

**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

# **Non-Small Cell Lung Cancer**

Version 4.2014

**NCCN.org**

**NCCN Guidelines for Patients® available at [www.nccn.org/patients](http://www.nccn.org/patients)**

**Continue**



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014 Panel Members

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

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

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

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

**Lyudmila A. Bazhenova, MD † ‡**  
UC San Diego Moores Cancer Center

**Hossein Borghaei, DO, MS † ‡**  
Fox Chase Cancer Center

**D. Ross Camidge, MD, PhD †**  
University of Colorado Cancer Center

**Richard T. Cheney, MD ≠**  
Roswell Park Cancer Institute

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

**Thomas A. D'Amico, MD ¶**  
Duke Cancer Institute

**Todd L. Demmy, MD ¶**  
Roswell Park Cancer Institute

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

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

**Stefan C. Grant, MD, JD † ‡**  
University of Alabama at Birmingham  
Comprehensive Cancer Center

**Leora Horn, MD, MSc †**  
Vanderbilt-Ingram Cancer Center

**Thierry M. Jahan, MD † ‡**  
UCSF Helen Diller Family  
Comprehensive Cancer Center

**Ritsuko Komaki, MD §**  
The University of Texas  
MD Anderson Cancer Center

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

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

**Rudy P. Lackner, MD**  
Fred & Pamela Buffett Cancer Center at  
The Nebraska Medical Center

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

**Jules Lin, MD ¶**  
University of Michigan Comprehensive Cancer  
Center

**Billy W. Loo, Jr., MD, PhD §**  
Stanford Cancer Institute

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

**Gregory A. Otterson, MD †**  
The Ohio State University Comprehensive  
Cancer Center - James Cancer Hospital  
and Solove Research Institute

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

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

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

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

**Eric Rohren, MD, PhD ϕ**  
The University of Texas  
MD Anderson Cancer Center

**Theresa A. Shapiro, MD, PhD ≠**  
The Sidney Kimmel Comprehensive  
Cancer Center at Johns Hopkins

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

**Kurt Tauer, MD**  
University of Tennessee Health Science Center

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

**NCCN**  
**Kristina Gregory, RN, MSN**  
**Miranda Hughes, PhD**

† Medical oncology  
¶ Surgery/Surgical oncology  
§ Radiation oncology/Radiotherapy  
≠ Pathology  
‡ Hematology/Hematology oncology  
ϕ Diagnostic/Interventional radiology  
≠ Patient advocate  
\*Writing committee member

**Continue**

[NCCN Guidelines Panel Disclosures](#)



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014 Table of Contents

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

### [NCCN Non-Small Cell Lung Cancer Panel Members](#)

#### [Summary of Guidelines Updates](#)

#### [Lung Cancer Prevention and Screening \(PREV-1\)](#)

#### [Clinical Presentation and Risk Assessment \(DIAG-1\)](#)

#### [Initial Evaluation and Clinical Stage \(NSCL-1\)](#)

#### [Evaluation and Treatment:](#)

- [Stage I \(T1ab-2a, N0\), Stage II \(T1ab-2ab, N1; T2b, N0\), and Stage IIB \(T3, N0\) \(NSCL-2\)](#)
- [Stage IIB \(T3 invasion, N0\) and Stage IIIA \(T4 extension, N0-1; T3, N1\) \(NSCL-4\)](#)
- [Stage IIIA \(T1-3, N2\) and Separate Pulmonary Nodules \(Stage IIB, IIIA, IV\) \(NSCL-7\)](#)
- [Multiple Lung Cancers \(NSCL-10\)](#)
- [Stage IIIB \(T1-3, N3\) \(NSCL-11\)](#)
- [Stage IIIB \(T4 extension, N2-3\) and Stage IV \(M1a\) \(pleural or pericardial effusion\) \(NSCL-12\)](#)
- [Stage IV \(M1b: solitary site\) \(NSCL-13\)](#)

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

#### [Therapy for Recurrence and Metastasis \(NSCL-15\)](#)

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

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

#### [Principles of Surgical Therapy \(NSCL-B\)](#)

#### [Principles of Radiation Therapy \(NSCL-C\)](#)

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

#### [Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#)

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

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

#### [Targeted Agents for Patients with Other Genetic Alterations \(NSCL-H\)](#)

#### [Staging \(ST-1\)](#)

**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. ©2014.



# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

Updates in the 4.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 3.2014 version include:

### [NSCL-18](#)

- Second-line therapy, brain (isolated lesion and multiple lesions) and systemic (isolated lesion): “...continue crizotinib” changed to “...continue ALK inhibitor.”
- Second-line therapy, systemic (multiple lesions): “Consider platinum doublet ± bevacizumab” changed to “Ceritinib or consider platinum doublet ± bevacizumab.”
- Second-line therapy, asymptomatic: “Continue crizotinib” changed to “Continue crizotinib or switch to ceritinib depending on degree of progression.”
- Footnote “nn” is new to the page: Patients who are intolerant to crizotinib may be switched to ceritinib.
- Footnote “oo” is new to the page: See third-line therapy (NSCL-21) for progressive disease with multiple symptomatic systemic lesions after treatment with crizotinib, ceritinib, and/or platinum doublet ± bevacizumab.
- Footnote “pp” is new to the page: For rapid radiologic progression or threatened organ function, alternate therapy should be instituted.
- The following statement was added after “second-line therapy”: Symptomatic systemic progression after local therapies and/or after switching to ceritinib, see third-line therapy (NSCL-21)

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

- Second-line therapy, bullet 1, sub-bullet 5 added: Ceritinib is indicated for select patients with ALK rearrangements who have disease progression on or are intolerant to crizotinib.
- Continuation after disease progression: ceritinib added to the list of targeted agents.

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

- Ceritinib added with the following reference: Shaw 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.

### [NSCL-H](#)

- Ceritinib added for ALK rearrangements with the following reference: Shaw 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.



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

Updates in the 3.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2014 version include:

**[MS-1](#)** - The Discussion section updated to reflect the changes in the algorithm.

Updates in the 2.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 1.2014 version include:

**[NSCL-3](#)**

- Stage IB, IIA, margins negative: adjuvant chemotherapy recommendation changed from a category 2B to a category 2A for high risk patients.

Updates in the 1.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2013 version include:

**[DIAG-2](#)**

- >10 mm non-solid or part-solid nodule, options modified after LDCT: increase in size *or increase in solid component*.

**[NSCL-1](#)**

- Initial evaluation: “Supportive care” changed to “Integrate palliative care.” A link to the NCCN Guidelines for Palliative Care added.

**[NSCL-2](#)**

- Stage IA, medically inoperable treatment recommendation modified: Definitive RT *including* SABR.
- Stage IB, I, II, IIB, medically inoperable treatment recommendations modified.
  - ▶ Nodal status added
  - ▶ N0 is recommended to receive definitive RT including SABR, followed by adjuvant chemotherapy (category 2B) for high-risk stages IB-II.
  - ▶ N1 is recommended to receive definitive chemoradiation.
  - ▶ High-risk footnote added from NSCL-3: Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.

**[NSCL-3](#)**

- Adjuvant treatment recommendations for Stage IIA, IIB, margins positive modified.
  - ▶ R1 resection separated out with the following recommendations: resection + chemotherapy or chemoradiation (sequential or concurrent).
  - ▶ R2 resection separated out with the following recommendations: resection + chemotherapy or concurrent chemoradiation.
- Adjuvant treatment recommendations for Stage IIIA modified.
  - ▶ R0 resection clarified as *chemotherapy (category 1) or sequential chemotherapy + RT (N2 only)*.
  - ▶ R1 resection separated out with the following recommendations: chemoradiation (sequential or concurrent).
  - ▶ R2 resection separated out with the following recommendations: concurrent chemoradiation.
- Previous footnote “j” deleted: Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.
- Footnote “l” modified: ~~Examples of high-risk patients-factors may include~~ *are defined by* poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular invasion, wedge resection, tumors >4 cm, visceral pleural involvement, and incomplete lymph node sampling (Nx). These factors independently may not be an indication and may be considered when determining treatment with adjuvant chemotherapy.
- Previous footnote “p” deleted: The panel recommends concurrent chemoradiation for R2 resections and sequential chemoradiation for R1 resections. This information is now delineated in the algorithm. (also applies to NSCL-5, NSCL-6, NSCL-8, NSCL-9)

**[NSCL-5](#)**

- Superior sulcus tumor (T4 extension, N0-1): marginally resectable changed to possibly resectable.
- Footnote “q” modified: If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy. (also applies to NSCL-6, NSCL-12)



# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

Updates in the 1.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2013 version include:

### [NSCL-6](#)

- Chest wall, proximal airway, or mediastinum: T4 clarified as “resectable.”
- Surgery as initial treatment, margins positive:
  - ▶ R1 resection separated out with the following recommendations: resection + chemotherapy or chemoradiation (sequential or concurrent).
  - ▶ R2 resection separated out with the following recommendations: resection + chemotherapy or concurrent chemoradiation.

### [NSCL-8](#)

- T1-3, N0-1: unresectable changed to medically inoperable.
- Surgery as initial treatment, margins positive:
  - ▶ R1 resection separated out with the following recommendations: chemoradiation (sequential or concurrent).
  - ▶ R2 resection separated out with the following recommendations: concurrent chemoradiation.
- Footnote “s” is new to the page: Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

### [NSCL-9](#)

- Surgery as initial treatment, margins positive:
  - ▶ R1 resection separated out with the following recommendations: chemoradiation (sequential or concurrent).
  - ▶ R2 resection separated out with the following recommendations: concurrent chemoradiation.

### [NSCL-10](#)

- Footnote “v” modified: Lesions at low risk of becoming symptomatic can be observed (*eg, small subsolid nodules with slow growth*). However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms (*eg, subsolid nodules with accelerating growth or increasing solid component or increasing FDG uptake, even while small*), treatment should be considered.

### [NSCL-13](#)

- T1-2, N0-1; T3, N0: SABR of the lung lesion added as a treatment option after chemotherapy.

### [NSCL-14](#)

- H&P and chest CT recommendations in surveillance changed from a category 2B to a category 2A.

### [NSCL-15](#)

- Mediastinal lymph node recurrence: treatment recommendations listed according to prior treatment with RT. If patients received prior RT, the recommendation of systemic chemotherapy added.

### [NSCL-16](#)

- Establish histologic subtype with adequate tissue for molecular testing: “consider rebiopsy if appropriate” added.
- “Integrate palliative care” added with footnote “b”. A link to the NCCN Guidelines for Palliative Care added.
- Adenocarcinoma, large cell, NSCLC NOS; the following added:
  - ▶ Category 1 added to ALK testing.
  - ▶ EGFR ± ALK testing should be conducted as part of a multiplex/next-generation sequencing.
- Squamous cell carcinoma; the following modified/added:
  - ▶ ~~Consider~~ EGFR mutation and ALK testing ~~are not routinely recommended except especially~~ in never smokers ~~and/or~~ small biopsy specimens, or mixed histology.
  - ▶ EGFR ± ALK testing should be conducted as part of a multiplex/next-generation sequencing.
- Footnote “cc” added with direction to a new page, Targeted Agents for Patients with Other Genetic Alterations (NSCL-H).
- EGFR mutation and ALK negative: “or unknown” added.





# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

Updates in the 1.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2013 version include:

### NSCL-16

- Footnote “dd” modified: In patients with squamous cell carcinoma, the observed incidence of *EGFR mutations* is 2.7% with a confidence that the true incidence of mutations is less than 3.6% ~~in patients with squamous cell carcinoma~~. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharmha G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
- Footnote “ff” modified: ~~Consider ROS1 testing, if positive~~ **Consider ROS1 testing, if positive** ~~if ROS1 mutation status is known and positive~~, may treat with crizotinib. [http://www.nccn.org/disclosures/panel\\_list.asp?ID=40](http://www.nccn.org/disclosures/panel_list.asp?ID=40) 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. (also applies to NSCL-18)

### NSCL-17

- First-line therapy, EGFR mutation discovered prior to first-line chemotherapy: afatinib added as a category 1 recommendation.
- First-line therapy, EGFR mutation discovered during first-line chemotherapy: recommended treatment options modified to **“Interrupt or complete planned chemotherapy, start erlotinib or afatinib or May add erlotinib or afatinib to current chemotherapy (category 2B)”**
- Second-line therapy: afatinib added as a treatment option.
- Second-line therapy, symptomatic brain: footnote “II” added: Consider pulse erlotinib for carcinomatosis meningitis.
- Second-line therapy, systemic multiple lesions: Consider systemic therapy changed to Consider **platinum doublet ± bevacizumab ± erlotinib**.
- Footnote “mm” added: 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.

### NSCL-18

- Treatment recommendations for ALK positive modified to be consistent with EGFR-positive mutations.

### NSCL-19

- First-line therapy: the combination regimen cisplatin/pemetrexed was deleted from this page, as it is included in doublet chemotherapy.
- Maintenance therapy:
  - Continuation of current regimen until disease progression removed as an option.
  - Continuation maintenance with gemcitabine changed from a category 2A recommendation to a category 2B recommendation.
  - Switch maintenance with pemetrexed or erlotinib changed from a category 2A recommendation to a category 2B recommendation.
- Footnote “nn” added: Consider additional mutational testing if only EGFR and ALK were performed. See Targeted Agents for Patients with Other Genetic Alterations (NSCL-H).
- Previous footnote “ii” removed: There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients who do not have squamous histology, in comparison to cisplatin/gemcitabine. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. J Clin Oncol 2008;26:3543-3551.
- Previous footnote “jj” removed: Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open label randomised phase III trial. Lancet 2009;373:1525-1531. (also applies to NSCL-20)
- Previous footnote “II” removed: Pérol M, Chouaid C, Pérol D, et al. Randomized, phase III study of gemcitabine or erlotinib maintenance therapy versus observation, with predefined second-line treatment, after cisplatin-gemcitabine induction chemotherapy in advanced non-small-cell lung cancer. J Clin Oncol 2012;30:3516-3524. (also applies to NSCL-20)
- Second-line therapy
  - The qualifying statement “if not already given” added.
  - Gemcitabine added as a treatment option.



# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

Updates in the 1.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2013 version include:

### [NSCL-20](#)

- Maintenance therapy:
  - ▶ “Continuation of current regimen until disease progression” removed as an option.
  - ▶ Continuation maintenance with gemcitabine changed from a category 2A recommendation to a category 2B recommendation.
  - ▶ Switch maintenance with docetaxel or erlotinib changed from a category 2A recommendation to a category 2B recommendation.
- Second-line therapy
  - ▶ The qualifying statement “if not already given” added.
  - ▶ Gemcitabine added as a treatment option.

### [NSCL-21](#)

- Third-line therapy: Gemcitabine added as an option.
- Footnote “ss” is new to the page: Pemetrexed, docetaxel, and gemcitabine are category 2B if patient did not receive erlotinib or crizotinib in first- or second-line therapy.

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

- Previous bullet 5 removed: Although formalin-fixed paraffin-embedded tumor may be used for most molecular analyses, acquisition of fresh cryopreserved tumor tissue for advanced molecular studies should be considered.
- Current bullet 5 modified: 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) and *one adenocarcinoma marker* (eg, TTF-1) should suffice for most diagnostic problems.

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

- EGFR and KRAS, sub-bullets 2 and 7 modified:
  - ▶ L861 added to exon 21 and G719 added to exon 18.
  - ▶ Primary resistance to 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, sub-bullets 2 and 3 modified:
  - ▶ 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. However, for the most part, ALK translocations and EGFR mutations are mutually exclusive. ~~ALK translocations tend to occur in younger patients and in those with more advanced NSCLC, though this relationship has not been reported for EGFR mutant NSCLC.~~
  - ▶ 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 adenocarcinoma ~~cancer~~. 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 ~~with lung adenocarcinoma are~~ have ALK-positive *lung cancer*.



# NCCN Guidelines Version 4.2014 Updates

## Non-Small Cell Lung Cancer

Updates in the 1.2014 version of the Guidelines for Non-Small Cell Lung Cancer from the 2.2013 version include:

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

- Evaluation
  - ▶ Previous bullet 6 removed: In current smokers who stop smoking, consider waiting 4 weeks before surgery to maximize outcomes after surgery.
- Resection
  - ▶ Bullet 5 modified: VATS or *minimally invasive surgery should be strongly considered* ~~is a reasonable and acceptable approach~~ for patients with no anatomic or surgical contraindications, as long as there is no compromise of standard oncologic and dissection principles of thoracic surgery.

### [NSCL-C \(1 of 9\)](#)

- Early-stage NSCLC (Stage I)
  - ▶ Bullet 2 modified with the removal of the following sentence: A prospective randomized cooperative group trial of sublobar resection versus SABR is ongoing.

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

- Locally advanced stage/conventionally fractionated RT
  - ▶ Bullet 2 modified: The final results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy are pending, but preliminarily, 74 Gy ~~was not associated with improved overall survival at 1 year~~ *does not improve overall survival. A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens, and individualized accelerated RT dose intensification is now being evaluated in a randomized trial (RTOG 1106).*

### [NSCL-E](#)

- Concurrent chemotherapy/RT followed by chemotherapy: Weekly paclitaxel/carboplatin regimen changed from a category 2B to a category 2A recommendation.
- Previous footnote “\*” removed: There are data that support full dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

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

- First-line therapy
  - ▶ Bullet 3 modified: 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.*
  - ▶ Bullet 4 added: Afatinib is indicated for select patients with sensitizing EGFR mutations.

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

- Maintenance therapy: category 2B added to continuation maintenance with gemcitabine and switch maintenance with erlotinib or pemetrexed.
- Second-line therapy: Sub-bullet 4 added: Afatinib is indicated for select patients with sensitizing EGFR mutations.
- Third-line therapy: “Erlotinib is superior to best supportive care” replaced with “If not already given, options for PS 0-2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).”

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

- Afatinib added to systemic therapy options with reference.

### [NSCL-G](#)

- Link to NCCN Guidelines for Cervical Cancer Screening removed.

### [NSCL-H](#)

- New page added listing targeted agents for patients with genetic alterations.



# NCCN Guidelines Version 4.2014

## 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](http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf)) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk of lung cancer from second-hand smoke exposure associated with living with a smoker (<http://surgeongeneral.gov/library/reports/smokeexposure/fullreport.pdf>). Every person should be informed of the health consequences, addictive nature, and mortal threat posed by tobacco consumption and exposure to tobacco smoke, and effective legislative, executive, administrative, or other measures should be contemplated at the appropriate governmental level to protect all persons from exposure to tobacco smoke ([www.who.int/tobacco/framework/final\\_text/en/](http://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 & Quality (AHRQ) Guidelines ([www.ahrq.gov/path/tobacco.htm#Clinic](http://www.ahrq.gov/path/tobacco.htm#Clinic)) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the [NCCN Guidelines for Lung Cancer Screening](#)).

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

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

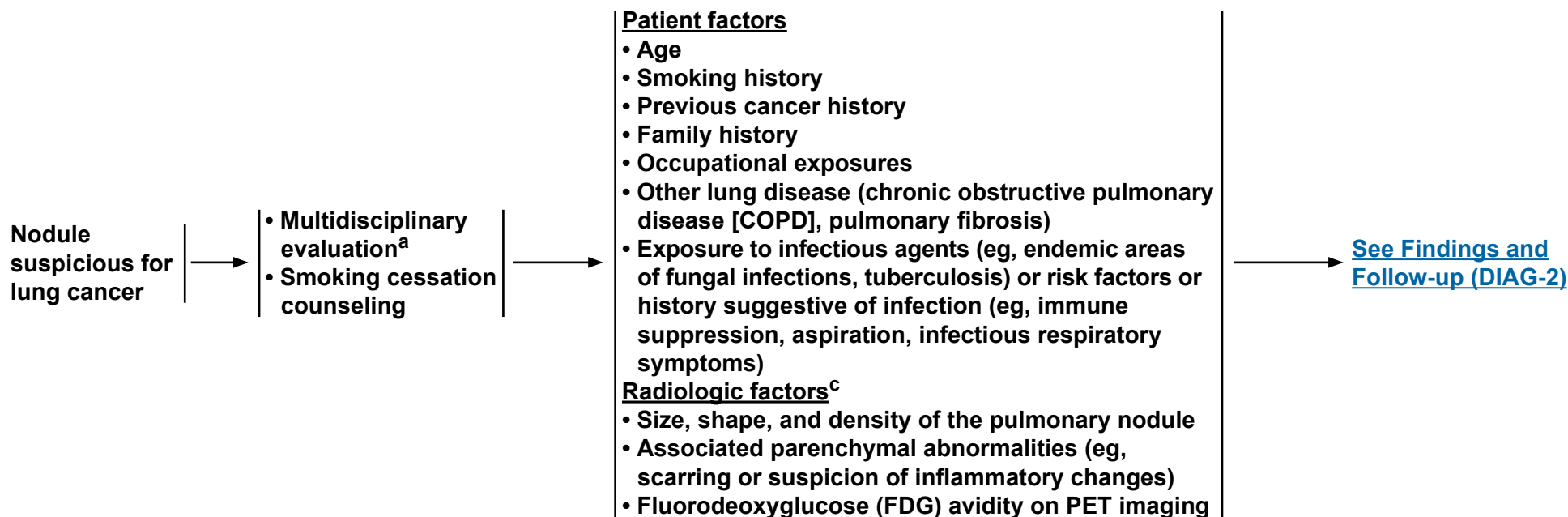


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL PRESENTATION

### RISK ASSESSMENT<sup>b</sup>



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

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

<sup>c</sup>[See Principles of Diagnostic Evaluation \(DIAG-A 1 of 2\).](#)

**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.

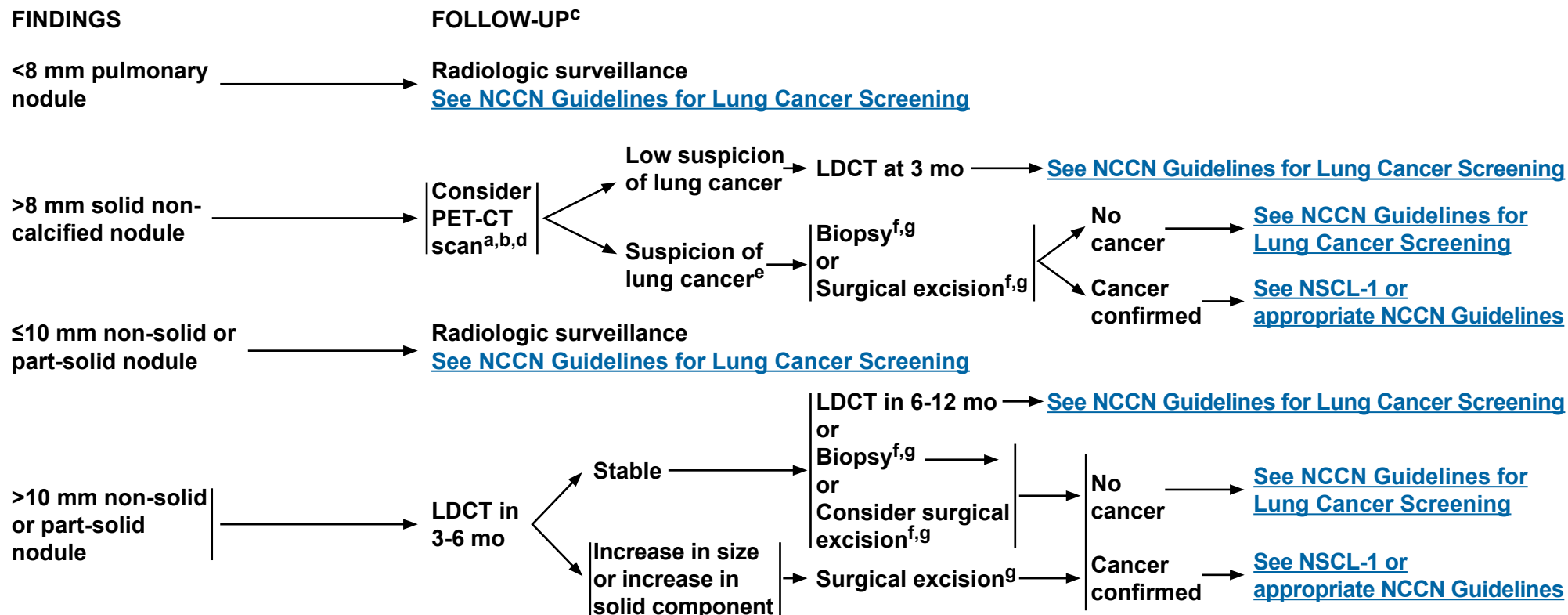


National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)



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

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

<sup>c</sup>[See Principles of Diagnostic Evaluation \(DIAG-A 1 of 2\).](#)

<sup>d</sup>A positive PET result is defined as a standardized uptake value (SUV) in the lung nodule greater than the baseline mediastinal blood pool. A positive PET scan finding can be caused by infection or inflammation, including absence of lung cancer with localized infection, presence of lung cancer with associated (eg, postobstructive) infection, and presence of lung cancer with related inflammation (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).

<sup>e</sup>Patients with a suspicion of lung cancer after PET-CT require histologic confirmation before any nonsurgical therapy.

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

<sup>g</sup>Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.

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

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



# NCCN Guidelines Version 4.2014

## 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 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 or 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 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 aspiration (TTNA)
    - ◊ 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
    - ◊ 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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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).**
    - ◊ **Technologies and expertise available**
  - ▶ **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 may also benefit from involvement of a pulmonologist with experience in advanced bronchoscopic techniques for diagnosis, depending on local expertise.**
  - ▶ **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 should have navigational bronchoscopy, radial EBUS, or TTNA.**
    - ◊ **Patients with suspected nodal disease should be biopsied by EBUS, navigational bronchoscopy, or mediastinoscopy.**
      - **Esophageal ultrasound (EUS)–guided biopsy provides additional access to station 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.**
    - ◊ **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 preferably 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.**

**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### **PATHOLOGIC DIAGNOSIS OF NSCLC**

### **INITIAL EVALUATION**

### **CLINICAL STAGE**

Non-Small Cell  
Lung Cancer  
(NSCLC)

- Pathology review<sup>a</sup>
- H&P (include performance status + weight loss)
- 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<sup>b</sup>  
([See NCCN Guidelines for Palliative Care](#))

- Stage IA, peripheral<sup>c</sup> (T1ab, N0)  
Mediastinal CT negative (lymph nodes <1 cm) → [See Pretreatment Evaluation \(NSCL-2\)](#)
- Stage I, peripheral<sup>c</sup> (T2a, N0); central<sup>c</sup> (T1ab-T2a, N0);  
Stage II (T1ab-T2ab, N1; T2b, N0); stage IIB (T3, N0)<sup>d</sup>  
Mediastinal CT negative (lymph nodes <1 cm) → [See Pretreatment Evaluation \(NSCL-2\)](#)
- Stage IIB<sup>e</sup> (T3 invasion, N0);  
Stage IIIA<sup>e</sup> (T4 extension, N0-1; T3, N1) → [See Pretreatment Evaluation \(NSCL-4\)](#)
- Stage IIIA<sup>e</sup> (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 Pretreatment Evaluation \(NSCL-9\)](#)
- Stage IIIB<sup>e</sup> (T1-3, N3) mediastinal CT positive  
Contralateral (lymph nodes ≥1 cm) or palpable supraclavicular lymph nodes → [See Pretreatment Evaluation \(NSCL-11\)](#)
- Stage IIIB<sup>e</sup> (T4 extension, N2-3) on CT → [See Pretreatment Evaluation \(NSCL-12\)](#)
- Stage IV (M1a)<sup>b</sup> (pleural or pericardial effusion) → [See Pretreatment Evaluation \(NSCL-12\)](#)
- Stage IV (M1b)<sup>b</sup>  
Solitary metastasis with resectable lung lesion → [See Pretreatment Evaluation \(NSCL-13\)](#)
- Stage IV (M1b)<sup>b</sup> disseminated metastases → [See Systemic Therapy \(NSCL-16\)](#)

<sup>a</sup>[See Principles of Pathologic Review \(NSCL-A\)](#).

<sup>b</sup>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.

<sup>c</sup>Based on the CT of the chest: Peripheral = outer third of lung. Central = inner two thirds of lung.

<sup>d</sup>T3, N0 related to size or satellite nodules.

