2011;1:14-24.
- ¹⁶Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
- ¹⁷Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500.
- ¹⁸Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. Oncologist 2007;12:90-98.
- ¹⁹Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-495.
- ²⁰Lund-Iverson M, Kleinber L, Fjellbirkeland L, Helland A, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. J Thorac Oncol 2012;7:1471-1413.
- ²¹Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small cell lung cancer: preclinical data and clinical implications. Lancet Oncol 2012;13:e23-31.
- ²²Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. Clin Cancer Res 2006;12:7232-7241.
- ²³Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-262.
- ²⁴Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. J Mol Diagn 2007;9:320-326.
- ²⁵Cataldo KA, Jalal SM, Law ME, et al. Detection of t(2;5) in anaplastic large cell lymphoma: comparison of immunohistochemical studies, FISH, and RT-PCR in paraffin-embedded tissue. Am J Surg Pathol 1999;23:1386-1392.
- ²⁶Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-1703.
- ²⁷Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. J Clin Oncol 2009;27:4247-4253.
- ²⁸Koivunen JP, Kim J, Lee J, et al. Mutations in the LKB1 tumour suppressor are frequently detected in tumours from Caucasian but not Asian lung cancer patients. Br J Cancer 2008;99:245-252.
- ²⁹Koivunen JP, Mermel C, Zejnullahu K, et al. EML4-ALK fusion gene and efficacy of an ALK kinase inhibitor in lung cancer. Clin Cancer Res 2008;14:4275-4283.
- ³⁰Soda M, Takada S, Takeuchi K, et al. A mouse model for EML4-ALK-positive lung cancer. Proc Natl Acad Sci U S A 2008;105:19893-19897.
- ³¹Inamura K, Takeuchi K, Togashi Y, et al. EML4-ALK lung cancers are characterized by rare other mutations, a TTF-1 cell lineage, an acinar histology, and young onset. Mod Pathol 2009;22:508-515.
- ³²Wynes MW, Sholl LM, Dietel M, et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. J Thorac Oncol 2014;9(5):631-638.

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PRINCIPLES OF SURGICAL THERAPY (1 of 4)

Evaluation

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

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥ 2 cm or \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

- ¹Martins RG, D'Amico TA, Loo BW Jr, et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. J Natl Compr Canc Netw 2012;10:599-613.
- ²Albain K, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomized controlled trial. Lancet 2009;374:379-386.
- ³van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. J Natl Cancer Inst 2007;99:442-450.
- ⁴Farjah F, Flum DR, Varghese TK Jr, et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. Ann Thorac Surg 2009;87:995-1006.
- ⁵Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomised trial in stage III non-small-cell lung cancer. Lancet Oncol 2008;9:607-608.
- ⁶Andre F, Grunenwald D, Pignon J, et al. Survival of patients with resected N2 non-small-cell lung Cancer: Evidence for a subclassification and implications. J Clin Oncol 2000;18:2981-2989.
- ⁷Decaluwé H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. Eur J Cardiothorac Surg 2009;36:433-439.
- ⁸Bueno R, Richards WG, Swanson SJ, et al. Nodal stage after induction therapy for stage IIIA lung cancer determines patient survival. Ann Thorac Surg 2000;70:1826-1831.
- ⁹Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2009;75:1462-1467.
- ¹⁰de Cabanyes Candela S, Detterbeck FC. A systematic review of restaging after induction therapy for stage IIIa lung cancer: prediction of pathologic stage. J Thorac Oncol 2010;5:389-398.
- ¹¹Bauman JE, Mulligan MS, Martins RG, et al. Salvage Lung Resection After Definitive Radiation (>59 Gy) for Non-Small Cell Lung Cancer: Surgical and Oncologic Outcomes. Ann Thorac Surg 2008;86:1632-1639.
- ¹²Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary Resection After Curative Intent Radiotherapy (>59 Gy) and Concurrent Chemotherapy in Non-Small-Cell Lung Cancer. Ann Thorac Surg 2004;78:1200-1205.
- ¹³Evans NR 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary lung cancer. J Thorac Cardiovasc Surg 2010;139:991-996.
- ¹⁴Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy—Influence of preoperative induction therapy. J Thorac Cardiovasc Surg 2009;138:289-294.
- ¹⁵Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! Eur J Cardiothorac Surg 2007;31:181-185.
- ¹⁶Weder W, Collaud S, Eberhardt WEE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. J Thorac Cardiovasc Surg 2010;139:1424-1430.
- ¹⁷Shah AA, Berry M, Tzao C, et al. Induction chemoradiotherapy is not superior to induction chemotherapy alone in stage IIIA lung cancer: a systematic review and meta-analysis. Ann Thorac Surg 2012;93:1807-1812.

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PRINCIPLES OF RADIATION THERAPY (1 of 9)

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

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

Early-Stage NSCLC (Stage I)

- SABR (also known as SBRT) is recommended for patients who are medically inoperable or who refuse to have surgery after thoracic surgery evaluation. SABR has achieved primary tumor control rates and overall survival, comparable to lobectomy and higher than 3D-CRT in nonrandomized and population-based comparisons in medically inoperable or older patients.⁵⁻¹⁰
- SABR is also an appropriate option for patients with high surgical risk (able to tolerate sublobar resection but not lobectomy [eg, age ≥75 years], poor lung function). SABR and sublobar resection achieve comparable cancer-specific survival and primary tumor control.¹⁰⁻¹²
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are alternatives.¹³⁻¹⁴
- In patients treated with surgery, postoperative radiotherapy (PORT) is not recommended unless there are positive margins or upstaging to N2 (see *Locally Advanced NSCLC* below).

Locally Advanced NSCLC (Stage II-III)

- The standard of care for patients with inoperable stage II and stage III is concurrent chemoRT.¹⁵⁻¹⁷
(<http://www.acr.org/~media/ACR/Documents/AppCriteria/Oncology/NonsurgicalTreatmentForNSCLCGoodPerformanceStatusDefinitiveIntent.pdf>) RT interruptions and dose reductions for manageable acute toxicities should be avoided by employing supportive care.
- Sequential chemoRT or RT alone is appropriate for frail patients unable to tolerate concurrent therapy.^{18,19}
(<http://www.acr.org/~media/ACR/Documents/AppCriteria/OncologyNonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf>)

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PRINCIPLES OF RADIATION THERAPY (2 of 9)

Locally Advanced NSCLC (Stage II-III) (continued)

- Accelerated RT regimens may be beneficial, particularly if not concurrent with chemotherapy (ie, in a sequential or RT-only approach).^{20,21}
- RT has a role before or after surgery.
<http://www.acr.org/~media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf>
 - ▶ Preoperative concurrent chemoRT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)²² and is recommended for resectable superior sulcus tumors.²³⁻²⁴
 - ▶ Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.^{25,26}
 - ▶ The determination of resectability in trimodality therapy should be made prior to initiation of all treatment.
 - ▶ 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.^{27,28} 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 patients²⁹⁻³¹ and is recommended for positive resection margins.
 - ▶ 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.³²

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.^{33,34}
- See the [NCCN Guidelines for Central Nervous System Cancers](#) regarding RT for brain metastases.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints (See Tables 2–5 on NSCL-C 6 of 9 and NSCL-C 7 of 9)

- 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.^{35,36} Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.³⁷⁻⁴¹

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PRINCIPLES OF RADIATION THERAPY (3 of 9)

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.⁴² 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.^{42,43} 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,^{43,44} while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.⁴⁵ The dose for 5-fraction regimens is being studied prospectively in RTOG 0813.
- SABR is most commonly used for tumors up to 5 cm in size, though selected larger isolated tumors can be treated safely if normal tissue constraints are respected.⁴⁶
- 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.^{47,48} All of these must be considered when interpreting or emulating regimens from prior studies.

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.⁴⁹⁻⁵³ One randomized trial found improved survival for IFI versus ENI, possibly because it enabled dose escalation.⁵⁴ IFI is reasonable in order to optimize definitive dosing to the tumor.
- 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.⁵⁵ Dose escalation in RT alone,⁵⁶ sequential chemoRT,⁵⁷ or concurrent chemoRT⁵⁸ 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,⁵⁹⁻⁶² preliminary results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy, found that 74 Gy does not improve overall survival, and therefore is not currently a standard dose.⁶³ A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,⁶⁴ and individualized accelerated RT dose intensification is now being evaluated in a randomized trial (RTOG 1106).
- Doses of 45 to 50 Gy in 1.8 to 2 Gy fractions are standard preoperative doses. Definitive RT doses delivered as preoperative chemoRT can safely be administered and achieve promising nodal clearance and survival rates,⁶⁵⁻⁶⁸ 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.⁶⁹ 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.^{29,30} 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.⁷⁰

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PRINCIPLES OF RADIATION THERAPY (4 of 9)

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,⁷¹⁻⁷⁴ 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.⁷⁵ When higher doses (>30 Gy) are warranted, 3D-CRT should be used to reduce normal tissue irradiation.

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,⁷⁶ 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.⁷⁷ Given the potential for rapid progression of NSCLC,^{78,79} PET/CT should be obtained preferably within 4 weeks before treatment. It is ideal to obtain PET/CT in the treatment position.
- Tumor and organ motion, especially owing to breathing, should be assessed or accounted for at simulation. Options include fluoroscopy, inhale/exhale or slow scan CT, or, ideally, 4D-CT.
- Photon beam energy should be individualized based on the anatomic location of the tumors and beam paths. In general, photon energies between 4 to 10 MV are recommended for beams passing through low-density lung tissue before entering the tumor. When there is no air gap before the beam enters the tumor (such as for some large mediastinal tumors or tumors attached to chest wall), higher energies may improve the dose distribution, especially when using a smaller number of fixed beam angles.
- Tissue heterogeneity correction and accurate dose calculation algorithms that account for buildup and lateral electron scatter effects in heterogeneous density tissues are recommended. Heterogeneity correction with simple pencil beam algorithms is not recommended.⁴⁸
- 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 76.⁸⁰
- 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 (5 of 9)

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
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

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

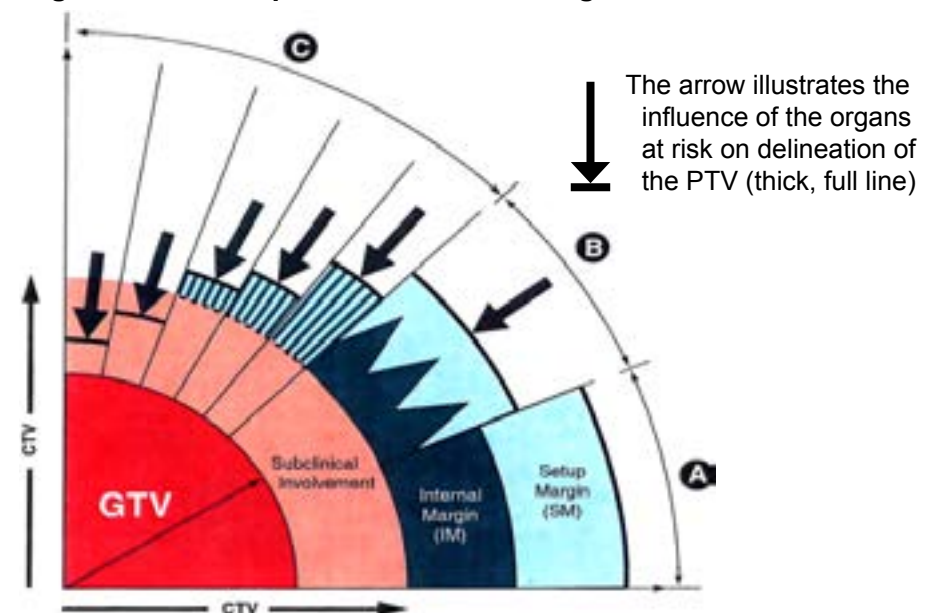
*[NCCN Guidelines for Central Nervous System Cancers](#)

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

OAR	Constraints in 30–35 Fractions
Spinal cord	Max ≤50 Gy
Lung	V20 ≤35%; V5 ≤65%; MLD ≤20 Gy
Heart	V40 ≤80%; V45 ≤60%; V60 ≤30%; Mean ≤35 Gy
Esophagus	Mean ≤34 Gy; Max ≤105% of prescription dose
Brachial plexus	Max ≤66 Gy

V_{xx} = % of the whole OAR receiving ≥xx Gy.

Figure 1. ICRU Report 62 Schema of Target Volume Definitions



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

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- ¹Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *J Clin Oncol* 2011;29:2305-2311.
- ²Liao ZX, Komaki RR, Thames HD, et al. Influence of Technologic Advances on Outcomes in Patients With Unresectable, Locally Advanced Non-Small-Cell Lung Cancer Receiving Concomitant Chemoradiotherapy. *Int J Radiat Oncol Biol Phys* 2010;76:775-781.
- ³Sejpal S, Komaki R, Tsao A, et al. Early findings on toxicity of proton beam therapy with concurrent chemotherapy for non-small cell lung cancer. *Cancer* 2011;117:3004-3013.
- ⁴Chang JY, Komaki R, Lu C, et al. Phase 2 study of high-dose proton therapy with concurrent chemotherapy for unresectable stage III non-small cell lung cancer. *Cancer* 2011;117:4707-4713.
- ⁵Timmerman R, Paulus R, Galvin J, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA* 2010;303:1070-1076.
- ⁶Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-3296.
- ⁷Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352-1358.
- ⁸Grutters JPC, Kessels AGH, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010;95:32-40.
- ⁹Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol* 2010;28:5153-5159.
- ¹⁰Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. *Int J Radiat Oncol Biol Phys* 2012;84:1060-1070.
- ¹¹Grills IS, Mangona VS, Welsh R, et al. Outcomes After Stereotactic Lung Radiotherapy or Wedge Resection for Stage I Non-Small-Cell Lung Cancer. *J Clin Oncol* 2010;28:928-935.
- ¹²Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg* 2010;140:377-386.
- ¹³Bogart JA, Hodgson L, Seagren SL, et al. Phase I study of accelerated conformal radiotherapy for stage I non-small-cell lung cancer in patients with pulmonary dysfunction: CALGB 39904. *J Clin Oncol* 2010;28:202-206.
- ¹⁴Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;68:103-110.
- ¹⁵Aupérin A, Le Péchoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181-2190.
- ¹⁶O'Rourke N, Roqué I, Figuls M, Farré Bernadó N, Macbeth F. Concurrent chemoradiotherapy in non-small cell lung cancer. *Cochrane Database Syst Rev* 2010;CD002140.
- ¹⁷Curran 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.
- ¹⁸Sause W, Kolesar P, Taylor S IV, et al. Final results of phase III trial in regionally advanced unresectable non-small cell lung cancer: Radiation Therapy Oncology Group, Eastern Cooperative Oncology Group, and Southwest Oncology Group. *Chest* 2000;117:358-364.
- ¹⁹Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210-1215.
- ²⁰Baumann M, Herrmann T, Koch R, et al. Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). *Radiother Oncol* 2011;100:76-85.
- ²¹Mauguen A, Le Péchoux C, Saunders MI, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797.
- ²²Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet* 2009;374:379-386.
- ²³Kunitoh H, Kato H, Tsuboi M, et al. Phase II trial of preoperative chemoradiotherapy followed by surgical resection in patients with superior sulcus non-small-cell lung cancers: report of Japan Clinical Oncology Group trial 9806. *J Clin Oncol* 2008;26:644-649.
- ²⁴Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol* 2007;25:313-318.
- ²⁵Thomas M, Rube C, Hoffknecht P, et al. Effect of preoperative chemoradiation in addition to preoperative chemotherapy: a randomized trial in stage III non-small-cell lung cancer. *Lancet Oncol* 2008;9:607-608.
- ²⁶Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Biol Phys* 2009;75:1462-1467.
- ²⁷Douillard J-Y, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. *Int J Radiat Oncol Biol Phys* 2008;72:695-701.
- ²⁸Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998-3006.
- ²⁹Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. *J Thorac Oncol* 2007;2:287-292.
- ³⁰Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group–RTOG 9705. *J Clin Oncol* 2005;23:3480-3487.
- ³¹Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. *N Engl J Med* 2000;343:1217-1222.
- ³²Burdett S, Stewart L, Group PM-a. Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis. *Lung Cancer* 2005;47:81-83.
- ³³Milano MT, Katz AW, Okunieff P. Patterns of recurrence after curative-intent radiation for oligometastases confined to one organ. *Am J Clin Oncol* 2010;33:157-163.
- ³⁴Salama JK, Chmura SJ, Mehta N, et al. An initial report of a radiation dose-escalation trial in patients with one to five sites of metastatic disease. *Clin Cancer Res* 2008;14:5255-5259.
- ³⁵Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. *Semin Radiat Oncol* 2007;17:108-120.
- ³⁶Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008;18:215-222.
- ³⁷Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. *Int J Radiat Oncol Biol Phys* 2010;76:S10-19.
- ³⁸Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76:S70-76.
- ³⁹Werner-Wasik M, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. *Int J Radiat Oncol Biol Phys* 2010;76:S86-93.
- ⁴⁰Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010;76:S77-85.
- ⁴¹Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. *Int J Radiat Oncol Biol Phys* 2010;76:S42-49.
- ⁴²Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007; 2:S94-100.
- ⁴³Lagerwaard FJ, Haasbeek CJA, Smit EF, et al. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2008;70:685-692.

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PRINCIPLES OF RADIATION THERAPY - References (9 of 9)

- ⁴⁴Chang JY, Li QQ, Xu QY, et al. Stereotactic body radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small-cell lung cancer: how to fly in a "no fly zone". *Int J Radiat Oncol Biol Phys* 2014;88:1120-1128.
- ⁴⁵Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol* 2006; 24:4833-4839.
- ⁴⁶Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677-682.
- ⁴⁷Xiao Y, Papiez L, Paulus R, et al. Dosimetric evaluation of heterogeneity corrections for RTOG 0236: stereotactic body radiotherapy of inoperable stage I-II non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;73:1235-1242.
- ⁴⁸Liu MB, Eclow NC, Trakul N, et al. Clinical impact of dose overestimation by effective path length calculation in stereotactic ablative radiation therapy of lung tumors. *Practical Radiation Oncology* 2012 In press.
- ⁴⁹Belderbos JS, Kepka L, Kong FM, et al. Report from the International Atomic Energy Agency (IAEA) consultants' meeting on elective nodal irradiation in lung cancer: non-small cell lung cancer (NSCLC). *Int J Radiat Oncol Biol Phys* 2008;72:335-342.
- ⁵⁰Bradley J, Bae K, Choi N, et al. A phase II comparative study of gross tumor volume definition with or without PET/CT fusion in dosimetric planning for non-small-cell lung cancer (NSCLC): primary analysis of radiation therapy oncology group (RTOG) 0515. *Int J Radiat Oncol Biol Phys* 2012;82:435-441.
- ⁵¹Sanuki-Fujimoto N, Sumi M, Ito Y, et al. Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol* 2009; 91:433-437.
- ⁵²Sulman EP, Komaki R, Klopp AH, et al. Exclusion of elective nodal irradiation is associated with minimal elective nodal failure in non-small cell lung cancer. *Radiat Oncol* 2009;4:5-11.
- ⁵³Rosenzweig KE, Sura S, Jackson A, Yorke E. Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557-5561.
- ⁵⁴Yuan S, Sun X, Li M, et al. A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer. *Am J Clin Oncol* 2007;30:239-244.
- ⁵⁵Perez CA, Pajak TF, Rubin P, et al. Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59:1874-1881.
- ⁵⁶Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324-333.
- ⁵⁷Rengan R, Rosenzweig KE, Venkatraman E, et al. Improved local control with higher doses of radiation in large-volume stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004;60:741-747.
- ⁵⁸Machtay M, Bae K, Movsas B, et al. Higher biologically effective dose of radiotherapy is associated with improved Outcomes for Locally Advanced Non-Small Cell Lung Carcinoma Treated with Chemoradiation: An Analysis of the radiation therapy oncology group. *Int J Radiat Oncol Biol Phys* 2012;82:425-434.
- ⁵⁹Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006; 65:1106-1111.
- ⁶⁰Socinski MA, Blackstock AW, Bogart JA, et al. Randomized phase II trial of induction chemotherapy followed by concurrent chemotherapy and dose-escalated thoracic conformal radiotherapy (74 Gy) in stage III non-small-cell lung cancer: CALGB 30105. *J Clin Oncol* 2008;26:2457-2463.
- ⁶¹Stinchcombe TE, Lee CB, Moore DT, et al. Long-term follow-up of a phase I/II trial of dose escalating three-dimensional conformal thoracic radiation therapy with induction and concurrent carboplatin and paclitaxel in unresectable stage IIIA/B non-small cell lung cancer. *J Thorac Oncol* 2008; 3:1279-1285.
- ⁶²Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480.
- ⁶³Bradley JD, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy +/- cetuximab for stage III non-small cell lung cancer: results on radiation dose in RTOG 0617. *J Clin Oncol* 2013;31(suppl; abstr 7501).
- ⁶⁴Maugen A, Le Pechoux C, Saunders M, et al. Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis. *J Clin Oncol* 2012;30:2788-2797.
- ⁶⁵Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg* 2009; 35:718-723; discussion 723.
- ⁶⁶Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. *J Thorac Cardiovasc Surg* 2005;129:1250-1257.
- ⁶⁷Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg* 2004;78:1200-1205.
- ⁶⁸Suntharalingam M, Paulus R, Edelman MJ, et al. Radiation therapy oncology group protocol 02-29: a phase II trial of neoadjuvant therapy with concurrent chemotherapy and full-dose radiation therapy followed by surgical resection and consolidative therapy for locally advanced non-small cell carcinoma of the lung. *Int J Radiat Oncol Biol Phys* 2012;84:456-463.
- ⁶⁹Kelsey CR, Light KL, Marks LB. Patterns of failure after resection of non-small-cell lung cancer: implications for postoperative radiation therapy volumes. *Int J Radiat Oncol Biol Phys* 2006;65:1097-1105.
- ⁷⁰Spiegel FO, Senan S, Le Pechoux C, et al. Variations in target volume definition for postoperative radiotherapy in stage III non-small-cell lung cancer: analysis of an international contouring study. *Int J Radiat Oncol Biol Phys* 2010; 76:1106-1113.
- ⁷¹Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007;25:1423-1436.
- ⁷²Lutz S, Berk L, Chang E, et al. Palliative radiotherapy for bone metastases: an ASTRO evidence-based guideline. *Int J Radiat Oncol Biol Phys* 2011;79:965-976.
- ⁷³Cross CK, Berman S, Buswell L, et al. Prospective study of palliative hypofractionated radiotherapy (8.5 Gy x 2) for patients with symptomatic non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2004; 58:1098-1105.
- ⁷⁴Medical Research Council Lung Cancer Working Party. A Medical Research Council (MRC) randomised trial of palliative radiotherapy with two fractions or a single fraction in patients with inoperable non-small-cell lung cancer (NSCLC) and poor performance status. Medical Research Council Lung Cancer Working Party. *Br J Canc* 1992; 65:934-941.
- ⁷⁵Rodrigues G, Videtic GMM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol* 2011;1:60-71.
- ⁷⁶MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. *Radiother Oncol* 2009;91:85-94.
- ⁷⁷Ung YC, Gu C-S, Cline K, et al. An Ontario Clinical Oncology Group (OCOG) randomized trial (PET START) of FDG PET/CT in patients with stage 3 non-small cell lung cancer (NSCLC): impact of PET on radiation treatment volumes [Abstract]. *J Thorac Oncol* 2011;6:S428.
- ⁷⁸Everitt S, Herschtal A, Callahan J, et al. High rates of tumor growth and disease progression detected on serial pretreatment positrooxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. *Cancer* 2010;116:5030-5037.
- ⁷⁹Mohammed N, Kestin LL, Grills IS, et al. Rapid disease progression with delay in treatment of non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2011;79:466-472.
- ⁸⁰Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874-3900.

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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 80 mg/m² days 1, 22, 43, 64; vinblastine 4 mg/m² days 1, 8, 15, 22, 29 then every 2 wks after day 43, every 21 days for 4 cycles^b
- Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles^d
- Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for nonsquamous (without specific histologic subtype) every 21 days for 4 cycles^e

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^f

^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.

^dFossella 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.

^eKreuter 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.

^fStrauss 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 (preferred)*
- Cisplatin 100 mg/m² days 1 and 29; vinblastine 5 mg/m²/weekly x 5; concurrent thoracic RT^b (preferred)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 4 cycles; concurrent thoracic RT^c (nonsquamous)
- Cisplatin 75 mg/m² on day 1, pemetrexed 500 mg/m² on day 1 every 21 days for 3 cycles; concurrent thoracic RT^d (nonsquamous)

Sequential Chemotherapy/RT Regimens

- 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^e

Concurrent Chemotherapy/RT Followed by Chemotherapy

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

*This regimen can be used as neoadjuvant chemoradiotherapy. Cisplatin and etoposide is the preferred regimen. If weekly carboplatin and paclitaxel is used because the patient is not able to tolerate concurrent full-dose cisplatin and radiotherapy, the treating physician should consider 2 cycles of full-dose platinum therapy after local treatment is completed.

^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.

^dVokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. Clin Lung Cancer 2009;10:193-198.

^eBelani 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 3)

ADVANCED DISEASE:

- The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.
- Stage, weight loss, performance status, and gender predict survival.
- Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.
- Histology of NSCLC is important in the selection of systemic therapy.
- New agent/platinum combinations have generated a plateau in overall response rate ($\approx 25\%$ – 35%), time to progression (4–6 mo), median survival (8–10 mo), 1-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 for *EGFR* mutation-positive patients.

First-line Therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Erlotinib is recommended as a first-line therapy in patients with sensitizing *EGFR* mutations and should not be given as first-line therapy to patients negative for these *EGFR* mutations or with unknown *EGFR* status.
- Afatinib is indicated for patients with sensitizing *EGFR* mutations.
- Crizotinib is indicated for patients with *ALK* rearrangements.
- 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.
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, etoposide, vinblastine, vinorelbine, pemetrexed, or albumin-bound paclitaxel.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine).
- Response assessment after 1-2 cycles, then every 2-4 cycles.

[See Maintenance Chemotherapy, Subsequent Therapy NSCL-F \(2 of 3\)](#)

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Non-Small Cell Lung Cancer

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

Maintenance Therapy

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

- Continuation Maintenance: Bevacizumab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
 - ▶ Continuation of bevacizumab after 4–6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
 - ▶ Continuation of pemetrexed after 4–6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (category 1).
 - ▶ Continuation of bevacizumab + pemetrexed after 4 to 6 cycles of bevacizumab, pemetrexed, cisplatin/carboplatin, for patients with histologies other than squamous cell carcinoma.
 - ▶ Continuation of gemcitabine after 4–6 cycles of platinum-doublet chemotherapy (category 2B).
- Switch Maintenance: Two studies have shown a benefit in progression-free and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy, in patients without disease progression after 4–6 cycles of therapy.
 - ▶ Initiation of pemetrexed after 4–6 cycles of first-line platinum-doublet chemotherapy, for patients with histologies other than squamous cell carcinoma (category 2B).
 - ▶ Initiation of erlotinib after 4–6 cycles of first-line platinum-doublet chemotherapy (category 2B).
 - ▶ Initiation of docetaxel after 4–6 cycles of first-line platinum-doublet chemotherapy in patients with squamous cell carcinoma (category 2B).
- Close surveillance of patients without therapy is a reasonable alternative to maintenance.

Subsequent Therapy

- In patients who have experienced disease progression either during or after first-line therapy, single-agent docetaxel, pemetrexed, or erlotinib are established second-line agents.
 - ▶ Docetaxel is superior to vinorelbine or ifosfamide.
 - ▶ Pemetrexed is considered equivalent to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
 - ▶ Ramucirumab + docetaxel improves survival when compared to docetaxel alone.
 - ▶ Erlotinib is superior to best supportive care.
 - ▶ Afatinib is indicated for patients with sensitizing *EGFR* mutations.
 - ▶ Ceritinib is indicated for patients with *ALK* rearrangements who have disease progression on or are intolerant to crizotinib.

Continuation After Disease Progression

- With the exception of targeted agents (erlotinib, gefitinib, afatinib, crizotinib, ceritinib) in patients with *EGFR*-sensitizing mutations or *ALK* rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section)

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

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Non-Small Cell Lung Cancer

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

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

- Cisplatin¹⁻⁹
- Carboplatin^{4,6-11}
- Paclitaxel^{1,4,6,8-11}
- Docetaxel^{5,7,8,12,13}
- Vinorelbine^{7,9,10}
- Gemcitabine^{3,5,6,8,9,13}
- Etoposide⁴
- Irinotecan⁹
- Vinblastine
- Mitomycin
- Ifosfamide¹²
- Pemetrexed^{14,15}
- Erlotinib¹⁶
- Bevacizumab¹⁷
- Albumin-bound paclitaxel¹⁸⁻²⁰ †
- Crizotinib²¹
- Afatinib²²
- Ceritinib²³
- Ramucirumab²⁴

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

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

³Cardenal 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.

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

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

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

⁷Fossella 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.

⁸Schiller 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.

⁹Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. Ann Oncol 2007;18:317-323.

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

¹¹Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008;26:468-473.

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

¹³Pujol 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.

¹⁴Hanna NH, Sheperd FA, Fossella FV, et al. Randomized phase III study of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597.

¹⁵Scagliotti 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.

¹⁶Shepherd FA, Pereira JR, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-32.

¹⁷Sandler AB, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. N Engl J Med 2006;355:2542-2550.

¹⁸Green 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.

¹⁹Rizvi 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.

²⁰Socinski 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.

²¹Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011;12:1004-1012.

²²Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol 2013;31:3327-3334.

²³Shaw AT, Kim D-W, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. N Engl J Med 2014;370:1189-1197.

²⁴Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-673.

†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.

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

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



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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 Wellness¹
- 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/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED (Accessed September 24, 2014)

²Memorial Sloan Kettering Cancer Center Screening Guidelines: <http://www.mskcc.org/mskcc/html/65279.cfm> (Accessed September 24, 2014)

³American Cancer Society Guidelines for Early Detection of Cancer:

http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed September 24, 2014)

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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*	vemurafenib ¹ dabrafenib ²
<i>MET</i> amplification	crizotinib ^{3,4}
<i>ROS1</i> rearrangements	crizotinib ⁵
<i>HER2</i> mutations	trastuzumab ⁶ (category 2B) afatinib ⁷ (category 2B)
<i>RET</i> rearrangements	cabozantinib ⁸ (category 2B)

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

¹Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 2012;7:e23-24.

²Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15): Abstract 8009.

³Ou 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.

⁴Camidge RD, Ou S-HI, Shapiro G, et al. Efficacy and safety of crizotinib in patients with advanced c-MET-amplified non-small cell lung cancer. J Clin Oncol 2014;32(Suppl 5): Abstract 8001.

⁵Shaw 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.

⁶Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621.

⁷Mazieres 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.

⁸Drilon A, Wang L, Hasanovic A, et al. Response to cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013; 3:630-635.

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

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



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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. In 2015, an estimated 221,200 new cases (115,610 in men and 105,590 in women) of lung and bronchial cancer will be diagnosed, and 158,040 deaths (86,380 in men and 71,660 in women) are estimated to occur because of the disease.¹ Only 16.8% of all patients with lung cancer are alive 5 years or more after diagnosis.² However, much progress has been made recently for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, advances in radiation therapy (RT) including stereotactic ablative radiotherapy (SABR), and targeted therapies.³⁻⁶ Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; patients with symptoms are more likely to have chronic obstructive pulmonary disease.⁷

The NCCN Guidelines® for Non-Small Cell Lung Cancer are updated at least once a year by the NCCN Panel. With the 2015 update, these NCCN Guidelines® have now been published for 20 years. 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. Exceptions to the rule were discussed among the NCCN Panel during the process of developing these guidelines.

Literature Search Criteria and Guidelines Update Methodology

Before the update of this version of the NCCN Guidelines for Non-Small Cell Lung Cancer, an electronic search of the PubMed database was performed to obtain key literature in non-small cell lung cancer (NSCLC), published between June 1, 2013 and June 1, 2014, using the following search term: NSCLC. The PubMed database was chosen,

because it is the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature. The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 333 citations and their potential relevance was examined. The data from key PubMed articles selected by the panel for review during the Guidelines update meeting, as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the 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.⁸⁻¹² Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).^{11,13} 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).^{9,13-16}

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).^{17,18} 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.¹⁹⁻²¹ 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.²² Asbestos also causes malignant pleural mesothelioma (see the NCCN Guidelines for Malignant Pleural Mesothelioma). Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.^{8,23-26} A review conducted by the International Agency for Research on Cancer of the WHO concluded that outdoor air pollution is a leading environmental cause of lung cancer deaths.²⁷

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,²⁸ 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.²⁸ In women who received estrogen alone, the incidence or risk of death from lung cancer did not increase.²⁹

Smoking Cessation

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.¹⁰ 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.¹⁰ Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.³⁰ Those who live with someone who smokes have an increased risk for lung cancer.¹⁴ Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer.³¹⁻³⁴ The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange).³⁵ It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.³⁶ Some surgeons will not operate on a current smoker. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA) can be very useful.³⁷ For example, the American Cancer Society (ACS) has a *Guide to Quitting Smoking* as well as The E-Quit Study, which uses email to help smokers quit smoking.