<sup>e</sup>For patients considered to have stage IIB and stage III tumors, where more than one treatment modality (surgery, radiation therapy, or chemotherapy) is usually considered, a multidisciplinary evaluation should be performed.

**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.



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014

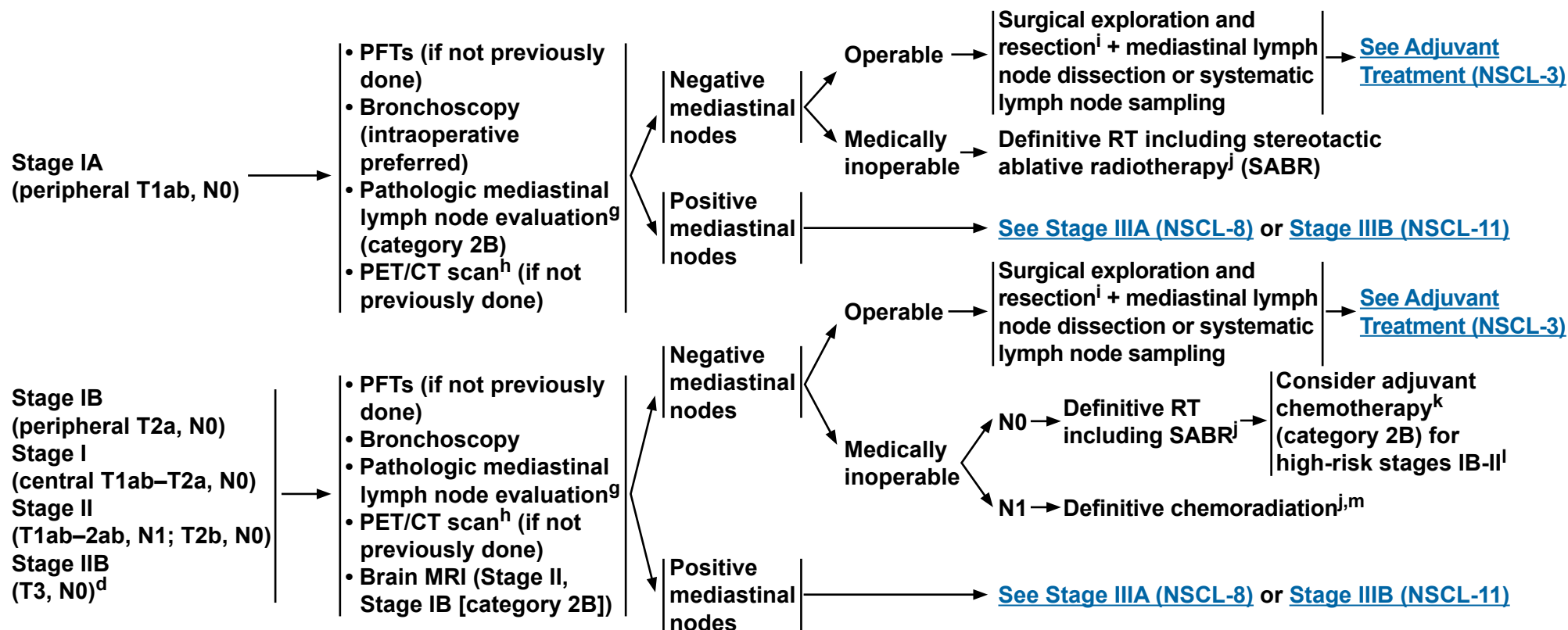
## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION<sup>f</sup>

### INITIAL TREATMENT



<sup>d</sup>T3, N0 related to size or satellite nodules.

<sup>f</sup>Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.

<sup>g</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>i</sup>[See Principles of Surgical Therapy \(NSCL-B\).](#)

<sup>j</sup>[See Principles of Radiation Therapy \(NSCL-C\).](#)

<sup>k</sup>[See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-D\).](#)

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

<sup>m</sup>[See 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.

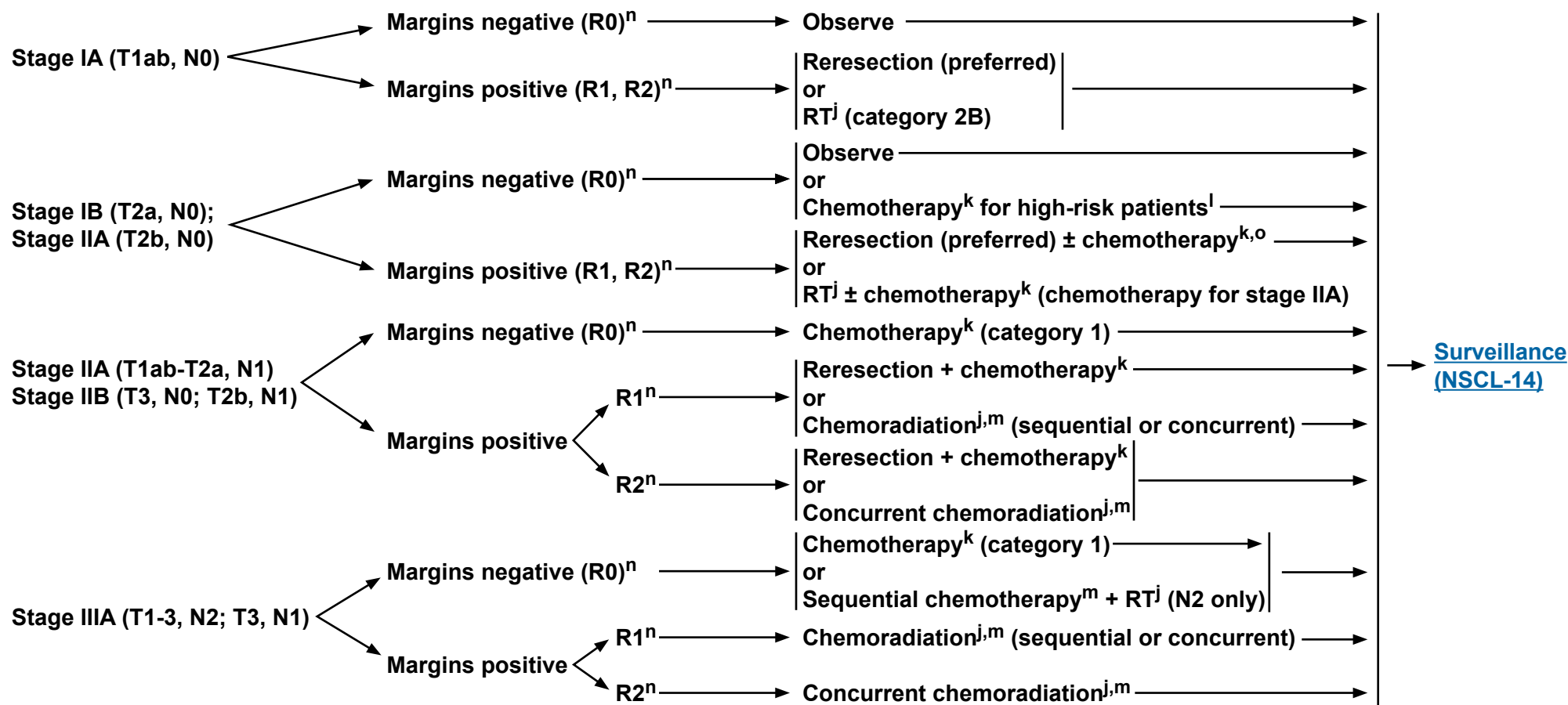


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### FINDINGS AT SURGERY

### ADJUVANT TREATMENT


<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>k</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

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

<sup>m</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>n</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>o</sup>Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

**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.



# NCCN Guidelines Version 4.2014

## 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<sup>g</sup>
- Brain MRI
- MRI of spine + thoracic inlet for superior sulcus lesions abutting the spine or subclavian vessels
- PET/CT scan<sup>h</sup> (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 solitary site \(NSCL-13\) or distant disease \(NSCL-15\)](#)

<sup>g</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

**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.



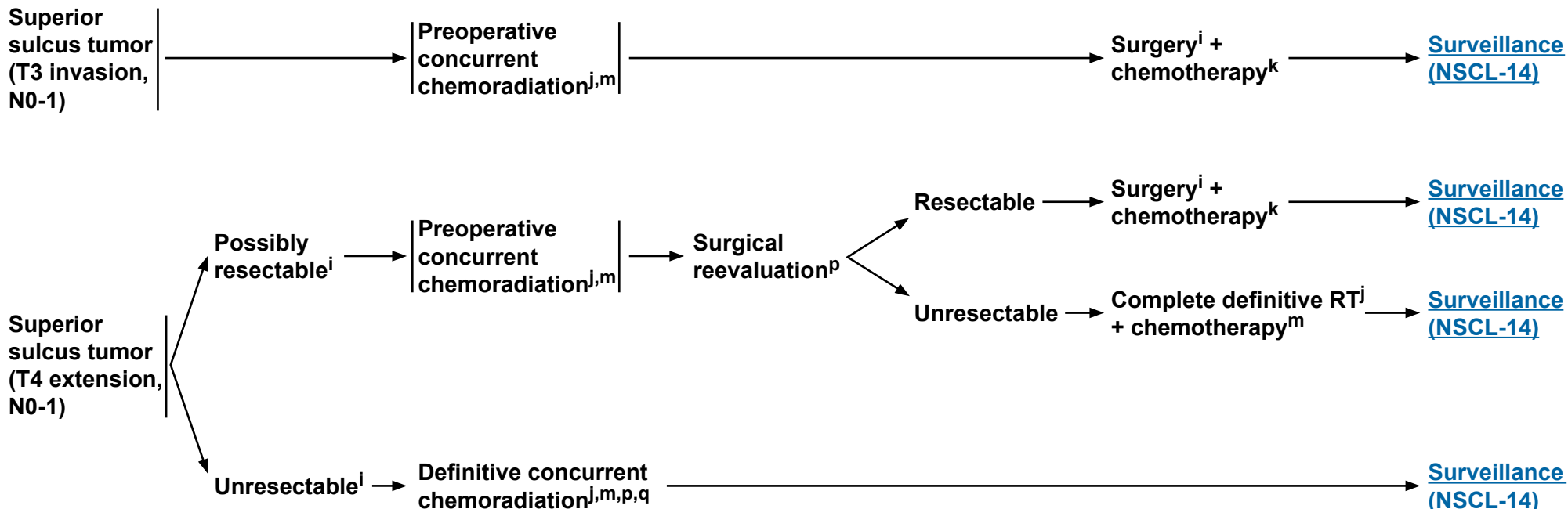
# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL PRESENTATION

### INITIAL TREATMENT

### ADJUVANT TREATMENT



<sup>i</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>k</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>m</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>p</sup>RT should continue to definitive dose without interruption if patient is not a surgical candidate.

<sup>q</sup>If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

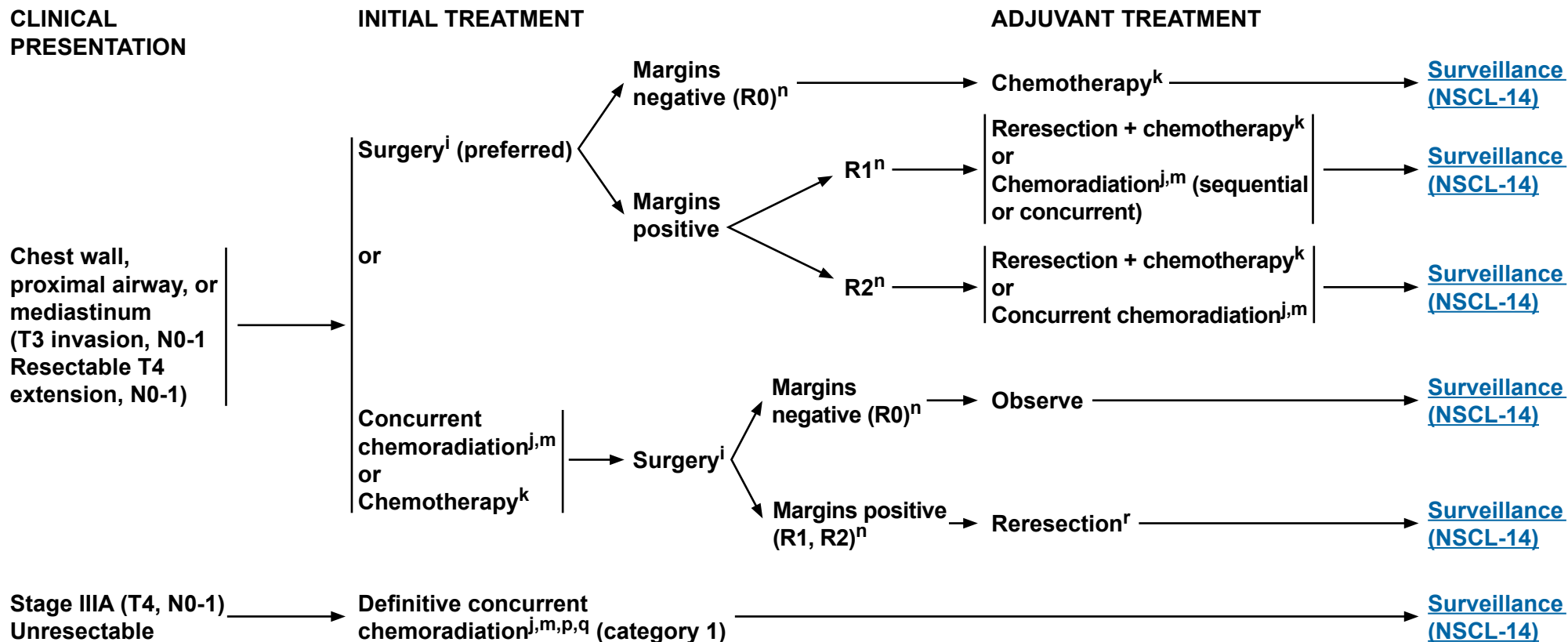
**Note:** All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer


<sup>i</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>k</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>m</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>n</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>p</sup>PRT should continue to definitive dose without interruption if patient is not a surgical candidate.

<sup>q</sup>If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

<sup>r</sup>Consider RT boost if chemoradiation is given as initial treatment.