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline.^{38,39} A recent study suggests that cytisine is more efficacious than nicotine replacement therapy, although more side effects were reported with cytisine such as nausea, vomiting, and sleep disorders.⁴⁰ Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.⁴¹⁻⁴³ The effectiveness of varenicline for preventing relapse has not been clearly established.⁴⁴ 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.⁴⁵⁻⁴⁸ Other side effects with varenicline include nausea, abnormal dreams, insomnia,



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and headache.^{43,49,50} Bupropion may also be associated with similar serious neuropsychiatric symptoms. Nicotine replacement has fewer adverse effects than varenicline or bupropion.⁵¹ However, in spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.⁵¹

Lung Cancer Screening

Lung cancer is the leading cause of cancer death worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes.^{52,53} 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 assessing the risks and benefits of low-dose CT scans compared with chest radiographs for detecting lung cancer.⁵⁴ 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%.⁵⁵ 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.^{54,56} The NCCN, ACS, U.S. Preventive Services Task Force, American College of Chest Physicians, European Society for Medical Oncology (ESMO), and other organizations recommend lung cancer screening using low-dose CT for select high-risk current and former smokers (see the NCCN Guidelines for Lung Cancer Screening).⁵⁷⁻⁶⁰ It is important to note that low-dose CT is not a substitute for smoking cessation; patients should be offered

smoking cessation counseling. NCCN is currently developing a smoking cessation guideline, which will be published in the spring of 2015.

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). NSCLC accounts for more than 85% of all lung cancer cases, and it includes 2 major types: 1) non-squamous carcinoma (including adenocarcinoma, large-cell carcinoma, and other cell types); and 2) squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most common type of lung cancer seen in the United States and is also the most frequently occurring histology in nonsmokers. In 2011, an international panel revised the classification of lung adenocarcinoma (see the *Pathologic Evaluation of Lung Cancer* in this Discussion).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 of Lung Nodules

A section on evaluating suspicious lung nodules was recently added to the NCCN Guidelines (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁶³ This diagnostic section describes the evaluation of suspicious pulmonary nodules that are seen on low-dose CT scans.⁶³ The diagnostic algorithm for pulmonary nodules in the NCCN Guidelines for NSCLC incorporates information from the NCCN Guidelines for Lung Cancer Screening. Risk assessment is used to determine which individuals are at high risk for lung cancer and thus are candidates for low-dose CT.



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Solid and subsolid nodules are the 2 main types of pulmonary nodules that may be seen on low-dose CT scans. The Fleischner Society has recommendations for patients with solid and subsolid nodules.^{64,65}

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.^{64,66-68} 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.^{61,64,66,67,69,70} 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.^{71,72} Solid and part-solid nodules are more likely to be invasive, faster-growing cancers, factors that are reflected in the increased suspicion and follow-up of these nodules (see *Follow-up* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{63-65,73,74}

All findings and patient factors need to be carefully evaluated in a multidisciplinary diagnostic team before establishing a diagnosis of lung cancer and before starting treatment. The NCCN Guidelines recommend biopsy or surgical excision for highly suspicious nodules seen on low-dose CT scans or further surveillance for nodules with a low suspicion of cancer depending on the type of nodule and a multidisciplinary evaluation of other patient factors (see *Risk Assessment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients having repeat scans, the most important radiologic factor is change or stability of a nodule when compared with a previous imaging study. False-positive results (eg, benign intrapulmonary lymph nodes, noncalcified granulomas) frequently occurred with low-dose CT when using the original cutoffs from the NLST.⁵⁵ However, it is anticipated that

the revised cutoff values recently recommended by the American College of Radiology will decrease the rate of false-positive results from low-dose CT.^{75,76}

The NCCN Guidelines recommend that the diagnostic strategy should be individualized for each patient depending on the size and location of the tumor, the presence of mediastinal or distant disease, patient characteristics (eg, comorbidities), and local expertise. The diagnostic strategy needs to be decided in a multidisciplinary setting. Decisions regarding whether a biopsy (including what type of biopsy) or surgical excision is appropriate depend on several factors as outlined in the NSCLC algorithm (see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For example, a preoperative biopsy may be appropriate if an intraoperative diagnosis seems to be difficult or very risky. The preferred biopsy technique depends on the site of disease and is described in the NSCLC algorithm (see *Principles of Diagnostic Evaluation*). For example, radial endobronchial ultrasound (EBUS), navigational bronchoscopy, or transthoracic needle aspiration (TTNA) are recommended for patients with suspected peripheral nodules.⁷⁷ PET imaging is useful before selecting a biopsy site, because it is better to biopsy the site that will confer the highest stage. Patients with suspected nodal disease should be assessed by endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA), EBUS–guided transbronchial needle aspiration (EBUS-TBNA), navigational bronchoscopy, or mediastinoscopy (see *Mediastinoscopy* in this Discussion and *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

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



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Staging in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer). Diagnosis, staging, and planned resection (eg, lobectomy) are ideally one operative procedure for patients with early-stage disease (see the *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A preoperative or intraoperative tissue diagnosis of lung cancer should be established before doing a lobectomy.

Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify the histologic type of the lung cancer, determine the extent of invasion, determine whether it is primary lung cancer or metastatic cancer, establish the cancer involvement status of the surgical margins (ie, positive or negative margins), and do molecular diagnostic studies to determine whether certain gene alterations are present (eg, epidermal growth factor receptor [EGFR] mutations) (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁷⁸ Data show that targeted therapy is potentially very effective in patients with specific gene mutations or rearrangements (see *EGFR Mutations* and *ALK Gene Rearrangements* in this Discussion).^{5,79-84} Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, FNA biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.^{77,85} Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC.^{86,87} However, diagnosis may be more difficult when using small biopsies and cytology.⁶⁹ In addition, the mediastinal lymph nodes are systematically sampled to assess the staging and therapeutic options. Other lung diseases also need to be ruled out (eg, tuberculosis, sarcoidosis).^{88,89}

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.⁹⁰ In 2011, the classification for lung adenocarcinoma was revised by an international panel (see *Adenocarcinoma* in this Discussion).⁶¹ The revised classification requires immunohistochemical, histochemical, and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁹¹ 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, the term *former BAC* is used. The categories for adenocarcinoma include: 1) AIS (formerly BAC), which is a preinvasive lesion; 2) MIA; 3) invasive adenocarcinoma (includes formerly nonmucinous BAC); and 4) variants of invasive adenocarcinoma (includes formerly mucinous BAC). Both AIS and MIA are associated with excellent survival if they are resected. The international panel and NCCN recommend that all patients with adenocarcinoma be tested for EGFR mutations; the NCCN Panel also recommends that these patients be tested for anaplastic lymphoma kinase (ALK) gene rearrangements and other genetic alterations. The terms *AIS*, *MIA*, and *large cell carcinoma* should not be used for small samples because of challenges with cytology specimens.⁶¹



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Immunohistochemical Staining

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung (eg, breast, prostate, colorectal), to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the NSCLC algorithm (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). However, limited use of immunohistochemistry in small tissue samples is recommended to conserve tumor tissue for molecular studies, especially in patients with advanced disease.^{87,92} Although cytology can be used to distinguish adenocarcinomas from squamous cell carcinomas, immunohistochemistry is also useful for poorly differentiated NSCLC in small biopsy and/or cytology specimens.^{61,93} 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.^{61,93} Other markers (eg, p40, napsin A) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.^{94,95}

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma.^{96,97} 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.⁹⁸ Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin antibody),⁹⁹ HMBW-1, and cytokeratin 5/6.^{96,97} 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).^{96,97,100}

TTF-1 is very important in distinguishing primary lung adenocarcinoma from metastatic adenocarcinoma, because most primary adenocarcinomas are TTF-1 positive. TTF-1 is typically negative for squamous cell carcinoma.⁹³ However, TTF-1 is positive in tumors from patients with thyroid cancer.¹⁰¹ In addition, thyroglobulin is present in tumors from patients with thyroid cancer, while it is negative in lung cancer tumors. Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20-, whereas metastatic adenocarcinoma of the colorectum is usually CK7- and CK20+. CDX2 is a marker for metastatic gastrointestinal malignancies that can be used to differentiate them from primary lung tumors. All typical and atypical carcinoid tumors are positive for chromogranin and synaptophysin, whereas SCLC is negative in 25% of cases.

Although the cytologic diagnosis of NSCLC is generally reliable, it is more difficult to diagnose SCLC.^{77,93,102} 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.^{103,104} 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.¹⁰⁵ Data suggest that microRNA expression can be used to distinguish SCLC from NSCLC.¹⁰⁶

Staging

The NCCN Guidelines use the AJCC (7th edition) staging system for lung cancer.¹⁰⁷ The stage grouping is summarized in Table 2 of the



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staging tables (see *Staging* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The descriptors of the TNM classification scheme are summarized in Table 3 of the staging tables (see *Staging*). The lung cancer staging system was revised by the International Association for the Study of Lung Cancer (IASLC)^{108,109} and was adopted by the AJCC.^{110,111} 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 2004 to 2010, the overall 5-year relative survival rate for lung cancer was 16.8% in the United States.² Of lung and bronchial cancer cases, 15% 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 6% the staging information was unknown. The corresponding 5-year relative survival rates were 54% for localized, 26.5% for regional, 4.0% for distant, and 7.4% for unstaged.² However, these data include SCLC, which has a poorer prognosis.

Five-year survival after lobectomy for pathologic stage I NSCLC ranges from 45% to 65%, depending on whether the patient has stage 1A or 1B disease and on the location of the tumor.¹¹³ 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%.¹¹⁴ Of patients with stage I disease who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Predictive and Prognostic Biomarkers

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

Predictive biomarkers include the ALK fusion oncogene (fusion between ALK and other genes [eg, echinoderm microtubule-associated protein-like 4]) and sensitizing EGFR mutations (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Emerging biomarkers include HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and MET amplification (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines). The presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy; therefore, these mutations are referred to as *sensitizing* EGFR mutations (see *EGFR Mutations* in this Discussion).^{115,116} However, the presence of the EGFR exon 19 deletion (LREA) or exon 21 L858R mutation does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.¹¹⁷ The ALK fusion oncogene (ie, ALK gene rearrangement) is a predictive biomarker that has been identified in a small subset of patients with NSCLC (see *ALK Gene Rearrangements* in this Discussion and *Principles of Pathologic Review* in the NCCN Guidelines). Other gene rearrangements (ie, gene fusions) have recently been identified (such as ROS1, RET) that are susceptible to targeted therapies.¹¹⁸⁻¹²²



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Testing for ALK gene rearrangements and EGFR mutations is recommended (category 1) in the NSCLC algorithm for patients with adenocarcinoma so that patients with these genetic abnormalities can receive effective treatment with targeted agents such as erlotinib, afatinib, crizotinib, and ceritinib (see *Targeted Therapies* in this Discussion and in the NCCN Guidelines for Non-Small Cell Lung Cancer).¹²³⁻¹²⁵ Although rare, patients with ALK rearrangements or sensitizing EGFR mutations can have mixed squamous cell histology.^{126,127} Therefore, testing for ALK rearrangements and EGFR mutations can be considered in patients with squamous cell histology if they are never smokers, small biopsy specimens were used for testing, or mixed histology was reported. EGFR, KRAS, and ALK genetic alterations do not usually overlap.¹²⁸

Patients with NSCLC may have other genetic alterations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{79,129,130} Mutation screening assays for detecting multiple biomarkers simultaneously (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) have been developed that can detect more than 50 point mutations, including EGFR.^{131,132} However, these multiplex polymerase chain reaction (PCR) systems do not detect gene rearrangements, because they are not point mutations. ALK gene rearrangements can be detected using fluorescence in situ hybridization (FISH) (see *ALK Gene Rearrangements* in this Discussion). Next-generation sequencing (NGS) can detect panels of mutations and gene rearrangements.¹³³⁻¹³⁵ Other driver mutations and gene rearrangements (ie, driver events) are being identified such as HER2 (also known as ERBB2) and BRAF V600E mutations, ROS1 and RET gene rearrangements, and MET amplification.^{118,120,122,136-143} Targeted agents are available for patients with NSCLC who have these other genetic alterations, although they

are FDA approved for other indications (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{133,144} Thus, the NCCN Panel strongly endorses broader molecular profiling to identify rare driver mutations using multiplex/NGS to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these targeted agents.¹²⁴ Several online resources are available that describe NSCLC driver events such as DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment)¹⁴⁵ and *My Cancer Genome*.^{131,146} 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).¹⁴⁷ KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.^{115,148,149} EGFR, KRAS, and ALK genetic alterations do not usually overlap.¹²⁸ TKI therapy is not effective in patients with KRAS mutations and ALK gene rearrangements.

EGFR Mutations

In patients with NSCLC, the most commonly found EGFR mutations are deletions in exon 19 (Exon19del [with conserved deletion of the LREA sequence] in 45% of patients) 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).¹⁵⁰ Thus, these mutations are referred to as sensitizing EGFR mutations. Erlotinib is commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib may be used if available. Afatinib is an oral TKI that inhibits the entire ErbB/HER family of receptors



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including EGFR and HER2.^{151,152} The FDA has approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.^{153,154}

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.¹⁵⁵ Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).¹⁵⁶ Primary resistance to TKI therapy is associated with KRAS mutations and ALK gene rearrangements. Patients with exon 20 insertion mutations are also resistant to TKIs.¹⁵⁷⁻¹⁶⁰ The EGFR T790M mutation is associated with acquired resistance to TKI therapy and has been reported in about 50% of patients with disease progression after initial response to erlotinib.¹⁶¹⁻¹⁶⁶ Most patients with sensitizing EGFR mutations become resistant to erlotinib (or gefitinib) after about 8 to 16 months of TKI therapy.¹⁶¹ However, studies suggest the T790M mutation may also occur in patients who have not previously received TKI therapy.¹⁶⁷ Acquired resistance may be associated with histologic transformation from NSCLC to SCLC and with epithelial to mesenchymal transition (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).¹⁶⁸⁻¹⁷⁰

DNA mutational analysis is the preferred method to assess for EGFR status.¹⁷¹⁻¹⁷³ Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18 to 21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available.^{155,172,174-176} Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY® system, SNaPshot® Multiplex System) can detect more than 50 point mutations, including EGFR.¹³² NGS can also be used to detect EGFR mutations.¹³⁴

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.¹⁵⁰ Retrospective studies have shown an objective response rate of approximately 80% with a median progression-free survival (PFS) of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and a sensitizing EGFR mutation.¹¹⁵ 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, 21% other mutations) is 55% with a median PFS of 9.2 months.¹¹⁶ 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.¹²⁶ Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.¹²⁶

Recent data suggest that erlotinib (or 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.^{154,177-182} Data show that PFS is improved with use of EGFR TKI in patients with sensitizing EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.^{154,177} Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.^{177,183} Based on this data and the FDA approval, erlotinib (or gefitinib) is recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.¹⁷⁷ In a recent phase 3 randomized trial, patients receiving afatinib had decreased cough,



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decreased dyspnea, and improved health-related quality of life when compared with those receiving cisplatin/pemetrexed.¹⁸³ Based on this data and the FDA approval, afatinib is recommended (category 1) as first-line systemic therapy in patients with sensitizing EGFR mutations.¹⁵⁴ However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.¹⁵⁴

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.⁸⁴ These patients are resistant to EGFR TKIs but have similar clinical characteristics to those with EGFR mutations (ie, adenocarcinoma histology, never smokers, or light smokers) except they are more likely to be men and may be younger.¹³⁰ In these selected populations, estimates are that about 30% of patients will have ALK rearrangements.^{130,184} 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.¹²⁷ It can be challenging to accurately determine histology in small biopsy specimens; thus, patients may have mixed squamous cell histology (or squamous components) instead of pure squamous cell. The NCCN Panel recommends testing for ALK rearrangements if small biopsy specimens were used to assess histology, mixed histology was reported, or patients never smoked. A molecular diagnostic test (using FISH) has been approved by the FDA for detecting ALK rearrangements and is a prerequisite before treatment with crizotinib. Studies suggest that immunohistochemistry can be used to screen for ALK rearrangements; if positive, FISH analysis can be done to confirm ALK positivity.^{125,128,185-191} NGS can also be used to assess whether ALK rearrangements are present.^{192,193}

Crizotinib—an inhibitor of ALK, ROS1, and MET tyrosine kinases—is approved by the FDA for patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements (ie, ALK-positive disease).¹⁹⁴⁻¹⁹⁸ Crizotinib yields very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements.^{84,194,199,200} Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).^{199,201,202} However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.¹⁹⁶ Patients have responded rapidly to crizotinib with improvement in symptoms (eg, cough, dyspnea, pain); median time to progression on crizotinib is about 7 months to 1 year.^{203,204} Randomized phase 3 trials have compared crizotinib with standard second-line (ie, subsequent) chemotherapy (PROFILE 1007) and with standard first-line therapy (PROFILE 1014).^{5,194,205} 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).¹⁹⁴ Based on this trial, crizotinib is recommended (category 1) for first-line therapy in patients with ALK-positive NSCLC (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Subsequent therapy with crizotinib improved PFS (7.7 vs. 3.0 months; $P < .001$) and response rate (65% vs. 20%; $P < .001$) when compared with single-agent therapy (either docetaxel or pemetrexed) in patients with ALK-positive NSCLC who had progressed after first-line chemotherapy.¹⁹⁵ Based on this trial, crizotinib is recommended as subsequent therapy in patients with ALK-positive disease. For the 2015 update, the phrase *subsequent* therapy was substituted for the terms *second-line* or *third-line* systemic therapy, because the line of therapy may vary depending on previous treatment with targeted agents.



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Newer ALK inhibitors are in development.²⁰⁶⁻²¹⁴ Ceritinib is an orally active TKI of ALK, which also inhibits the insulin-like growth factor--1 (IGF-1) receptor but not MET. A recent expanded phase I trial showed that ceritinib was very active in 122 patients with locally advanced or metastatic NSCLC who have ALK gene rearrangements.²⁰⁸ The overall response rate to ceritinib was 56% in patients who had previously received crizotinib; the median PFS was 7 months. Based on this study, ceritinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who progress on or are intolerant to crizotinib. The NCCN Panel recommends ceritinib for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib based on the data from Shaw et al and the recent FDA approval.²⁰⁸

ALK rearrangements and sensitizing EGFR mutations are generally mutually exclusive.^{128,215,216} Thus, erlotinib (or gefitinib) or afatinib is not recommended as subsequent therapy in patients with ALK rearrangements who relapse on crizotinib (see *ALK Positive: Subsequent Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{129,130} Likewise, crizotinib or ceritinib is not recommended for patients with sensitizing EGFR mutations who relapse on erlotinib (or gefitinib) or afatinib. For patients who progress on crizotinib, subsequent treatment for ALK-positive NSCLC includes ceritinib (see *Ceritinib* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer).^{199,217,218} Continuing crizotinib may also be appropriate for patients who progress on crizotinib.²¹⁹

KRAS Mutations

Data suggest that approximately 25% of adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation.^{82,115,133,144,149} KRAS mutation prevalence is associated with

cigarette smoking.²²⁰ Patients with KRAS mutations appear to have a shorter survival than patients with wild-type KRAS.^{147,149,221} KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.^{82,115,148} Overlapping EGFR and KRAS mutations generally do not occur (<1%).^{128,222} Therefore, KRAS testing may identify patients who may not benefit from further molecular testing.^{124,148} Targeted therapy is not currently available for patients with KRAS mutations, although MEK inhibitors are in clinical trials.^{144,207,223}

Treatment Approaches

Surgery, RT, and chemotherapy 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.²²⁴ However, thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated. 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.²²⁴⁻²²⁸ Although frailty is an increasingly recognized predictor of surgical and other treatment morbidity, a preferred frailty assessment system has not been established.^{229,230}



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The *Principles of Surgical Therapy* are described in the NSCLC algorithm and are summarized here (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who should participate in multidisciplinary clinics and/or tumor boards for patients with lung cancer. Surgery may be appropriate for select patients with uncommon types of lung cancer (eg, superior sulcus, chest wall involvement) (see the NCCN Guidelines for Non-Small Cell Lung Cancer).²³¹ 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.^{224,232,233} Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).²³⁴⁻²³⁸ Resection (including wedge resection) is preferred over ablation.^{224,233} Wide wedge resection may improve outcomes.²³⁹ Patients with medically inoperable disease may be candidates for SABR, also known as stereotactic body RT (SBRT). If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended.²⁴⁰ (see *Stereotactic Ablative Radiotherapy* in this Discussion).²⁴¹

Lymph Node Dissection

A randomized trial (ACOSOG Z0030) compared systematic mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in patients with N0 (no demonstrable metastasis to regional lymph nodes) or N1 (metastasis to lymph nodes in the ipsilateral peribronchial and/or hilar region, including direct extension) NSCLC disease. In patients with early-stage disease who had negative nodes by systematic lymph node dissection, complete mediastinal lymph node dissection did not improve survival.²⁴²⁻²⁴⁴ 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.²⁴² 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.²⁴⁵ Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because it would substantially increase the surgical risk.

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



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Stage IIIA N2 Disease

The role of surgery in patients with pathologically documented stage IIIA (N2) disease is discussed in the NSCLC algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer) and is 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).^{246,247} Randomized controlled trials suggest that surgery does not increase survival in these patients.^{248,249} However, one of these trials (EORTC) only enrolled patients with unresectable disease.²⁴⁹ Most clinicians agree that resection is appropriate for patients with a negative preoperative mediastinum and with a single positive node (<3 cm) found at thoracotomy.²⁵⁰ Neoadjuvant therapy is recommended for select patients. In patients with N2 disease, 50% of the NCCN Member Institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.²⁵¹ 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.²⁵² Clinicians also agree that resection is not appropriate for patients with multiple pathologically proven malignant lymph nodes greater than 3 cm; definitive chemoradiotherapy is recommended for these patients.

The NCCN Panel believes that surgery may be appropriate for select patients with N2 disease, especially those who respond to induction chemotherapy (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{246,253} However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.^{248,253-259} Patients with resectable N2

disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.^{253,260}

Thorascopic Lobectomy

Video-assisted thoracic surgery (VATS), which is also known as thorascopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{261,262} Published studies suggest that thorascopic lobectomy has several advantages over the standard thoracotomy.²⁶³⁻²⁶⁷ Acute and chronic pain associated with thorascopic lobectomy are minimal; thus, this procedure requires a shorter length of hospitalization.^{268,269} Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.²⁷⁰⁻²⁷⁴ Thorascopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.²⁷⁵⁻²⁷⁸

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.²⁷⁹⁻²⁸³ Thorascopic lobectomy has also been shown to improve discharge independence in older populations and in patients at high risk.^{284,285} Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.^{286,287} Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy (including robotic-assisted approaches) is recommended in the NSCLC algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as standard principles of thoracic surgery are not compromised (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).²⁸⁸⁻²⁹¹



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Robotic VATS seems to be more expensive with longer operating times than conventional VATS.^{292,293}

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.²⁹⁴⁻²⁹⁹ These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery (SRS) for brain metastases are also discussed in this section. The abbreviations for RT are defined in the NSCLC algorithm (see Table 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

General Principles

Treatment recommendations should be made by a multidisciplinary team. Because RT has a potential role in all stages of NSCLC, as either definitive or palliative therapy, input from board-certified radiation oncologists who perform lung cancer RT as a prominent part of their practice should be part of the multidisciplinary evaluation or discussion for all patients with NSCLC. Uses of RT for NSCLC include: 1) definitive therapy for locally advanced NSCLC, generally combined with chemotherapy; 2) definitive therapy for early-stage NSCLC in patients with contraindications for surgery; 3) preoperative or postoperative therapy for selected patients treated with surgery; 4) salvage therapy for limited recurrences and metastases; and/or 5) palliative therapy for patients with incurable NSCLC.^{240,300-307} 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.³⁰⁸⁻³¹² 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).^{240,307,313,314} Interventional radiology ablation is an option for selected patients who are medically inoperable.^{224,315,316} By extrapolation from surgical data, adjuvant chemotherapy (category 2B) may be considered after definitive RT/SABR in patients with high-risk factors (eg, large tumors >4 cm in size). SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy (eg, major medical comorbidity or severely limited lung function). However, resection is recommended for patients with early-stage NSCLC who are medically fit (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).³¹⁷ Definitive chemoradiation is recommended for patients with locally advanced (ie, stage II–III) disease who are not appropriate surgical candidates.³¹⁸

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.^{307,319-321} Shorter courses of palliative RT are preferred for patients with poor PS and/or shorter life expectancy (eg, 17 Gy in 8.5 Gy fractions) for patients with symptomatic chest disease (see Table 4 in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Higher dose and longer course thoracic RT (eg, ≥30 Gy in 10 fractions) are associated with modestly improved survival and symptoms, especially in patients with good PS.³¹⁹ The RT recommendations for patients with stages I to IV are described in the



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NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

The indications for using preoperative or postoperative chemoradiation or RT alone are described in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with clinical stage I or II NSCLC who are upstaged to N2+ after surgery, postoperative chemotherapy can be administered followed by postoperative RT depending on the margin status (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{296,322} For clinical stage III NSCLC, definitive concurrent chemoradiation is recommended (category 1). However, the optimal management of patients with potentially operable stage IIIA NSCLC is controversial and is discussed in detail in the algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{246,248,258,323} For patients undergoing preoperative therapy before surgical resection of stage IIIA NSCLC, some prefer chemotherapy alone rather than chemoradiotherapy for the preoperative treatment;²⁵² RT should generally be given postoperatively if not given preoperatively. NCCN Member Institutions are evenly split in their use of neoadjuvant chemotherapy versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.²⁴⁶ 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,²⁴⁸ 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.³²⁴⁻³²⁶ When giving preoperative RT to less than definitive doses (eg, 45 Gy), one should be prepared up front to continue to a full definitive dose of RT without interruption if the patient does not proceed to surgery for some reason. For these reasons, when considering trimodality therapy, the treatment plan—including assessment for resectability and the type of resection—should be decided before initiation of any therapy.

Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints

The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in the *Principles of Radiation Therapy* in the NSCLC algorithm (see Table 4 in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{295,297,304,324-327} After surgery, lung tolerance to RT is much less than for patients with intact lungs. Although the dose volume constraints for conventionally fractionated RT for normal lungs are a useful guide (see Table 5 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer), more conservative constraints should be used for postoperative RT.

For definitive RT, the commonly prescribed dose is 60 to 70 Gy in 2 Gy fractions over 6 to 7 weeks.³²⁸ The use of higher RT doses is discussed in the NSCLC algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).³²⁹⁻³³⁴ 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.³³⁴⁻³³⁸



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Reports 50, 62, and 83 from the International Commission on Radiation Units and Measurements provide a formalism for defining RT target volumes based on grossly visible disease, potential microscopic extension, and margins for target motion and daily positioning uncertainty (see Figure 1 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer);^{339,340} the ACR-ASTRO guidelines are also a helpful reference.^{308,341,342} 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*).³⁴³ These constraints are mainly empirical and have for the most part not been validated rigorously.³⁴⁴⁻³⁵¹ However, the QUANTEC review provides the most comprehensive estimates from clinical data of dose-response relationships for normal tissue complications.³⁵²⁻³⁵⁶ For patients receiving postoperative RT, more strict 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 with nodal involvement. PET/CT can significantly improve target delineation accuracy, especially when there is atelectasis or contraindications to intravenous CT contrast.³⁵⁷ In the NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or IMRT (see *Radiation Therapy Simulation, Planning, and Delivery* in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{311,358-362} Respiratory motion should be managed. The report from the AAPM Task Group 76

is a useful reference for implementing a broad range of motion management strategies as described in the NSCLC algorithm (see *Radiation Therapy Simulation, Planning, and Delivery* in the NCCN Guidelines for Non-Small Cell Lung Cancer).³⁶³

Stereotactic Ablative Radiotherapy

SABR (also known as SBRT) uses short courses of very conformal and dose-intensive RT precisely delivered to limited-size targets.³⁶⁴⁻³⁶⁶

Clinical literature, including prospective multi-institutional trials, has demonstrated the efficacy of SABR for patients with inoperable stage I NSCLC or for those who refuse surgery.^{240,367-370} 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%.³¹⁴ 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.^{224,314,316,317,362,369,371-376} Substantially higher survival has been observed in patients with potentially operable disease who are treated with SABR; survival is comparable in population-based comparisons to surgical outcomes.^{317,368,377-381}

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 who are high risk, elderly, or refuse surgery after appropriate consultation (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{224,370,372,382} SABR can also be used for patients with limited lung metastases or limited metastases to other body sites.^{364,370,383-389} After SABR, assessment of recurrences by imaging can be challenging because of benign inflammatory/fibrotic changes that can remain FDG avid for 2 or more years after treatment, emphasizing the importance of follow-up by a team with experience interpreting such post-treatment effects.^{390,391} This is particularly



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relevant, because selected patients with localized recurrences after SABR may benefit from salvage surgery or re-treatment with SABR.³⁹²⁻³⁹⁶

SABR fractionation regimens and normal tissue constraints are provided in the NSCLC algorithm (see Tables 2 and 3 in the *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{367,369,376,397-404} 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. Aggressive local therapy of oligometastatic disease in the adrenal gland remains controversial and thus is a category 2B recommendation; SRS or SABR for oligometastases to the brain or other body sites, respectively, may be useful in these settings (see *Stage IV, M1b: Limited Sites/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{231,370,405,406} However, local therapy combined with targeted therapy is a category 2A recommendation for patients with ALK rearrangements or sensitizing EGFR mutations.^{407,408} 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.⁴⁰⁹ 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.^{224,240,316}

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.^{7,410} Options for treatment of single brain metastases include surgery followed by whole brain RT (category 1) for selected patients (eg, with symptomatic metastases or when

tumor tissue is needed), surgery followed by SRS, SRS followed by WBRT (category 1), or SRS alone (see the NCCN Guidelines for Central Nervous System Cancers and for Non-Small Cell Lung Cancer).^{386,410-417} Decisions about whether to recommend surgery, whole brain RT, SRS, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.^{411,418-420} Treatment should be individualized for patients with recurrent or progressive brain lesions.⁴²¹

For multiple metastases (eg, >3), WBRT is a standard option, although SRS is also an option (see the NCCN Guidelines for Central Nervous System Cancers).⁴²²⁻⁴²⁴ WBRT is associated with measurable declines in neurocognitive function in clinical trials, particularly with increasing dose and advanced age of the patient.⁴²⁵⁻⁴²⁷ On the other hand, control of brain metastases confers improved neurocognitive function.^{428,429} For limited metastases, randomized trials have found that the addition of WBRT to SRS decreases intracranial recurrence but does not improve survival and may increase the risk of cognitive decline.^{429,430} Thus, an approach of SRS alone may strike an appropriate balance in patients with limited volume metastases.⁴³¹ Similarly, some have suggested that resection followed by SRS to the cavity (instead of resection followed by WBRT) will decrease the risk of neurocognitive problems.^{432,433} A recent study suggests that using IMRT to avoid the hippocampus may help decrease memory impairment after WBRT.⁴³⁴

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



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disease is node negative (see *Stereotactic Ablative Radiotherapy* in this Discussion and see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.⁴³⁵⁻⁴³⁷ Some studies suggested that neoadjuvant chemotherapy (which is the administration of chemotherapy before surgery) is as effective as and better tolerated than adjuvant chemotherapy (see *Neoadjuvant Chemotherapy Followed by Surgery: Trial Data* in this Discussion).^{246,438-445} However, a recent randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.⁴⁴⁶ Neoadjuvant chemotherapy is also referred to as induction chemotherapy or preoperative chemotherapy. 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.^{224,447} Concurrent chemoradiation is superior to sequential therapy for patients with unresectable stage III disease.⁴⁴⁸⁻⁴⁵¹

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.⁴⁵²⁻⁴⁵⁷ Data show that early palliative care combined with standard care improves quality of life, mood, and survival in patients with metastatic NSCLC, even though these patients had less aggressive therapy when compared with those receiving standard care alone.⁴⁵⁸ Patients should receive treatment for debilitating symptoms.^{7,459,460} A recent study also suggests that social support, such as being married, is as effective as chemotherapy.⁴⁶¹ Surgery is rarely done for patients with stage IV disease. However, surgical resection of a solitary brain metastasis may improve survival in selected patients with stage IV disease and is recommended in the NCCN Guidelines for Non-Small Cell Lung Cancer (see also the NCCN Guidelines for Central Nervous System Cancers).⁴⁶² Local therapy of a solitary metastasis

located in sites other than the brain remains controversial and thus is a category 2B recommendation; however, SRS or SABR may be useful in these settings (see *Stage IV, M1b: Solitary Site/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{231,370} The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

Surgery Followed by Chemotherapy: Trial Data

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

The International Adjuvant Lung Cancer Trial (IALT) reported a statistically significant survival benefit with cisplatin-based adjuvant therapy in patients with completely resected stage I, II, or III NSCLC.⁴³⁵ The study included 1867 patients with surgically resected lung cancer who were randomly assigned either to cisplatin-based adjuvant chemotherapy or to observation, with a median follow-up duration of 56 months. A significantly higher survival rate (45% vs. 40% at 5 years; HR for death, 0.86; 95% CI, 0.76–0.98; $P < .03$) and disease-free survival rate (39% vs. 34% at 5 years; HR, 0.83; 95% CI, 0.74–0.94; $P < .003$) were observed for patients assigned to chemotherapy when compared with observation. IALT data suggest that cisplatin-based adjuvant chemotherapy improves survival 5 years after treatment in patients with completely resected NSCLC. However, after 7.5 years of follow-up, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.⁴⁶³ Data show that adjuvant chemotherapy prevents recurrences.



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The NCIC CTG JBR.10 trial and the ANITA trial compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in early-stage NSCLC. In the JBR.10 trial, 482 patients (ECOG PS of 0–1) with completely resected stage IB (T2, N0) or stage II (T1, N1, or T2, N1) NSCLC were randomly assigned either to vinorelbine plus cisplatin or to observation.⁴³⁶ 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 ($P = .03$). However, updated data from JBR.10 after 9 years of follow-up show that when compared with observation alone, adjuvant chemotherapy is beneficial for patients with stage II disease but not for stage IB disease.⁴⁶⁴ 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 plus cisplatin or to observation.⁴³⁷ 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.⁴³⁷ 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,⁴⁶⁵ however, others prefer to use regimens with less toxicity.^{466,467}

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).⁴⁶⁸ A subgroup analysis found that cisplatin/vinorelbine also increased survival.⁴⁶⁵ 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.^{227,469}

The CALGB 9633 trial assessed paclitaxel/carboplatin in patients with T2, N0, M0, stage IB lung cancer;⁴⁷⁰ updated results have been reported.^{471,472} In this trial, 344 patients were randomly assigned either to paclitaxel/carboplatin or to observation (within 4–8 weeks of resection) with a median follow-up duration of 74 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 6 years was not significantly different, although 3-year survival was significant (80% vs. 73%, $P = .02$).^{471,472} The original results from CALGB suggested that the paclitaxel/carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors 4 cm or more). Thus, the carboplatin/paclitaxel regimen is only recommended for early-stage disease if patients cannot tolerate cisplatin (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁴⁷³ However, it is important to note that the CALGB trial was underpowered for patients with stage 1B disease.⁴⁷⁴

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



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after surgery often make it difficult for patients to tolerate therapy. This problem was demonstrated in the NATCH phase 3 trial (which compared surgery alone to preoperative or postoperative chemotherapy with paclitaxel/carboplatin), because 90% of the preoperative cohort completed 3 cycles of chemotherapy but only 61% of the postoperative cohort completed chemotherapy; however, survival was equivalent among all 3 arms.⁴⁴³ A recent randomized trial found no difference in 3-year overall survival (67.4% vs. 67.7%) with preoperative versus postoperative chemotherapy in patients with early-stage NSCLC; response rate and quality of life were similar in both arms.⁴⁴⁶ Postoperative chemotherapy is considered the standard of care for early-stage disease.²²⁴

Several trials suggest that neoadjuvant therapy is beneficial in patients with N2 disease.^{246,252,442} Other trials suggest that neoadjuvant therapy is beneficial in patients with earlier stage disease.^{439,440,445} 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.⁴⁴⁵

Scagliotti et al published a phase 3 trial of preoperative cisplatin and 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).⁴³⁹ Song et al published a meta-analysis of all available randomized clinical trials evaluating preoperative chemotherapy in resectable NSCLCs. This meta-analysis evaluated 13

randomized trials and found improvement in overall survival in the neoadjuvant chemotherapy arm when compared with the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92; $P = .0001$).⁴³⁸ These results are similar to those recently reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; $P = .02$).⁴³⁹ The benefit from neoadjuvant chemotherapy is similar to that attained with postoperative chemotherapy.^{439,446,468}

Chemoradiation: Trial Data

The major controversies in NSCLC relate to the management of patients with stage IIIA disease (see the *Role of Surgery in Patients with Stage IIIA (N2) NSCLC* [in *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer]). All 3 treatment modalities—surgical resection, chemotherapy, and radiation—may be used in treating stage III disease. The ongoing debate centers on which modalities to use and in what sequence.^{475–479} For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.^{475,476,478,479} Concurrent chemoradiation is superior to sequential chemoradiation.^{448–451} However, concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential chemoradiation. Selection of patients should be based not only on the response to therapy but also on how well the patient tolerates therapy. Frail patients may not be able to tolerate concurrent chemoradiation.^{225,480}

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide, cisplatin/vinblastine, and carboplatin/paclitaxel (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{335,448,450,481–484} For non-squamous NSCLC, other concurrent chemoradiation regimens include carboplatin/pemetrexed and cisplatin/pemetrexed.^{485,486}



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Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.⁴⁵⁴⁻⁴⁵⁶ Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, albumin-bound paclitaxel, and docetaxel), vinorelbine, vinblastine, etoposide, pemetrexed, and gemcitabine (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Combinations using many of these drugs produce 1-year survival rates of 30% to 40% and are superior to single agents. Regimens include carboplatin/paclitaxel, cisplatin/paclitaxel, cisplatin/vinorelbine, gemcitabine/cisplatin, cisplatin/pemetrexed, and docetaxel/cisplatin.^{473,487-490} 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.^{491,492} Gemcitabine/cisplatin is used for patients with squamous cell carcinoma.⁴⁹⁰⁻⁴⁹³ These regimens are commonly used based on phase 3 randomized trials (ie, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).^{490,494}

Recently, many oncologists have been using pemetrexed-based regimens for adenocarcinomas (if patients are not candidates for targeted therapy), because taxane-based regimens are associated with more toxicity (eg, neurotoxicity).^{490,495,496} There are no agents for the prevention of peripheral neuropathy, and few agents are useful for treatment.⁴⁹⁷ 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.^{496,498} However, the POINTBREAK trial showed that both regimens are similar in regard to overall survival rates;

therefore, oncologists may return to using taxane-based regimens, which are well established.⁴⁹⁶ 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.⁴⁹⁹ For patients with advanced NSCLC who have a PS of 2 (ie, poor PS), single-agent chemotherapy or platinum-based combinations are recommended in the NCCN Guidelines.⁵⁰⁰ Single-agent chemotherapy includes vinorelbine, gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.⁵⁰¹⁻⁵⁰³ However, patients with a PS of 2 are often just treated with one chemotherapy agent because of concerns about toxicity.⁵⁰⁴ Results from a recent trial reported that treatment with carboplatin/pemetrexed increased median overall survival when compared with pemetrexed alone (9.3 vs. 5.3 months, $P = .001$) in patients with a PS of 2; however, 4 treatment-related deaths occurred in the carboplatin/pemetrexed arm.^{501,505}

Phase 3 randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.^{506,507} The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.^{493,508,509} Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;^{487,510-512} non-platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.⁵¹³⁻⁵¹⁶ 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;



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or 2) in whom the standard premedications (ie, dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.^{517,518} 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.⁵¹⁹ The FDA has approved albumin-bound paclitaxel/carboplatin for patients with locally advanced or metastatic NSCLC who are not candidates for curative surgery or RT. Based on the recent trial and the FDA approval, the NCCN Panel recommends an albumin-bound paclitaxel/carboplatin regimen as first-line therapy for patients with advanced NSCLC and good PS (0–1).

Targeted Therapies

Specific targeted therapies have been developed for the treatment of advanced NSCLC (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{123,520,521} Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor. Erlotinib, gefitinib, and afatinib are small molecule inhibitors of EGFR. Crizotinib is a small molecule inhibitor that targets ALK, ROS1, and MET. Ceritinib is a small molecule inhibitor that targets ALK and IGF-1 receptor. Erlotinib, afatinib, crizotinib, ceritinib, and gefitinib are oral TKIs.

Bevacizumab

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC. The ECOG recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced non-squamous NSCLC based on the results of phase 2 to 3 clinical trials (ECOG 4599).⁴⁹⁴ To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: non-squamous NSCLC and no recent history

of hemoptysis. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab. For patients with non-squamous NSCLC or NSCLC not otherwise specified (NOS) and PS 0 to 1 who are negative for either ALK gene rearrangements or sensitizing EGFR mutations, bevacizumab in combination with chemotherapy is one of the recommended options (see *Sensitizing EGFR Mutation Positive/First-Line Therapy* or *ALK Positive/First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Erlotinib

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. Recently, the FDA approved the use of erlotinib as first-line therapy in patients with sensitizing EGFR mutations.⁵²² Erlotinib is recommended (category 1) in the NSCLC algorithm as first-line therapy in patients with advanced, recurrent, or metastatic non-squamous NSCLC who have known active sensitizing EGFR mutations regardless of their PS (see *Sensitizing EGFR Mutation Positive* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{82,523-}

⁵²⁵ This recommendation is based on the results of a phase 3 randomized trial (IPASS) in which patients with sensitizing EGFR mutations who received gefitinib had increased PFS (24.9% vs. 6.7%), response rate (71.2% vs. 47.3%), and quality of life with fewer side effects (eg, neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).⁵²⁴ Updated results from the IPASS study show that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of sensitizing EGFR mutation status.⁵²⁶ 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



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EGFR mutations. TKIs are recommended in patients with sensitizing EGFR mutations, because quality of life is improved when compared with chemotherapy. Gefitinib is not readily available in the United States, so erlotinib is often used. Erlotinib is an orally active TKI that is very well tolerated by most patients.

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.⁵²⁷ The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced non-squamous NSCLC.⁵²⁸ Survival was increased in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib first followed by subsequent chemotherapy (11.6 vs. 8.7 months). The OPTIMAL trial found that PFS was increased in patients with sensitizing EGFR mutations who received erlotinib.^{180,181} ASCO recommends that patients be tested for EGFR mutations.⁵²⁹ However, the ESMO Guidelines specify that only patients with non-squamous NSCLC (eg, adenocarcinoma) be assessed for EGFR mutations.⁵⁰⁰ Patients with pure squamous cell carcinoma are unlikely to have sensitizing EGFR mutations; however, those with adenosquamous carcinoma may have mutations.¹²⁶

An updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.^{530,531} 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 switch to erlotinib therapy in patients found to have sensitizing EGFR mutations during chemotherapy (see *EGFR Mutation Positive/ First-Line Therapy* in the NCCN Guidelines for Non-Small Cell

Lung Cancer). Based on this trial, the NCCN Panel considers erlotinib or afatinib plus chemotherapy as a category 2B recommendation.

Afatinib

A randomized phase 3 trial showed that afatinib improved PFS when compared with cisplatin/pemetrexed in patients with metastatic adenocarcinoma who have sensitizing EGFR mutations (11.1 vs. 6.9 months, $P = .001$).¹⁵⁴ The FDA has approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.^{153,532} Based on this phase 3 randomized trial and the FDA approval, the NCCN Panel recommends afatinib for first-line therapy (category 1) in patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{151,154,218} Afatinib is also recommended for subsequent therapy based on data showing efficacy in patients who have progressed after first-line chemotherapy (see *Second-Line and Third-Line (Subsequent) Systemic Therapy* in this Discussion).¹⁵⁰

Crizotinib

Crizotinib is approved by the FDA for patients with locally advanced or metastatic NSCLC who are positive for the ALK gene rearrangement. The approval is based on a phase 2 trial that showed dramatic response rates (>80%) to crizotinib in patients who had previously progressed.^{196,197} Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough. A recent phase 3 trial compared first-line crizotinib versus chemotherapy in patients with ALK rearrangements; patients receiving crizotinib had improved PFS, quality of life, and response rates when compared with those receiving chemotherapy.¹⁹⁴ For the 2015 update, the NCCN Panel revised the recommendation for first-line therapy with crizotinib to category 1 from category 2A based on this phase 3 trial; the panel also feels that crizotinib is appropriate for patients with PS 0 to 4. Crizotinib is also



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recommended as subsequent therapy for patients with ALK rearrangements who have progressed after first-line systemic therapy.¹⁹⁵

Ceritinib

Ceritinib was recently approved by the FDA for patients with ALK-positive metastatic NSCLC who have progressed on or are intolerant to crizotinib. The approval is based on a recent expanded phase I study showing overall response rates of 56% to ceritinib in patients who had previously received crizotinib.²⁰⁸ 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 ceritinib.

Cetuximab

Cetuximab is a monoclonal antibody that targets EGFR. A large phase 3 randomized trial (FLEX) assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC (most patients had stage IV disease).⁵³³ Adding cetuximab slightly increased overall survival (11.3 vs. 10.1 months, $P = .04$). Patients receiving cetuximab had increased grade 4 events versus control (62% vs. 52%, $P < .01$); cetuximab was also associated with grade 2 acne-like rash.

For the 2015 update, cetuximab was removed from the NCCN Guidelines. The benefits of the cetuximab/cisplatin/vinorelbine 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.⁴⁵² Patients may also have comorbid conditions that prevent them from receiving cisplatin such as poor kidney function. The cetuximab/cisplatin/vinorelbine regimen is generally not used in the

United States because of concerns about toxicity.^{452,466,533} Some feel that although the FLEX trial results were statistically significant they were not clinically significant.⁴⁵²

Ramucirumab

A recent phase 3 randomized trial (REVEL) assessed ramucirumab/docetaxel versus docetaxel alone in patients with metastatic NSCLC that had progressed.⁵³⁴ The median overall survival was slightly increased with ramucirumab/docetaxel versus docetaxel alone (10.5 vs. 9.1 mo; $P < .023$). Ramucirumab in combination with docetaxel was recently approved by the FDA for patients with metastatic NSCLC with disease progression on or after platinum-based chemotherapy. For the 2015 update, the NCCN Panel added ramucirumab/docetaxel (category 2A) as an option for subsequent therapy for metastatic NSCLC that has progressed based on the phase 3 randomized trial and the recent FDA approval. The NCCN Panel initially added ramucirumab/docetaxel as a category 2B recommendation (Version 1.2015); however, this recommendation was revised to category 2A with the recent FDA approval (Version 3.2015). Patients with [or without] ALK rearrangements or sensitizing EGFR mutations are eligible for ramucirumab/docetaxel if they have progressed after receiving the appropriate targeted therapy. Contraindications for ramucirumab/docetaxel therapy include risk for severe hemorrhage, grade 3 to 4 gastrointestinal bleeding, gastrointestinal perforation or fistula, and poorly controlled hypertension.

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.⁵³⁵ However, patients are only candidates for maintenance therapy if they have responded to their previous treatment



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(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* therapy refers to the initiation of a different agent that was not included as part of the first-line regimen. Selection of appropriate maintenance therapy depends on several factors (eg, histologic type, presence of mutations or gene rearrangements, PS). Maintenance therapy is an option in the NCCN Guidelines for select patients with tumor response or stable disease and is not considered the standard of care for all patients (eg, not recommended for PS 3–4, those with progression); close observation is also a valid treatment option (see the NCCN Guidelines for Non-Small Cell Lung Cancer).⁵³⁶

Continuation Maintenance Therapy

For continuation maintenance therapy, select agents (which were initially given in combination with conventional chemotherapy) may be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. Single-agent bevacizumab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, platinum-doublet chemotherapy given with bevacizumab) in patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations.^{494,537,538} Single-agent pemetrexed (category 1) may also be given as continuation maintenance therapy in patients with non-squamous NSCLC (who are negative for ALK rearrangements or sensitizing EGFR mutations).^{537,539} A recent phase 3 randomized trial (PARAMOUNT) found that continuation maintenance therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 vs. 2.8 months).^{539,540} Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).^{541,542} Based on the recent trial and the FDA approval, the NCCN Panel recommends

single-agent pemetrexed as continuation maintenance therapy (category 1) in patients with non-squamous NSCLC but without ALK rearrangements or sensitizing EGFR mutations. For the 2015 update, continuation maintenance therapy with cetuximab was removed from the NCCN Guidelines because the first-line regimen of cetuximab/cisplatin/vinorelbine was removed (see *Cetuximab* in this Discussion).

Continuation maintenance therapy using bevacizumab/pemetrexed is also an option in patients with non-squamous NSCLC (who are negative for ALK rearrangements or sensitizing EGFR mutations); this is a category 2A recommendation. Data from the recent POINTBREAK study showed a very slight improvement in PFS (6 vs. 5.6 months) when comparing bevacizumab/pemetrexed versus bevacizumab alone as maintenance therapy; the initial regimens were either bevacizumab/carboplatin/pemetrexed or bevacizumab/carboplatin/paclitaxel.^{496,498} It is important to note that the pemetrexed-based arm was associated with less toxicity (eg, less neurotoxicity, less neutropenia, less hair loss) than the paclitaxel-based arm. When using bevacizumab/pemetrexed versus bevacizumab alone as maintenance therapy, data from the recent AVAPERL study showed a 3.7-month increase in PFS (7.4 vs. 3.7 months); the initial regimen was bevacizumab/cisplatin/pemetrexed.^{543,544}

A phase 3 randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Data show that continuation maintenance therapy with single-agent gemcitabine increased PFS to a greater extent (3.8 months) than switch maintenance therapy with erlotinib (2.9 months) when compared with observation (1.9 months).^{545,546} Another phase 3 randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of



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cisplatin/gemcitabine.⁵⁴⁷ The data showed a slight difference in PFS but no difference in overall survival. The NCCN Guidelines recommend using gemcitabine (category 2B) as continuation maintenance therapy regardless of histology in patients negative for ALK rearrangements or sensitizing EGFR mutations.

Use of continuation maintenance therapy depends on several factors such as whether the patient had minimal toxicity during treatment. A drug vacation may be more appropriate for some patients.⁴⁹⁵ 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.^{495,548} 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).^{548,549}

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.^{495,550} Therefore, switch maintenance therapy is a category 2B recommendation in the NCCN Guidelines. Two phase 3 randomized trials have shown a benefit in PFS and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4–6 cycles) in patients with no apparent disease progression.^{551,552} Switch maintenance therapy with pemetrexed may be initiated in patients with histologies other than squamous cell carcinoma who are negative for ALK rearrangements or sensitizing EGFR mutations.⁵⁵² The FDA has approved maintenance therapy with pemetrexed.⁵⁵³ Likewise, switch

maintenance therapy with erlotinib may be initiated in patients 1) without ALK rearrangements or sensitizing EGFR mutations; or 2) with squamous cell carcinoma.^{546,551}

Both erlotinib and pemetrexed have a category 2B recommendation for switch maintenance therapy in the NCCN Guidelines, although pemetrexed is not recommended for squamous cell carcinoma. The FDA has approved maintenance therapy with erlotinib.⁵⁵⁴ A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.⁵⁵⁵ Switch maintenance therapy with docetaxel is a category 2B recommendation in the NCCN Guidelines for patients with squamous cell carcinoma, because many patients in the delayed chemotherapy arm did not receive docetaxel.

Clinical Evaluation

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

After patients are confirmed to have NSCLC based on a pathologic diagnosis, a clinical evaluation needs to be done (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with symptoms, the clinical stage is initially determined from disease history (ie, cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests (see *Evaluation* and *Clinical Stage* in the



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NCCN Guidelines for Non-Small Cell Lung Cancer). Note that for some patients, the diagnosis, staging, and surgical resection are done during the same operative procedure. A multidisciplinary evaluation should be done before treatment. The NCCN Panel also recommends that smoking cessation advice, counseling, and pharmacotherapy be provided to patients.^{32,556-558} Based on the initial evaluation, the clinical stage is determined and the patient is assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

Additional Pretreatment Evaluation

Mediastinoscopy

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease); however, CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer (see *Mediastinoscopy* and *Other Imaging Studies* in this Discussion).⁵⁵⁹⁻⁵⁶² 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 PET/CT scan does not suggest mediastinal node involvement. Mediastinoscopy may also be appropriate to confirm mediastinal node involvement in patients with a positive PET/CT scan. In contrast, because of the low prior probability of lymph node involvement in patients with peripheral T1ab, N0 lesions,⁵⁶³ some NCCN Member Institutions do not use routine mediastinoscopy in these patients, which is reflected in the category 2B recommendation.

However, in patients with peripheral T2a, central T1ab, or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy and/or EUS-FNA and EBUS-TBNA are recommended (see *Other Imaging Studies* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer).

Dillemans et al have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT.⁵⁶⁴ 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.⁵⁶⁵

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.⁵⁶⁰ 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.^{559,566,567} However, PET/CT is even more sensitive and is recommended by NCCN.^{568–570}

The NCCN Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.⁵⁷¹ Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.⁵⁷² 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.⁵⁷³ 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%.⁵⁷⁴ Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.^{575,576} The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% vs. 65%). PET/CT has been shown to be useful in restaging patients after adjuvant therapy.^{577,578}

When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.⁵⁶⁸ However, positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation (eg, MRI of bone). If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation.^{559,579} 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.^{580–583} 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.⁵⁸⁴ In patients with positive nodes on CT or PET, EBUS-TBNA can be used to clarify the results.^{585,586} However, in patients with negative findings on EBUS-TBNA, conventional mediastinoscopy can be done to confirm the results.^{581,586–588} Note that EBUS is also known as endosonography.

The routine use of bone scans (to exclude bone metastases) is not recommended. Brain MRI (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.⁵⁸⁹ Patients with stage IB NSCLC are less likely to have brain metastases; therefore, brain MRI is only a category 2B recommendation in this setting. Note that PET scans are not recommended for assessing the presence of brain metastases (see the NCCN Guidelines for Central Nervous System Cancers).

Initial Therapy

Before treatment, it is strongly recommended that determination of tumor resectability be made by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). *Principles of Radiation Therapy* recommends doses for RT (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In addition, the NCCN Guidelines also recommend regimens for chemotherapy and chemoradiation (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy*, *Chemotherapy Regimens Used with Radiation Therapy*, and *Systemic Therapy for Advanced or Metastatic Disease*).



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Stage I, Stage II, and Stage IIIA Disease

Depending on the extent and type of comorbidity present, patients with stage I or a subset of stage II (T1–2, N1) tumors are generally candidates for surgical resection and mediastinal lymph node dissection. Definitive RT, particularly SABR, is recommended for patients with early-stage NSCLC who are medically inoperable or refuse surgery, and can be considered as an alternative to surgery in patients at high risk of complications (see *Stereotactic Ablative Radiotherapy* in this Discussion and see *Initial Treatment* for Stage I and II in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{224,240,307,313,314,590} 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 includes 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 and 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.²³¹ For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

For patients with resectable tumors (T3 invasion, N0–1) in the superior sulcus, the NCCN Panel recommends preoperative concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see *Initial Treatment for Superior Sulcus Tumors* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Preoperative concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.^{231,325,327,591-594} The overall 5-year survival rate is approximately 40%.³²⁷ Patients with possibly resectable superior sulcus tumors should undergo preoperative concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T4 extension, N0–1) in the superior sulcus, definitive concurrent chemoradiation is recommended followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.^{484,595}

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.^{248,448} If full-dose chemotherapy was not given initially as concurrent treatment, then an additional 2 cycles of full-dose chemotherapy can be administered (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{248,448,484}

Multimodality therapy is recommended for most patients with stage III NSCLC.⁴⁸⁰ For patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with negative mediastinal biopsy findings are candidates for surgery. For those patients with resectable lesions, mediastinal lymph node



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dissection or lymph node sampling should be performed during the operation. Those individuals who are medically inoperable should be treated according to the clinical stage (see the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients with (T1–2 or T3) N2 node-positive disease, a brain MRI and PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the NCCN Panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{306,449} Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread (see the NCCN Guidelines for Non-Small Cell Lung Cancer).

When a lung metastasis is present, it usually occurs in patients with other systemic metastases; the prognosis is poor. Therefore, many of these patients are not candidates for surgery; however, systemic therapy is recommended. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery (see *Multiple Lung Cancers* in this Discussion).⁵⁹⁶ 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%.⁵⁹⁷ Intrapulmonary metastases were downstaged in the TNM staging (ie, AJCC 7th edition).^{111,597,598} 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 institutions favor concurrent chemoradiation for positive margins, but sequential chemoradiation is reasonable in frailer patients. For those with N2 nodes and negative margins, sequential chemotherapy (category 1) with RT is recommended. Chemotherapy alone is

recommended for those with N0-1 nodes (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with synchronous solitary nodules (contralateral lung), the NCCN Panel recommend treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the NCCN Guidelines for Non-Small Cell Lung Cancer).⁵⁹⁹

Multiple Lung Cancers

Patients with a history of lung cancer or those with biopsy-proven synchronous lesions may be suspected of having multiple lung cancers (see *Clinical Presentation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{600,601} 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.^{61,231,602,603} Therefore, it is essential to determine the histology of the lung tumor (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Infection and other benign diseases also need to be ruled out (eg, inflammatory granulomas).^{604,605} Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.⁶⁰⁵⁻⁶⁰⁸ The Martini and Melamed criteria are often used to diagnose multiple lung cancers as follows: 1) the histologies are different; 2) the histologies are the same but there is no lymph node involvement and no extrathoracic metastases.⁶⁰⁸

Treatment of multiple lung cancers depends on status of the lymph nodes (eg, N0–1) and on whether the lung cancers are asymptomatic, symptomatic, or at high risk of becoming symptomatic (see *Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{602,609-611} In patients eligible for definitive local therapy, parenchymal-sparing resection is preferred (see the *Principles of*



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Surgical Therapy in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{601,602} VATS or SABR are reasonable options depending on the number and distribution of the tumors requiring local treatment.⁶¹²

Multiple lung nodules (eg, solid, subsolid nodules) may also be detected on low-dose CT scans; some of these nodules can be followed with imaging, whereas others need to be biopsied or excised (see the NCCN Guidelines for Lung Cancer Screening).⁶¹³

Stage IIIB Disease

Stage IIIB tumors comprise 2 groups, including: 1) T1–3, N3 tumors; and 2) T4, N2–3 tumors, which are unresectable and include contralateral mediastinal nodes (T4, N3). Surgical resection is not recommended in patients with T1–3, N3 disease. However, in patients with suspected N3 disease, the NCCN Guidelines recommend pathologic confirmation of nodal status (see *Pretreatment Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{614,615} In addition, PET/CT scans (if not previously done) and brain MRI should also be included in the pretreatment evaluation. If these tests are negative, then treatment options for the appropriate nodal status should be followed (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If N3 disease is confirmed, definitive concurrent chemoradiation (category 1) is recommended followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not initially given concurrently with RT.^{248,448,484,616,617} For metastatic disease that is confirmed by PET/CT scan and brain MRI, treatment is described in the NCCN Guidelines.

For patients with T4, N2–3 disease (stage IIIB), surgical resection is not generally recommended. The initial workup includes biopsies of the N3 and N2 nodes. If these biopsies are negative, the same treatment options may be used as for stage IIIA (T4, N0–1) disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If either the

contralateral or ipsilateral mediastinal node is positive, definitive concurrent chemoradiation therapy is recommended (category 1) followed by 2 cycles of full-dose chemotherapy if full-dose chemotherapy was not given concurrently with RT as initial treatment (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{248,448,484,616-618}

Stage IV Disease

In general, systemic therapy is recommended for patients with metastatic disease (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). This section focuses on patients with limited metastatic disease; management of widespread distant metastases is described in another section (see *Treatment of Recurrences and Distant Metastases* in this Discussion and *Systemic Therapy for Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Pleural or pericardial effusion is a criterion for stage IV, M1a disease. T4 with pleural effusion is classified as stage IV, M1a (see Table 3 in *Staging* in the NCCN Guidelines for Non-Small Cell Lung Cancer).¹¹¹ Although pleural effusions are malignant in 90% to 95% of patients, they may be related to obstructive pneumonitis, atelectasis, lymphatic or venous obstruction, or a pulmonary embolus. Therefore, pathologic confirmation of a malignant effusion by using thoracentesis or pericardiocentesis is recommended. In certain cases where thoracentesis is inconclusive, thoracoscopy may be performed. In the absence of nonmalignant causes (eg, obstructive pneumonia), an exudate or sanguinous effusion is considered malignant no matter what the results of cytologic examination. If the pleural effusion is considered negative, recommended treatment is based on the confirmed T and N stage (see the NCCN Guidelines for Non-Small Cell Lung Cancer). However, all pleural effusions, whether malignant or not, are associated with



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unresectable disease in 95% of cases.⁶¹⁹ In patients with effusions that are positive for malignancy, the tumor is treated as M1a with local therapy (ie, ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer).⁶²⁰

Management of patients with distant metastasis in limited sites (ie, stage IV, M1b) depends on the location of the metastases—a few nodules in the brain or adrenal gland—the diagnosis of which is aided by mediastinoscopy, bronchoscopy, PET/CT scan, and brain MRI. The increased sensitivity of PET/CT scans, compared with other imaging methods, may identify additional metastases and, thus, spare some patients from unnecessary surgery. However, positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Patients with limited oligometastatic disease (eg, single brain or adrenal metastasis) and otherwise limited disease in the chest may benefit from aggressive local therapy to both the primary chest and metastatic sites.^{621,622} Aggressive local therapy may comprise surgery or definitive RT including SABR to each site, and may be preceded or followed by chemotherapy. Recent data suggest that erlotinib combined with SABR or SRS may also be useful.⁴⁰⁷

Metastases to the adrenal gland from lung cancer are a common occurrence, with approximately 33% of patients having such disease at autopsy. In patients with otherwise resectable primary tumors, however, many solitary adrenal masses are not malignant. Any adrenal mass found on a preoperative CT scan in a patient with lung cancer should be biopsied to rule out benign adenoma. Local therapy (category 2B) of the adrenal lesion has produced some long-term survivors when an adrenal metastasis has been found and the lung lesion has been curable (see

the NCCN Guidelines for Non-Small Cell Lung Cancer).⁶²³⁻⁶²⁶ Some NCCN Panel Members feel that local therapy for adrenal metastases is only advisable if the synchronous lung disease is stage I or possibly stage II (ie, resectable). Systemic therapy is another treatment option for adrenal metastasis.

Adjuvant Treatment

Chemotherapy or Chemoradiation

Post-surgical treatment options for patients with stage IA tumors (T1ab, N0) and with positive surgical margins (R1, R2) include re-resection (preferred) or RT (category 2B). Observation is recommended for patients with T1ab, N0 tumors and with negative surgical margins (R0). Patients with T2ab, N0 tumors with negative surgical margins are usually observed. However, chemotherapy now has a category 2A recommendation as adjuvant treatment for patients with high-risk features (including poorly differentiated tumors, vascular invasion, wedge resection, tumors greater than 4 cm, visceral pleural involvement, and incomplete lymph node sampling [Nx]) (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{472,627} 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).^{296,472}

The NCCN Panel recommends chemotherapy (category 1) for patients with negative surgical margins and stage II disease, including 1) T1ab–2a, N1; 2) T2b, N1; or 3) T3, N0 disease.^{468,628} 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. Patients with T1–3,



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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 radiation is recommended for an R2 resection (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Most NCCN Member Institutions favor concurrent chemoradiation for positive margins, but sequential is reasonable in frailer patients. Patients with negative margins may be treated with either 1) chemotherapy (category 1); or 2) sequential chemotherapy plus RT (for N2 only).⁴⁶⁸

As with stage IB and stage II surgically resected disease, adjuvant chemotherapy can be used in patients with stage III NSCLC who have had surgery (see the NCCN Guidelines for Non-Small Cell Lung Cancer). For superior sulcus tumors (T4 extension, N0–1) that convert to a resectable status (ie, become resectable) after preoperative concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If the lesion remains unresectable after preoperative concurrent chemoradiation, the full course of definitive chemo/RT should be completed, followed by chemotherapy as an adjuvant treatment if full doses were not given with concurrent therapy. Among patients with chest wall lesions with T3 invasion–T4 extension, N0–1 disease, those who are initially treated with surgery (preferred) may receive chemotherapy alone if the surgical margins are negative. When surgical margins are positive, they may receive either 1) sequential or concurrent chemoradiation, depending on whether the resection is R1 or R2; 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. A

similar treatment plan is recommended for resectable tumors of the proximal airway or mediastinum (T3–4, N0–1).

For patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2) with no apparent disease progression after initial treatment, recommended treatment includes surgery with (or without) RT (if not given preoperatively) and/or with (or without) chemotherapy (category 2B for chemotherapy) (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Alternatively, if the disease progresses, patients may be treated with either 1) local therapy using RT (if not given previously) with (or without) chemotherapy; or 2) systemic treatment (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with separate pulmonary nodules in the same lobe (T3, N0-1) or ipsilateral non-primary lobe (T4, N0-1), surgery is recommended (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with N2 disease, if the margins are negative, sequential chemotherapy (category 1) with radiation is recommended. If the resection margins are positive in patients with N2 disease, concurrent chemoradiation is recommended for an R2 resection, whereas either concurrent or sequential chemoradiation is recommended for an R1 resection. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients.

Because patients with stage III disease have both local and distant failures, theoretically, the use of chemotherapy may eradicate micrometastatic disease obviously present but undetectable at diagnosis. The timing of this chemotherapy varies (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Such chemotherapy may be given alone, sequentially, or concurrently with RT. In addition, chemotherapy could be given preoperatively or postoperatively in appropriate patients.



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On the basis of clinical studies on neoadjuvant and adjuvant chemotherapy for NSCLC,⁴³⁵⁻⁴³⁷ the NCCN Panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with pemetrexed (for nonsquamous NSCLC), gemcitabine, or docetaxel (see *Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{473,487,490} For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel is an option.^{473,629} A recent 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).⁶³⁰ However, data are conflicting regarding whether bevacizumab benefits elderly patients.^{499,631} A number of phase 2 studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.⁶³²⁻⁶³⁴

Three phase 3 trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.^{442,635-637} 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 and 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.^{636,637} All 3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase 3 studies had a small number of patients, while the SWOG study was stopped early because of the positive results of the IALT study. However, the induction

chemotherapy-surgery approach needs to be compared with induction chemotherapy-RT in large, randomized clinical trials.

Radiation Therapy

After complete resection of clinical early-stage NSCLC, postoperative RT has been found to be detrimental in the context of pathological N0 or N1 stage disease in a meta-analysis of small randomized trials using older techniques and dosing regimens and a population-based analysis of data from SEER.⁶³⁸ However, there was an apparent survival benefit of PORT in patients with N2 nodal stage diagnosed surgically.³²² The analysis of the ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.²⁹⁶ Postoperative adjuvant sequential chemotherapy with RT is recommended for patients with T1–3, N2 disease and negative margins (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A meta-analysis assessed postoperative chemotherapy with (or without) postoperative RT in patients mainly with stage III disease.⁶²⁸ In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemo/RT. Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide. The ACR Appropriateness Criteria® provide specific recommendations for postoperative adjuvant therapy.^{639,640}

Either concurrent or sequential chemoradiation may be used for postoperative adjuvant therapy, depending on the type of resection and the setting (eg, N2 disease) (see *Adjuvant Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Concurrent chemo/RT is recommended for R2 resections, whereas either sequential or concurrent chemo/RT is recommended for R1 resections. Concurrent chemoradiation is often used for positive margins, but sequential is reasonable in frailer patients. Cisplatin/etoposide, cisplatin/vinorelbine, and carboplatin/paclitaxel are chemoradiation regimens recommended



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by the NCCN Panel (see *Chemotherapy Regimens Used with Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁴⁸³ Pemetrexed with either cisplatin or carboplatin may be used for concurrent chemoradiation in patients with non-squamous cell histology. Chemoradiation regimens cited in the NCCN Guidelines may also be used for stage II to III disease.^{297,298,448,449,484-486}

Surveillance

The surveillance guidelines for patients with no clinical or radiographic evidence of disease are as follows (see *Surveillance* in the NCCN Guidelines for Non-Small Cell Lung Cancer). A chest CT scan with (or without) contrast is recommended every 6 to 12 months postoperatively for 2 years;⁶⁴¹⁻⁶⁴⁶ a low-dose non-contrast-enhanced chest CT is recommended annually thereafter. For the 2015 update, the NCCN Panel revised the screening recommendation to include low-dose CT. However, patients treated with chemotherapy with (or without) RT who have residual abnormalities may require more frequent imaging. PET/CT or brain MRI are not recommended for routine surveillance in patients without symptoms. But, PET may be useful for assessing CT scans that appear to show malignant neoplasms but may be radiation fibrosis, atelectasis, or other benign conditions. It is important to note that areas previously treated with RT may remain FDG avid for up to 2 years and therefore histologic confirmation of apparent *recurrent* disease is needed.⁶⁴⁷

Recent data show that low-dose CT screening of select current and former smokers at high risk for lung cancer (ie, ≥ 30 pack-years of smoking) decreased the mortality from lung cancer.⁵⁵ Information about smoking cessation (eg, advice, counseling, therapy) should be provided to aid the treatment of lung cancer and to improve the quality of life of the patients.

The NCCN Guidelines include information about the long-term follow-up care of NSCLC survivors (see *Cancer Survivorship Care* in the NCCN Guidelines for Non-Small Cell Lung Cancer). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening. A recent analysis suggests that patients who survive lung cancer have a high symptom burden 1 year after diagnosis and therefore need management after treatment.⁶⁴⁸

Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (eg, endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁷ For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in patients who are severely compromised, and may improve the quality of life.⁶⁴⁹ After the treatment for the locoregional recurrence, observation or systemic therapy (category 2B for systemic therapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic therapy is recommended. The type of systemic therapy depends on the histologic type, whether any genetic alterations are present, and PS (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

Management of distant metastases (eg, localized symptoms; bone, limited, diffuse brain, or disseminated metastases) is described in the NCCN Guidelines (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Palliation of



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symptoms can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bone metastasis.^{304,650,651}

Of note, recurrent and metastatic disease have historically been regarded as incurable. However, selected limited locoregional recurrences may be treated with curative intent salvage therapy (surgery or RT with [or without] chemotherapy) (see *Therapy for Recurrence and Metastasis* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Similarly, patients with limited-site oligometastatic disease may benefit from aggressive local therapies to the metastatic and primary sites, with clinical data suggesting the possibility of long-term survival (see *Initial Treatment for Stage IV, M1b: Limited Sites* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{383,384,387,652-656} In addition, emerging clinical data suggest the feasibility of definitive re-irradiation 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.^{301,394-396,657-660}

Denosumab or intravenous bisphosphonate therapy can be considered in patients with bone metastasis.^{123,661-664} In patients with NSCLC who have bone metastases, data suggest that denosumab increases median overall survival when compared with zoledronic acid (9.5 vs. 8 months).⁶⁶⁵ 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.^{666,667}

For patients with recurrent and metastatic disease, the NCCN Guidelines recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see *Metastatic Disease: Histologic Subtype* in the NCCN Guidelines for Non-Small Cell Lung Cancer).⁴⁹⁰ In addition, testing for genetic alterations (ie, driver events) is now recommended in select patients with NSCLC, because targeted therapy has been shown to decrease tumor burden, decrease symptoms, and dramatically improve the quality of life for patients with specific genetic alterations. The number of available targeted agents is increasing. Several targeted agents have category 1 recommendations for first-line therapy based on larger trials such as erlotinib (or gefitinib), afatinib, and crizotinib.

Additional targeted therapies for patients with other genetic alterations are also recommended, although there is less evidence for these agents (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The following targeted agents are recommended (category 2A) for patients with specific genetic alterations: crizotinib (for ROS1 rearrangements and MET amplification), and dabrafenib and vemurafenib (for BRAF V600E mutations); category 2B recommendations include trastuzumab and afatinib (both for HER2 mutations), and cabozantinib (for RET rearrangements) because response rates are lower and treatment is less effective when these agents are used for patients with the indicated genetic alterations (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{79,84,118-120,133,139,142,143,152,154,523,668-673} Other targeted therapies (such as ceritinib) are recommended or being developed as subsequent therapies for patients who become resistant to first-line targeted therapies.



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EGFR mutation testing (category 1) is recommended in patients with non-squamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in NSCLC NOS, because erlotinib and afatinib (category 1 for both) are recommended for patients who are positive for sensitizing EGFR mutations (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{82,150,179,524,674} Testing for ALK rearrangements (category 1) is also recommended in patients with non-squamous NSCLC, because crizotinib is recommended for patients who are positive for ALK rearrangements.^{125,675} Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification (see *Emerging Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{118,120,142,676} Ceritinib is recommended for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib.²⁰⁸ The NCCN Panel recommends that EGFR mutation testing be done as part of multiplex mutation screening assays or NGS. Testing for ALK gene rearrangements can be done with either FISH or NGS.¹³³⁻¹³⁵

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 or sensitizing EGFR mutations; therefore, routine testing is not recommended in these patients.^{126,677-679} However, testing for ALK rearrangements or EGFR mutations can be considered in patients with squamous cell carcinomas who never smoked and those whose histology was determined using small biopsy specimens or mixed histology specimens.¹²⁶ Treatment recommendations and eligibility criteria for patients with non-squamous NSCLC (or NSCLC NOS) who are negative for ALK rearrangements or

sensitizing EGFR mutations are described in the NCCN Guidelines. Treatment recommendations and eligibility criteria for patients with squamous cell carcinoma are also described in the NCCN Guidelines. These recommendations are briefly summarized in the following paragraphs. Data supporting these recommendations are described in the following section (see *Trial Data* in this Discussion).

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

Doublet chemotherapy regimens, such as cisplatin/pemetrexed, are recommended (category 1) for patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations if eligibility criteria are met (ie, they do not have squamous cell carcinoma); these regimens are also recommended in patients who have not had testing for mutations or rearrangements.⁴⁹⁰ Bevacizumab/chemotherapy is another option for patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations if eligibility criteria are met.⁶⁸⁰ 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.⁶⁸¹ Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on histology, PS, and other factors (see



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Trial Data in this Discussion, *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer, and the NCCN Drugs & Biologics Compendium [NCCN Compendium®]).

Cisplatin/gemcitabine (category 1) is an option for patients with squamous cell carcinoma.⁴⁹⁰ Carboplatin/paclitaxel, cisplatin/vinorelbine (category 1 for both), and other regimens listed in the NSCLC algorithm may also be used (see *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer and the NCCN Compendium®). As previously indicated, regimens containing pemetrexed or bevacizumab are not recommended for squamous cell carcinoma. Currently, there are fewer treatment options for patients with squamous cell carcinoma when compared with non-squamous NSCLC. Research is ongoing to find newer options.^{5,79,135,682,683}

Trial Data

In a phase 2/3 trial (ECOG 4599), 878 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.^{494,684} 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 and carboplatin alone.⁴⁹⁴ 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.⁴⁹⁴ However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and 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 and 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).⁶⁸⁰ However, a trial (AVAiL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.^{685,686}

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.⁴⁹⁰ 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.⁶⁸⁷

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 any of the following agents: docetaxel, etoposide, gemcitabine, paclitaxel (and albumin-bound paclitaxel), pemetrexed, vinblastine, and vinorelbine.^{473,487-490,510,511,519} Non-platinum regimens (eg,



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gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives, because data show they are active and less toxic than platinum-based regimens.^{513-516,688}

Number of Cycles of First-Line Systemic Therapy

Patients receiving first-line systemic therapy for advanced disease should be evaluated for tumor response with a CT scan. Approximately 25% of patients show disease progression after the initial cycle of chemotherapy; subsequent therapy is recommended for these patients (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of systemic therapy.^{453,549,689} 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;⁵³⁹ 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.⁴⁹⁵ 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.⁶⁹⁰ 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.^{548,549} In this phase 3 trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.⁵⁴⁹

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.⁴⁹⁵ 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.^{537,549}

Maintenance Therapy

In patients with advanced NSCLC, maintenance therapy is another option for those with responsive or stable disease after first-line systemic therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer). For patients with non-squamous NSCLC who are negative for ALK rearrangements or sensitizing EGFR mutations, continuation maintenance therapy regimens include bevacizumab (category 1), pemetrexed (category 1), bevacizumab/pemetrexed, or gemcitabine (category 2B) (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{494,496,533,539,540,544-546} Switch maintenance therapy regimens for these patients include pemetrexed or erlotinib (both are category 2B).^{545,546,551,552} 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.⁵⁵² 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) can be used as continuation maintenance therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).^{546,551} Switch maintenance therapy for these patients includes erlotinib or docetaxel (category 2B



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for both). 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).^{545,546} However, the benefits of maintenance therapy were very slight; therefore, the recommendation is only category 2B for maintenance therapy with gemcitabine or erlotinib. A phase 3 trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.⁵⁵⁵ 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.⁶⁹¹

Continuation of Erlotinib, Gefitinib, or Afatinib After Progression

Erlotinib is commonly used in the United States in patients with sensitizing EGFR mutations because of restrictions on the use of gefitinib. However, gefitinib may be used if available. Patients may continue to derive benefit from erlotinib or gefitinib after disease progression; discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).⁶⁹² 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.⁶⁹³ Data support the continued use of erlotinib in patients with lung adenocarcinoma with sensitizing *EGFR* mutations after development of

acquired resistance to erlotinib.⁶⁹⁴ The NCCN Panel recommends continuing either erlotinib or afatinib in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see *Sensitizing EGFR Mutation Positive: Subsequent Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).^{670,695,696} In most cases, erlotinib or afatinib is continued for these patients; however, additional therapy may be added or substituted (eg, whole brain RT, local therapy, systemic therapy).

Accumulating data suggest how cancers become resistant to EGFR inhibitors.⁶⁹⁷ The most common known mechanism is the acquisition of the T790M mutation (which is a secondary mutation in EGFR), that renders the kinase resistant to erlotinib and gefitinib.^{698,699} 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.^{692,700} Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.⁶⁹⁴

Second-Line and Third-Line (Subsequent) Systemic Therapy

For the 2015 update, the phrase *subsequent* therapy was substituted for the terms *second-line* or *third-line* 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



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histologic subtype, and whether the patient has symptoms (see the NCCN Guidelines for Non-Small Cell Lung Cancer).⁷⁰¹⁻⁷¹⁰

For patients with sensitizing EGFR mutations who progress during or after first-line targeted therapy, subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes: 1) erlotinib with local therapy or WBRT; 2) afatinib with local therapy or WBRT; or 3) systemic therapy with [or without] erlotinib. For patients with ALK rearrangements who progress during or after first-line targeted therapy, subsequent therapy depends on whether the progression is asymptomatic or symptomatic and includes either 1) ALK inhibitors with [or without] local therapy or WBRT; or 2) systemic therapy. After further progression on subsequent targeted therapy, first-line combination chemotherapy options for wild-type adenocarcinoma or squamous cell carcinoma are recommended (category 1) for patients with PS of 0 to 1 such as cisplatin/pemetrexed or cisplatin/gemcitabine, respectively.^{123,711} Other chemotherapy options are also recommended for patients with PS 2 (see the NCCN Guidelines for Non-Small Cell Lung Cancer).

For all histologic subtypes without ALK rearrangements or sensitizing EGFR mutations, docetaxel with (or without) ramucirumab, erlotinib, or gemcitabine are recommended if not already given as subsequent systemic therapy regimens for patients with PS of 0 to 2 who have disease progression during or after first-line therapy. For patients with non-squamous NSCLC but without sensitizing EGFR mutations, pemetrexed is also recommended as subsequent therapy. For the 2015 update, the NCCN Panel added ramucirumab/docetaxel as an additional option for subsequent therapy based on a recent phase 3 randomized trial.⁵³⁴ 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. In an interim update, the NCCN Panel recently revised the recommendation for ramucirumab/docetaxel from category 2B to category 2A based on the recent FDA approval.

Pemetrexed (non-squamous only), docetaxel (with or without ramucirumab), gemcitabine, or erlotinib are recommended options for subsequent therapy in patients with advanced NSCLC if these agents have not already been given.^{702,712,713} Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.^{707,708} When compared with docetaxel, pemetrexed has similar median survival but less toxicity.^{709,714} Pemetrexed is recommended in patients with adenocarcinoma or large cell carcinoma (ie, non-squamous NSCLC).⁵⁵² Docetaxel is preferred for patients with wild-type EGFR tumors based on 2 randomized trials comparing erlotinib versus docetaxel.^{715,716} Proteomic testing can be used to determine whether erlotinib should be used in patients with unknown EGFR status.⁷¹⁷

Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.⁷¹⁰ In patients with PS of 3 to 4 who have sensitizing EGFR mutations, erlotinib is recommended for subsequent therapy for progressive disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Doublet chemotherapy with (or without) bevacizumab is recommended for patients with non-squamous NSCLC who have progressed with symptomatic systemic multiple lesions after therapy with erlotinib (or gefitinib), afatinib, crizotinib, or ceritinib.⁴⁹⁴ Erlotinib (or gefitinib) or afatinib is recommended as subsequent therapy in patients with sensitizing EGFR mutations who have progressed after first-line therapy based on several studies.^{150,670,695,696} Ceritinib is recommended as subsequent therapy in patients with ALK-positive NSCLC who have



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progressed after first-line therapy with crizotinib or are intolerant to crizotinib.²⁰⁸

In a randomized trial (NCIC CTG trial), 731 patients (stage IIIB or IV, PS 0–3) were randomly assigned (2:1) to receive either erlotinib or placebo, following failure of first-line or subsequent chemotherapy.⁷¹⁰ Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (HR, 0.70; $P < .001$). PFS was 2.2 months for the erlotinib group versus 1.8 months for placebo (HR, 0.61; $P < .001$). However, 5% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first-line or subsequent systemic therapy. A randomized phase 3 trial in 829 patients found that oral topotecan was not inferior to docetaxel as subsequent therapy for patients with advanced NSCLC.⁷¹⁸

Pemetrexed (non-squamous only), docetaxel, gemcitabine, or erlotinib are recommended for subsequent therapy after second disease progression in patients with advanced NSCLC and PS 0–2 if these agents have not already been given; except for erlotinib, all these agents are category 2B in this setting.^{702,712,713,716} If second disease progression occurs after a subsequent systemic therapy, patients with PS of 3 to 4 may be treated with erlotinib (if they have sensitizing EGFR mutations) or best supportive care (see the NCCN Guidelines for Palliative Care).^{7,459,460} Patients often have a limited response to subsequent systemic therapy, although it may serve a useful palliative role.⁷¹⁹



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References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25559415>.
2. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2011, based on November 2013 SEER data submission, posted to the SEER web site, April 2014. Bethesda, MD: National Cancer Institute; 2014. Available at: http://seer.cancer.gov/csr/1975_2011/.
3. Johnson DH, Schiller JH, Bunn PA, Jr. Recent clinical advances in lung cancer management. J Clin Oncol 2014;32:973-982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24567433>.
4. Reck M, Heigener DF, Mok T, et al. Management of non-small-cell lung cancer: recent developments. Lancet 2013;382:709-719. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23972814>.
5. Forde PM, Ettinger DS. Targeted therapy for non-small-cell lung cancer: past, present and future. Expert Rev Anticancer Ther 2013;13:745-758. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23773106>.
6. Ettinger DS. Ten years of progress in non-small cell lung cancer. J Natl Compr Canc Netw 2012;10:292-295. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22393190>.
7. Simoff MJ, Lally B, Slade MG, et al. Symptom management in patients with lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e455S-497S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649452>.
8. Alberg AJ, Brock MV, Ford JG, et al. Epidemiology of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e1S-29S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649439>.
9. Subramanian J, Govindan R. Lung cancer in never smokers: a review. J Clin Oncol 2007;25:561-570. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17290066>.
10. The Health Consequences of Smoking: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services. Centers for Disease Control and Prevention (US); 2004.
11. Secretan B, Straif K, Baan R, et al. A review of human carcinogens-Part E: tobacco, areca nut, alcohol, coal smoke, and salted fish. Lancet Oncol 2009;10:1033-1034. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19891056>.
12. Doll R, Peto R. Mortality in relation to smoking: 20 years' observations on male British doctors. Br Med J 1976;2:1525-1536. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1009386>.
13. Taylor R, Najafi F, Dobson A. Meta-analysis of studies of passive smoking and lung cancer: effects of study type and continent. Int J Epidemiol 2007;36:1048-1059. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17690135>.
14. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. (ed 2010/07/30). Atlanta (GA): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention; 2006.
15. Hackshaw AK, Law MR, Wald NJ. The accumulated evidence on lung cancer and environmental tobacco smoke. BMJ 1997;315:980-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9365295>.
16. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? Br Med J (Clin Res



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

Ed) 1986;293:1217-1222. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/3096439>.

17. Fraumeni JF, Jr. Respiratory carcinogenesis: an epidemiologic appraisal. J Natl Cancer Inst 1975;55:1039-1046. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/1107567>.

18. Janerich DT, Thompson WD, Varela LR, et al. Lung cancer and exposure to tobacco smoke in the household. N Engl J Med 1990;323:632-636. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/2385268>.

19. Straif K, Benbrahim-Tallaa L, Baan R, et al. A review of human carcinogens--part C: metals, arsenic, dusts, and fibres. Lancet Oncol 2009;10:453-454. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19418618>.

20. Driscoll T, Nelson DI, Steenland K, et al. The global burden of disease due to occupational carcinogens. Am J Ind Med 2005;48:419-431. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16299703>.

21. Humans IWGoTEoCRt. Arsenic, metals, fibres, and dusts. IARC Monogr Eval Carcinog Risks Hum 2012;100:11-465. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23189751>.

22. Omenn GS, Merchant J, Boatman E, et al. Contribution of environmental fibers to respiratory cancer. Environ Health Perspect 1986;70:51-56. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/3830113>.

23. El Ghissassi F, Baan R, Straif K, et al. A review of human carcinogens--part D: radiation. Lancet Oncol 2009;10:751-752. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19655431>.

24. Darby S, Hill D, Deo H, et al. Residential radon and lung cancer--detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe. Scand J Work Environ Health

2006;32 Suppl 1:1-83. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16538937>.

25. Krewski D, Lubin JH, Zielinski JM, et al. A combined analysis of North American case-control studies of residential radon and lung cancer. J Toxicol Environ Health A 2006;69:533-597. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16608828>.

26. Schrump DS, Carter D, Kelsey CR, et al. Non-small cell lung cancer. In: DeVita Jr. VT, Lawrence TS, Rosenberg SA, et al., eds. DeVita, Hellman, and Rosenberg's Cancer: Principles and Practice of Oncology, 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2011.

27. Loomis D, Grosse Y, Lauby-Secretan B, et al. The carcinogenicity of outdoor air pollution. Lancet Oncol 2013;14:1262-1263. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25035875>.

28. Chlebowski RT, Schwartz AG, Wakelee H, et al. Oestrogen plus progestin and lung cancer in postmenopausal women (Women's Health Initiative trial): a post-hoc analysis of a randomised controlled trial. Lancet 2009;374:1243-1251. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19767090>.

29. Chlebowski RT, Anderson GL, Manson JE, et al. Lung cancer among postmenopausal women treated with estrogen alone in the women's health initiative randomized trial. J Natl Cancer Inst 2010;102:1413-1421. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20709992>.

30. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. N Engl J Med 2013;368:351-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343064>.

31. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. J Clin Oncol 2014;32:3989-3995. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25385740>.



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NCCN Guidelines Version 4.2015 Non-Small Cell Lung Cancer

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32. Leone FT, Evers-Casey S, Toll BA, Vachani A. Treatment of tobacco use in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e61S-77S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649454>.

33. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. N Engl J Med 2013;368:341-350. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23343063>.

34. Rigotti NA. Strategies to help a smoker who is struggling to quit. JAMA 2012;308:1573-1580. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23073954>.

35. Five Major Steps to Intervention (The "5 A's"). Vol. December. Rockville, MD: Agency for Healthcare Research and Quality; 2012. Available at: <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/5steps.html>.

36. Tao L, Wang R, Gao YT, Yuan JM. Impact of postdiagnosis smoking on long-term survival of cancer patients: the Shanghai cohort study. Cancer Epidemiol Biomarkers Prev 2013;22:2404-2411. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24319070>.

37. Treating Tobacco Use and Dependence. Vol. April. Rockville, MD: Agency for Healthcare Research and Quality; 2013. Available at: <http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/clinicians/update/index.html>.

38. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane Database Syst Rev 2013;5:CD009329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23728690>.

39. Koegelenberg CF, Noor F, Bateman ED, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. JAMA

2014;312:155-161. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25005652>.

40. Walker N, Howe C, Glover M, et al. Cytisine versus Nicotine for Smoking Cessation. N Engl J Med 2014;371:2353-2362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25517706>.

41. Aubin HJ, Bobak A, Britton JR, et al. Varenicline versus transdermal nicotine patch for smoking cessation: results from a randomised open-label trial. Thorax 2008;63:717-724. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18263663>.

42. Jorenby DE, Hays JT, Rigotti NA, et al. Efficacy of varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs placebo or sustained-release bupropion for smoking cessation: a randomized controlled trial. JAMA 2006;296:56-63. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16820547>.

43. Gonzales D, Rennard SI, Nides M, et al. Varenicline, an alpha4beta2 nicotinic acetylcholine receptor partial agonist, vs sustained-release bupropion and placebo for smoking cessation: a randomized controlled trial. JAMA 2006;296:47-55. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16820546>.

44. Cahill K, Stead LF, Lancaster T. Nicotine receptor partial agonists for smoking cessation. Cochrane Database Syst Rev 2011:CD006103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21328282>.

45. Ware JH, Vetrovec GW, Miller AB, et al. Cardiovascular safety of varenicline: patient-level meta-analysis of randomized, blinded, placebo-controlled trials. Am J Ther 2013;20:235-246. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23615317>.

46. Haber SL, Boomershine V, Raney E. Safety of varenicline in patients with cardiovascular disease. J Pharm Pract 2014;27:65-70. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24080536>.



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NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

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47. Mills EJ, Thorlund K, Eapen S, et al. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014;129:28-41. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24323793>.

48. Xi ZX. Preclinical Pharmacology, Efficacy and Safety of Varenicline in Smoking Cessation and Clinical Utility in High Risk Patients. *Drug Healthc Patient Saf* 2010;2010:39-48. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21278851>.

49. Gonzales D, Hajek P, Pliamm L, et al. Retreatment with varenicline for smoking cessation in smokers who have previously taken varenicline: a randomized, placebo-controlled trial. *Clin Pharmacol Ther* 2014;96:390-396. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24911368>.

50. Garrison GD, Dugan SE. Varenicline: a first-line treatment option for smoking cessation. *Clin Ther* 2009;31:463-491. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19393839>.

51. Hays JT, Ebbert JO. Adverse effects and tolerability of medications for the treatment of tobacco use and dependence. *Drugs* 2010;70:2357-2372. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21142259>.

52. Carney DN. Lung cancer--time to move on from chemotherapy. *N Engl J Med* 2002;346:126-128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11784881>.

53. Chute JP, Chen T, Feigal E, et al. Twenty years of phase III trials for patients with extensive-stage small-cell lung cancer: perceptible progress. *J Clin Oncol* 1999;17:1794-1801. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561217>.

54. National Lung Screening Trial Research T, Aberle DR, Berg CD, et al. The National Lung Screening Trial: overview and study design. *Radiology* 2011;258:243-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21045183>.

55. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *N Engl J Med* 2011;365:395-409. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21714641>.

56. National Lung Screening Trial Research T, Aberle DR, Adams AM, et al. Baseline characteristics of participants in the randomized national lung screening trial. *J Natl Cancer Inst* 2010;102:1771-1779. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21119104>.

57. Detterbeck FC, Mazzone PJ, Naidich DP, Bach PB. Screening for lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e78S-92S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649455>.

58. Vansteenkiste J, Crino L, Doooms C, et al. 2nd ESMO Consensus Conference on Lung Cancer: early-stage non-small-cell lung cancer consensus on diagnosis, treatment and follow-up. *Ann Oncol* 2014;25:1462-1474. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24562446>.

59. Smith RA, Brooks D, Cokkinides V, et al. Cancer screening in the United States, 2013: a review of current American Cancer Society guidelines, current issues in cancer screening, and new guidance on cervical cancer screening and lung cancer screening. *CA Cancer J Clin* 2013;63:88-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23378235>.

60. Moyer VA, Force USPST. Screening for lung cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2014;160:330-338. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24378917>.

61. Travis WD, Brambilla E, Noguchi M, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung



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NCCN Guidelines Version 4.2015

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adenocarcinoma. J Thorac Oncol 2011;6:244-285. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21252716>.

62. Finkelstein DM, Ettinger DS, Ruckdeschel JC. Long-term survivors in metastatic non-small-cell lung cancer: an Eastern Cooperative Oncology Group Study. J Clin Oncol 1986;4:702-709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3701389>.

63. Gould MK, Donington J, Lynch WR, et al. Evaluation of individuals with pulmonary nodules: when is it lung cancer? Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e93S-120S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649456>.

64. Naidich DP, Bankier AA, MacMahon H, et al. Recommendations for the management of subsolid pulmonary nodules detected at CT: a statement from the Fleischner Society. Radiology 2013;266:304-317. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23070270>.

65. 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16244247>.

66. Gardiner N, Jogai S, Wallis A. The revised lung adenocarcinoma classification-an imaging guide. J Thorac Dis 2014;6:S537-546. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25349704>.

67. Seidelman JL, Myers JL, Quint LE. Incidental, subsolid pulmonary nodules at CT: etiology and management. Cancer Imaging 2013;13:365-373. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24061063>.

68. Hansell DM, Bankier AA, MacMahon H, et al. Fleischner Society: glossary of terms for thoracic imaging. Radiology 2008;246:697-722. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18195376>.

69. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung cancer in small biopsies and cytology: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:668-684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22970842>.

70. Kim HY, Shim YM, Lee KS, et al. Persistent pulmonary nodular ground-glass opacity at thin-section CT: histopathologic comparisons. Radiology 2007;245:267-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17885195>.

71. Marshall HM, Bowman RV, Yang IA, et al. Screening for lung cancer with low-dose computed tomography: a review of current status. J Thorac Dis 2013;5 Suppl 5:S524-539. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163745>.

72. Brawley OW, Flanagan EL. Low-dose spiral CT screening and evaluation of the solitary pulmonary nodule. Oncology (Williston Park) 2014;28:441-446. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25004661>.

73. Chang B, Hwang JH, Choi YH, et al. Natural history of pure ground-glass opacity lung nodules detected by low-dose CT scan. Chest 2013;143:172-178. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22797081>.

74. Lindell RM, Hartman TE, Swensen SJ, et al. Five-year lung cancer screening experience: CT appearance, growth rate, location, and histologic features of 61 lung cancers. Radiology 2007;242:555-562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17255425>.

75. McKee BJ, Regis SM, McKee AB, et al. Performance of ACR Lung-RADS in a Clinical CT Lung Screening Program. J Am Coll Radiol 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25176499>.

76. Kazerooni EA, Austin JH, Black WC, et al. ACR-STR practice parameter for the performance and reporting of lung cancer screening



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

thoracic computed tomography (CT): 2014 (Resolution 4). J Thorac Imaging 2014;29:310-316. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24992501>.

77. Rivera MP, Mehta AC, Wahidi MM. Establishing the diagnosis of lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e142S-165S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649436>.

78. Schwartz AM, Rezaei MK. Diagnostic surgical pathology in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e251S-262S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649441>.

79. Oxnard GR, Binder A, Janne PA. New targetable oncogenes in non-small-cell lung cancer. J Clin Oncol 2013;31:1097-1104. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401445>.

80. Cooper WA, O'Toole S, Boyer M, et al. What's new in non-small cell lung cancer for pathologists: the importance of accurate subtyping, EGFR mutations and ALK rearrangements. Pathology 2011;43:103-115. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21233671>.

81. Fossella FV, Putnam JB, Komaki R, eds. Lung Cancer. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.

82. Eberhard DA, Johnson BE, Amler LC, et al. Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib. J Clin Oncol 2005;23:5900-5909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16043828>.

83. Cappuzzo F, Ligorio C, Toschi L, et al. EGFR and HER2 gene copy number and response to first-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). J Thorac Oncol

2007;2:423-429. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17473658>.