**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.





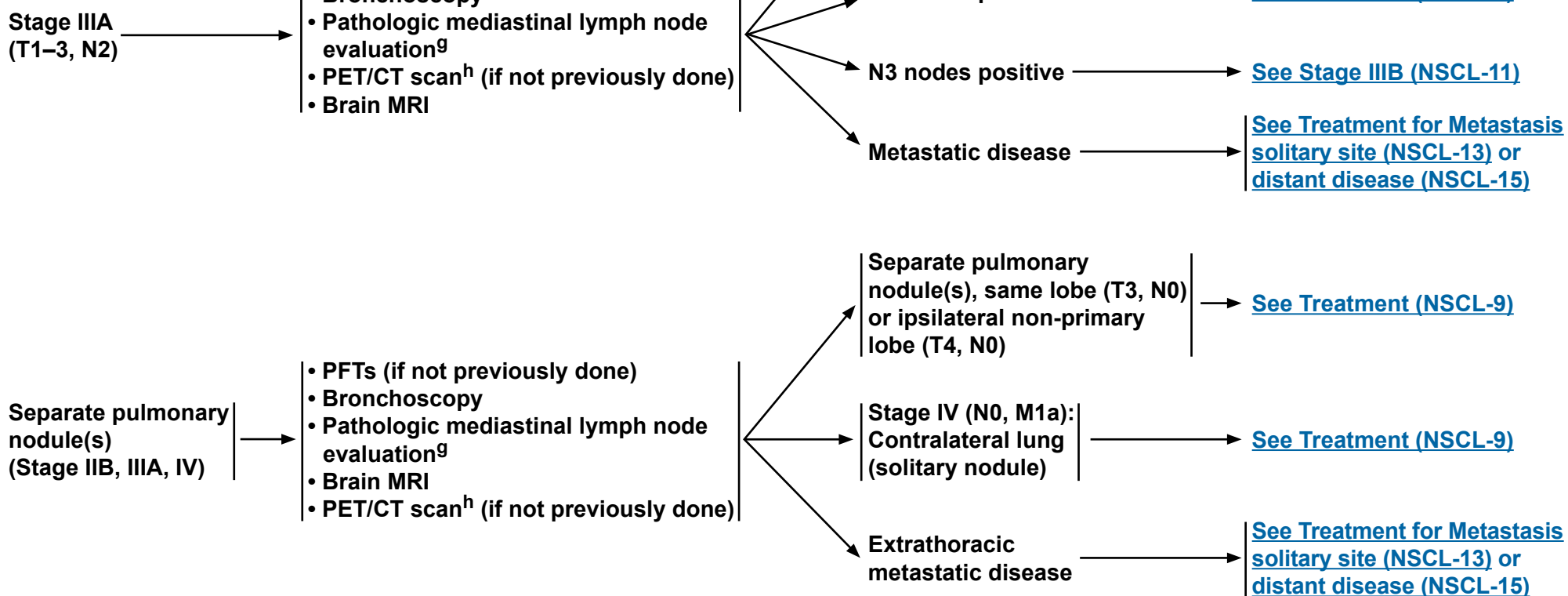
# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION

### MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY



<sup>g</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

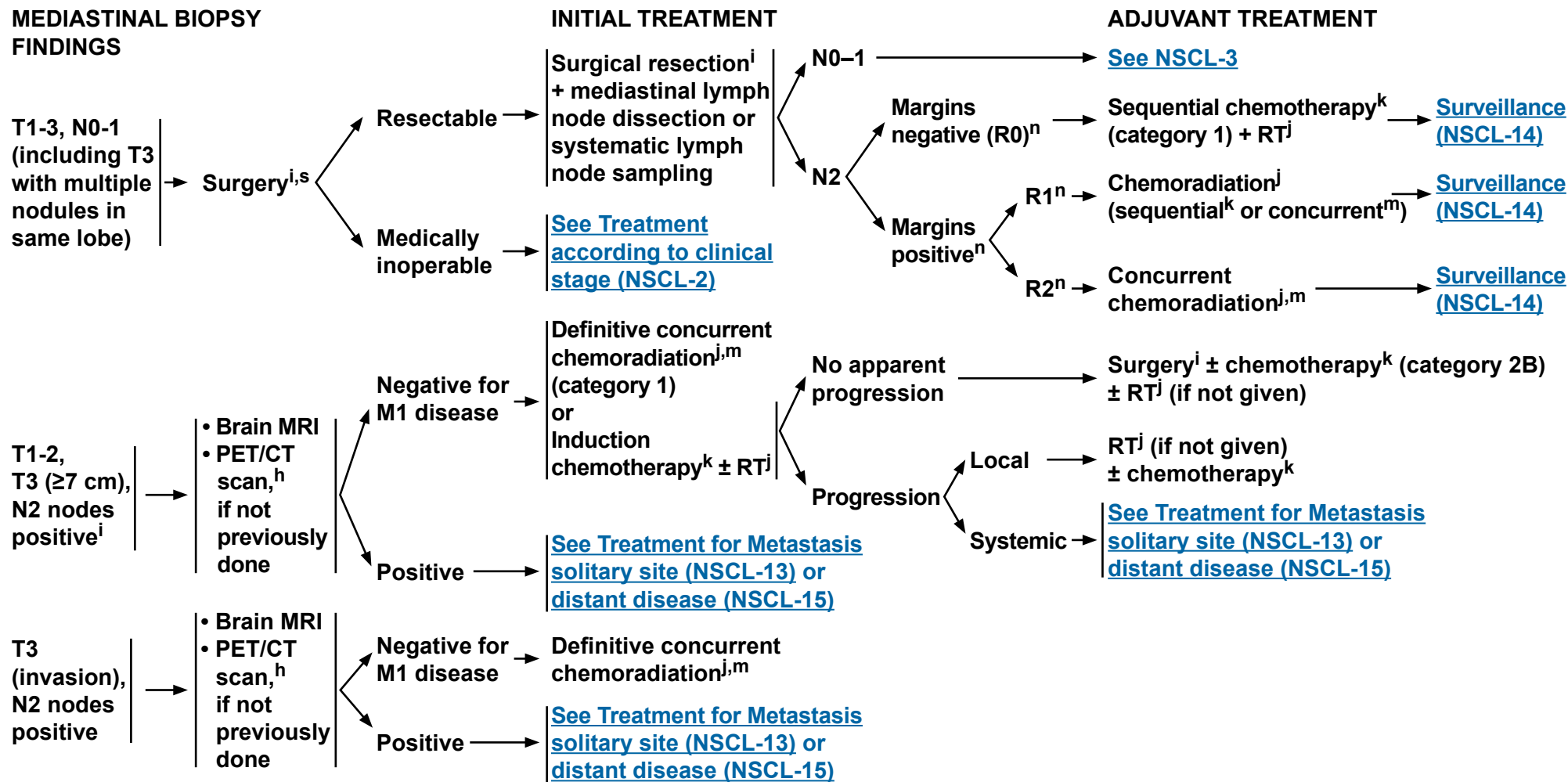
**Note:** All recommendations are category 2A unless otherwise indicated.

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

# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### MEDIASTINAL BIOPSY FINDINGS



<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>i</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>k</sup>See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).

<sup>m</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>n</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

<sup>s</sup>Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

**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.

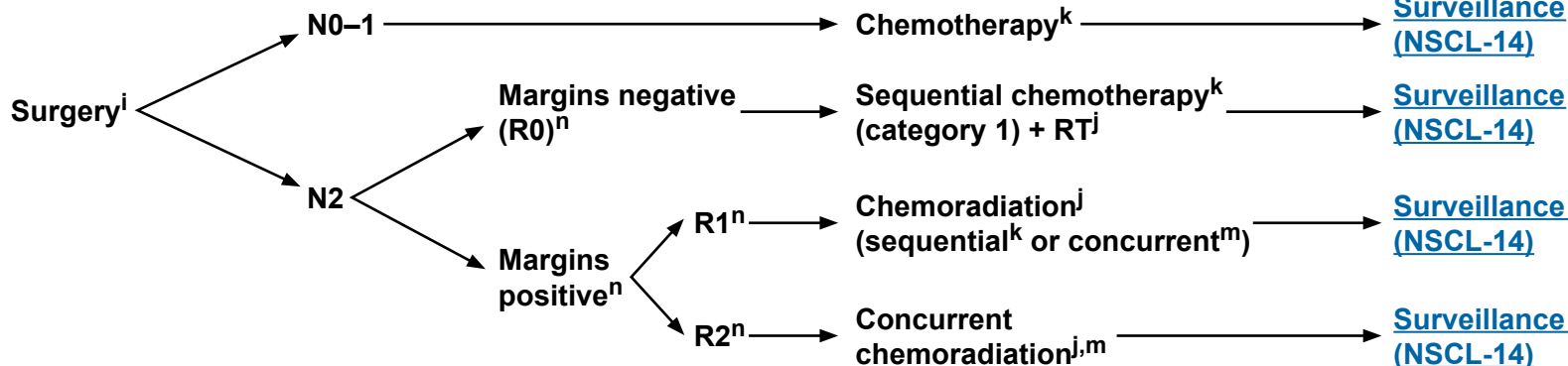


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL PRESENTATION

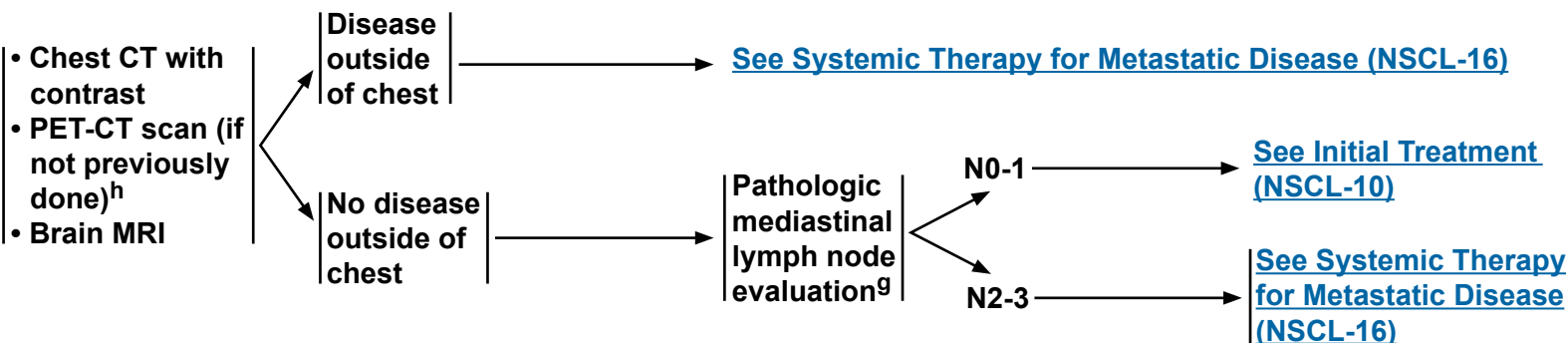
Separate pulmonary nodule(s), same lobe (T3, N0), or ipsilateral non-primary lobe (T4, N0)



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)<sup>t,u</sup>



<sup>g</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>i</sup>[See Principles of Surgical Therapy \(NSCL-B\)](#).

<sup>j</sup>[See Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>k</sup>[See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy \(NSCL-D\)](#).

<sup>m</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

<sup>n</sup>R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

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

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

**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.

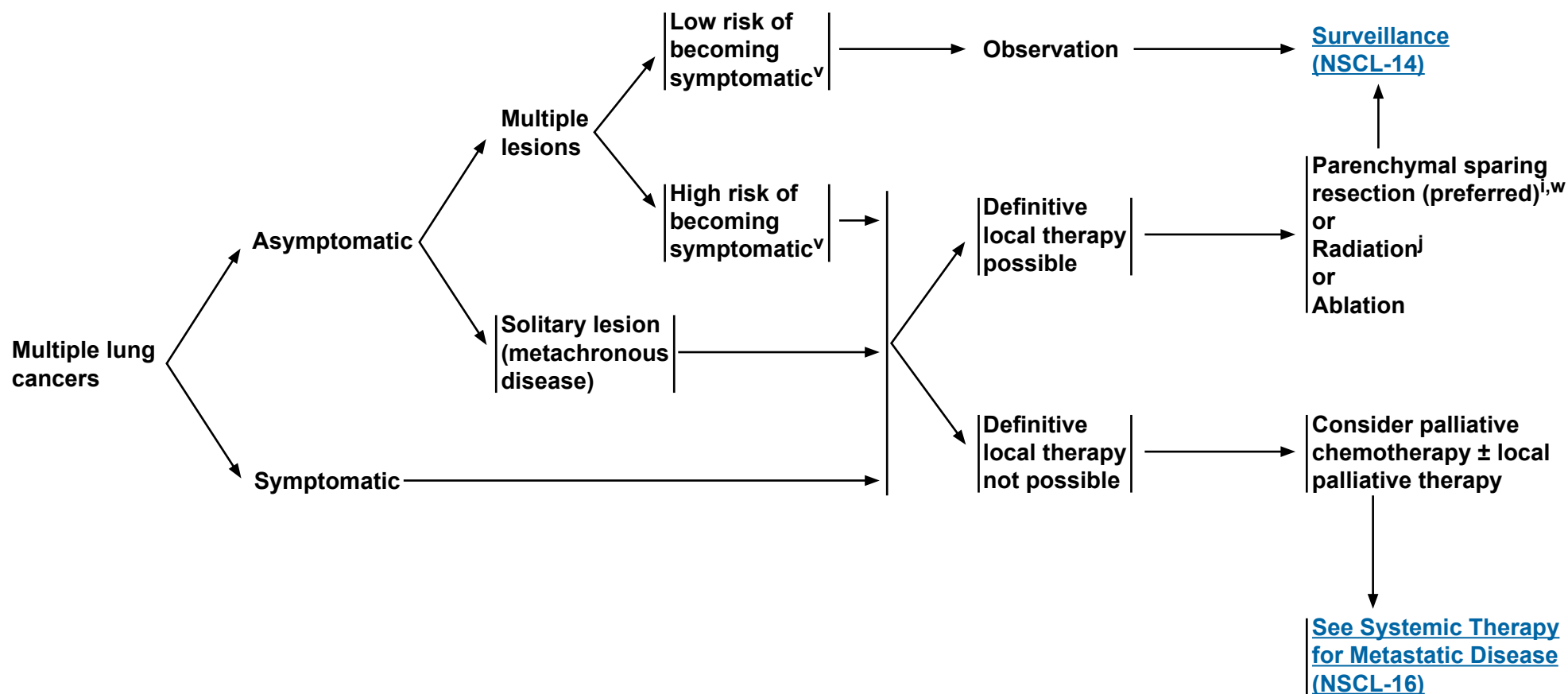


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL PRESENTATION

### INITIAL TREATMENT



<sup>i</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>v</sup>Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms (eg, subsolid nodules with accelerating growth or increasing solid component or increasing FDG uptake, even while small), treatment should be considered.