84. Kwak EL, Bang YJ, Camidge DR, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med 2010;363:1693-1703. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20979469>.

85. Travis WD, Brambilla E, Noguchi M, et al. Diagnosis of lung adenocarcinoma in resected specimens: implications of the 2011 International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification. Arch Pathol Lab Med 2013;137:685-705. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22913371>.

86. Cameron SE, Andrade RS, Pambuccian SE. Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of the art review. Cytopathology 2010;21:6-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20015257>.

87. Moreira AL, Thornton RH. Personalized medicine for non-small-cell lung cancer: implications of recent advances in tissue acquisition for molecular and histologic testing. Clin Lung Cancer 2012;13:334-339. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22424871>.

88. Iannuzzi MC, Fontana JR. Sarcoidosis: clinical presentation, immunopathogenesis, and therapeutics. JAMA 2011;305:391-399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21266686>.

89. Centers for Disease C, Prevention. CDC Grand Rounds: the TB/HIV syndemic. MMWR Morb Mortal Wkly Rep 2012;61:484-489. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22763886>.

90. Travis WD, Brambilla E, Muller-Hermelink HK, Harris CC. Pathology and genetics of tumours of the lung, pleura, thymus and heart, World Health Organization Classification of Tumours. Lyon, France: IARC Press; 2004.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

91. Travis WD, Brambilla E, Riely GJ. New pathologic classification of lung cancer: relevance for clinical practice and clinical trials. *J Clin Oncol* 2013;31:992-1001. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401443>.
92. Travis WD, Rekhtman N. Pathological diagnosis and classification of lung cancer in small biopsies and cytology: strategic management of tissue for molecular testing. *Semin Respir Crit Care Med* 2011;32:22-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21500121>.
93. Rekhtman N, Ang DC, Sima CS, et al. Immunohistochemical algorithm for differentiation of lung adenocarcinoma and squamous cell carcinoma based on large series of whole-tissue sections with validation in small specimens. *Mod Pathol* 2011;24:1348-1359. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21623384>.
94. Mukhopadhyay S, Katzenstein AL. Subclassification of non-small cell lung carcinomas lacking morphologic differentiation on biopsy specimens: Utility of an immunohistochemical panel containing TTF-1, napsin A, p63, and CK5/6. *Am J Surg Pathol* 2011;35:15-25. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21164283>.
95. Terry J, Leung S, Laskin J, et al. Optimal immunohistochemical markers for distinguishing lung adenocarcinomas from squamous cell carcinomas in small tumor samples. *Am J Surg Pathol* 2010;34:1805-1811. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21107086>.
96. Husain AN, Colby T, Ordonez N, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2013;137:647-667. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22929121>.
97. Husain AN, Colby TV, Ordonez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: a consensus statement from the International Mesothelioma Interest Group. *Arch Pathol Lab Med* 2009;133:1317-1331. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19653732>.
98. King JE, Thatcher N, Pickering CA, Hasleton PS. Sensitivity and specificity of immunohistochemical markers used in the diagnosis of epithelioid mesothelioma: a detailed systematic analysis using published data. *Histopathology* 2006;48:223-232. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16430468>.
99. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. *Hum Pathol* 2005;36:372-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15891998>.
100. Ordonez NG. The immunohistochemical diagnosis of mesothelioma: a comparative study of epithelioid mesothelioma and lung adenocarcinoma. *Am J Surg Pathol* 2003;27:1031-1051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12883236>.
101. Ordonez NG. Thyroid transcription factor-1 is a marker of lung and thyroid carcinomas. *Adv Anat Pathol* 2000;7:123-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10721419>.
102. Rivera MP, Mehta AC, American College of Chest P. Initial diagnosis of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). *Chest* 2007;132:131S-148S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17873165>.
103. Tan D, Zander DS. Immunohistochemistry for assessment of pulmonary and pleural neoplasms: a review and update. *Int J Clin Exp Pathol* 2008;1:19-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18784820>.
104. Zhang H, Liu J, Cagle PT, et al. Distinction of pulmonary small cell carcinoma from poorly differentiated squamous cell carcinoma: an immunohistochemical approach. *Mod Pathol* 2005;18:111-118. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15309021>.
105. Guinee DG, Jr., Fishback NF, Koss MN, et al. The spectrum of immunohistochemical staining of small-cell lung carcinoma in specimens from transbronchial and open-lung biopsies. *Am J Clin*



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

Pathol 1994;102:406-414. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/7524299>.

106. Du L, Schageman JJ, Irnov, et al. MicroRNA expression distinguishes SCLC from NSCLC lung tumor cells and suggests a possible pathological relationship between SCLCs and NSCLCs. J Exp Clin Cancer Res 2010;29:75. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20624269>.

107. Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.

108. 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 tumours. J Thorac Oncol 2007;2:706-714. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17762336>.

109. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260-271. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19584208>.

110. Rami-Porta R, Bolejack V, Goldstraw P. The new tumor, node, and metastasis staging system. Semin Respir Crit Care Med 2011;32:44-51. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21500123>.

111. Rami-Porta R, Crowley JJ, Goldstraw P. The revised TNM staging system for lung cancer. Ann Thorac Cardiovasc Surg 2009;15:4-9. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19262443>.

112. Greene FL, Page DL, Fleming ID, et al. AJCC Cancer Staging Manual, 6th ed. New York: Springer-Verlag; 2002.

113. Ou SH, Zell JA, Ziogas A, Anton-Culver H. Prognostic factors for survival of stage I nonsmall cell lung cancer patients : a population-based analysis of 19,702 stage I patients in the California Cancer Registry from 1989 to 2003. Cancer 2007;110:1532-1541. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17702091>.

114. Raz DJ, Zell JA, Ou SH, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007;132:193-199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17505036>.

115. Miller VA, Riely GJ, Zakowski MF, et al. Molecular characteristics of bronchioloalveolar carcinoma and adenocarcinoma, bronchioloalveolar carcinoma subtype, predict response to erlotinib. J Clin Oncol 2008;26:1472-1478. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18349398>.

116. Sequist LV, Martins RG, Spigel D, et al. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol 2008;26:2442-2449. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18458038>.

117. Tsao MS, Sakurada A, Cutz JC, et al. Erlotinib in lung cancer - molecular and clinical predictors of outcome. N Engl J Med 2005;353:133-144. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16014883>.

118. Shaw AT, Ou SH, Bang YJ, et al. Crizotinib in ROS1-rearranged non-small-cell lung cancer. N Engl J Med 2014;371:1963-1971. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25264305>.

119. Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. Cancer Discov 2013;3:630-635. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23533264>.

120. Bergethon K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22215748>.

121. Ou SH, Tan J, Yen Y, Soo RA. ROS1 as a 'druggable' receptor tyrosine kinase: lessons learned from inhibiting the ALK pathway. Expert Rev Anticancer Ther 2012;12:447-456. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22500682>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

122. Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012;18:378-381. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22327623>.

123. Besse B, Adjei A, Baas P, et al. 2nd ESMO Consensus Conference on Lung Cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. *Ann Oncol* 2014;25:1475-1484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24669016>.

124. Kerr KM, Bubendorf L, Edelman MJ, et al. Second ESMO consensus conference on lung cancer: pathology and molecular biomarkers for non-small-cell lung cancer. *Ann Oncol* 2014;25:1681-1690. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24718890>.

125. Lindeman NI, Cagle PT, Beasley MB, et al. Molecular testing guideline for selection of lung cancer patients for EGFR and ALK tyrosine kinase inhibitors: guideline from the College of American Pathologists, International Association for the Study of Lung Cancer, and Association for Molecular Pathology. *J Thorac Oncol* 2013;8:823-859. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23552377>.

126. Paik PK, Varghese AM, Sima CS, et al. Response to erlotinib in patients with EGFR mutant advanced non-small cell lung cancers with a squamous or squamous-like component. *Mol Cancer Ther* 2012;11:2535-2540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22896669>.

127. Wong DW, Leung EL, So KK, et al. The EML4-ALK fusion gene is involved in various histologic types of lung cancers from nonsmokers with wild-type EGFR and KRAS. *Cancer* 2009;115:1723-1733. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19170230>.

128. Ali G, Proietti A, Pelliccioni S, et al. ALK rearrangement in a large series of consecutive non-small cell lung cancers: comparison between a new immunohistochemical approach and fluorescence in situ hybridization for the screening of patients eligible for crizotinib

treatment. *Arch Pathol Lab Med* 2014;138:1449-1458. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24885803>.

129. Shaw AT, Forcione DG, Digumarthy SR, Iafrate AJ. Case records of the Massachusetts General Hospital. Case 21-2011. A 31-year-old man with ALK-positive adenocarcinoma of the lung. *N Engl J Med* 2011;365:158-167. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21751909>.

130. Shaw AT, Yeap BY, Mino-Kenudson M, et al. Clinical features and outcome of patients with non-small-cell lung cancer who harbor EML4-ALK. *J Clin Oncol* 2009;27:4247-4253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19667264>.

131. Lovly CM, Horn L. Molecular profiling of lung cancer. *My Cancer Genome*; 2014 (updated March 31). Available at: <http://www.mycancergenome.org/content/disease/lung-cancer>.

132. Dias-Santagata D, Akhavanfard S, David SS, et al. Rapid targeted mutational analysis of human tumours: a clinical platform to guide personalized cancer medicine. *EMBO Mol Med* 2010;2:146-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20432502>.

133. Cardarella S, Ortiz TM, Joshi VA, et al. The introduction of systematic genomic testing for patients with non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1767-1774. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23154547>.

134. Li T, Kung HJ, Mack PC, Gandara DR. Genotyping and genomic profiling of non-small-cell lung cancer: implications for current and future therapies. *J Clin Oncol* 2013;31:1039-1049. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401433>.

135. Planchard D. Identification of driver mutations in lung cancer: first step in personalized cancer. *Target Oncol* 2013;8:3-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23371030>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

136. Villaruz LC, Socinski MA, Abberbock S, et al. Clinicopathologic features and outcomes of patients with lung adenocarcinomas harboring BRAF mutations in the Lung Cancer Mutation Consortium. Cancer 2015;121:448-456. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25273224>.

137. Cardarella S, Ogino A, Nishino M, et al. Clinical, pathologic, and biologic features associated with BRAF mutations in non-small cell lung cancer. Clin Cancer Res 2013;19:4532-4540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23833300>.

138. Kelly RJ, Carter CA, Giaccone G. HER2 mutations in non-small-cell lung cancer can be continually targeted. J Clin Oncol 2012;30:3318-3319. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22649146>.

139. Gautschi O, Pauli C, Strobel K, et al. A patient with BRAF V600E lung adenocarcinoma responding to vemurafenib. J Thorac Oncol 2012;7:e23-24. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22743296>.

140. Paik PK, Arcila ME, Fara M, et al. Clinical characteristics of patients with lung adenocarcinomas harboring BRAF mutations. J Clin Oncol 2011;29:2046-2051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21483012>.

141. Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. Nat Med 2012;18:382-384. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22327622>.

142. Ou 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21623265>.

143. Cappuzzo F, Bemis L, Varella-Garcia M. HER2 mutation and response to trastuzumab therapy in non-small-cell lung cancer. N Engl J Med 2006;354:2619-2621. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16775247>.

144. Sequist LV, Heist RS, Shaw AT, et al. Implementing multiplexed genotyping of non-small-cell lung cancers into routine clinical practice. Ann Oncol 2011;22:2616-2624. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22071650>.

145. Pao W. New approaches to targeted therapy in lung cancer. Proc Am Thorac Soc 2012;9:72-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22550248>.

146. Pao W, Girard N. New driver mutations in non-small-cell lung cancer. Lancet Oncol 2011;12:175-180. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21277552>.

147. Slebos RJ, Kibbelaar RE, Dalesio O, et al. K-ras oncogene activation as a prognostic marker in adenocarcinoma of the lung. N Engl J Med 1990;323:561-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2199829>.

148. Roberts PJ, Stinchcombe TE. KRAS mutation: should we test for it, and does it matter? J Clin Oncol 2013;31:1112-1121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401440>.

149. Tsao MS, Aviel-Ronen S, Ding K, et al. Prognostic and predictive importance of p53 and RAS for adjuvant chemotherapy in non small-cell lung cancer. J Clin Oncol 2007;25:5240-5247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18024870>.

150. Langer CJ. Epidermal growth factor receptor inhibition in mutation-positive non-small-cell lung cancer: is afatinib better or simply newer? J Clin Oncol 2013;31:3303-3306. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23980079>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

151. Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. *Onco Targets Ther* 2013;6:135-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23493883>.

152. De Greve J, Teugels E, Geers C, et al. Clinical activity of afatinib (BIBW 2992) in patients with lung adenocarcinoma with mutations in the kinase domain of HER2/neu. *Lung Cancer* 2012;76:123-127. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22325357>.

153. Dungo RT, Keating GM. Afatinib: first global approval. *Drugs* 2013;73:1503-1515. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23982599>.

154. Sequist LV, Yang JC, Yamamoto N, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327-3334. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23816960>.

155. Hirsch FR, Bunn PA, Jr. EGFR testing in lung cancer is ready for prime time. *Lancet Oncol* 2009;10:432-433. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19410185>.

156. Riely GJ, Politi KA, Miller VA, Pao W. Update on epidermal growth factor receptor mutations in non-small cell lung cancer. *Clin Cancer Res* 2006;12:7232-7241. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17189394>.

157. Arcila ME, Nafa K, Chaft JE, et al. EGFR exon 20 insertion mutations in lung adenocarcinomas: prevalence, molecular heterogeneity, and clinicopathologic characteristics. *Mol Cancer Ther* 2013;12:220-229. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23371856>.

158. Oxnard GR, Lo PC, Nishino M, et al. Natural history and molecular characteristics of lung cancers harboring EGFR exon 20 insertions. *J Thorac Oncol* 2013;8:179-184. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23328547>.

159. Lund-Iversen M, Kleinberg L, Fjellbirkeland L, et al. Clinicopathological characteristics of 11 NSCLC patients with EGFR-exon 20 mutations. *J Thorac Oncol* 2012;7:1471-1473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22895145>.

160. Yasuda H, Kobayashi S, Costa DB. EGFR exon 20 insertion mutations in non-small-cell lung cancer: preclinical data and clinical implications. *Lancet Oncol* 2012;13:e23-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21764376>.

161. Yu HA, Arcila ME, Rekhtman N, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. *Clin Cancer Res* 2013;19:2240-2247. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23470965>.

162. Finlay MR, Anderton M, Ashton S, et al. Discovery of a potent and selective EGFR inhibitor (AZD9291) of both sensitizing and T790M resistance mutations that spares the wild type form of the receptor. *J Med Chem* 2014;57:8249-8267. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25271963>.

163. Gainor JF, Shaw AT. Emerging paradigms in the development of resistance to tyrosine kinase inhibitors in lung cancer. *J Clin Oncol* 2013;31:3987-3996. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24101047>.

164. Pao W, Miller VA, Politi KA, et al. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005;2:e73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15737014>.

165. Kosaka T, Yatabe Y, Endoh H, et al. Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib. *Clin Cancer Res* 2006;12:5764-5769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17020982>.

166. Onitsuka T, Uramoto H, Nose N, et al. Acquired resistance to gefitinib: the contribution of mechanisms other than the T790M, MET,



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

and HGF status. Lung Cancer 2010;68:198-203. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19589612>.

167. Rosell R, Molina MA, Costa C, et al. Pretreatment EGFR T790M mutation and BRCA1 mRNA expression in erlotinib-treated advanced non-small-cell lung cancer patients with EGFR mutations. Clin Cancer Res 2011;17:1160-1168. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21233402>.

168. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med 2011;3:75ra26. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21430269>.

169. Oxnard GR. Strategies for overcoming acquired resistance to epidermal growth factor receptor: targeted therapies in lung cancer. Arch Pathol Lab Med 2012;136:1205-1209. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23020725>.

170. Suda K, Mizuuchi H, Maehara Y, Mitsudomi T. Acquired resistance mechanisms to tyrosine kinase inhibitors in lung cancer with activating epidermal growth factor receptor mutation--diversity, ductility, and destiny. Cancer Metastasis Rev 2012;31:807-814. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22736441>.

171. Han SW, Kim TY, Jeon YK, et al. Optimization of patient selection for gefitinib in non-small cell lung cancer by combined analysis of epidermal growth factor receptor mutation, K-ras mutation, and Akt phosphorylation. Clin Cancer Res 2006;12:2538-2544. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/16638863>.

172. Dacic S. EGFR assays in lung cancer. Adv Anat Pathol 2008;15:241-247. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18580100>.

173. Sholl LM, Xiao Y, Joshi V, et al. EGFR mutation is a better predictor of response to tyrosine kinase inhibitors in non-small cell lung carcinoma than FISH, CISH, and immunohistochemistry. Am J Clin

Pathol 2010;133:922-934. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20472851>.

174. Eberhard DA, Giaccone G, Johnson BE, Non-Small-Cell Lung Cancer Working G. Biomarkers of response to epidermal growth factor receptor inhibitors in Non-Small-Cell Lung Cancer Working Group: standardization for use in the clinical trial setting. J Clin Oncol 2008;26:983-994. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18281673>.

175. Pao W, Ladanyi M. Epidermal growth factor receptor mutation testing in lung cancer: searching for the ideal method. Clin Cancer Res 2007;13:4954-4955. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17785543>.

176. Shepherd FA, Tsao MS. Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an enigma. J Clin Oncol 2010;28:903-905. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20100955>.

177. Rosell R, Carcereny E, Gervais R, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 2012;13:239-246. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22285168>.

178. Mitsudomi T, Morita S, Yatabe Y, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 2010;11:121-128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20022809>.

179. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 2010;362:2380-2388. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20573926>.



NCCN Guidelines Version 4.2015

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180. Zhou C, Wu YL, Chen G, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. *Lancet Oncol* 2011;12:735-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21783417>.

181. Zhou C, Wu YL, Chen G, et al. Updated efficacy and quality-of-life (QoL) analyses in OPTIMAL, a phase III, randomized, open-label study of first-line erlotinib versus gemcitabine/carboplatin in patients with EGFR-activating mutation-positive (EGFR Act Mut+) advanced non-small cell lung cancer (NSCLC) [abstract]. *J Clin Oncol* 2011;29(Suppl 15):Abstract 7520. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7520.

182. Rosell R, Gervais R, Vergnenegre A, et al. Erlotinib versus chemotherapy (CT) in advanced non-small cell lung cancer (NSCLC) patients (p) with epidermal growth factor receptor (EGFR) mutations: Interim results of the European Erlotinib Versus Chemotherapy (EURTAC) phase III randomized trial [abstract]. *J Clin Oncol* 2011;29(Suppl 15):Abstract 7503. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7503.

183. Yang JC, Hirsh V, Schuler M, et al. Symptom control and quality of life in LUX-Lung 3: a phase III study of afatinib or cisplatin/pemetrexed in patients with advanced lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3342-3350. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23816967>.

184. Sun JM, Lira M, Pandya K, et al. Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. *Lung Cancer* 2014;83:259-264. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24300132>.

185. von Laffert M, Warth A, Penzel R, et al. Multicenter immunohistochemical ALK-testing of non-small-cell lung cancer shows high concordance after harmonization of techniques and interpretation criteria. *J Thorac Oncol* 2014;9:1685-1692. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25436802>.

186. Wynes MW, Sholl LM, Dietel M, et al. An international interpretation study using the ALK IHC antibody D5F3 and a sensitive detection kit demonstrates high concordance between ALK IHC and ALK FISH and between evaluators. *J Thorac Oncol* 2014;9:631-638. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24722153>.

187. Zhou J, Zhao J, Sun K, et al. Accurate and economical detection of ALK positive lung adenocarcinoma with semiquantitative immunohistochemical screening. *PLoS One* 2014;9:e92828. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24667320>.

188. Thunnissen E, Bubendorf L, Dietel M, et al. EML4-ALK testing in non-small cell carcinomas of the lung: a review with recommendations. *Virchows Arch* 2012;461:245-257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22825000>.

189. Kim H, Yoo SB, Choe JY, et al. Detection of ALK gene rearrangement in non-small cell lung cancer: a comparison of fluorescence in situ hybridization and chromogenic in situ hybridization with correlation of ALK protein expression. *J Thorac Oncol* 2011;6:1359-1366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21587085>.

190. Rodig SJ, Mino-Kenudson M, Dacic S, et al. Unique clinicopathologic features characterize ALK-rearranged lung adenocarcinoma in the western population. *Clin Cancer Res* 2009;15:5216-5223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19671850>.

191. Mino-Kenudson M, Chirieac LR, Law K, et al. A novel, highly sensitive antibody allows for the routine detection of ALK-rearranged lung adenocarcinomas by standard immunohistochemistry. *Clin Cancer Res* 2010;16:1561-1571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20179225>.

192. Wallander ML, Geiersbach KB, Tripp SR, Layfield LJ. Comparison of reverse transcription-polymerase chain reaction, immunohistochemistry, and fluorescence in situ hybridization



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Non-Small Cell Lung Cancer

methodologies for detection of echinoderm microtubule-associated proteinlike 4-anaplastic lymphoma kinase fusion-positive non-small cell lung carcinoma: implications for optimal clinical testing. Arch Pathol Lab Med 2012;136:796-803. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22742552>.

193. Weickhardt AJ, Aisner DL, Franklin WA, et al. Diagnostic assays for identification of anaplastic lymphoma kinase-positive non-small cell lung cancer. Cancer 2013;119:1467-1477. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23280244>.

194. Solomon BJ, Mok T, Kim D-W, et al. First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer. New England Journal of Medicine 2014;371:2167-2177. Available at: <http://www.nejm.org/doi/full/10.1056/NEJMoa1408440>.

195. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med 2013;368:2385-2394. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23724913>.

196. Crino L, Kim D, Riely GJ, et al. Initial phase II results with crizotinib in advanced ALK-positive non-small cell lung cancer (NSCLC): PROFILE 1005 [abstract]. J Clin Oncol 2011;29 (Suppl 15):Abstract 7514. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7514.

197. Camidge DR, Bang Y, Kwak EL, et al. Progression-free survival (PFS) from a phase I study of crizotinib (PF-02341066) in patients with ALK-positive non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 2501. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/2501.

198. Rodig SJ, Shapiro GI. Crizotinib, a small-molecule dual inhibitor of the c-Met and ALK receptor tyrosine kinases. Curr Opin Investig Drugs 2010;11:1477-1490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21154129>.

199. Camidge DR, Bang YJ, Kwak EL, et al. Activity and safety of crizotinib in patients with ALK-positive non-small-cell lung cancer: updated results from a phase 1 study. Lancet Oncol 2012;13:1011-1019. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22954507>.

200. Shaw AT, Yeap BY, Solomon BJ, et al. Impact of crizotinib on survival in patients with advanced, ALK-positive NSCLC compared with historical controls [abstract]. J Clin Oncol 2011;29(Suppl 15):Abstract 7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7507.

201. Rothenstein JM, Letarte N. Managing treatment-related adverse events associated with ALK inhibitors. Curr Oncol 2014;21:19-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24523601>.

202. Brosnan EM, Weickhardt AJ, Lu X, et al. Drug-induced reduction in estimated glomerular filtration rate in patients with ALK-positive non-small cell lung cancer treated with the ALK inhibitor crizotinib. Cancer 2014;120:664-674. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24258622>.

203. Bang YJ. Treatment of ALK-positive non-small cell lung cancer. Arch Pathol Lab Med 2012;136:1201-1204. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23020724>.

204. Choi YL, Soda M, Yamashita Y, et al. EML4-ALK mutations in lung cancer that confer resistance to ALK inhibitors. N Engl J Med 2010;363:1734-1739. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20979473>.

205. Frampton JE. Crizotinib: a review of its use in the treatment of anaplastic lymphoma kinase-positive, advanced non-small cell lung cancer. Drugs 2013;73:2031-2051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24288180>.

206. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

002JG): results from the dose-finding portion of a phase 1/2 study. *Lancet Oncol* 2014;15:1119-1128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25153538>.

207. Stinchcombe TE. Novel agents in development for advanced non-small cell lung cancer. *Ther Adv Med Oncol* 2014;6:240-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25342991>.

208. Shaw AT, Kim DW, Mehra R, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;370:1189-1197. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24670165>.

209. Solomon B, Wilner KD, Shaw AT. Current status of targeted therapy for anaplastic lymphoma kinase-rearranged non-small cell lung cancer. *Clin Pharmacol Ther* 2014;95:15-23. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24091716>.

210. Savas P, Hughes B, Solomon B. Targeted therapy in lung cancer: IPASS and beyond, keeping abreast of the explosion of targeted therapies for lung cancer. *J Thorac Dis* 2013;5 Suppl 5:S579-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163750>.

211. Katayama R, Khan TM, Benes C, et al. Therapeutic strategies to overcome crizotinib resistance in non-small cell lung cancers harboring the fusion oncogene EML4-ALK. *Proc Natl Acad Sci U S A* 2011;108:7535-7540. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21502504>.

212. Sequist LV, Gettinger S, Senzer NN, et al. Activity of IPI-504, a novel heat-shock protein 90 inhibitor, in patients with molecularly defined non-small-cell lung cancer. *J Clin Oncol* 2010;28:4953-4960. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20940188>.

213. Zhang S, Wang F, Keats F. AP26113, a potent ALK inhibitor, overcomes mutations in EML4-ALK that confer resistance to PF-02341066 (PF1066) [abstract]. Presented at the Proceedings of the 101st Annual Meeting of the American Association for Cancer Research; Washington, DC. Abstract LB-298.

214. Cheng M, Ott GR. Anaplastic lymphoma kinase as a therapeutic target in anaplastic large cell lymphoma, non-small cell lung cancer and neuroblastoma. *Anticancer Agents Med Chem* 2010;10:236-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20406193>.

215. Gainor JF, Varghese AM, Ou SH, et al. ALK rearrangements are mutually exclusive with mutations in EGFR or KRAS: an analysis of 1,683 patients with non-small cell lung cancer. *Clin Cancer Res* 2013;19:4273-4281. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23729361>.

216. Takahashi T, Sonobe M, Kobayashi M, et al. Clinicopathologic features of non-small-cell lung cancer with EML4-ALK fusion gene. *Ann Surg Oncol* 2010;17:889-897. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20183914>.

217. Browning ET, Weickhardt AJ, Camidge DR. Response to crizotinib rechallenge after initial progression and intervening chemotherapy in ALK lung cancer. *J Thorac Oncol* 2013;8:e21. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23407562>.

218. West H, Oxnard GR, Doebele RC. Acquired resistance to targeted therapies in advanced non-small cell lung cancer: new strategies and new agents. *Am Soc Clin Oncol Educ Book* 2013:272-278. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23714521>.

219. Ou SH, Janne PA, Bartlett CH, et al. Clinical benefit of continuing ALK inhibition with crizotinib beyond initial disease progression in patients with advanced ALK-positive NSCLC. *Ann Oncol* 2014;25:415-422. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24478318>.

220. Slebos RJ, Hruban RH, Dalesio O, et al. Relationship between K-ras oncogene activation and smoking in adenocarcinoma of the human lung. *J Natl Cancer Inst* 1991;83:1024-1027. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2072410>.

221. Mitsudomi T, Steinberg SM, Oie HK, et al. ras gene mutations in non-small cell lung cancers are associated with shortened survival



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irrespective of treatment intent. Cancer Res 1991;51:4999-5002.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1654209>.

222. Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. J Natl Compr Canc Netw 2011;9 Suppl 5:S1-32; quiz S33. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22138009>.

223. Janne PA, Shaw AT, Pereira JR, et al. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. Lancet Oncol 2013;14:38-47. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23200175>.

224. Howington JA, Blum MG, Chang AC, et al. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e278S-313S. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23649443>.

225. Handforth C, Clegg A, Young C, et al. The prevalence and outcomes of frailty in older cancer patients: a systematic review. Ann Oncol 2014. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25403592>.

226. Caillet P, Laurent M, Bastuji-Garin S, et al. Optimal management of elderly cancer patients: usefulness of the Comprehensive Geriatric Assessment. Clin Interv Aging 2014;9:1645-1660. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25302022>.

227. Pallis AG, Gridelli C, Wedding U, et al. Management of elderly patients with NSCLC; updated expert's opinion paper: EORTC Elderly Task Force, Lung Cancer Group and International Society for Geriatric Oncology. Ann Oncol 2014;25:1270-1283. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24638905>.

228. Brunelli A, Kim AW, Berger KI, Addrizzo-Harris DJ. Physiologic evaluation of the patient with lung cancer being considered for

resectional surgery: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e166S-190S. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23649437>.

229. Vairaktarakis C, Tsiamis V, Soursou G, et al. A computer-aided diagnosis system for geriatrics assessment and frailty evaluation. Adv Exp Med Biol 2015;820:69-77. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25417017>.

230. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. J Clin Oncol 2014;32:2595-2603. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25071125>.

231. Kozower BD, Lerner JM, Detterbeck FC, Jones DR. Special treatment issues in non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e369S-399S. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23649447>.

232. Boffa DJ, Allen MS, Grab JD, et al. Data from The Society of Thoracic Surgeons General Thoracic Surgery database: the surgical management of primary lung tumors. J Thorac Cardiovasc Surg 2008;135:247-254. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18242243>.

233. Scott WJ, Howington J, Feigenberg S, et al. Treatment of non-small cell lung cancer stage I and stage II: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:234S-242S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17873171>.

234. Villamizar N, Swanson SJ. Lobectomy vs. segmentectomy for NSCLC (T<2 cm). Ann Cardiothorac Surg 2014;3:160-166. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24790839>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

235. Landreneau RJ, Normolle DP, Christie NA, et al. Recurrence and survival outcomes after anatomic segmentectomy versus lobectomy for clinical stage I non-small-cell lung cancer: a propensity-matched analysis. *J Clin Oncol* 2014;32:2449-2455. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24982447>.

236. Altorki NK, Yip R, Hanaoka T, et al. Sublobar resection is equivalent to lobectomy for clinical stage 1A lung cancer in solid nodules. *J Thorac Cardiovasc Surg* 2014;147:754-762; Discussion 762-754. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24280722>.

237. Sienel W, Dango S, Kirschbaum A, et al. Sublobar resections in stage IA non-small cell lung cancer: segmentectomies result in significantly better cancer-related survival than wedge resections. *Eur J Cardiothorac Surg* 2008;33:728-734. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18261918>.

238. Sienel W, Stremmel C, Kirschbaum A, et al. Frequency of local recurrence following segmentectomy of stage IA non-small cell lung cancer is influenced by segment localisation and width of resection margins--implications for patient selection for segmentectomy. *Eur J Cardiothorac Surg* 2007;31:522-527; discussion 527-528. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17229574>.

239. Narsule CK, Ebright MI, Fernando HC. Sublobar versus lobar resection: current status. *Cancer J* 2011;17:23-27. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21263263>.

240. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest* 2012;142:1620-1635. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23208335>.

241. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol* 2010;28:928-935. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20065181>.

242. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. *J Thorac Cardiovasc Surg* 2011;141:662-670. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21335122>.

243. Allen MS, Darling GE, Pechet TT, et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial. *Ann Thorac Surg* 2006;81:1013-1019; discussion 1019-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16488712>.

244. Allen MS, Darling GE, Decker PA, et al. Number of lymph nodes harvested from a mediastinal lymphadenectomy: Results of the randomized, prospective ACOSOG Z0030 trial [abstract]. *J Clin Oncol* 2007;25 (Suppl 18):Abstract 7555. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7555.

245. Rusch VW, Asamura H, Watanabe H, et al. The IASLC lung cancer staging project: a proposal for a new international lymph node map in the forthcoming seventh edition of the TNM classification for lung cancer. *J Thorac Oncol* 2009;4:568-577. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19357537>.

246. Martins RG, D'Amico TA, Loo BW, Jr., et al. The management of patients with stage IIIA non-small cell lung cancer with N2 mediastinal node involvement. *J Natl Compr Canc Netw* 2012;10:599-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22570291>.

247. Farjah F, Flum DR, Varghese TK, Jr., et al. Surgeon specialty and long-term survival after pulmonary resection for lung cancer. *Ann Thorac Surg* 2009;87:995-1004; discussion 1005-1006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19324119>.

248. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet*



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

2009;374:379-386. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19632716>.

249. van Meerbeeck JP, Kramer GW, Van Schil PE, et al. Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer. *J Natl Cancer Inst* 2007;99:442-450. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17374834>.

250. Cerfolio RJ, Bryant AS. Survival of patients with unsuspected N2 (stage IIIA) nonsmall-cell lung cancer. *Ann Thorac Surg* 2008;86:362-366; discussion 366-367. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18640297>.