<sup>w</sup>Lung-sparing resection is preferred, but tumor distribution and institutional expertise should guide individual treatment planning.

**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.



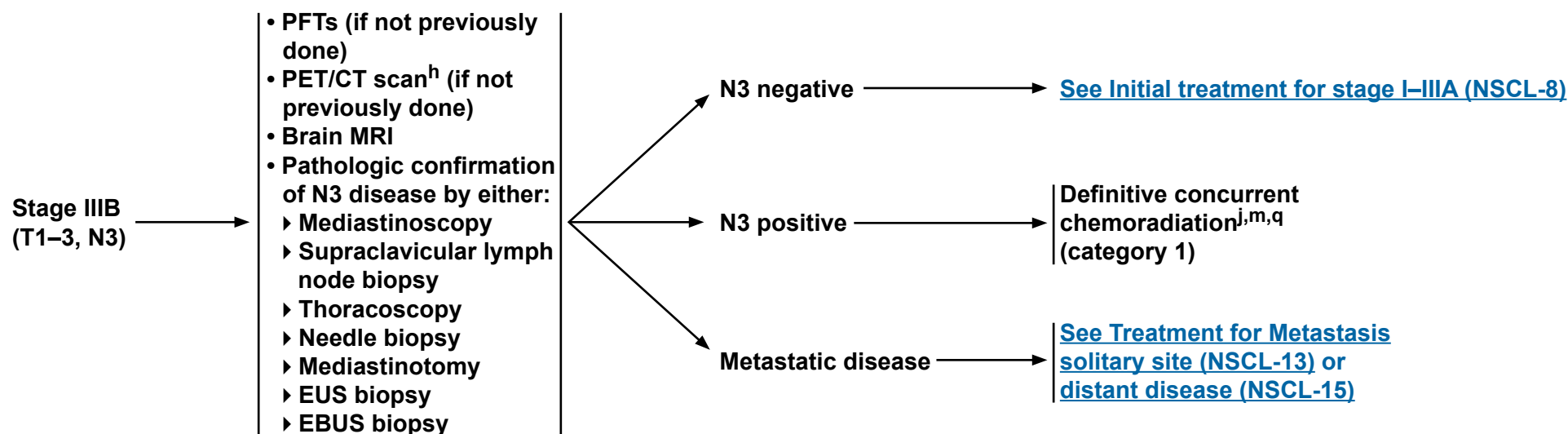
# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION

### INITIAL TREATMENT



<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>j</sup>[See Principles of Radiation Therapy \(NSCL-C\).](#)

<sup>m</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\).](#)

<sup>q</sup>If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

**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.



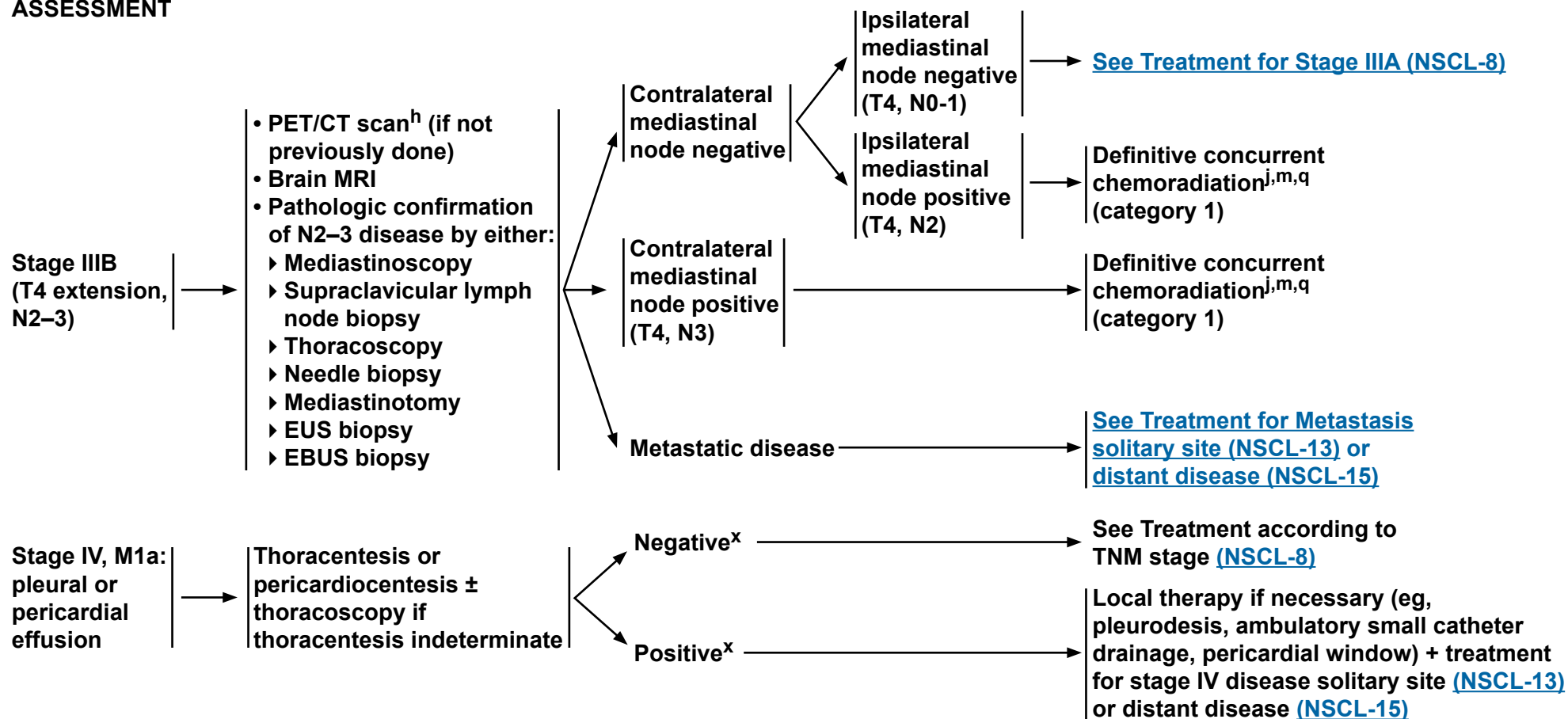
# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION

### INITIAL TREATMENT



<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>j</sup>[See Principles of Radiation Therapy \(NSCL-C\)](#).

<sup>m</sup>[See Chemotherapy Regimens Used with Radiation Therapy \(NSCL-E\)](#).

<sup>q</sup>If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

<sup>x</sup>While most pleural effusions associated with lung cancer are due to tumor, there are a few patients in whom multiple cytopathologic examinations of pleural fluid are negative for tumor and fluid is non-bloody and not an exudate. When these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element. Pericardial effusion is classified using the same criteria.

**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.





National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014

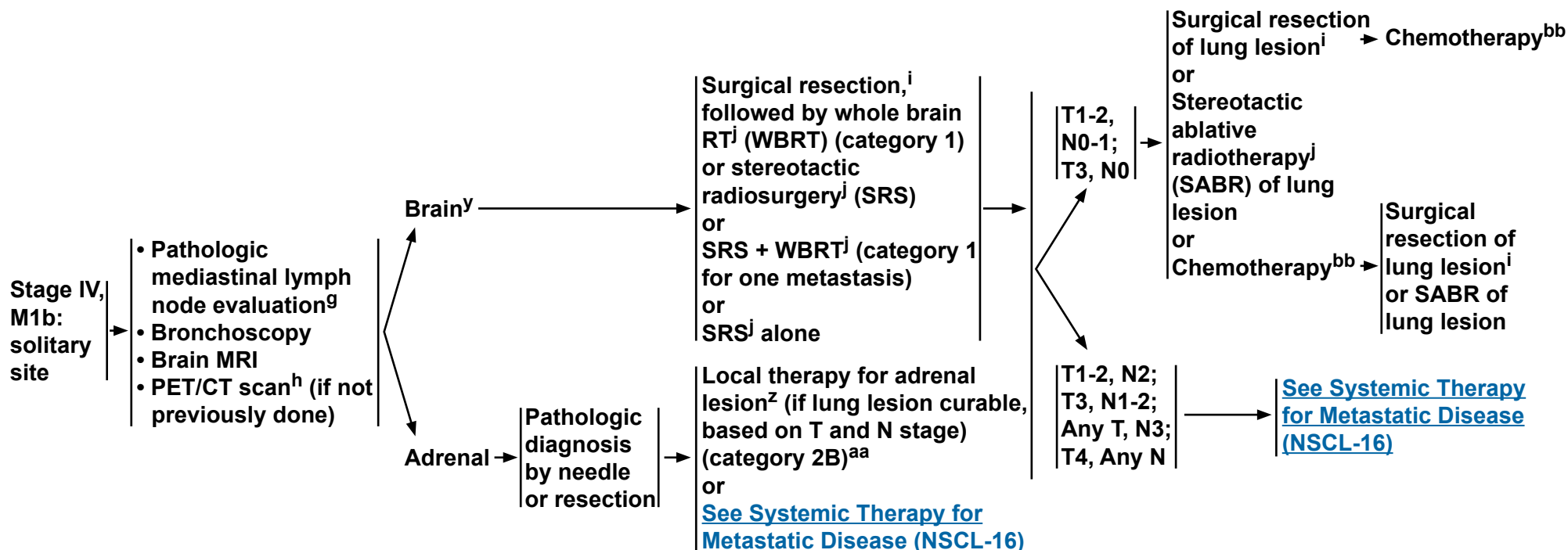
## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

### CLINICAL ASSESSMENT

### PRETREATMENT EVALUATION

### INITIAL TREATMENT



<sup>g</sup>Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.

<sup>h</sup>Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

<sup>i</sup>[See Principles of Surgical Therapy \(NSCL-B\).](#)

<sup>j</sup>[See Principles of Radiation Therapy \(NSCL-C\).](#)

<sup>y</sup>[See NCCN Guidelines for Central Nervous System Cancers.](#)

<sup>z</sup>May include adrenalectomy or RT (including SABR).

<sup>aa</sup>Patients with N2 disease have a poor prognosis and systemic therapy should be considered.

<sup>bb</sup>[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)

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

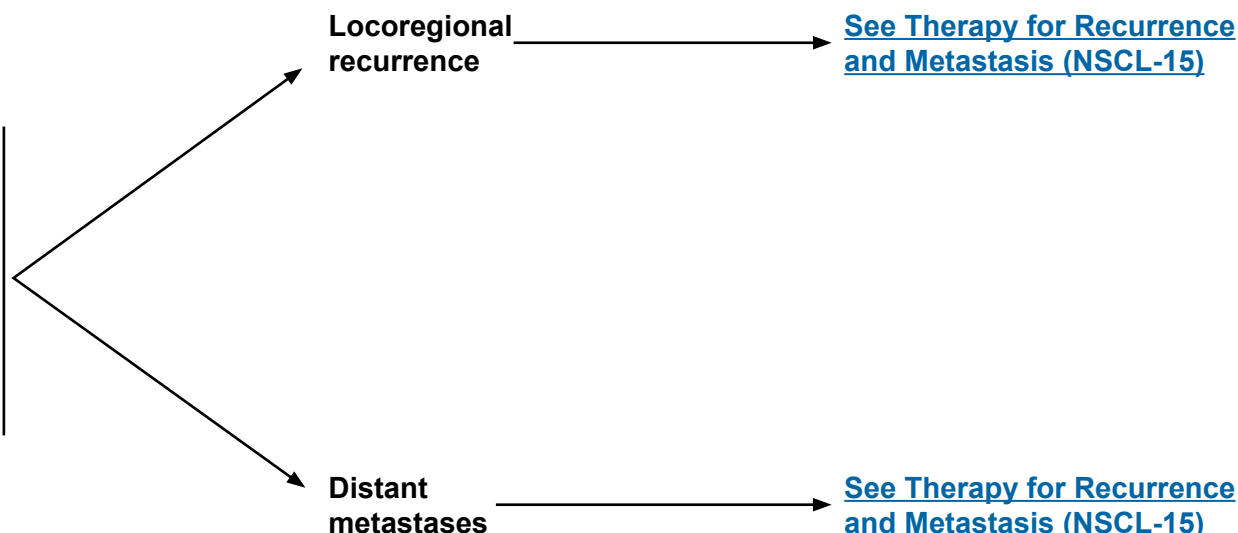
**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



### SURVEILLANCE

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

- H&P and chest CT ± contrast every 6-12 mo for 2 y, then H&P and a non-contrast-enhanced chest CT annually
- Smoking cessation advice, counseling, and pharmacotherapy
- PET or brain MRI is not indicated
- [See Cancer Survivorship Care \(NSCL-G\)](#).



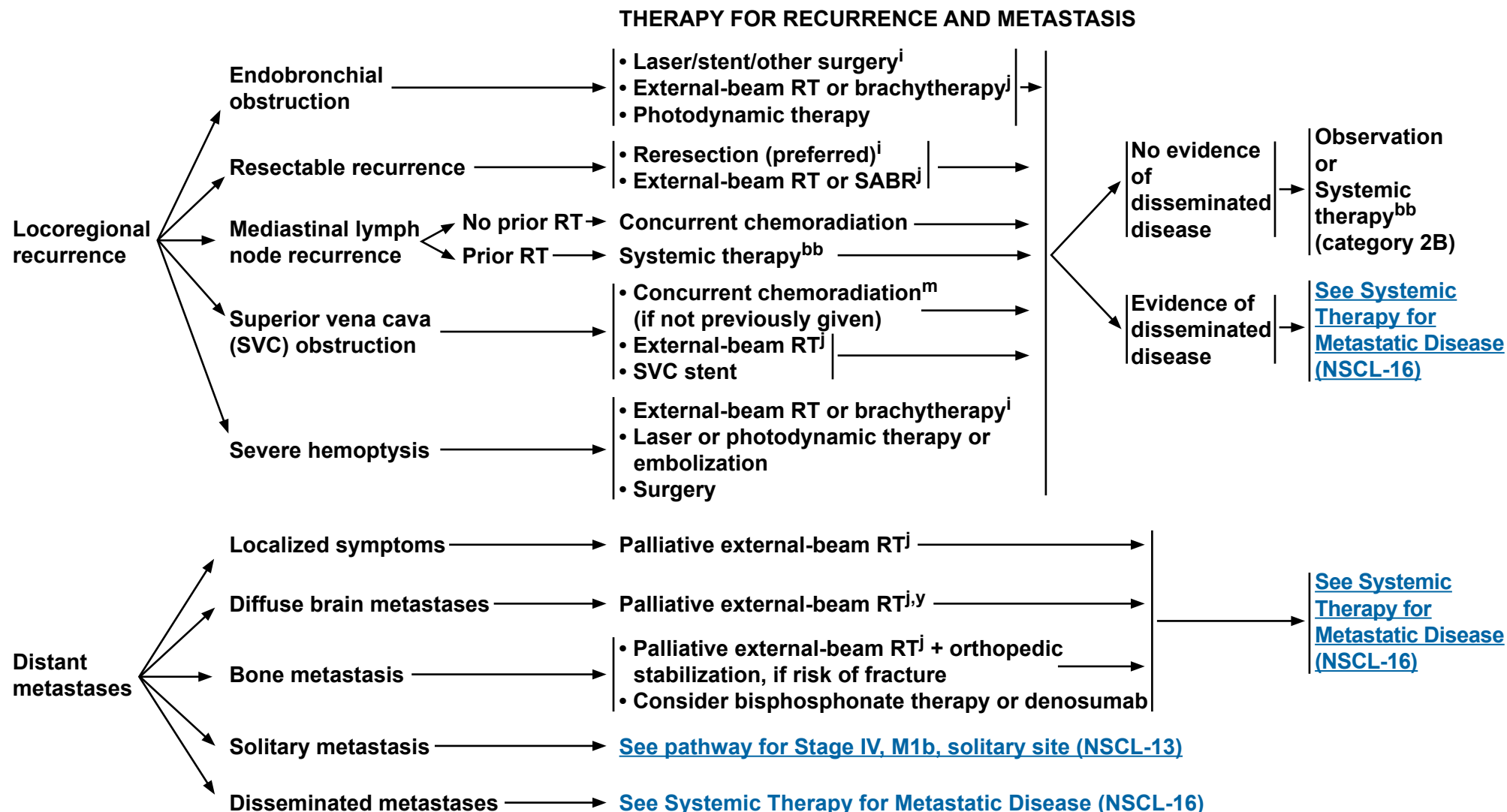
**Note:** All recommendations are category 2A unless otherwise indicated.

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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer



<sup>i</sup>See Principles of Surgical Therapy (NSCL-B).

<sup>j</sup>See Principles of Radiation Therapy (NSCL-C).

<sup>m</sup>See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

<sup>y</sup>See NCCN Guidelines for Central Nervous System Cancers.

<sup>bb</sup>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.

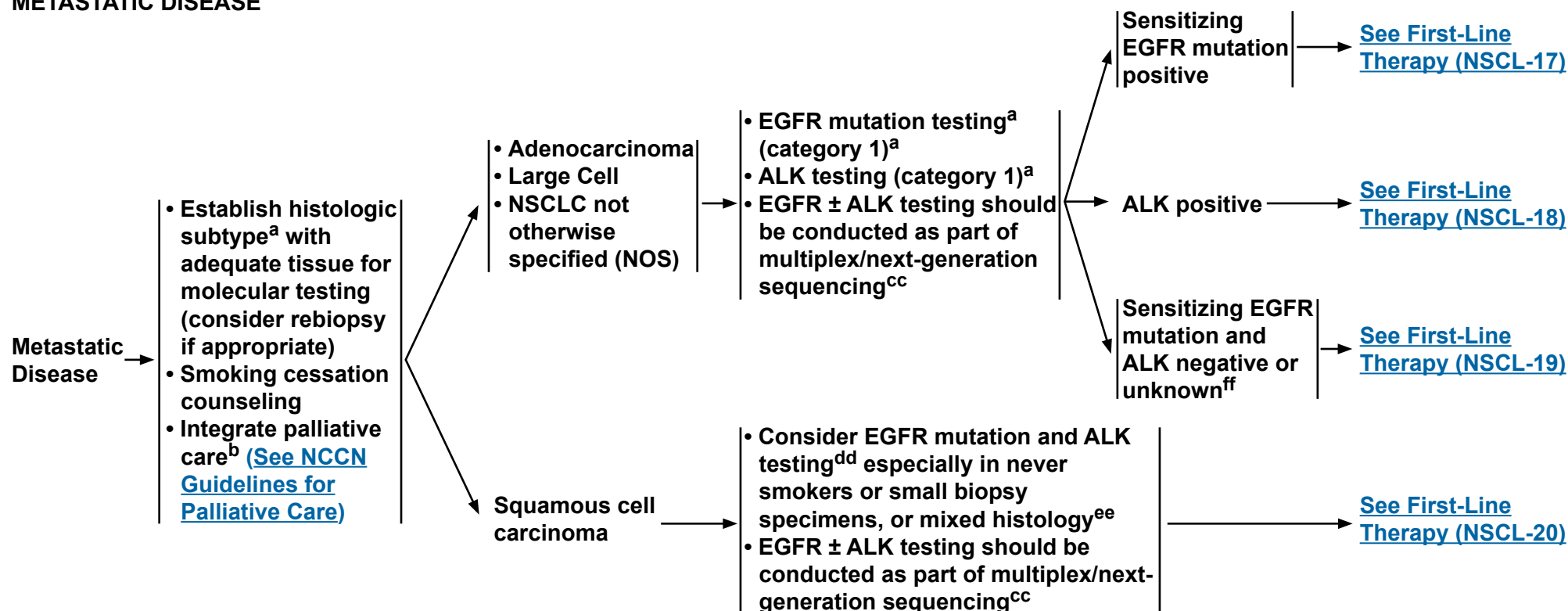


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### SYSTEMIC THERAPY FOR METASTATIC DISEASE

### HISTOLOGIC SUBTYPE



<sup>a</sup>[See Principles of Pathologic Review \(NSCL-A\).](#)

<sup>b</sup>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.

<sup>cc</sup>[See Targeted Agents for Patients with Other Genetic Alterations \(NSCL-H\).](#)

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

<sup>ee</sup>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.

<sup>ff</sup>Consider ROS1 testing; if positive, may treat with crizotinib. 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.

**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.

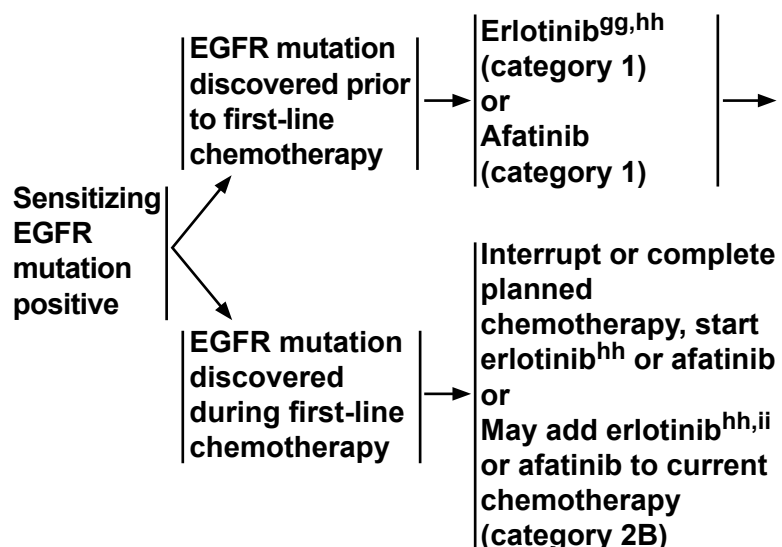


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

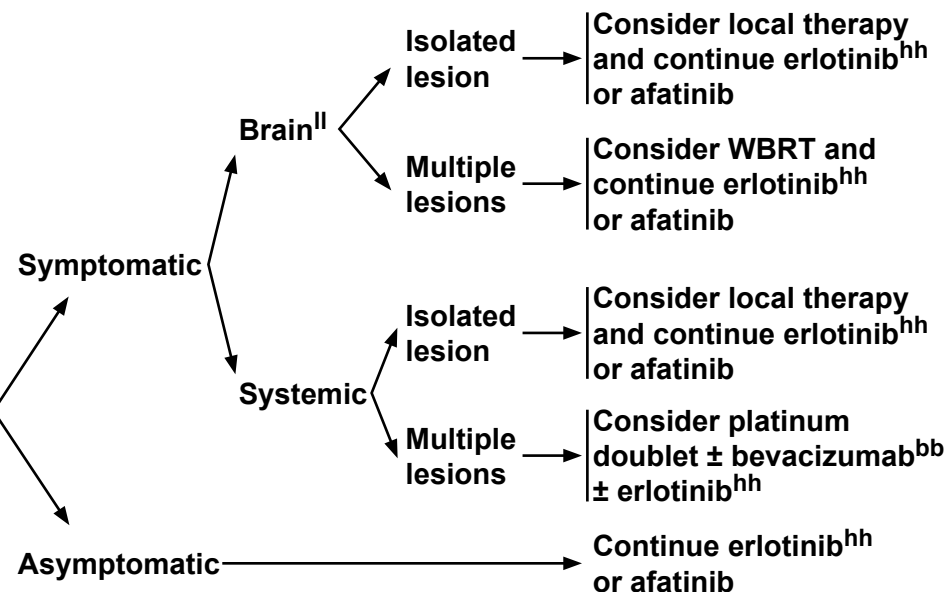
### ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE<sup>a</sup>

#### FIRST-LINE THERAPY<sup>bb</sup>



Progression<sup>jj,kk</sup>

#### SECOND-LINE THERAPY<sup>bb,mm</sup>



[Progression, See third-line therapy \(NSCL-21\)](#)

<sup>a</sup>See [Principles of Pathologic Review \(NSCL-A\)](#).

<sup>bb</sup>See [Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

<sup>gg</sup>For performance status 0-4.

<sup>hh</sup>In areas of the world where gefitinib is available, it may be used in place of erlotinib.

<sup>ii</sup>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.

<sup>jj</sup>Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression.

<sup>kk</sup>Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.

<sup>ll</sup>Consider pulse erlotinib for carcinomatosis meningitis.

<sup>mm</sup>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.

**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.

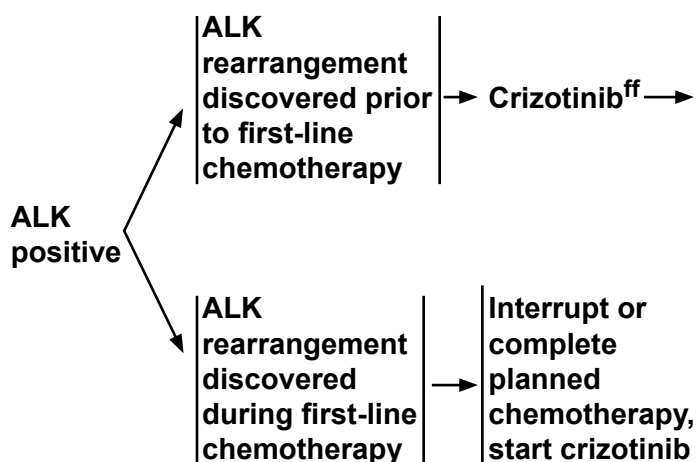


# NCCN Guidelines Version 4.2014

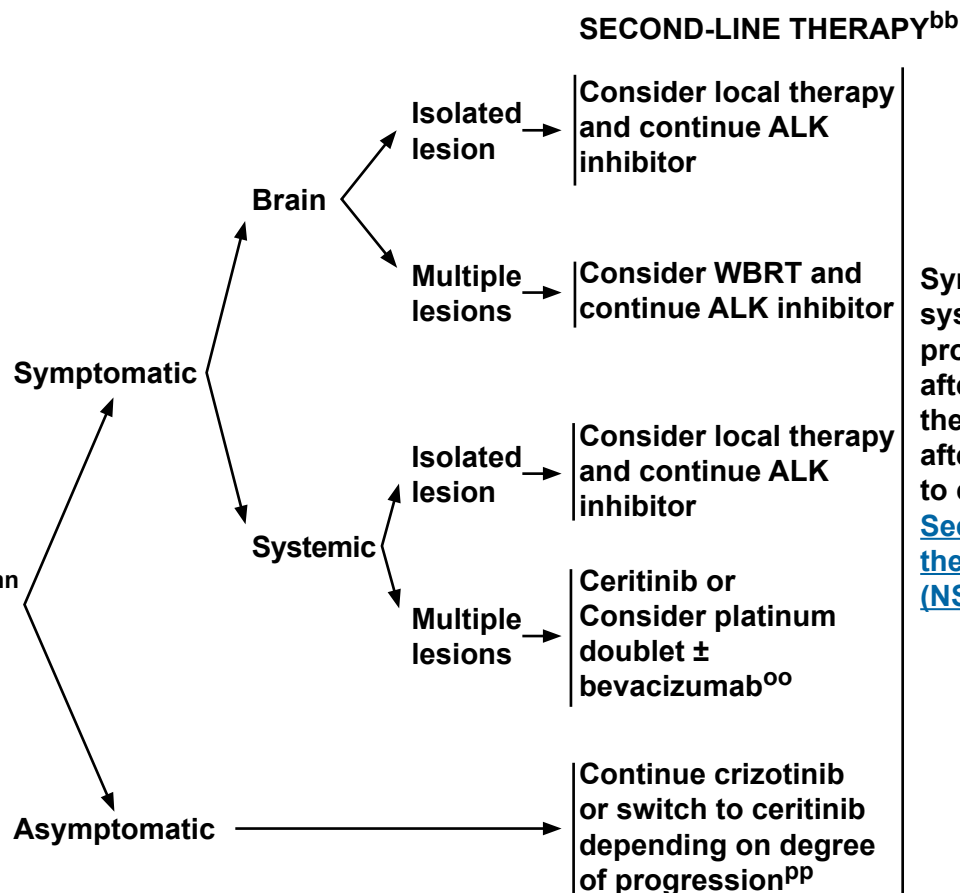
## Non-Small Cell Lung Cancer

### ADENOCARCINOMA, LARGE CELL, NSCLC NOS: ALK POSITIVE<sup>a</sup>

#### FIRST-LINE THERAPY<sup>bb</sup>



#### Progression<sup>nn</sup>



Symptomatic systemic progression after local therapies and/or after switching to ceritinib, [See third-line therapy \(NSCL-21\)](#)

<sup>a</sup>See Principles of Pathologic Review (NSCL-A).