251. Higgins K, Chino JP, Marks LB, et al. Preoperative chemotherapy versus preoperative chemoradiotherapy for stage III (N2) non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;75:1462-1467. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19467798>.

252. Shah AA, Berry MF, Tzao C, et al. Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer. *Ann Thorac Surg* 2012;93:1807-1812. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22632486>.

253. Stefani A, Alifano M, Bobbio A, et al. Which patients should be operated on after induction chemotherapy for N2 non-small cell lung cancer? Analysis of a 7-year experience in 175 patients. *J Thorac Cardiovasc Surg* 2010;140:356-363. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20381815>.

254. Gopal RS, Dubey S, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) on Induction and Adjuvant Therapy for Stage N2 Non-Small-Cell Lung Cancer: expert panel on radiation oncology-lung. *Int J Radiat Oncol Biol Phys* 2010;78:969-974. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20813465>.

255. Evans NR, 3rd, Li S, Wright CD, et al. The impact of induction therapy on morbidity and operative mortality after resection of primary

lung cancer. *J Thorac Cardiovasc Surg* 2010;139:991-996 e991-992.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20304144>.

256. Gaissert HA, Keum DY, Wright CD, et al. POINT: Operative risk of pneumonectomy--influence of preoperative induction therapy. *J Thorac Cardiovasc Surg* 2009;138:289-294. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19619768>.

257. Mansour Z, Kochetkova EA, Ducrocq X, et al. Induction chemotherapy does not increase the operative risk of pneumonectomy! *Eur J Cardiothorac Surg* 2007;31:181-185. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17141515>.

258. Weder W, Collaud S, Eberhardt WE, et al. Pneumonectomy is a valuable treatment option after neoadjuvant therapy for stage III non-small-cell lung cancer. *J Thorac Cardiovasc Surg* 2010;139:1424-1430.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20416887>.

259. Kappers I, van Sandick JW, Burgers SA, et al. Surgery after induction chemotherapy in stage IIIA-N2 non-small cell lung cancer: why pneumonectomy should be avoided. *Lung Cancer* 2010;68:222-227. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19664843>.

260. Decaluwe H, De Leyn P, Vansteenkiste J, et al. Surgical multimodality treatment for baseline resectable stage IIIA-N2 non-small cell lung cancer. Degree of mediastinal lymph node involvement and impact on survival. *Eur J Cardiothorac Surg* 2009;36:433-439. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19502079>.

261. Swanson SJ, Batirel HF. Video-assisted thoracic surgery (VATS) resection for lung cancer. *Surg Clin North Am* 2002;82:541-559.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12371584>.

262. Mahtabifard A, Fuller CB, McKenna RJ, Jr. Video-assisted thoracic surgery sleeve lobectomy: a case series. *Ann Thorac Surg* 2008;85:S729-732. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18222205>.



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263. Shaw JP, Dembitzer FR, Wisnivesky JP, et al. Video-assisted thoracoscopic lobectomy: state of the art and future directions. *Ann Thorac Surg* 2008;85:S705-709. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18222201>.

264. Cheng D, Downey RJ, Kernstine K, et al. Video-assisted thoracic surgery in lung cancer resection: a meta-analysis and systematic review of controlled trials. *Innovations (Phila)* 2007;2:261-292. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22437196>.

265. Alam N, Flores RM. Video-assisted thoracic surgery (VATS) lobectomy: the evidence base. *JSLs* 2007;11:368-374. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17931521>.

266. Whitson BA, Andrade RS, Boettcher A, et al. Video-assisted thoracoscopic surgery is more favorable than thoracotomy for resection of clinical stage I non-small cell lung cancer. *Ann Thorac Surg* 2007;83:1965-1970. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17532379>.

267. Whitson BA, Groth SS, Duval SJ, et al. Surgery for early-stage non-small cell lung cancer: a systematic review of the video-assisted thoracoscopic surgery versus thoracotomy approaches to lobectomy. *Ann Thorac Surg* 2008;86:2008-2016; discussion 2016-2008. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19022040>.

268. Scott WJ, Allen MS, Darling G, et al. Video-assisted thoracic surgery versus open lobectomy for lung cancer: a secondary analysis of data from the American College of Surgeons Oncology Group Z0030 randomized clinical trial. *J Thorac Cardiovasc Surg* 2010;139:976-981; discussion 981-973. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20172539>.

269. Atkins BZ, Harpole DH, Jr., Mangum JH, et al. Pulmonary segmentectomy by thoracotomy or thoracoscopy: reduced hospital length of stay with a minimally-invasive approach. *Ann Thorac Surg* 2007;84:1107-1112; discussion 1112-1103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17888955>.

270. Swanson SJ, Herndon JE, 2nd, D'Amico TA, et al. Video-assisted thoracic surgery lobectomy: report of CALGB 39802--a prospective, multi-institution feasibility study. *J Clin Oncol* 2007;25:4993-4997. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17971599>.

271. Ohtsuka T, Nomori H, Horio H, et al. Is major pulmonary resection by video-assisted thoracic surgery an adequate procedure in clinical stage I lung cancer? *Chest* 2004;125:1742-1746. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15136385>.

272. McKenna RJ, Jr. New approaches to the minimally invasive treatment of lung cancer. *Cancer J* 2005;11:73-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15831227>.

273. Demmy TL, Nwogu C. Is video-assisted thoracic surgery lobectomy better? Quality of life considerations. *Ann Thorac Surg* 2008;85:S719-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18222204>.

274. Cattaneo SM, Park BJ, Wilton AS, et al. Use of video-assisted thoracic surgery for lobectomy in the elderly results in fewer complications. *Ann Thorac Surg* 2008;85:231-235; discussion 235-236. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18154816>.

275. Cao C, Manganas C, Ang SC, et al. Video-assisted thoracic surgery versus open thoracotomy for non-small cell lung cancer: a meta-analysis of propensity score-matched patients. *Interact Cardiovasc Thorac Surg* 2013;16:244-249. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23169877>.

276. Ilonen IK, Rasanen JV, Knuuttila A, et al. Anatomic thoracoscopic lung resection for non-small cell lung cancer in stage I is associated with less morbidity and shorter hospitalization than thoracotomy. *Acta Oncol* 2011;50:1126-1132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21314296>.

277. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with



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NCCN Guidelines Version 4.2015 Non-Small Cell Lung Cancer

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thoracotomy. J Thorac Cardiovasc Surg 2009;138:419-425. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19619789>.

278. Paul S, Altorki NK, Sheng S, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg 2010;139:366-378. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20106398>.

279. Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. J Thorac Cardiovasc Surg 2014;147:747-752; Discussion 752-743. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24290575>.

280. Lee PC, Nasar A, Port JL, et al. Long-term survival after lobectomy for non-small cell lung cancer by video-assisted thoracic surgery versus thoracotomy. Ann Thorac Surg 2013;96:951-960; discussion 960-951. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23866808>.

281. Thomas P, Doddoli C, Yena S, et al. VATS is an adequate oncological operation for stage I non-small cell lung cancer. Eur J Cardiothorac Surg 2002;21:1094-1099. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12048091>.

282. Roviato G, Varoli F, Vergani C, et al. Long-term survival after videothoracoscopic lobectomy for stage I lung cancer. Chest 2004;126:725-732. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15364748>.

283. Solaini L, Prusciano F, Bagioni P, Poddie DB. Long-term results of video-assisted thoracic surgery lobectomy for stage I non-small cell lung cancer: a single-centre study of 104 cases. Interact Cardiovasc Thorac Surg 2004;3:57-62. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17670176>.

284. Demmy TL, Plante AJ, Nwogu CE, et al. Discharge independence with minimally invasive lobectomy. Am J Surg 2004;188:698-702. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15619486>.

285. Demmy TL. VATS lobectomy for frail or complex patients. Chest Meeting Abstracts 2003;124:234S. Available at: <http://meeting.chestpubs.org/cgi/reprint/124/4/234S.pdf>.

286. Nicastrì DG, Wisnivesky JP, Little VR, et al. Thoracoscopic lobectomy: report on safety, discharge independence, pain, and chemotherapy tolerance. J Thorac Cardiovasc Surg 2008;135:642-647. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18329487>.

287. Petersen RP, Pham D, Burfeind WR, et al. Thoracoscopic lobectomy facilitates the delivery of chemotherapy after resection for lung cancer. Ann Thorac Surg 2007;83:1245-1249; discussion 1250. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17383320>.

288. Hanna JM, Berry MF, D'Amico TA. Contraindications of video-assisted thoracoscopic surgical lobectomy and determinants of conversion to open. J Thorac Dis 2013;5 Suppl 3:S182-189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24040521>.

289. Yan TD, Cao C, D'Amico TA, et al. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. Eur J Cardiothorac Surg 2014;45:633-639. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24130372>.

290. Yan TD, Black D, Bannon PG, McCaughan BC. Systematic review and meta-analysis of randomized and nonrandomized trials on safety and efficacy of video-assisted thoracic surgery lobectomy for early-stage non-small-cell lung cancer. J Clin Oncol 2009;27:2553-2562. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19289625>.

291. Cao C, Manganas C, Ang SC, Yan TD. A meta-analysis of unmatched and matched patients comparing video-assisted thoracoscopic lobectomy and conventional open lobectomy. Ann



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

Cardiothorac Surg 2012;1:16-23. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23977459>.

292. Nakamura H. Systematic review of published studies on safety and efficacy of thoracoscopic and robot-assisted lobectomy for lung cancer. Ann Thorac Cardiovasc Surg 2014;20:93-98. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24583699>.

293. Swanson SJ, Miller DL, McKenna RJ, Jr., et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database (Premier). J Thorac Cardiovasc Surg 2014;147:929-937. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24210834>.

294. Effects of postoperative mediastinal radiation on completely resected stage II and stage III epidermoid cancer of the lung. The Lung Cancer Study Group. N Engl J Med 1986;315:1377-1381. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/2877397>.

295. Keller SM, Adak S, Wagner H, et al. A randomized trial of postoperative adjuvant therapy in patients with completely resected stage II or IIIA non-small-cell lung cancer. Eastern Cooperative Oncology Group. N Engl J Med 2000;343:1217-1222. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/11071672>.

296. Douillard JY, Rosell R, De Lena M, et al. Impact of postoperative radiation therapy on survival in patients with complete resection and stage I, II, or IIIA non-small-cell lung cancer treated with adjuvant chemotherapy: the adjuvant Navelbine International Trialist Association (ANITA) Randomized Trial. Int J Radiat Oncol Biol Phys 2008;72:695-701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18439766>.

297. Bradley JD, Paulus R, Graham MV, et al. Phase II trial of postoperative adjuvant paclitaxel/carboplatin and thoracic radiotherapy in resected stage II and IIIA non-small-cell lung cancer: promising long-term results of the Radiation Therapy Oncology Group--RTOG 9705. J

Clin Oncol 2005;23:3480-3487. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15908657>.

298. Feigenberg SJ, Hanlon AL, Langer C, et al. A phase II study of concurrent carboplatin and paclitaxel and thoracic radiotherapy for completely resected stage II and IIIA non-small cell lung cancer. J Thorac Oncol 2007;2:287-292. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17409799>.

299. Jaklitsch MT, Herndon JE, 2nd, DeCamp MM, Jr., et al. Nodal downstaging predicts survival following induction chemotherapy for stage IIIA (N2) non-small cell lung cancer in CALGB protocol #8935. J Surg Oncol 2006;94:599-606. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17039491>.

300. Lutz ST, Jones J, Chow E. Role of radiation therapy in palliative care of the patient with cancer. J Clin Oncol 2014;32:2913-2919. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25113773>.

301. McAvoy S, Ciura K, Wei C, et al. Definitive Reirradiation for Locoregionally Recurrent Non-Small Cell Lung Cancer With Proton Beam Therapy or Intensity Modulated Radiation Therapy: Predictors of High-Grade Toxicity and Survival Outcomes. Int J Radiat Oncol Biol Phys 2014. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25220718>.

302. Expert Panel on Radiation Oncology-Brain M, Lo SS, Gore EM, et al. ACR Appropriateness Criteria(R) pre-irradiation evaluation and management of brain metastases. J Palliat Med 2014;17:880-886. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24971478>.

303. Expert Panel on Radiation Oncology-Bone M, Lo SS, Lutz ST, et al. ACR Appropriateness Criteria (R) spinal bone metastases. J Palliat Med 2013;16:9-19. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23167547>.

304. Expert Panel On Radiation Oncology-Bone M, Lutz ST, Lo SS, et al. ACR Appropriateness Criteria(R) non-spine bone metastases. J



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Palliat Med 2012;15:521-526. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22536988>.

305. Patel SH, Robbins JR, Gore EM, et al. ACR Appropriateness Criteria(R) follow-up and retreatment of brain metastases. Am J Clin Oncol 2012;35:302-306. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22609733>.

306. Chang JY, Kestin LL, Barriger RB, et al. ACR Appropriateness Criteria(R) nonsurgical treatment for locally advanced non-small-cell lung cancer: good performance status/definitive intent. Oncology (Williston Park) 2014;28:706-710, 712, 714 passim. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/25140629>.

307. Rosenzweig KE, Chang JY, Chetty IJ, et al. ACR appropriateness criteria nonsurgical treatment for non-small-cell lung cancer: poor performance status or palliative intent. J Am Coll Radiol 2013;10:654-664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23890874>.

308. Gregoire V, Mackie TR. State of the art on dose prescription, reporting and recording in Intensity-Modulated Radiation Therapy (ICRU report No. 83). Cancer Radiother 2011;15:555-559. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21802333>.

309. Teoh M, Clark CH, Wood K, et al. Volumetric modulated arc therapy: a review of current literature and clinical use in practice. Br J Radiol 2011;84:967-996. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22011829>.

310. Chen AB, Neville BA, Sher DJ, et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. J Clin Oncol 2011;29:2305-2311. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21537034>.

311. Liao ZX, Komaki RR, Thames HD, Jr., et al. Influence of technologic advances on outcomes in patients with unresectable, locally advanced non-small-cell lung cancer receiving concomitant

chemoradiotherapy. Int J Radiat Oncol Biol Phys 2010;76:775-781. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19515503>.

312. Terasawa T, Dvorak T, Ip S, et al. Systematic review: charged-particle radiation therapy for cancer. Ann Intern Med 2009;151:556-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19755348>.

313. Taremi M, Hope A, Dahele M, et al. Stereotactic body radiotherapy for medically inoperable lung cancer: prospective, single-center study of 108 consecutive patients. Int J Radiat Oncol Biol Phys 2012;82:967-973. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21377293>.

314. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-1076. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20233825>.

315. Ambroggi MC, Fanucchi O, Cioni R, et al. Long-term results of radiofrequency ablation treatment of stage I non-small cell lung cancer: a prospective intention-to-treat study. J Thorac Oncol 2011;6:2044-2051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22052222>.

316. Bilal H, Mahmood S, Rajashanker B, Shah R. Is radiofrequency ablation more effective than stereotactic ablative radiotherapy in patients with early stage medically inoperable non-small cell lung cancer? Interact Cardiovasc Thorac Surg 2012;15:258-265. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22581864>.

317. Shirvani SM, Jiang J, Chang JY, et al. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. Int J Radiat Oncol Biol Phys 2012;84:1060-1070. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22975611>.

318. Gewanter RM, Rosenzweig KE, Chang JY, et al. ACR Appropriateness Criteria: nonsurgical treatment for non-small-cell lung cancer: good performance status/definitive intent. Curr Probl Cancer 2010;34:228-249. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20541060>.



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NCCN Guidelines Version 4.2015 Non-Small Cell Lung Cancer

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319. Rodrigues G, Videtic GM, Sur R, et al. Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline. *Pract Radiat Oncol* 2011;1:60-71. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24174996>.

320. Rodrigues G, Macbeth F, Burmeister B, et al. Consensus statement on palliative lung radiotherapy: third international consensus workshop on palliative radiotherapy and symptom control. *Clin Lung Cancer* 2012;13:1-5. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21729656>.

321. Chen AB, Cronin A, Weeks JC, et al. Palliative radiation therapy practice in patients with metastatic non-small-cell lung cancer: a Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. *J Clin Oncol* 2013;31:558-564. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23295799>.

322. Lally BE, Zelterman D, Colasanto JM, et al. Postoperative radiotherapy for stage II or III non-small-cell lung cancer using the surveillance, epidemiology, and end results database. *J Clin Oncol* 2006;24:2998-3006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16769986>.

323. Albain KS, Rusch VW, Crowley JJ, et al. Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995;13:1880-1892. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7636530>.

324. Cerfolio RJ, Bryant AS, Jones VL, Cerfolio RM. Pulmonary resection after concurrent chemotherapy and high dose (60Gy) radiation for non-small cell lung cancer is safe and may provide increased survival. *Eur J Cardiothorac Surg* 2009;35:718-723; discussion 723. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19233668>.

325. Kwong KF, Edelman MJ, Suntharalingam M, et al. High-dose radiotherapy in trimodality treatment of Pancoast tumors results in high pathologic complete response rates and excellent long-term survival. *J Thorac Cardiovasc Surg* 2005;129:1250-1257. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15942564>.

326. Sonett JR, Suntharalingam M, Edelman MJ, et al. Pulmonary resection after curative intent radiotherapy (>59 Gy) and concurrent chemotherapy in non-small-cell lung cancer. *Ann Thorac Surg* 2004;78:1200-1205; discussion 1206. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15464470>.

327. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for superior sulcus non-small-cell lung carcinomas: long-term results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Clin Oncol* 2007;25:313-318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17235046>.

328. Bradley J, Graham MV, Winter K, et al. Toxicity and outcome results of RTOG 9311: a phase I-II dose-escalation study using three-dimensional conformal radiotherapy in patients with inoperable non-small-cell lung carcinoma. *Int J Radiat Oncol Biol Phys* 2005;61:318-328. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15667949>.

329. Kong FM, Ten Haken RK, Schipper MJ, et al. High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 2005;63:324-333. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16168827>.

330. Zhao L, West BT, Hayman JA, et al. High radiation dose may reduce the negative effect of large gross tumor volume in patients with medically inoperable early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2007;68:103-110. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17363189>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

331. Wang L, Correa CR, Zhao L, et al. The effect of radiation dose and chemotherapy on overall survival in 237 patients with Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2009;73:1383-1390. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18929449>.

332. Rosenman JG, Halle JS, Socinski MA, et al. High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002;54:348-356. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12243807>.

333. Schild SE, McGinnis WL, Graham D, et al. Results of a Phase I trial of concurrent chemotherapy and escalating doses of radiation for unresectable non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1106-1111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16730134>.

334. Bradley JD, Moughan J, Graham MV, et al. A phase I/II radiation dose escalation study with concurrent chemotherapy for patients with inoperable stages I to III non-small-cell lung cancer: phase I results of RTOG 0117. *Int J Radiat Oncol Biol Phys* 2010;77:367-372. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20457350>.

335. Bradley JD, Paulus R, Komaki R, et al. Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. *The Lancet Oncology* 2015. Available at: [http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045\(14\)71207-0/abstract](http://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(14)71207-0/abstract).

336. Bradley JD, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy with or without cetuximab for stage III non-small cell lung cancer: Results on radiation dose in RTOG 0617 [abstract]. *J Clin Oncol* 2013;31(Suppl 15):Abstract 7501. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7501.

337. Bradley J, Paulus R, Komaki R, et al. A randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal chemoradiotherapy+/-cetuximab for stage IIIa/IIb non-small cell lung cancer: preliminary findings on radiation dose in RTOG 0617 [abstract]. Presented at the 53rd Annual Meeting of the American Society of Radiation Oncology; 2011. Abstract LBA2.

338. Bradley JD, Bae K, Graham MV, et al. Primary analysis of the phase II component of a phase I/II dose intensification study using three-dimensional conformal radiation therapy and concurrent chemotherapy for patients with inoperable non-small-cell lung cancer: RTOG 0117. *J Clin Oncol* 2010;28:2475-2480. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20368547>.

339. ICRU. ICRU Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.

340. ICRU. Prescribing, Recording and Reporting Photon Beam Therapy (Report 62) (Supplement to ICRU Report 50). Bethesda, MD: ICRU; 1999.

341. ICRU Report 83: Prescribing, Recording, and Reporting Intensity-Modulated Photon-Beam Therapy (IMRT). Bethesda, MD: International Commission on Radiation Units and Measurements; 2010. Available at: <http://www.icru.org/testing/reports/prescribing-recording-and-reporting-intensity-modulated-photon-beam-therapy-imrt-icru-report-83>.

342. Group IDW, Holmes T, Das R, et al. American Society of Radiation Oncology recommendations for documenting intensity-modulated radiation therapy treatments. *Int J Radiat Oncol Biol Phys* 2009;74:1311-1318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19616738>.

343. Kong FM, Ritter T, Quint DJ, et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. *Int J Radiat*



NCCN Guidelines Version 4.2015

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Oncol Biol Phys 2011;81:1442-1457. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20934273>.

344. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat Oncol 2007;17:108-120. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17395041>.

345. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer (NSCLC). Int J Radiat Oncol Biol Phys 1999;45:323-329. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10487552>.

346. Kong FM, Hayman JA, Griffith KA, et al. Final toxicity results of a radiation-dose escalation study in patients with non-small-cell lung cancer (NSCLC): predictors for radiation pneumonitis and fibrosis. Int J Radiat Oncol Biol Phys 2006;65:1075-1086. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16647222>.

347. Hernando ML, Marks LB, Bentel GC, et al. Radiation-induced pulmonary toxicity: a dose-volume histogram analysis in 201 patients with lung cancer. Int J Radiat Oncol Biol Phys 2001;51:650-659. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11597805>.

348. Kim TH, Cho KH, Pyo HR, et al. Dose-volumetric parameters for predicting severe radiation pneumonitis after three-dimensional conformal radiation therapy for lung cancer. Radiology 2005;235:208-215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15703313>.

349. Wang S, Liao Z, Wei X, et al. Analysis of clinical and dosimetric factors associated with treatment-related pneumonitis (TRP) in patients with non-small-cell lung cancer (NSCLC) treated with concurrent chemotherapy and three-dimensional conformal radiotherapy (3D-CRT). Int J Radiat Oncol Biol Phys 2006;66:1399-1407. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16997503>.

350. Rose J, Rodrigues G, Yaremko B, et al. Systematic review of dose-volume parameters in the prediction of esophagitis in thoracic

radiotherapy. Radiother Oncol 2009;91:282-287. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18950881>.

351. Hall WH, Guiou M, Lee NY, et al. Development and validation of a standardized method for contouring the brachial plexus: preliminary dosimetric analysis among patients treated with IMRT for head-and-neck cancer. Int J Radiat Oncol Biol Phys 2008;72:1362-1367. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18448267>.

352. Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-19. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20171502>.

353. Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76:S70-76. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20171521>.

354. Werner-Wasik M, Yorke E, Deasy J, et al. Radiation dose-volume effects in the esophagus. Int J Radiat Oncol Biol Phys 2010;76:S86-93. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20171523>.

355. Gagliardi G, Constone LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. Int J Radiat Oncol Biol Phys 2010;76:S77-85. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20171522>.

356. Kirkpatrick JP, van der Kogel AJ, Schultheiss TE. Radiation dose-volume effects in the spinal cord. Int J Radiat Oncol Biol Phys 2010;76:S42-49. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20171517>.

357. MacManus M, Nestle U, Rosenzweig KE, et al. Use of PET and PET/CT for radiation therapy planning: IAEA expert report 2006-2007. Radiother Oncol 2009;91:85-94. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19100641>.

358. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional



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Non-Small Cell Lung Cancer

conformal or intensity-modulated radiation therapy in Stage I or Stage III non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:1087-1096. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16682145>.

359. Na. Abstracts. *Journal of Thoracic Oncology* 2008;3:S263-S301. Available at: <http://journals.lww.com/jto/toc/2008/11001>.

360. Bush DA, Slater JD, Shin BB, et al. Hypofractionated proton beam radiotherapy for stage I lung cancer. *Chest* 2004;126:1198-1203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15486383>.

361. Nihei K, Ogino T, Ishikura S, Nishimura H. High-dose proton beam therapy for Stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys* 2006;65:107-111. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16458447>.

362. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol* 2010;95:32-40. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19733410>.

363. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76. *Med Phys* 2006;33:3874-3900. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17089851>.

364. Dahele M, Senan S. The role of stereotactic ablative radiotherapy for early-stage and oligometastatic non-small cell lung cancer: evidence for changing paradigms. *Cancer Res Treat* 2011;43:75-82. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21811422>.

365. Heinzerling JH, Kavanagh B, Timmerman RD. Stereotactic ablative radiation therapy for primary lung tumors. *Cancer J* 2011;17:28-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21263264>.

366. Potters L, Kavanagh B, Galvin JM, et al. American Society for Therapeutic Radiology and Oncology (ASTRO) and American College

of Radiology (ACR) practice guideline for the performance of stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2010;76:326-332. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20117285>.

367. Guckenberger M, Andratschke N, Alheit H, et al. Definition of stereotactic body radiotherapy: principles and practice for the treatment of stage I non-small cell lung cancer. *Strahlenther Onkol* 2014;190:26-33. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24052011>.

368. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys* 2011;81:1352-1358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20638194>.

369. Baumann P, Nyman J, Hoyer M, et al. Outcome in a prospective phase II trial of medically inoperable stage I non-small-cell lung cancer patients treated with stereotactic body radiotherapy. *J Clin Oncol* 2009;27:3290-3296. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19414667>.

370. Iyengar P, Westover K, Timmerman RD. Stereotactic ablative radiotherapy (SABR) for non-small cell lung cancer. *Semin Respir Crit Care Med* 2013;34:845-854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24258574>.

371. Nagata Y, Hiraoka M, Shibata T, et al. Stereotactic Body Radiation Therapy For T1N0M0 Non-small Cell Lung Cancer: First Report for Inoperable Population of a Phase II Trial by Japan Clinical Oncology Group (JCOG 0403). *International Journal of Radiation Oncology*Biophysics*Physics* 2012;84:S46. Available at: [http://www.redjournal.org/article/S0360-3016\(12\)01274-6/abstract](http://www.redjournal.org/article/S0360-3016(12)01274-6/abstract).

372. Palma D, Visser O, Lagerwaard FJ, et al. Impact of introducing stereotactic lung radiotherapy for elderly patients with stage I non-small-cell lung cancer: a population-based time-trend analysis. *J Clin Oncol*



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

2010;28:5153-5159. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21041709>.

373. Widder J, Postmus D, Ubbels JF, et al. Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer. *Int J Radiat Oncol Biol Phys* 2011;81:e291-297.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21640503>.

374. Bradley JD, El Naqa I, Drzymala RE, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung cancer: the pattern of failure is distant. *Int J Radiat Oncol Biol Phys* 2010;77:1146-1150.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19800181>.

375. Senti S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. *Lancet Oncol* 2012;13:802-809. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22727222>.

376. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys* 2009;75:677-682. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19251380>.

377. Versteegen NE, Oosterhuis JW, Palma DA, et al. Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis. *Ann Oncol* 2013;24:1543-1548. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23425947>.

378. Nagata Y, Hiraoka M, Shibata T, et al. A Phase II Trial of Stereotactic Body Radiation Therapy for Operable T1N0M0 Non-small Cell Lung Cancer: Japan Clinical Oncology Group (JCOG0403). *International Journal of Radiation Oncology*Biophysics* 2010;78:S27-S28. Available at: [http://www.redjournal.org/article/S0360-3016\(10\)01078-3/abstract](http://www.redjournal.org/article/S0360-3016(10)01078-3/abstract).

379. Lagerwaard FJ, Versteegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012;83:348-353. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22104360>.

380. Shirvani SM, Jiang J, Chang JY, et al. Lobectomy, Sublobar Resection, and Stereotactic Ablative Radiotherapy for Early-Stage Non-Small Cell Lung Cancers in the Elderly. *JAMA Surg* 2014. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25321323>.

381. Timmerman RD, Paulus R, Pass H. I., et al. RTOG 0618: Stereotactic body radiation therapy (SBRT) to treat operable early-stage lung cancer patients [abstract]. *J Clin Oncol* 2013;31(Suppl 15):Abstract 7523. Available at:

382. Kunkler IH, Audisio R, Belkacemi Y, et al. Review of current best practice and priorities for research in radiation oncology for elderly patients with cancer: the International Society of Geriatric Oncology (SIOG) task force. *Ann Oncol* 2014;25:2134-2146. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24625455>.

383. Shultz DB, Filippi AR, Thariat J, et al. Stereotactic Ablative Radiotherapy for Pulmonary Oligometastases and Oligometastatic Lung Cancer. *J Thorac Oncol* 2014. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25170641>.

384. Filippi AR, Badellino S, Guarneri A, et al. Outcomes of single fraction stereotactic ablative radiotherapy for lung metastases. *Technol Cancer Res Treat* 2014;13:37-45. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23819496>.

385. Chan NK, Abdullah KG, Lubelski D, et al. Stereotactic radiosurgery for metastatic spine tumors. *J Neurosurg Sci* 2014;58:37-44. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24614791>.

386. Ojerholm E, Lee JY, Kolker J, et al. Gamma Knife radiosurgery to four or more brain metastases in patients without prior intracranial



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

radiation or surgery. Cancer Med 2014;3:565-571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24510602>.

387. Timmerman RD, Herman J, Cho LC. Emergence of stereotactic body radiation therapy and its impact on current and future clinical practice. J Clin Oncol 2014;32:2847-2854. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25113761>.

388. Salazar OM, Sandhu TS, Lattin PB, et al. Once-weekly, high-dose stereotactic body radiotherapy for lung cancer: 6-year analysis of 60 early-stage, 42 locally advanced, and 7 metastatic lung cancers. Int J Radiat Oncol Biol Phys 2008;72:707-715. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18455322>.

389. Guckenberger M, Wulf J, Mueller G, et al. Dose-response relationship for image-guided stereotactic body radiotherapy of pulmonary tumors: relevance of 4D dose calculation. Int J Radiat Oncol Biol Phys 2009;74:47-54. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18977095>.

390. Zhang X, Liu H, Balter P, et al. Positron emission tomography for assessing local failure after stereotactic body radiotherapy for non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:1558-1565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22572078>.

391. Hoopes DJ, Tann M, Fletcher JW, et al. FDG-PET and stereotactic body radiotherapy (SBRT) for stage I non-small-cell lung cancer. Lung Cancer 2007;56:229-234. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17353064>.

392. Chen F, Matsuo Y, Yoshizawa A, et al. Salvage lung resection for non-small cell lung cancer after stereotactic body radiotherapy in initially operable patients. J Thorac Oncol 2010;5:1999-2002. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21102261>.

393. Neri S, Takahashi Y, Terashi T, et al. Surgical treatment of local recurrence after stereotactic body radiotherapy for primary and

metastatic lung cancers. J Thorac Oncol 2010;5:2003-2007. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21102262>.

394. Hearn JW, Videtic GM, Djemil T, Stephans KL. Salvage Stereotactic Body Radiation Therapy (SBRT) for Local Failure After Primary Lung SBRT. Int J Radiat Oncol Biol Phys 2014;90:402-406. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25017480>.

395. Trakul N, Harris JP, Le QT, et al. Stereotactic ablative radiotherapy for reirradiation of locally recurrent lung tumors. J Thorac Oncol 2012;7:1462-1465. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22895143>.

396. Kilburn JM, Kuremsky JG, Blackstock AW, et al. Thoracic re-irradiation using stereotactic body radiotherapy (SBRT) techniques as first or second course of treatment. Radiother Oncol 2014;110:505-510. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24444530>.

397. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone". Int J Radiat Oncol Biol Phys 2014;88:1120-1128. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24661665>.

398. Hadziahmetovic M, Loo BW, Timmerman RD, et al. Stereotactic body radiation therapy (stereotactic ablative radiotherapy) for stage I non-small cell lung cancer--updates of radiobiology, techniques, and clinical outcomes. Discov Med 2010;9:411-417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20515609>.

399. Hara R, Itami J, Kondo T, et al. Clinical outcomes of single-fraction stereotactic radiation therapy of lung tumors. Cancer 2006;106:1347-1352. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16475150>.

400. Chang JY, Balter PA, Dong L, et al. Stereotactic body radiation therapy in centrally and superiorly located stage I or isolated recurrent non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2008;72:967-971. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18954709>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

401. Takeda A, Sanuki N, Kunieda E, et al. Stereotactic body radiotherapy for primary lung cancer at a dose of 50 Gy total in five fractions to the periphery of the planning target volume calculated using a superposition algorithm. *Int J Radiat Oncol Biol Phys* 2009;73:442-448. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18990507>.

402. Stephans KL, Djemil T, Reddy CA, et al. A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience. *J Thorac Oncol* 2009;4:976-982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19633473>.

403. Jin JY, Kong FM, Chetty IJ, et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. *Int J Radiat Oncol Biol Phys* 2010;76:782-788. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19577855>.

404. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;2:S94-100. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17603311>.

405. Chawla S, Chen Y, Katz AW, et al. Stereotactic body radiotherapy for treatment of adrenal metastases. *Int J Radiat Oncol Biol Phys* 2009;75:71-75. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19250766>.

406. Scorsetti M, Alongi F, Filippi AR, et al. Long-term local control achieved after hypofractionated stereotactic body radiotherapy for adrenal gland metastases: a retrospective analysis of 34 patients. *Acta Oncol* 2012;51:618-623. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22263925>.

407. Iyengar P, Kavanagh BD, Wardak Z, et al. Phase II trial of stereotactic body radiation therapy combined with erlotinib for patients with limited but progressive metastatic non-small-cell lung cancer. *J Clin*

Oncol 2014;32:3824-3830. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25349291>.

408. Takeda M, Okamoto I, Nakagawa K. Clinical impact of continued crizotinib administration after isolated central nervous system progression in patients with lung cancer positive for ALK rearrangement. *J Thorac Oncol* 2013;8:654-657. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23584297>.

409. Sura S, Yorke E, Jackson A, Rosenzweig KE. High-dose radiotherapy for the treatment of inoperable non-small cell lung cancer. *Cancer J* 2007;13:238-242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17762758>.

410. Hu C, Chang EL, Hassenbusch SJ, 3rd, et al. Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. *Cancer* 2006;106:1998-2004. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16572401>.

411. Kalkanis SN, Kondziolka D, Gaspar LE, et al. The role of surgical resection in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:33-43. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19960230>.

412. Gaspar LE, Mehta MP, Patchell RA, et al. The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. *J Neurooncol* 2010;96:17-32. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19960231>.

413. Mintz A, Perry J, Spithoff K, et al. Management of single brain metastasis: a practice guideline. *Curr Oncol* 2007;14:131-143. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17710205>.

414. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med*



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

1990;322:494-500. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/2405271>.

415. Linskey ME, Andrews DW, Asher AL, et al. The role of stereotactic radiosurgery in the management of patients with newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:45-68. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19960227>.

416. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 2006;295:2483-2491. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16757720>.

417. Abe E, Aoyama H. The role of whole brain radiation therapy for the management of brain metastases in the era of stereotactic radiosurgery. Curr Oncol Rep 2012;14:79-84. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22006098>.

418. Mehta MP, Paleologos NA, Mikkelsen T, et al. The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 2010;96:71-83. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19960229>.

419. Ellis TL, Neal MT, Chan MD. The role of surgery, radiosurgery and whole brain radiation therapy in the management of patients with metastatic brain tumors. Int J Surg Oncol 2012;2012:952345. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22312545>.

420. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. JAMA 1998;280:1485-1489. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/9809728>.

421. Ammirati M, Cobbs CS, Linskey ME, et al. The role of retreatment in the management of recurrent/progressive brain metastases: a

systematic review and evidence-based clinical practice guideline. J

Neurooncol 2010;96:85-96. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19957016>.

422. Reck M, Popat S, Reinmuth N, et al. Metastatic non-small-cell lung cancer (NSCLC): ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014;25 Suppl 3:iii27-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25115305>.

423. Tsao MN, Lloyd N, Wong RK, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. Cochrane Database Syst Rev 2012;4:CD003869. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22513917>.

424. Chang WS, Kim HY, Chang JW, et al. Analysis of radiosurgical results in patients with brain metastases according to the number of brain lesions: is stereotactic radiosurgery effective for multiple brain metastases? J Neurosurg 2010;113 Suppl:73-78. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21121789>.

425. Wolfson AH, Bae K, Komaki R, et al. Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer. Int J Radiat Oncol Biol Phys 2011;81:77-84. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20800380>.

426. Sun A, Bae K, Gore EM, et al. Phase III trial of prophylactic cranial irradiation compared with observation in patients with locally advanced non-small-cell lung cancer: neurocognitive and quality-of-life analysis. J Clin Oncol 2011;29:279-286. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21135267>.

427. Tallet AV, Azria D, Barlesi F, et al. Neurocognitive function impairment after whole brain radiotherapy for brain metastases: actual assessment. Radiat Oncol 2012;7:77. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22640600>.



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428. Li J, Bentzen SM, Renschler M, Mehta MP. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007;25:1260-1266. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17401015>.

429. Aoyama H, Tago M, Kato N, et al. Neurocognitive function of patients with brain metastasis who received either whole brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. *Int J Radiat Oncol Biol Phys* 2007;68:1388-1395. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17674975>.

430. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol* 2009;10:1037-1044. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19801201>.

431. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387-395. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24621620>.

432. Suh JH, Videtic GM, Aref AM, et al. ACR Appropriateness Criteria: single brain metastasis. *Curr Probl Cancer* 2010;34:162-174. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20541055>.

433. Marsh JC, Gielda BT, Herskovic AM, Abrams RA. Cognitive Sparing during the Administration of Whole Brain Radiotherapy and Prophylactic Cranial Irradiation: Current Concepts and Approaches. *J Oncol* 2010;2010:198208. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20671962>.

434. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014;32:3810-3816. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25349290>.

435. Arriagada R, Bergman B, Dunant A, et al. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. *N Engl J Med* 2004;350:351-360. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/14736927>.

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

<http://www.ncbi.nlm.nih.gov/pubmed/15972865>.

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

<http://www.ncbi.nlm.nih.gov/pubmed/16945766>.

438. Song WA, Zhou NK, Wang W, et al. Survival benefit of neoadjuvant chemotherapy in non-small cell lung cancer: an updated meta-analysis of 13 randomized control trials. *J Thorac Oncol* 2010;5:510-516. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20107424>.

439. Scagliotti GV, Pastorino U, Vansteenkiste JF, et al. Randomized phase III study of surgery alone or surgery plus preoperative cisplatin and gemcitabine in stages IB to IIIa non-small-cell lung cancer. *J Clin Oncol* 2012;30:172-178. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22124104>.

440. Depierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with primary surgery in resectable stage I (except T1N0), II, and IIIa non-small-cell lung cancer. *J Clin Oncol* 2002;20:247-253. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/11773176>.

441. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIa non-small-cell lung cancer: a 7-year



NCCN Guidelines Version 4.2015

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assessment of a randomized controlled trial. Lung Cancer 1999;26:7-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10574676>.

442. Roth JA, Fossella F, Komaki R, et al. A randomized trial comparing perioperative chemotherapy and surgery with surgery alone in resectable stage IIIA non-small-cell lung cancer. J Natl Cancer Inst 1994;86:673-680. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8158698>.

443. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery alone in early-stage non-small-cell lung cancer. J Clin Oncol 2010;28:3138-3145. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20516435>.

444. Felip E, Massuti B, Alonso G, et al. Surgery (S) alone, preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy followed by S, or S followed by adjuvant (adj) PC chemotherapy in early-stage non-small cell lung cancer (NSCLC): Results of the NATCH multicenter, randomized phase III trial [abstract]. J Clin Oncol 2009;27(Suppl 15):Abstract CRA7500. Available at:

445. Pisters KM, Vallieres E, Crowley JJ, et al. Surgery with or without preoperative paclitaxel and carboplatin in early-stage non-small-cell lung cancer: Southwest Oncology Group Trial S9900, an intergroup, randomized, phase III trial. J Clin Oncol 2010;28:1843-1849. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20231678>.

446. Westeel V, Quoix E, Puyraveau M, et al. A randomised trial comparing preoperative to perioperative chemotherapy in early-stage non-small-cell lung cancer (IFCT 0002 trial). Eur J Cancer 2013;49:2654-2664. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23735703>.

447. Group NM-aC. Preoperative chemotherapy for non-small-cell lung cancer: a systematic review and meta-analysis of individual participant data. Lancet 2014;383:1561-1571. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24576776>.

448. Curran 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21903745>.

449. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. J Clin Oncol 2010;28:2181-2190. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20351327>.

450. Socinski MA, Rosenman JG, Halle J, et al. Dose-escalating conformal thoracic radiation therapy with induction and concurrent carboplatin/paclitaxel in unresectable stage IIIA/B nonsmall cell lung carcinoma: a modified phase I/II trial. Cancer 2001;92:1213-1223. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11571735>.

451. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. J Clin Oncol 1999;17:2692-2699. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561343>.

452. Socinski MA, Evans T, Gettinger S, et al. Treatment of stage IV non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e341S-368S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649446>.

453. Azzoli CG, Temin S, Aliff T, et al. 2011 Focused Update of 2009 American Society of Clinical Oncology Clinical Practice Guideline Update on Chemotherapy for Stage IV Non-Small-Cell Lung Cancer. J Clin Oncol 2011;29:3825-3831. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21900105>.

454. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

for stage IV non-small-cell lung cancer. J Clin Oncol 2009;27:6251-6266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19917871>.

455. Group NM-AC. Chemotherapy in addition to supportive care improves survival in advanced non-small-cell lung cancer: a systematic review and meta-analysis of individual patient data from 16 randomized controlled trials. J Clin Oncol 2008;26:4617-4625. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18678835>.

456. Souquet PJ, Chauvin F, Boissel JP, et al. Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 1993;342:19-21. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8100290>.

457. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Non-small Cell Lung Cancer Collaborative Group. BMJ 1995;311:899-909. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7580546>.

458. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. N Engl J Med 2010;363:733-742. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20818875>.

459. Yates P, Schofield P, Zhao I, Currow D. Supportive and palliative care for lung cancer patients. J Thorac Dis 2013;5 Suppl 5:S623-628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163753>.

460. Ford DW, Koch KA, Ray DE, Selecky PA. Palliative and end-of-life care in lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e498S-512S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649453>.

461. Aizer AA, Chen MH, McCarthy EP, et al. Marital status and survival in patients with cancer. J Clin Oncol 2013;31:3869-3876. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24062405>.

462. Magilligan DJ, Jr., Duvernoy C, Malik G, et al. Surgical approach to lung cancer with solitary cerebral metastasis: twenty-five years' experience. Ann Thorac Surg 1986;42:360-364. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3767508>.

463. Arriagada R, Dunant A, Pignon JP, et al. Long-term results of the international adjuvant lung cancer trial evaluating adjuvant Cisplatin-based chemotherapy in resected lung cancer. J Clin Oncol 2010;28:35-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19933916>.

464. Butts CA, Ding K, Seymour L, et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR-10. J Clin Oncol 2010;28:29-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19933915>.

465. Douillard JY, Tribodet H, Aubert D, et al. Adjuvant cisplatin and vinorelbine for completely resected non-small cell lung cancer: subgroup analysis of the Lung Adjuvant Cisplatin Evaluation. J Thorac Oncol 2010;5:220-228. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20027124>.

466. Kreuter M, Vansteenkiste J, Fischer 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23161898>.

467. Petrelli F, Barni S. Non-cancer-related mortality after cisplatin-based adjuvant chemotherapy for non-small cell lung cancer: a study-level meta-analysis of 16 randomized trials. Med Oncol 2013;30:641. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23813019>.

468. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-3559. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18506026>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

469. Wisnivesky JP, Smith CB, Packer S, et al. Survival and risk of adverse events in older patients receiving postoperative adjuvant chemotherapy for resected stages II-IIIa lung cancer: observational cohort study. *BMJ* 2011;343:d4013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21757436>.

470. Strauss GM, Herndon J, Maddaus MA, et al. Randomized clinical trial of adjuvant chemotherapy with paclitaxel and carboplatin following resection in stage IB non-small cell lung cancer (NSCLC): Report of Cancer and Leukemia Group B (CALGB) Protocol 9633 [abstract]. *J Clin Oncol* 2004;22 (Suppl 14):Abstract 7019. Available at: http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/7019.

471. Strauss GM, Herndon JE, II, Maddaus MA, et al. Adjuvant chemotherapy in stage IB non-small cell lung cancer (NSCLC): Update of Cancer and Leukemia Group B (CALGB) protocol 9633 [abstract]. *J Clin Oncol* 2006;24 (Suppl 18):Abstract 7007. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7007.

472. Strauss GM, Herndon JE, 2nd, 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18809614>.

473. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007;18:317-323. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17079694>.

474. Katz A, Saad ED. CALGB 9633: an underpowered trial with a methodologically questionable conclusion. *J Clin Oncol* 2009;27:2300-2301; author reply 2301-2302. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19332712>.

475. Dillman RO, Seagren SL, Propert KJ, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer. *N Engl J Med* 1990;323:940-945. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2169587>.

476. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in nonresectable non-small-cell lung cancer: first analysis of a randomized trial in 353 patients. *J Natl Cancer Inst* 1991;83:417-423. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1847977>.

477. Schaake-Koning C, van den Bogaert W, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small-cell lung cancer. *N Engl J Med* 1992;326:524-530. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1310160>.

478. Dillman RO, Seagren SL, Herndon J, et al. A randomized trial of induction chemotherapy plus high-dose radiation versus radiation alone in stage III non-small-cell lung cancer: Five-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Clin Oncol* (Meeting Abstracts) 1993;12:329. Available at:

479. Dillman RO, Herndon J, Seagren SL, et al. Improved survival in stage III non-small-cell lung cancer: seven-year follow-up of cancer and leukemia group B (CALGB) 8433 trial. *J Natl Cancer Inst* 1996;88:1210-1215. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8780630>.

480. Ramnath N, Dilling TJ, Harris LJ, et al. Treatment of stage III non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2013;143:e314S-340S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649445>.

481. Santana-Davila R, DeVistetty K, Szabo A, et al. Cisplatin and Etoposide Versus Carboplatin and Paclitaxel With Concurrent Radiotherapy for Stage III Non-Small-Cell Lung Cancer: An Analysis of Veterans Health Administration Data. *J Clin Oncol* 2014. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25422491>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

482. Ezer N, Smith CB, Galsky MD, et al. Cisplatin vs. carboplatin-based chemoradiotherapy in patients >65 years of age with stage III non-small cell lung cancer. *Radiother Oncol* 2014;112:272-278.

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25150635>.

483. Albain KS, Crowley JJ, Turrisi AT, 3rd, 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. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12177106>.

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

<http://www.ncbi.nlm.nih.gov/pubmed/16087941>.

485. Govindan 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. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21747084>.

486. Vokes EE, Senan S, Treat JA, Iscoe NA. PROCLAIM: A phase III study of pemetrexed, cisplatin, and radiation therapy followed by consolidation pemetrexed versus etoposide, cisplatin, and radiation therapy followed by consolidation cytotoxic chemotherapy of choice in locally advanced stage III non-small-cell lung cancer of other than predominantly squamous cell histology. *Clin Lung Cancer* 2009;10:193-198. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19443340>.

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

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12837811>.

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

Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14581415>.

489. Zatloukal P, Petruzella L, Zemanova M, et al. Concurrent versus sequential chemoradiotherapy with cisplatin and vinorelbine in locally advanced non-small cell lung cancer: a randomized study. *Lung Cancer* 2004;46:87-98. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15364136>.

490. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage non-small-cell lung cancer. *J Clin Oncol* 2008;26:3543-3551. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18506025>.

491. Zornosa C, Vandergrift JL, Kalemkerian GP, et al. First-line systemic therapy practice patterns and concordance with NCCN guidelines for patients diagnosed with metastatic NSCLC treated at NCCN institutions. *J Natl Compr Canc Netw* 2012;10:847-856. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22773800>.

492. Pennell NA. Selection of chemotherapy for patients with advanced non-small cell lung cancer. *Cleve Clin J Med* 2012;79 Electronic Suppl 1:eS46-50. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22614966>.

493. Leigh NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. *Curr Oncol* 2012;19:S52-58. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22787411>.

494. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med*



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

2006;355:2542-2550. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17167137>.

495. Edelman MJ, Le Chevalier T, Soria JC. Maintenance therapy and advanced non-small-cell lung cancer: a skeptic's view. *J Thorac Oncol* 2012;7:1331-1336. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22895137>.

496. Patel J, Socinski MA, Garon EB, et al. A randomized, open-label, phase 3, superiority study of pemetrexed (Pem)+carboplatin (Cb)+bevacizumab (B) followed by maintenance Pem+B versus paclitaxel (Pac)+Cb+B followed by maintenance B in patients (pts) with stage IIIB or IV non-squamous non-small cell lung cancer (NS-NSCLC) [abstract]. *J Thorac Oncol* 2012;7:Abstract LBPL1. Available at:
<http://journals.lww.com/jto/toc/2012/09004#-1657960090>.

497. Hershman DL, Lacchetti C, Dworkin RH, et al. Prevention and management of chemotherapy-induced peripheral neuropathy in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2014;32:1941-1967. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24733808>.

498. Patel 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. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/24145346>.

499. Zhu J, Sharma DB, Gray SW, et al. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell lung cancer. *JAMA* 2012;307:1593-1601. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22511687>.

500. Felip E, Gridelli C, Baas P, et al. Metastatic non-small-cell lung cancer: consensus on pathology and molecular tests, first-line, second-line, and third-line therapy: 1st ESMO Consensus Conference in Lung

Cancer; Lugano 2010. *Ann Oncol* 2011;22:1507-1519. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21536661>.

501. Lilenbaum R, Zukin M, Pereira JR, et al. A randomized phase III trial of single-agent pemetrexed (P) versus carboplatin and pemetrexed (CP) in patients with advanced non-small cell lung cancer (NSCLC) and performance status (PS) of 2 [abstract]. *J Clin Oncol* 2012;30(Suppl 15):Abstract 7506. Available at:
http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/7506.

502. Langer CJ, O'Byrne KJ, Socinski MA, et al. Phase III trial comparing paclitaxel poliglumex (CT-2103, PPX) in combination with carboplatin versus standard paclitaxel and carboplatin in the treatment of PS 2 patients with chemotherapy-naïve advanced non-small cell lung cancer. *J Thorac Oncol* 2008;3:623-630. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/18520802>.

503. Lilenbaum R, Villafior VM, Langer C, et al. Single-agent versus combination chemotherapy in patients with advanced non-small cell lung cancer and a performance status of 2: prognostic factors and treatment selection based on two large randomized clinical trials. *J Thorac Oncol* 2009;4:869-874. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19487960>.

504. Roth BJ, Krilov L, Adams S, et al. Clinical cancer advances 2012: annual report on progress against cancer from the american society of clinical oncology. *J Clin Oncol* 2013;31:131-161. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23213095>.

505. Zukin M, Barrios CH, Pereira JR, et al. Randomized phase III trial of single-agent pemetrexed versus carboplatin and pemetrexed in patients with advanced non-small-cell lung cancer and Eastern Cooperative Oncology Group performance status of 2. *J Clin Oncol* 2013;31:2849-2853. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23775961>.

506. Kelly K, Crowley J, Bunn PA, Jr., et al. Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

treatment of patients with advanced non--small-cell lung cancer: a Southwest Oncology Group trial. J Clin Oncol 2001;19:3210-3218. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11432888>.

507. Schiller JH, Harrington D, Belani CP, et al. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 2002;346:92-98. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11784875>.

508. Grossi F, Kubota K, Cappuzzo F, et al. Future scenarios for the treatment of advanced non-small cell lung cancer: focus on taxane-containing regimens. Oncologist 2010;15:1102-1112. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20930102>.

509. de Marinis F, Rossi A, Di Maio M, et al. Treatment of advanced non-small-cell lung cancer: Italian Association of Thoracic Oncology (AIOT) clinical practice guidelines. Lung Cancer 2011;73:1-10. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21440325>.

510. Danson S, Middleton MR, O'Byrne KJ, et al. Phase III trial of gemcitabine and carboplatin versus mitomycin, ifosfamide, and cisplatin or mitomycin, vinblastine, and cisplatin in patients with advanced nonsmall cell lung carcinoma. Cancer 2003;98:542-553. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12879472>.

511. Booton R, Lorigan P, Anderson H, et al. A phase III trial of docetaxel/carboplatin versus mitomycin C/ifosfamide/cisplatin (MIC) or mitomycin C/vinblastine/cisplatin (MVP) in patients with advanced non-small-cell lung cancer: a randomised multicentre trial of the British Thoracic Oncology Group (BTOG1). Ann Oncol 2006;17:1111-1119. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16603599>.

512. Gronberg BH, Bremnes RM, Flotten O, et al. Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:3217-3224. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19433683>.

513. D'Addario G, Pintilie M, Leighl NB, et al. Platinum-based versus non-platinum-based chemotherapy in advanced non-small-cell lung cancer: a meta-analysis of the published literature. J Clin Oncol 2005;23:2926-2936. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15728229>.

514. Greco FA, Spigel DR, Kuzur ME, et al. Paclitaxel/Carboplatin/gemcitabine versus gemcitabine/vinorelbine in advanced non-small-cell lung cancer: a phase II/III study of the Minnie Pearl Cancer Research Network. Clin Lung Cancer 2007;8:483-487. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17922972>.

515. Herbst RS, Khuri FR, Lu C, et al. The novel and effective nonplatinum, nontaxane combination of gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: potential for decreased toxicity and combination with biological therapy. Cancer 2002;95:340-353. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12124835>.

516. Pujol JL, Breton JL, Gervais R, et al. Gemcitabine-docetaxel versus cisplatin-vinorelbine in advanced or metastatic non-small-cell lung cancer: a phase III study addressing the case for cisplatin. Ann Oncol 2005;16:602-610. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15741225>.

517. Rizvi NA, Riely GJ, Azzoli CG, 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18235124>.

518. Green MR, Manikhas GM, 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16740598>.

519. Socinski MA, Bondarenko I, Karaseva NA, et al. Weekly nab-paclitaxel in combination with carboplatin versus solvent-based



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

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. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22547591>.

520. Sandler AB, Johnson DH, Herbst RS. Anti-vascular endothelial growth factor monoclonals in non-small cell lung cancer. *Clin Cancer Res* 2004;10:4258s-4262s. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/15217970>.

521. Giaccone G. Epidermal growth factor receptor inhibitors in the treatment of non-small-cell lung cancer. *J Clin Oncol* 2005;23:3235-3242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15886311>.

522. Khozin S, Blumenthal GM, Jiang X, et al. U.S. Food and Drug Administration approval summary: Erlotinib for the first-line treatment of metastatic non-small cell lung cancer with epidermal growth factor receptor exon 19 deletions or exon 21 (L858R) substitution mutations. *Oncologist* 2014;19:774-779. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/24868098>.

523. Sequist LV, Joshi VA, Janne PA, et al. Response to treatment and survival of patients with non-small cell lung cancer undergoing somatic EGFR mutation testing. *Oncologist* 2007;12:90-98. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17285735>.

524. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947-957. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19692680>.

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

<http://www.ncbi.nlm.nih.gov/pubmed/19224850>.

526. Fukuoka M, Wu YL, Thongprasert S, et al. Biomarker analyses and final overall survival results from a phase III, randomized, open-label,

first-line study of gefitinib versus carboplatin/paclitaxel in clinically selected patients with advanced non-small-cell lung cancer in Asia (IPASS). *J Clin Oncol* 2011;29:2866-2874. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21670455>.

527. Jackman DM, Miller VA, Cioffredi LA, et al. Impact of epidermal growth factor receptor and KRAS mutations on clinical outcomes in previously untreated non-small cell lung cancer patients: results of an online tumor registry of clinical trials. *Clin Cancer Res* 2009;15:5267-5273. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19671843>.

528. Gridelli C, Ciardiello F, Gallo C, et al. First-line erlotinib followed by second-line cisplatin-gemcitabine chemotherapy in advanced non-small-cell lung cancer: the TORCH randomized trial. *J Clin Oncol* 2012;30:3002-3011. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22778317>.

529. Keedy VL, Temin S, Somerfield MR, et al. American Society of Clinical Oncology provisional clinical opinion: epidermal growth factor receptor (EGFR) Mutation testing for patients with advanced non-small-cell lung cancer considering first-line EGFR tyrosine kinase inhibitor therapy. *J Clin Oncol* 2011;29:2121-2127. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21482992>.

530. Janne PA, Wang X, Socinski MA, et al. Randomized phase II trial of erlotinib alone or with carboplatin and paclitaxel in patients who were never or light former smokers with advanced lung adenocarcinoma: CALGB 30406 trial. *J Clin Oncol* 2012;30:2063-2069. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22547605>.

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

http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7503.



NCCN Guidelines Version 4.2015 Non-Small Cell Lung Cancer

532. FDA approves afatinib for advanced lung cancer. Oncology (Williston Park) 2013;27:813-814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24133833>.

533. Pirker R, Pereira JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open-label randomised phase III trial. Lancet 2009;373:1525-1531. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19410716>.

534. Garon EB, Ciuleanu TE, Arrieta O, et al. Ramucirumab plus docetaxel versus placebo plus docetaxel for second-line treatment of stage IV non-small-cell lung cancer after disease progression on platinum-based therapy (REVEL): a multicentre, double-blind, randomised phase 3 trial. Lancet 2014;384:665-673. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24933332>.

535. Gridelli C, de Marinis F, Di Maio M, et al. Maintenance treatment of advanced non-small-cell lung cancer: results of an international expert panel meeting of the Italian association of thoracic oncology. Lung Cancer 2012;76:269-279. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22266040>.

536. Hashemi-Sadraei N, Pennell NA. Advanced non-small cell lung cancer (NSCLC): maintenance therapy for all? Curr Treat Options Oncol 2012;13:478-490. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22972369>.

537. Patel JD, Hensing TA, Rademaker A, et al. Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer. J Clin Oncol 2009;27:3284-3289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19433684>.

538. Nadler E, Yu E, Ravelo A, et al. Bevacizumab treatment to progression after chemotherapy: outcomes from a U.S. community practice network. Oncologist 2011;16:486-496. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21441299>.

539. Paz-Ares L, de Marinis F, Dediu M, et al. Maintenance therapy with pemetrexed plus best supportive care versus placebo plus best supportive care after induction therapy with pemetrexed plus cisplatin for advanced non-squamous non-small-cell lung cancer (PARAMOUNT): a double-blind, phase 3, randomised controlled trial. Lancet Oncol 2012;13:247-255. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22341744>.

540. Paz-Ares LG, De Marinis F, Dediu M, et al. PARAMOUNT: Phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo plus BSC immediately following induction treatment with pem plus cisplatin for advanced nonsquamous non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2011;29(Suppl 18):Abstract CRA7510. Available at: http://meeting.ascopubs.org/cgi/content/abstract/29/18_suppl/CRA7510.

541. Paz-Ares LG, de Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival results of the phase III study of maintenance pemetrexed versus placebo immediately after induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small-cell lung cancer. J Clin Oncol 2013;31:2895-2902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23835707>.

542. Paz-Ares L, De Marinis F, Dediu M, et al. PARAMOUNT: Final overall survival (OS) results of the phase III study of maintenance pemetrexed (pem) plus best supportive care (BSC) versus placebo (plb) plus BSC immediately following induction treatment with pem plus cisplatin (cis) for advanced nonsquamous (NS) non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2012;30(Suppl 18):Abstract LBA7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/18_suppl/LBA7507.

543. Barlesi 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 (MO22089). J Clin Oncol 2013;31:3004-3011. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23835708>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

544. Barlesi F, de Castro J, Dvornichenko V, et al. AVAPERL (MO22089): Final efficacy outcomes for patients with advanced non-squamous non-small cell lung cancer randomized to continuation maintenance with bevacizumab (bev) or bev + pemetrexed (pem) after first-line bev-cisplatin-pem treatment [abstract]. Eur J Cancer 2011;47 (Suppl 2):16 Abstract 34LBA. Available at: http://new.ecco-org.eu/ecco_content/2011StockholmLateBreakingflipbook/index.html#/20/.

545. Perol M, Chouaid C, Perol 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22949150>.

546. Perol M, Chouaid C, Milleron BJ, et al. Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatment after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study [abstract]. J Clin Oncol 2010;28(Suppl 15):Abstract 7507. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7507.

547. Brodowicz T, Krzakowski M, Zwitter M, et al. Cisplatin and gemcitabine first-line chemotherapy followed by maintenance gemcitabine or best supportive care in advanced non-small cell lung cancer: a phase III trial. Lung Cancer 2006;52:155-163. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16569462>.

548. Fidias P, Novello S. Strategies for prolonged therapy in patients with advanced non-small-cell lung cancer. J Clin Oncol 2010;28:5116-5123. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21041704>.

549. Socinski MA, Schell MJ, Peterman A, et al. Phase III trial comparing a defined duration of therapy versus continuous therapy followed by second-line therapy in advanced-stage IIIB/IV non-small-cell lung cancer. J Clin Oncol 2002;20:1335-1343. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11870177>.

550. Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea. J Clin Oncol 2013;31:1009-1020. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23401441>.

551. Cappuzzo F, Ciuleanu T, Stelmakh L, et al. Erlotinib as maintenance treatment in advanced non-small-cell lung cancer: a multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 2010;11:521-529. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20493771>.

552. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-1440. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19767093>.

553. Cohen MH, Cortazar P, Justice R, Pazdur R. Approval summary: pemetrexed maintenance therapy of advanced/metastatic nonsquamous, non-small cell lung cancer (NSCLC). Oncologist 2010;15:1352-1358. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21148615>.

554. Cohen MH, Johnson JR, Chattopadhyay S, et al. Approval summary: erlotinib maintenance therapy of advanced/metastatic non-small cell lung cancer (NSCLC). Oncologist 2010;15:1344-1351. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21148614>.

555. Fidias PM, Dakhil SR, Lyss AP, et al. Phase III study of immediate compared with delayed docetaxel after front-line therapy with gemcitabine plus carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2009;27:591-598. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19075278>.

556. Rigotti NA, Regan S, Levy DE, et al. Sustained care intervention and postdischarge smoking cessation among hospitalized adults: a randomized clinical trial. JAMA 2014;312:719-728. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25138333>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

557. Stead LF, Hartmann-Boyce J, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database Syst Rev 2013;8:CD002850. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23934971>.

558. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:CD008286. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23076944>.

559. Silvestri GA, Gonzalez AV, Jantz MA, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e211S-250S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649440>.

560. Patterson GA, Ginsberg RJ, Poon PY, et al. A prospective evaluation of magnetic resonance imaging, computed tomography, and mediastinoscopy in the preoperative assessment of mediastinal node status in bronchogenic carcinoma. J Thorac Cardiovasc Surg 1987;94:679-684. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3669696>.

561. Gonzalez-Stawinski GV, Lemaire A, Merchant F, et al. A comparative analysis of positron emission tomography and mediastinoscopy in staging non-small cell lung cancer. J Thorac Cardiovasc Surg 2003;126:1900-1905. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/14688703>.

562. Tournoy KG, Maddens S, Gosselin R, et al. Integrated FDG-PET/CT does not make invasive staging of the intrathoracic lymph nodes in non-small cell lung cancer redundant: a prospective study. Thorax 2007;62:696-701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17687098>.

563. Meyers BF, Haddad F, Siegel BA, et al. Cost-effectiveness of routine mediastinoscopy in computed tomography- and positron emission tomography-screened patients with stage I lung cancer. J

Thorac Cardiovasc Surg 2006;131:822-829; discussion 822-829. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16580440>.

564. Dillemans B, Deneffe G, Verschakelen J, Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non-small cell lung cancer. A study of 569 patients. Eur J Cardiothorac Surg 1994;8:37-42. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8136168>.

565. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. Thorax 1995;50:1267-1269. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8553299>.

566. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission tomography. N Engl J Med 2000;343:254-261. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10911007>.

567. Manente P, Vicario G, Piazza F, et al. Does PET/CT modify the therapeutic approach in medical oncology [abstract]? . J Clin Oncol 2008;26(Suppl 15):Abstract 17525. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/17525.

568. Maziak DE, Darling GE, Incullet RI, et al. Positron emission tomography in staging early lung cancer: a randomized trial. Ann Intern Med 2009;151:221-228, W-248. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19581636>.

569. Fischer B, Lassen U, Mortensen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32-39. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19571281>.

570. De Wever W, Stroobants S, Coolen J, Verschakelen JA. Integrated PET/CT in the staging of nonsmall cell lung cancer: technical aspects and clinical integration. Eur Respir J 2009;33:201-212. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19118231>.



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571. McLoud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. *Radiology* 1992;182:319-323. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/1732943>.