<sup>bb</sup>See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

<sup>ff</sup>Consider ROS1 testing; if positive, may treat with crizotinib. Bergethson K, Shaw AT, Ou SH, et al. ROS1 rearrangements define a unique molecular class of lung cancers. J Clin Oncol 2012;30:863-870.

<sup>nn</sup>Patients who are intolerant to crizotinib may be switched to ceritinib.

<sup>oo</sup>See third-line therapy (NSCL-21) for progressive disease with multiple symptomatic systemic lesions after treatment with crizotinib, ceritinib, and/or platinum doublet ± bevacizumab.

<sup>pp</sup>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.

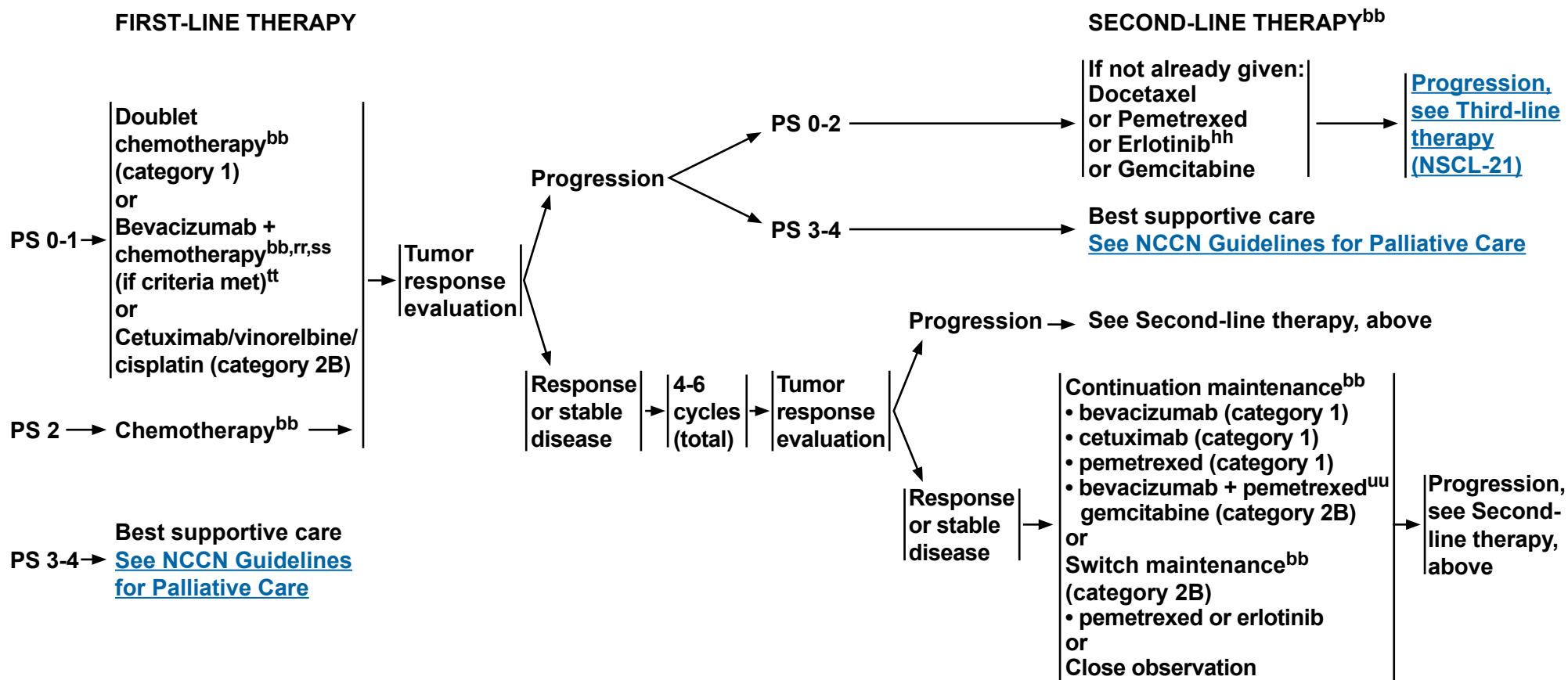




# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION AND ALK NEGATIVE OR UNKNOWN<sup>qq</sup>


<sup>bb</sup>[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)
<sup>hh</sup>In areas of the world where gefitinib is available, it may be used in place of erlotinib.

<sup>qq</sup>Consider additional mutational testing if only EGFR and ALK were performed. [See Targeted Agents for Patients with Other Genetic Alterations \(NSCL-H\).](#)
<sup>rr</sup>Bevacizumab should be given until progression.

<sup>ss</sup>Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.

<sup>tt</sup>Criteria for treatment with bevacizumab + chemotherapy: 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.

<sup>uu</sup>If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

**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.

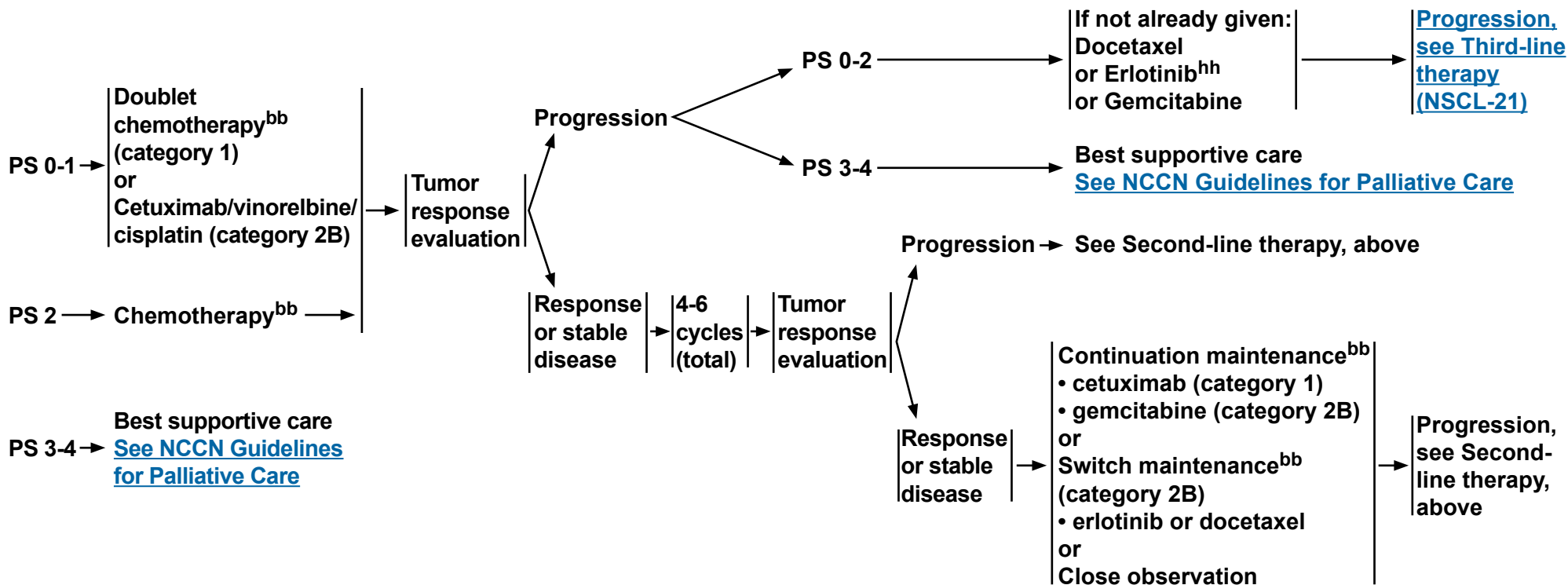


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### SQUAMOUS CELL CARCINOMA

#### FIRST-LINE THERAPY



<sup>bb</sup>[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\)](#).

<sup>hh</sup>In areas of the world where gefitinib is available, it may be used in place of erlotinib.

**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.

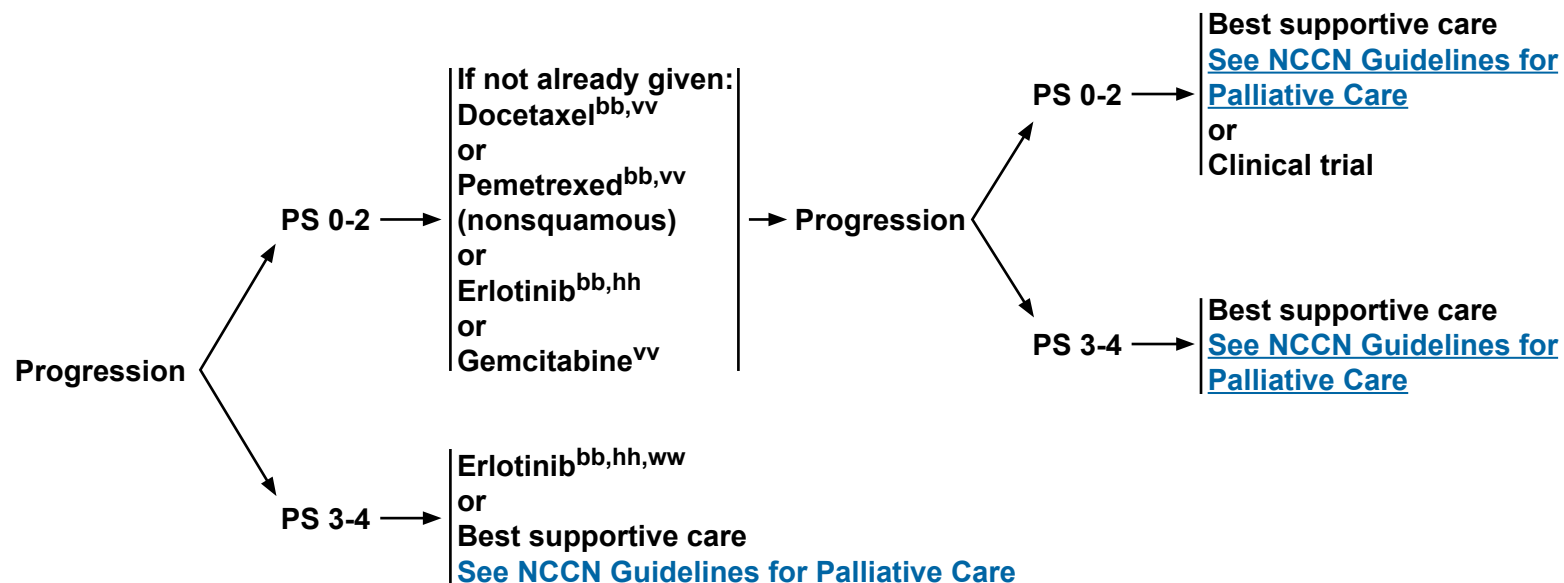


# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### ADENOCARCINOMA, LARGE CELL, NSCLC NOS, or SQUAMOUS CELL CARCINOMA

#### THIRD-LINE THERAPY



<sup>bb</sup>[See Systemic Therapy for Advanced or Metastatic Disease \(NSCL-F\).](#)

<sup>hh</sup>In areas of the world where gefitinib is available, it may be used in place of erlotinib.

<sup>vv</sup>Pemetrexed, docetaxel, and gemcitabine are category 2B if patient did not receive erlotinib or crizotinib in first- or second-line therapy.

<sup>ww</sup>Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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,<sup>1</sup> including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis.<sup>2,3</sup> 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 this section).<sup>4,5</sup>
- 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.<sup>6,7</sup>
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung with squamous morphology, neuroendocrine differentiation, and other variant carcinomas. The recently published classification of adenocarcinoma should be used for this tumor subtype in resection specimens and small biopsies.<sup>8</sup> 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.”<sup>8</sup> Mutational testing (eg, epidermal growth factor receptor [EGFR]) should be performed in this setting.
- Although formalin-fixed paraffin-embedded tumor may be used for most molecular analyses, acquisition of fresh cryopreserved tumor tissue for advanced molecular studies should be considered.
- 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) and one adenocarcinoma marker (eg, TTF-1) should suffice for most diagnostic problems.<sup>8</sup>

#### Adenocarcinoma Classification<sup>8</sup>

- 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.

**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.



# NCCN Guidelines Version 4.2014

## 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—and to determine whether neuroendocrine differentiation is present.<sup>9-11</sup>
- Primary pulmonary adenocarcinoma
  - ▶ An appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to the lung.<sup>12</sup>
  - ▶ 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 adenocarcinomas subtypes.<sup>13</sup> 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.<sup>12</sup>
  - ▶ The panel of TTF-1 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, not otherwise specified (NOS).<sup>8</sup>
- 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).<sup>11</sup>
    - ◊ Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma).<sup>14,15</sup>
  - ▶ Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (negative in mesothelioma).<sup>8,11</sup>

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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) and exon 18 (G719X, G719) mutations—and sensitivity to TKIs.<sup>16-19</sup>
- ▶ The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.<sup>20,21</sup>
- ▶ EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.<sup>22</sup>
- ▶ KRAS mutations are associated with intrinsic TKI resistance, and KRAS gene sequencing could be useful for the selection of patients as candidates for TKI therapy.<sup>23</sup>
- ▶ 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.<sup>24</sup> 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 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).<sup>25</sup> 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.<sup>26</sup> Crizotinib is an oral ALK inhibitor that is approved by the FDA for patients with locally advanced or 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.<sup>27,28</sup> However, for the most part, ALK translocations and EGFR mutations are mutually exclusive.<sup>27, 29-31</sup>
- ▶ 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.<sup>32,33</sup> 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.