572. Seely JM, Mayo JR, Miller RR, Muller NL. T1 lung cancer: prevalence of mediastinal nodal metastases and diagnostic accuracy of CT. *Radiology* 1993;186:129-132. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8416552>.

573. Kerr KM, Lamb D, Wathen CG, et al. Pathological assessment of mediastinal lymph nodes in lung cancer: implications for non-invasive mediastinal staging. *Thorax* 1992;47:337-341. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/1609375>.

574. Chin R, Jr., Ward R, Keyes JW, et al. Mediastinal staging of non-small-cell lung cancer with positron emission tomography. *Am J Respir Crit Care Med* 1995;152:2090-2096. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/8520780>.

575. Kernstine KH, Trapp JF, Croft DR, et al. Comparison of positron emission tomography (PET) and computed tomography (CT) to identify N2 and N3 disease in non small cell lung cancer (NSCLC). *J Clin Oncol* (Meeting Abstracts) 1998;17:458. Available at:

576. Kernstine KH, Stanford W, Mullan BF, et al. PET, CT, and MRI with Combidex for mediastinal staging in non-small cell lung carcinoma. *Ann Thorac Surg* 1999;68:1022-1028. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10510001>.

577. De Leyn P, Stroobants S, De Wever W, et al. Prospective comparative study of integrated positron emission tomography-computed tomography scan compared with remediastinoscopy in the assessment of residual mediastinal lymph node disease after induction chemotherapy for mediastinoscopy-proven stage IIIA-N2 Non-small-cell lung cancer: a Leuven Lung Cancer Group Study. *J Clin Oncol*

2006;24:3333-3339. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16849747>.

578. Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: a prospective study. *J Thorac Cardiovasc Surg* 2006;131:1229-1235. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16733150>.

579. Darling GE, Maziak DE, Inculet RI, et al. Positron emission tomography-computed tomography compared with invasive mediastinal staging in non-small cell lung cancer: results of mediastinal staging in the early lung positron emission tomography trial. *J Thorac Oncol* 2011;6:1367-1372. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21587082>.

580. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration compared with mediastinoscopy for mediastinal lymph node staging of lung cancer. *J Thorac Cardiovasc Surg* 2011;142:1393-1400 e1391. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21963329>.

581. Annema JT, van Meerbeeck JP, Rintoul RC, et al. Mediastinoscopy vs endosonography for mediastinal nodal staging of lung cancer: a randomized trial. *JAMA* 2010;304:2245-2252. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21098770>.

582. Tournoy KG, Keller SM, Annema JT. Mediastinal staging of lung cancer: novel concepts. *Lancet Oncol* 2012;13:e221-229. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22554550>.

583. Vilmann P, Krasnik M, Larsen SS, et al. Transesophageal endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) biopsy: a combined approach in the evaluation of mediastinal lesions. *Endoscopy* 2005;37:833-839. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/16116534>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

584. Yasufuku K, Nakajima T, Motoori K, et al. Comparison of endobronchial ultrasound, positron emission tomography, and CT for lymph node staging of lung cancer. *Chest* 2006;130:710-718. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16963667>.

585. Ernst A, Eberhardt R, Krasnik M, Herth FJ. Efficacy of endobronchial ultrasound-guided transbronchial needle aspiration of hilar lymph nodes for diagnosing and staging cancer. *J Thorac Oncol* 2009;4:947-950. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19590457>.

586. Rintoul RC, Tournoy KG, El Daly H, et al. EBUS-TBNA for the clarification of PET positive intra-thoracic lymph nodes-an international multi-centre experience. *J Thorac Oncol* 2009;4:44-48. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19096305>.

587. Defranchi SA, Edell ES, Daniels CE, et al. Mediastinoscopy in patients with lung cancer and negative endobronchial ultrasound guided needle aspiration. *Ann Thorac Surg* 2010;90:1753-1757. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21095301>.

588. Medford AR, Bennett JA, Free CM, Agrawal S. Mediastinal staging procedures in lung cancer: EBUS, TBNA and mediastinoscopy. *Curr Opin Pulm Med* 2009;15:334-342. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19395972>.

589. Mayr NA, Hussey DH, Yuh WT. Cost-effectiveness of high-contrast-dose MR screening of asymptomatic brain metastasis. *AJNR Am J Neuroradiol* 1995;16:215-217. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7755752>.

590. Videtic GM, Chang JY, Chetty IJ, et al. ACR appropriateness Criteria(R) early-stage non-small-cell lung cancer. *Am J Clin Oncol* 2014;37:201-207. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25180631>.

591. Rusch VW, Kraut MJ, Crowley J, et al. Induction chemoradiotherapy and surgical resection for non-small cell lung

carcinomas of the superior sulcus (pancoast tumors): Mature results of Southwest Oncology Group trial 9416 (Intergroup trial 0160) [abstract]. *Proc Am Soc Clin Oncol* 2003 22:Abstract 2548. Available at: http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=103854.

592. Barnes JB, Johnson SB, Dahiya RS, et al. Concomitant weekly cisplatin and thoracic radiotherapy for Pancoast tumors of the lung: pilot experience of the San Antonio Cancer Institute. *Am J Clin Oncol* 2002;25:90-92. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11823705>.

593. Rusch VW, Giroux DJ, Kraut MJ, et al. Induction chemoradiation and surgical resection for non-small cell lung carcinomas of the superior sulcus: Initial results of Southwest Oncology Group Trial 9416 (Intergroup Trial 0160). *J Thorac Cardiovasc Surg* 2001;121:472-483. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11241082>.

594. Pourel N, Santelmo N, Naafa N, et al. Concurrent cisplatin/etoposide plus 3D-conformal radiotherapy followed by surgery for stage IIB (superior sulcus T3N0)/III non-small cell lung cancer yields a high rate of pathological complete response. *Eur J Cardiothorac Surg* 2008;33:829-836. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18367406>.

595. Gandara DR, Chansky K, Albain KS, et al. Consolidation docetaxel after concurrent chemoradiotherapy in stage IIIB non-small-cell lung cancer: phase II Southwest Oncology Group Study S9504. *J Clin Oncol* 2003;21:2004-2010. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12743155>.

596. Nakagawa T, Okumura N, Miyoshi K, et al. Prognostic factors in patients with ipsilateral pulmonary metastasis from non-small cell lung cancer. *Eur J Cardiothorac Surg* 2005;28:635-639. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16126398>.

597. Lee JG, Lee CY, Kim DJ, et al. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging



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assessment. Eur J Cardiothorac Surg 2008;33:480-484. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18249000>.

598. Oliaro A, Filosso PL, Cavallo A, et al. The significance of intrapulmonary metastasis in non-small cell lung cancer: upstaging or downstaging? A re-appraisal for the next TNM staging system. Eur J Cardiothorac Surg 2008;34:438-443; discussion 443. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18502660>.

599. Bhaskarla A, Tang PC, Mashtare T, et al. Analysis of second primary lung cancers in the SEER database. J Surg Res 2010;162:1-6. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20400118>.

600. Aziz TM, Saad RA, Glasser J, et al. The management of second primary lung cancers. A single centre experience in 15 years. Eur J Cardiothorac Surg 2002;21:527-533. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11888775>.

601. Adebajo SA, Moritz DM, Danby CA. The results of modern surgical therapy for multiple primary lung cancers. Chest 1997;112:693-701. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9315801>.

602. Nakata M, Sawada S, Yamashita M, et al. Surgical treatments for multiple primary adenocarcinoma of the lung. Ann Thorac Surg 2004;78:1194-1199. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15464469>.

603. Ginsberg MS, Griff SK, Go BD, et al. Pulmonary nodules resected at video-assisted thoracoscopic surgery: etiology in 426 patients. Radiology 1999;213:277-282. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10540672>.

604. Allen MS. Multiple benign lung tumors. Semin Thorac Cardiovasc Surg 2003;15:310-314. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12973710>.

605. Asamura H. Multiple primary cancers or multiple metastases, that is the question. J Thorac Oncol 2010;5:930-931. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20581574>.

606. Girard N, Deshpande C, Azzoli CG, et al. Use of epidermal growth factor receptor/Kirsten rat sarcoma 2 viral oncogene homolog mutation testing to define clonal relationships among multiple lung adenocarcinomas: comparison with clinical guidelines. Chest 2010;137:46-52. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19376842>.

607. Han HS, Eom DW, Kim JH, et al. EGFR mutation status in primary lung adenocarcinomas and corresponding metastatic lesions: discordance in pleural metastases. Clin Lung Cancer 2011;12:380-386. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21729655>.

608. Martini N, Melamed MR. Multiple primary lung cancers. J Thorac Cardiovasc Surg 1975;70:606-612. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/170482>.

609. Chang YL, Wu CT, Lee YC. Surgical treatment of synchronous multiple primary lung cancers: experience of 92 patients. J Thorac Cardiovasc Surg 2007;134:630-637. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17723810>.

610. Tanvetyanon T, Robinson L, Sommers KE, et al. Relationship between tumor size and survival among patients with resection of multiple synchronous lung cancers. J Thorac Oncol 2010;5:1018-1024. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20453687>.

611. Rea F, Zuin A, Callegaro D, et al. Surgical results for multiple primary lung cancers. Eur J Cardiothorac Surg 2001;20:489-495. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11509268>.

612. Gibbs IC, Loo BW, Jr. CyberKnife stereotactic ablative radiotherapy for lung tumors. Technol Cancer Res Treat 2010;9:589-596. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21070081>.



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613. Godoy MC, Naidich DP. Subsolid pulmonary nodules and the spectrum of peripheral adenocarcinomas of the lung: recommended interim guidelines for assessment and management. *Radiology* 2009;253:606-622. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19952025>.

614. Pearson FG, DeLarue NC, Ilves R, et al. Significance of positive superior mediastinal nodes identified at mediastinoscopy in patients with resectable cancer of the lung. *J Thorac Cardiovasc Surg* 1982;83:1-11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7054602>.

615. Rice TW. Thoracoscopy in the staging of thoracic malignancies. In: Kaiser LR, Daniel TM, eds, eds. *Thoracoscopic Surgery*. Philadelphia: Lippincott Williams & Wilkins; 1993:153-162.

616. Gandara DR, Chansky K, Albain KS, et al. Long-term survival with concurrent chemoradiation therapy followed by consolidation docetaxel in stage IIIB non-small-cell lung cancer: a phase II Southwest Oncology Group Study (S9504). *Clin Lung Cancer* 2006;8:116-121. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17026812>.

617. Mina LA, Neubauer MA, Ansari RH, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023--Updated results [abstract]. *J Clin Oncol* 2008;26 (Suppl 15):Abstract 7519. Available at: http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7519.

618. Hanna NH, Neubauer M, Ansari R, et al. Phase III trial of cisplatin (P) plus etoposide (E) plus concurrent chest radiation (XRT) with or without consolidation docetaxel (D) in patients (pts) with inoperable stage III non-small cell lung cancer (NSCLC): HOG LUN 01-24/USO-023 [abstract]. *J Clin Oncol* 2007;25 (Suppl 18):Abstract 7512. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7512.

619. Decker DA, Dines DE, Payne WS, et al. The significance of a cytologically negative pleural effusion in bronchogenic carcinoma. *Chest* 1978;74:640-642. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/216532>.

620. Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). *J Natl Compr Canc Netw* 2012;10:975-982. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22878823>.

621. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer* 2014;15:346-355. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24894943>.

622. de Vin T, Engels B, Gevaert T, et al. Stereotactic radiotherapy for oligometastatic cancer: a prognostic model for survival. *Ann Oncol* 2014;25:467-471. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24355488>.

623. Raz DJ, Lanuti M, Gaissert HC, et al. Outcomes of patients with isolated adrenal metastasis from non-small cell lung carcinoma. *Ann Thorac Surg* 2011;92:1788-1792; discussion 1793. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21944257>.

624. Tanvetyanon T, Robinson LA, Schell MJ, et al. Outcomes of adrenalectomy for isolated synchronous versus metachronous adrenal metastases in non-small-cell lung cancer: a systematic review and pooled analysis. *J Clin Oncol* 2008;26:1142-1147. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18309950>.

625. Raviv G, Klein E, Yellin A, et al. Surgical treatment of solitary adrenal metastases from lung carcinoma. *J Surg Oncol* 1990;43:123-124. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1689433>.



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626. Reyes L, Parvez Z, Nemoto T, et al. Adrenalectomy for adrenal metastasis from lung carcinoma. J Surg Oncol 1990;44:32-34. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2342373>.

627. Park SY, Lee JG, Kim J, et al. Efficacy of platinum-based adjuvant chemotherapy in T2aN0 stage IB non-small cell lung cancer. J Cardiothorac Surg 2013;8:151. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23759129>.

628. Group NM-aC, Arriagada R, Auperin A, et al. Adjuvant chemotherapy, with or without postoperative radiotherapy, in operable non-small-cell lung cancer: two meta-analyses of individual patient data. Lancet 2010;375:1267-1277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20338627>.

629. Belani CP, Ramalingam S, Perry MC, et al. Randomized, phase III study of weekly paclitaxel in combination with carboplatin versus standard every-3-weeks administration of carboplatin and paclitaxel for patients with previously untreated advanced non-small-cell lung cancer. J Clin Oncol 2008;26:468-473. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18202422>.

630. Quoix E, Zalcman G, Oster JP, et al. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. Lancet 2011;378:1079-1088. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21831418>.

631. Langer CJ, Socinski MA, Patel JD, et al. Efficacy and safety of paclitaxel and carboplatin with bevacizumab for the first-line treatment of patients with nonsquamous non-small cell lung cancer (NSCLC): Analyses based on age in the phase III PointBreak and E4599 trials [abstract]. J Clin Oncol 2013;31(Suppl 15):Abstract 8073. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8073.

632. Burkes RL, Ginsberg RJ, Shepherd FA, et al. Induction chemotherapy with mitomycin, vindesine, and cisplatin for stage III unresectable non-small-cell lung cancer: results of the Toronto Phase II

Trial. J Clin Oncol 1992;10:580-586. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1312587>.

633. Bonomi P, Faber L. Neoadjuvant chemoradiation therapy in non-small cell lung cancer: The Rush University experience. Lung Cancer 1993;9:383-390. Available at:

634. Rusch VW, Albain KS, Crowley JJ, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent induction chemoradiotherapy. A Southwest Oncology Group trial. J Thorac Cardiovasc Surg 1993;105:97-104; discussion 104-106. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8380477>.

635. Rosell R, Gomez-Codina J, Camps C, et al. A randomized trial comparing preoperative chemotherapy plus surgery with surgery alone in patients with non-small-cell lung cancer. N Engl J Med 1994;330:153-158. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/8043059>.

636. Pisters K, Vallieres E, Bunn P, et al. S9900: A phase III trial of surgery alone or surgery plus preoperative (preop) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Preliminary results [abstract]. J Clin Oncol 2005;23 (Suppl 16):Abstract LBA7012. Available at: http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA7012.

637. Pisters K, Vallieres E, Bunn PA, Jr., et al. S9900: Surgery alone or surgery plus induction (ind) paclitaxel/carboplatin (PC) chemotherapy in early stage non-small cell lung cancer (NSCLC): Follow-up on a phase III trial [abstract]. J Clin Oncol 2007;25 (Suppl 18):Abstract 7520. Available at: http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7520.

638. Postoperative radiotherapy in non-small-cell lung cancer: systematic review and meta-analysis of individual patient data from nine randomised controlled trials. PORT Meta-analysis Trialists Group. Lancet 1998;352:257-263. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/9690404>.



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639. Decker RH, Langer CJ, Rosenzweig KE, et al. ACR Appropriateness Criteria(R) postoperative adjuvant therapy in non-small cell lung cancer. Am J Clin Oncol 2011;34:537-544. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21946673>.

640. Weisenburger TH, Graham MV, Sause WT, et al. Postoperative radiotherapy in non-small cell lung cancer. American College of Radiology. ACR Appropriateness Criteria. Radiology 2000;215 Suppl:1295-1318. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11037548>.

641. Hanna WC, Paul NS, Darling GE, et al. Minimal-dose computed tomography is superior to chest x-ray for the follow-up and treatment of patients with resected lung cancer. J Thorac Cardiovasc Surg 2014;147:30-33. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24139896>.

642. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81; discussion 81-72. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23127371>.

643. Calman L, Beaver K, Hind D, et al. Survival benefits from follow-up of patients with lung cancer: a systematic review and meta-analysis. J Thorac Oncol 2011;6:1993-2004. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21892108>.

644. Colt HG, Murgu SD, Korst RJ, et al. Follow-up and surveillance of the patient with lung cancer after curative-intent therapy: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:e437S-454S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23649451>.

645. Dane B, Grechushkin V, Plank A, et al. PET/CT vs. non-contrast CT alone for surveillance 1-year post lobectomy for stage I non-small-

cell lung cancer. Am J Nucl Med Mol Imaging 2013;3:408-416. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24116349>.

646. Henschke CI, McCauley DI, Yankelevitz DF, et al. Early Lung Cancer Action Project: overall design and findings from baseline screening. Lancet 1999;354:99-105. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10408484>.

647. Ulaner GA, Lyall A. Identifying and distinguishing treatment effects and complications from malignancy at FDG PET/CT. Radiographics 2013;33:1817-1834. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24108564>.

648. Shi Q, Smith TG, Michonski JD, et al. Symptom burden in cancer survivors 1 year after diagnosis: a report from the American Cancer Society's Studies of Cancer Survivors. Cancer 2011;117:2779-2790. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21495026>.

649. Gelb AF, Tashkin DP, Epstein JD, et al. Physiologic characteristics of malignant unilateral main-stem bronchial obstruction. Diagnosis and Nd-YAG laser treatment. Am Rev Respir Dis 1988;138:1382-1385. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2462389>.

650. Howell DD, James JL, Hartsell WF, et al. Single-fraction radiotherapy versus multifraction radiotherapy for palliation of painful vertebral bone metastases-equivalent efficacy, less toxicity, more convenient: a subset analysis of Radiation Therapy Oncology Group trial 97-14. Cancer 2013;119:888-896. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23165743>.

651. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. J Clin Oncol 2007;25:1423-1436. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17416863>.

652. Ashworth A, Rodrigues G, Boldt G, Palma D. Is there an oligometastatic state in non-small cell lung cancer? A systematic review of the literature. Lung Cancer 2013;82:197-203. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24051084>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

653. Griffioen GH, Toguri D, Dahele M, et al. Radical treatment of synchronous oligometastatic non-small cell lung carcinoma (NSCLC): patient outcomes and prognostic factors. Lung Cancer 2013;82:95-102. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23973202>.

654. Collen C, Christian N, Schallier D, et al. Phase II study of stereotactic body radiotherapy to primary tumor and metastatic locations in oligometastatic nonsmall-cell lung cancer patients. Ann Oncol 2014;25:1954-1959. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25114022>.

655. Tree AC, Khoo VS, Eeles RA, et al. Stereotactic body radiotherapy for oligometastases. Lancet Oncol 2013;14:e28-37. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23276369>.

656. De Ruyscher D, Wanders R, van Baardwijk A, et al. Radical treatment of non-small-cell lung cancer patients with synchronous oligometastases: long-term results of a prospective phase II trial (Nct01282450). J Thorac Oncol 2012;7:1547-1555. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22982655>.

657. Kelly P, Balter PA, Rebueno N, et al. Stereotactic body radiation therapy for patients with lung cancer previously treated with thoracic radiation. Int J Radiat Oncol Biol Phys 2010;78:1387-1393. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20381271>.

658. Meijneke TR, Petit SF, Wentzler D, et al. Reirradiation and stereotactic radiotherapy for tumors in the lung: dose summation and toxicity. Radiother Oncol 2013;107:423-427. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23647748>.

659. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. Radiother Oncol 2011;101:260-266. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22056534>.

660. Reyngold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT).

Radiat Oncol 2013;8:99. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23617949>.

661. Henry D, Vadhan-Raj S, Hirsh V, et al. Delaying skeletal-related events in a randomized phase 3 study of denosumab versus zoledronic acid in patients with advanced cancer: an analysis of data from patients with solid tumors. Support Care Cancer 2014;22:679-687. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24162260>.

662. Henry DH, Costa L, Goldwasser F, et al. Randomized, double-blind study of denosumab versus zoledronic acid in the treatment of bone metastases in patients with advanced cancer (excluding breast and prostate cancer) or multiple myeloma. J Clin Oncol 2011;29:1125-1132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21343556>.

663. Rosen LS, Gordon D, Tchekmedyian NS, et al. Long-term efficacy and safety of zoledronic acid in the treatment of skeletal metastases in patients with nonsmall cell lung carcinoma and other solid tumors: a randomized, Phase III, double-blind, placebo-controlled trial. Cancer 2004;100:2613-2621. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15197804>.

664. Henry DH, von Moos R, Hungria V, et al. Delaying skeletal-related events in a randomized phase III study of denosumab versus zoledronic acid in patients with advanced cancer [abstract]. J Clin Oncol 2010;28 (Suppl 15):Abstract 9133. Available at: http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/9133.

665. Scagliotti GV, Hirsh V, Siena S, et al. Overall survival improvement in patients with lung cancer and bone metastases treated with denosumab versus zoledronic acid: subgroup analysis from a randomized phase 3 study. J Thorac Oncol 2012;7:1823-1829. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23154554>.

666. Casas A, Llombart A, Martin M. Denosumab for the treatment of bone metastases in advanced breast cancer. Breast 2013;22:585-592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23759273>.



NCCN Guidelines Version 4.2015 Non-Small Cell Lung Cancer

667. Ibrahim A, Scher N, Williams G, et al. Approval summary for zoledronic acid for treatment of multiple myeloma and cancer bone metastases. Clin Cancer Res 2003;9:2394-2399. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12855610>.

668. Robinson SD, O'Shaughnessy JA, Cowey CL, Konduri K. BRAF V600E-mutated lung adenocarcinoma with metastases to the brain responding to treatment with vemurafenib. Lung Cancer 2014;85:326-330. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24888229>.

669. Mazieres 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23610105>.

670. Miller VA, Hirsh V, Cadranet J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-538. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22452896>.

671. Paez JG, Janne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. Science 2004;304:1497-1500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15118125>.

672. Peters S, Michielin O, Zimmermann S. Dramatic response induced by vemurafenib in a BRAF V600E-mutated lung adenocarcinoma. J Clin Oncol 2013;31:e341-344. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23733758>.

673. Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BRF113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. J Clin Oncol 2013;31(Suppl 15):Abstract 8009. Available at: http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8009.

674. Sakuma Y, Matsukuma S, Yoshihara M, et al. Distinctive evaluation of nonmucinous and mucinous subtypes of bronchioloalveolar carcinomas in EGFR and K-ras gene-mutation analyses for Japanese lung adenocarcinomas: confirmation of the correlations with histologic subtypes and gene mutations. Am J Clin Pathol 2007;128:100-108. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17580276>.

675. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer harbouring ALK gene rearrangement: a retrospective analysis. Lancet Oncol 2011;12:1004-1012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21933749>.

676. Roberts PJ. Clinical use of crizotinib for the treatment of non-small cell lung cancer. Biologics 2013;7:91-101. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23671386>.

677. Forbes SA, Bhamra G, Bamford S, et al. The Catalogue of Somatic Mutations in Cancer (COSMIC). Curr Protoc Hum Genet 2008;Chapter 10:Unit 10 11. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18428421>.

678. Lee SY, Kim MJ, Jin G, et al. Somatic mutations in epidermal growth factor receptor signaling pathway genes in non-small cell lung cancers. J Thorac Oncol 2010;5:1734-1740. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20881644>.

679. Rekhtman N, Paik PK, Arcila ME, et al. Clarifying the spectrum of driver oncogene mutations in biomarker-verified squamous carcinoma of lung: lack of EGFR/KRAS and presence of PIK3CA/AKT1 mutations. Clin Cancer Res 2012;18:1167-1176. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22228640>.

680. Sandler A, Yi J, Dahlberg S, et al. Treatment outcomes by tumor histology in Eastern Cooperative Group Study E4599 of bevacizumab with paclitaxel/carboplatin for advanced non-small cell lung cancer. J



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Thorac Oncol 2010;5:1416-1423. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/20686429>.

681. Socinski MA, Langer CJ, Huang JE, et al. Safety of bevacizumab in patients with non-small-cell lung cancer and brain metastases. J Clin Oncol 2009;27:5255-5261. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19738122>.

682. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 2012;366:2455-2465. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22658128>.

683. Heist RS, Sequist LV, Engelman JA. Genetic changes in squamous cell lung cancer: a review. J Thorac Oncol 2012;7:924-933. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22722794>.

684. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 2004;22:2184-2191. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/15169807>.

685. Reck M, von Pawel J, Zatloukal P, et al. Phase III trial of cisplatin plus gemcitabine with either placebo or bevacizumab as first-line therapy for nonsquamous non-small-cell lung cancer: AVAIL. J Clin Oncol 2009;27:1227-1234. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19188680>.

686. Mezger J, von Pawel J, Reck M. Bevacizumab (Bv) single-agent maintenance following Bv-based chemotherapy in patients with advanced non-small cell lung cancer (NSCLC): Results from an exploratory analysis of the AVAIL study [abstract]. J Clin Oncol 2009;27 (Suppl 15):Abstract e19001. Available at:
<http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e19001>.

687. Scagliotti G, Brodowicz T, Shepherd FA, et al. Treatment-by-histology interaction analyses in three phase III trials show superiority of pemetrexed in nonsquamous non-small cell lung cancer. J Thorac Oncol 2011;6:64-70. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21119545>.

688. Kubota K, Kawahara M, Ogawara M, et al. Vinorelbine plus gemcitabine followed by docetaxel versus carboplatin plus paclitaxel in patients with advanced non-small-cell lung cancer: a randomised, open-label, phase III study. Lancet Oncol 2008;9:1135-1142. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19013107>.

689. Pfister DG, Johnson DH, Azzoli CG, et al. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. J Clin Oncol 2004;22:330-353. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/14691125>.

690. Soon YY, Stockler MR, Askie LM, Boyer MJ. Duration of chemotherapy for advanced non-small-cell lung cancer: a systematic review and meta-analysis of randomized trials. J Clin Oncol 2009;27:3277-3283. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19470938>.

691. Coate LE, Shepherd FA. Maintenance therapy in advanced non-small cell lung cancer: evolution, tolerability and outcomes. Ther Adv Med Oncol 2011;3:139-157. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/21904577>.

692. Riely GJ, Kris MG, Zhao B, et al. Prospective assessment of discontinuation and reinitiation of erlotinib or gefitinib in patients with acquired resistance to erlotinib or gefitinib followed by the addition of everolimus. Clin Cancer Res 2007;13:5150-5155. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/17785570>.

693. von Minckwitz G, du Bois A, Schmidt M, et al. Trastuzumab beyond progression in human epidermal growth factor receptor 2-positive advanced breast cancer: a german breast group 26/breast



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international group 03-05 study. J Clin Oncol 2009;27:1999-2006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19289619>.

694. Becker K, Xu Y. Management of tyrosine kinase inhibitor resistance in lung cancer with EGFR mutation. World J Clin Oncol 2014;5:560-567. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25302160>.

695. Katakami N, Atagi S, Goto K, et al. LUX-Lung 4: a phase II trial of afatinib in patients with advanced non-small-cell lung cancer who progressed during prior treatment with erlotinib, gefitinib, or both. J Clin Oncol 2013;31:3335-3341. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23816963>.

696. Hirsh V, Cadranel J, Cong XJ, et al. Symptom and quality of life benefit of afatinib in advanced non-small-cell lung cancer patients previously treated with erlotinib or gefitinib: results of a randomized phase IIb/III trial (LUX-Lung 1). J Thorac Oncol 2013;8:229-237. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23328549>.

697. Ou SH. Second-generation irreversible epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs): a better mousetrap? A review of the clinical evidence. Crit Rev Oncol Hematol 2012;83:407-421. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22257651>.

698. Nguyen KS, Kobayashi S, Costa DB. Acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in non-small-cell lung cancers dependent on the epidermal growth factor receptor pathway. Clin Lung Cancer 2009;10:281-289. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19632948>.

699. Gazdar AF. Activating and resistance mutations of EGFR in non-small-cell lung cancer: role in clinical response to EGFR tyrosine kinase inhibitors. Oncogene 2009;28 Suppl 1:S24-31. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19680293>.

700. Chaft JE, Oxnard GR, Sima CS, et al. Disease flare after tyrosine kinase inhibitor discontinuation in patients with EGFR-mutant lung

cancer and acquired resistance to erlotinib or gefitinib: implications for clinical trial design. Clin Cancer Res 2011;17:6298-6303. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21856766>.

701. Meoni G, Cecere FL, Lucherini E, Di Costanzo F. Medical treatment of advanced non-small cell lung cancer in elderly patients: a review of the role of chemotherapy and targeted agents. J Geriatr Oncol 2013;4:282-290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24070465>.

702. Weiss JM, Stinchcombe TE. Second-Line Therapy for Advanced NSCLC. Oncologist 2013;18:947-953. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23918070>.

703. van Putten JW, Baas P, Codrington H, et al. Activity of single-agent gemcitabine as second-line treatment after previous chemotherapy or radiotherapy in advanced non-small-cell lung cancer. Lung Cancer 2001;33:289-298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11551424>.

704. Crino L, Mosconi AM, Scagliotti G, et al. Gemcitabine as second-line treatment for advanced non-small-cell lung cancer: A phase II trial. J Clin Oncol 1999;17:2081-2085. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10561261>.

705. Anderson H, Hopwood P, Stephens RJ, et al. Gemcitabine plus best supportive care (BSC) vs BSC in inoperable non-small cell lung cancer—a randomized trial with quality of life as the primary outcome. UK NSCLC Gemcitabine Group. Non-Small Cell Lung Cancer. Br J Cancer 2000;83:447-453. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10945489>.

706. Sculier JP, Lafitte JJ, Berghmans T, et al. A phase II trial testing gemcitabine as second-line chemotherapy for non small cell lung cancer. The European Lung Cancer Working Party. 101473.1044@compuserve.com. Lung Cancer 2000;29:67-73. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10880849>.



NCCN Guidelines Version 4.2015

Non-Small Cell Lung Cancer

707. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol 2000;18:2354-2362. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10856094>.

708. Shepherd FA, Dancey J, Ramlau R, et al. Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 2000;18:2095-2103. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10811675>.

709. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-1597. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15117980>.

710. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 2005;353:123-132. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16014882>.

711. Sacher AG, Janne PA, Oxnard GR. Management of acquired resistance to epidermal growth factor receptor kinase inhibitors in patients with advanced non-small cell lung cancer. Cancer 2014;120:2289-2298. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24752335>.

712. Langer CJ, Mok T, Postmus PE. Targeted agents in the third-/fourth-line treatment of patients with advanced (stage III/IV) non-small cell lung cancer (NSCLC). Cancer Treat Rev 2013;39:252-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22703830>.

713. Noble J, Ellis PM, Mackay JA, et al. Second-line or subsequent systemic therapy for recurrent or progressive non-small cell lung cancer: a systematic review and practice guideline. J Thorac Oncol

2006;1:1042-1058. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17409993>.

714. Demarinis F, Paul S, Hanna N, et al. Survival update for the phase III study of pemetrexed vs docetaxel in non-small cell lung cancer (NSCLC) [abstract]. J Clin Oncol 2006;24 (Suppl 18):Abstract 7133. Available at: http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7133.

715. Garassino MC, Martelli O, Brogini M, et al. Erlotinib versus docetaxel as second-line treatment of patients with advanced non-small-cell lung cancer and wild-type EGFR tumours (TAILOR): a randomised controlled trial. Lancet Oncol 2013;14:981-988. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23883922>.

716. Kawaguchi T, Ando M, Asami K, et al. Randomized phase III trial of erlotinib versus docetaxel as second- or third-line therapy in patients with advanced non-small-cell lung cancer: Docetaxel and Erlotinib Lung Cancer Trial (DELTA). J Clin Oncol 2014;32:1902-1908. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24841974>.

717. Gregorc V, Novello S, Lazzari C, et al. Predictive value of a proteomic signature in patients with non-small-cell lung cancer treated with second-line erlotinib or chemotherapy (PROSE): a biomarker-stratified, randomised phase 3 trial. Lancet Oncol 2014;15:713-721. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24831979>.

718. Ramlau R, Gervais R, Krzakowski M, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. J Clin Oncol 2006;24:2800-2807. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16682727>.

719. Eccles BK, Geldart TR, Laurence VM, et al. Experience of first- and subsequent-line systemic therapy in the treatment of non-small cell lung cancer. Ther Adv Med Oncol 2011;3:163-170. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21904578>.