**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

- <sup>1</sup>Edge SB, Byrd DR, Compton CC, et al. AJCC Cancer Staging Manual, 7th ed. New York: Springer; 2010.
- <sup>2</sup>Fossella FV, Putnam JB, Komaki R, eds. Lung Cancer. M.D. Anderson Cancer Care Series. New York: Springer; 2003:316.
- <sup>3</sup>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. Philadelphia: Lippincott Williams & Wilkins; 2011.
- <sup>4</sup>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.
- <sup>5</sup>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.
- <sup>6</sup>Travis WD. Pathology and genetics of tumours of the lung, pleura, thymus and heart Lyon: IARC Press; 2004.
- <sup>7</sup>Brambilla E, Travis WD, Colby TV, et al. The new World Health Organization classification of lung tumours. Eur Respir J 2001;18:1059-1068.
- <sup>8</sup>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 adenocarcinoma. J Thorac Oncol 2011;6:244-285.
- <sup>9</sup>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.
- <sup>10</sup>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, papsin A, p63, and CK5/6. Am J Surg Pathol 2011;35:15-25.
- <sup>11</sup>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 2012 Aug 28. [Epub ahead of print]
- <sup>12</sup>Jagirdar J. Application of immunohistochemistry to the diagnosis of primary and metastatic carcinoma to the lung. Arch Pathol Lab Med 2008;132:384-396.
- <sup>13</sup>Goldstein NS, Thomas M. Mucinous and nonmucinous bronchioloalveolar adenocarcinomas have distinct staining patterns with thyroid transcription factor and cytokeratin 20 antibodies. Am J Clin Pathol 2001;116:319-325.
- <sup>14</sup>Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant mesothelioma. Hum Pathol 2005;36:372-380.
- <sup>15</sup>Chirieac 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.
- <sup>16</sup>Cappuzzo F, Finocchiaro G, Metro G, et al. Clinical experience with gefitinib: an update. Crit Rev Oncol Hematol 2006;58:31-45.
- <sup>17</sup>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.
- <sup>18</sup>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.
- <sup>19</sup>Ji H, Li D, Chen L, et al. The impact of human EGFR kinase domain mutations on lung tumorigenesis and in vivo sensitivity to EGFR-targeted therapies. Cancer Cell 2006;9:485-495.
- <sup>20</sup>Lund-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.
- <sup>21</sup>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.
- <sup>22</sup>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.
- <sup>23</sup>Shigematsu H, Gazdar AF. Somatic mutations of epidermal growth factor receptor signaling pathway in lung cancers. Int J Cancer 2006;118:257-262.
- <sup>24</sup>Finberg KE, Sequist LV, Joshi VA, et al. Mucinous differentiation correlates with absence of EGFR mutation and presence of KRAS mutation in lung adenocarcinomas with bronchioloalveolar features. J Mol Diagn 2007;9:320-326.
- <sup>25</sup>Cataldo 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.
- <sup>26</sup>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.
- <sup>27</sup>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.
- <sup>28</sup>Koivunen 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.
- <sup>29</sup>Koivunen 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.
- <sup>30</sup>Soda 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.
- <sup>31</sup>Inamura 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.
- <sup>32</sup>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.
- <sup>33</sup>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.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF SURGICAL THERAPY (1 of 4)

#### Evaluation

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

#### Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins  $\geq 2$  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 nodule<sup>1</sup>  $\leq 2$  cm with at least one of the following:
    - ◊ Pure adenocarcinoma in situ (AIS) histology
    - ◊ Nodule has  $\geq 50\%$  ground-glass appearance on CT
    - ◊ Radiologic surveillance confirms a long doubling time ( $\geq 400$  days)
- VATS or minimally invasive surgery 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](#))

<sup>1</sup>Peripheral is defined as the outer one third of the lung parenchyma.

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

**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.



# NCCN Guidelines Version 4.2014

## 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, or 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.<sup>1</sup> Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.<sup>2,3</sup> 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.<sup>4</sup>
- 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](#)

**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.



# NCCN Guidelines Version 4.2014

## 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.<sup>5</sup>
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.<sup>1,6,7</sup>
- 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.<sup>7,8</sup>
- 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.<sup>5,9</sup> Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.<sup>10</sup> 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.<sup>11,12</sup> 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 resection.
- Data from a large multi-institutional trial indicate that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality.<sup>2</sup> 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.<sup>13-16</sup> 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.<sup>17</sup>

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%)

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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

- <sup>1</sup>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.
- <sup>2</sup>Albain 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.
- <sup>3</sup>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.
- <sup>4</sup>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;87:995-1006.
- <sup>5</sup>Thomas 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.
- <sup>6</sup>Andre 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.
- <sup>7</sup>Decaluwé 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.
- <sup>8</sup>Bueno 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.
- <sup>9</sup>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.
- <sup>10</sup>de 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.
- <sup>11</sup>Bauman 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.
- <sup>12</sup>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.
- <sup>13</sup>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.
- <sup>14</sup>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.
- <sup>15</sup>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.
- <sup>16</sup>Weder 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.
- <sup>17</sup>Shah 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.

**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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.<sup>1</sup>
- 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. Nonrandomized comparisons of using advanced technologies versus older techniques demonstrate reduced toxicity and improved survival.<sup>2-4</sup>
- 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 and 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.<sup>5-10</sup>
- 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.<sup>10-12</sup>
- For institutions without an established SABR program, more modestly hypofractionated or dose-intensified conventionally fractionated 3D-CRT regimens are alternatives.<sup>13-14</sup>
- 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 (Stages II-III)**

- The standard of care for patients with inoperable stage II and stage III is concurrent chemoRT.<sup>15-17</sup>  
(<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.<sup>18,19</sup>  
(<http://www.acr.org/~media/ACR/Documents/AppCriteria/OncologyNonsurgicalTreatmentForNSCLCPoorPerformanceStatusOrPalliativeIntent.pdf>)

**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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).<sup>20,21</sup>
- 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)<sup>22</sup> and is recommended for resectable superior sulcus tumors.<sup>23-24</sup>
  - ▶ Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.<sup>25,26</sup>
  - ▶ 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.<sup>27,28</sup> Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients<sup>29-31</sup> 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.<sup>32</sup>

#### 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.<sup>33-35</sup>
- 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 2-5. These are based on published experience, ongoing trials, historical data, modeling, and empirical judgment.<sup>37,38</sup> Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.<sup>39-43</sup>

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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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  $\geq 100$  Gy are associated with significantly better local control and survival than less intensive regimens.<sup>44</sup> In the United States, only regimens of  $\leq 5$  fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.<sup>44,45</sup> 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,<sup>45,46</sup> while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.<sup>47</sup> 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.<sup>48</sup>
- Prescription doses incompletely describe the actual delivered doses, which also depend strongly on how the dose is prescribed (to the isocenter vs. an isodose volume covering a proportion of the PTV), the degree of dose heterogeneity, whether tissue density heterogeneity corrections are used, and the type of dose calculation algorithm.<sup>49,50</sup> 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.<sup>51-55</sup> One randomized trial found improved survival for IFI versus ENI, possibly because it enabled dose escalation.<sup>56</sup> 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.<sup>57</sup> Dose escalation in RT alone,<sup>58</sup> sequential chemoRT,<sup>59</sup> or concurrent chemoRT<sup>60</sup> is associated with better survival in non-randomized comparisons. Doses of up to 74 Gy with concurrent chemotherapy can be delivered safely when normal tissue dose constraints are respected.<sup>61-64</sup> The final results from RTOG 0617, comparing 60 versus 74 Gy with concurrent chemotherapy are pending, but preliminarily, 74 Gy does not improve overall survival.<sup>65</sup> A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,<sup>66</sup> 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,<sup>67-70</sup> 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.<sup>71</sup> 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.<sup>29,30</sup> 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.<sup>72</sup>

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### 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,<sup>73-76</sup> and are preferred for patients with poor performance status and/or shorter life expectancy. 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,<sup>77</sup> 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.<sup>77</sup> Given the potential for rapid progression of NSCLC,<sup>79,80</sup> 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.<sup>50</sup>
- 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.<sup>81</sup>
- 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.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF RADIATION THERAPY (5 of 9)

**Table 1. Commonly Used Abbreviations in Radiation Therapy**

RT	Radiation Therapy or Radiotherapy	IFI	Involved Field Irradiation
2D-RT	2-Dimensional RT	IGRT	Image-Guided RT
3D-CRT	3-Dimensional Conformal RT	IMRT	Intensity-Modulated RT
4D-CT	4-Dimensional Computed Tomography	ITV*	Internal Target Volume
AAPM	American Association of Physicists in Medicine	MLD	Mean Lung Dose
ABC	Active Breathing Control	OAR	Organ at Risk
ACR	American College of Radiology	OBI	On-Board Imaging
ASTRO	American Society for Radiation Oncology	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
DVH	Dose-Volume Histogram	SABR	Stereotactic Ablative RT, also known as Stereotactic Body RT (SBRT)
ENI	Elective Nodal Irradiation	V20	% Volume of an OAR receiving $\geq 20$ Gy
GTV*	Gross Tumor Volume	VMAT	Volumetric Modulated Arc Therapy
ICRU	International Commission on Radiation Units and Measurements		

\*Refer to ICRU Report 83 for detailed definitions.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF RADIATION THERAPY (6 of 9)

**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	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Brachial Plexus	17.5 Gy	21 Gy (7 Gy/fx)	27.2 Gy (6.8 Gy/fx)	30 Gy (6 Gy/fx)
Heart/ Pericardium	22 Gy	30 Gy (10 Gy/fx)	34 Gy (8.5 Gy/fx)	35 Gy (7 Gy/fx)
Great Vessels	37 Gy	39 Gy (13 Gy/fx)	49 Gy (12.25 Gy/fx)	55 Gy (11 Gy/fx)
Trachea & Proximal Bronchi	20.2 Gy	30 Gy (10 Gy/fx)	34.8 Gy (8.7 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Rib	30 Gy	30 Gy (10 Gy/fx)	30 Gy (7.5 Gy/fx)	32.5 Gy (6.5 Gy/fx)
Skin	26 Gy	30 Gy (10 Gy/fx)	36 Gy (9 Gy/fx)	40 Gy (8 Gy/fx)
Stomach	12.4 Gy	27 Gy (9 Gy/fx)	30 Gy (7.5 Gy/fx)	35 Gy (7 Gy/fx)

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

**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF RADIATION THERAPY (7 of 9)

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

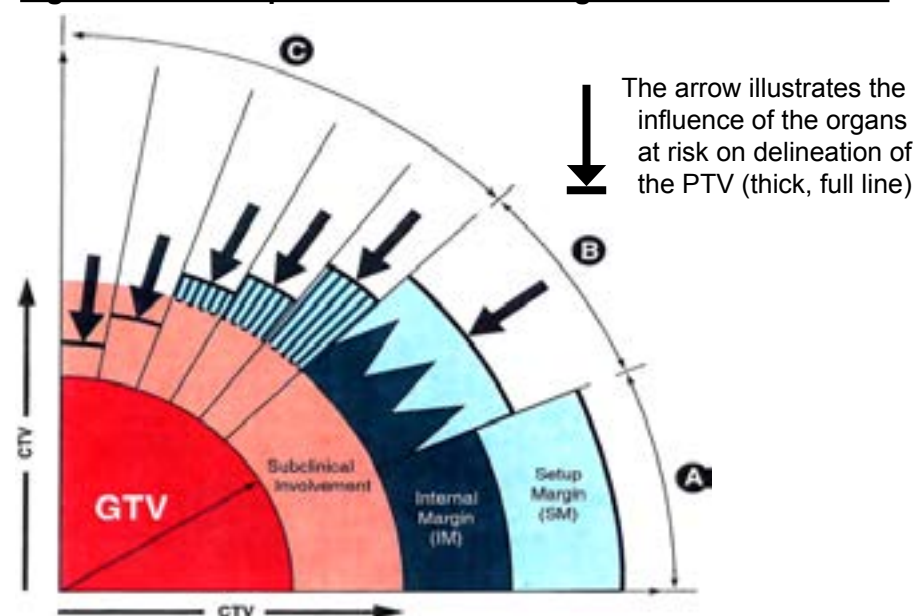
Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60-74 Gy	2 Gy	6-7.5 weeks
Preoperative RT	45-50 Gy	1.8-2 Gy	5 weeks
Postoperative RT • Negative margins • Extracapsular nodal extension or microscopic positive margins • Gross residual tumor	50-54 Gy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

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

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

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

**Figure 1. ICRU Report 62 Schema of Target Volume Definitions**



**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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF RADIATION THERAPY - References (8 of 9)

- <sup>1</sup>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.
- <sup>2</sup>Liao 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.
- <sup>3</sup>Sejpal 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.
- <sup>4</sup>Chang 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.
- <sup>5</sup>Timmerman R, Paulus R, Galvin J, et al. Stereotactic Body Radiation Therapy for Inoperable Early Stage Lung Cancer. *JAMA* 2010; 303:1070-1076.
- <sup>6</sup>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.
- <sup>7</sup>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.
- <sup>8</sup>Grutters 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.
- <sup>9</sup>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* 2010; 28:5153-5159.
- <sup>10</sup>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.
- <sup>11</sup>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.
- <sup>12</sup>Crabtree 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.
- <sup>13</sup>Bogart 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.
- <sup>14</sup>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.
- <sup>15</sup>Aupérin 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.
- <sup>16</sup>O'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.
- <sup>17</sup>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.
- <sup>18</sup>Sause 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.
- <sup>19</sup>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.
- <sup>20</sup>Baumann 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.
- <sup>21</sup>Mauguen 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.
- <sup>22</sup>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* 2009; 374:379-386.
- <sup>23</sup>Kunitoh 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.
- <sup>24</sup>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.
- <sup>25</sup>Thomas 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.
- <sup>26</sup>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 Biol Phys* 2009;75:1462-1467.
- <sup>27</sup>Douillard 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.
- <sup>28</sup>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.
- <sup>29</sup>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.
- <sup>30</sup>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.
- <sup>31</sup>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.
- <sup>32</sup>Burdett 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.
- <sup>33</sup>Milano 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.
- <sup>34</sup>Rusthoven KE, Kavanagh BD, Burri SH, et al. Multi-institutional phase I/II trial of stereotactic body radiation therapy for lung metastases. *J Clin Oncol* 2009; 27:1579-1584.
- <sup>35</sup>Salama 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.
- <sup>36</sup>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 Oncol Biol Phys* 2011;81:1442-1457.
- <sup>37</sup>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.
- <sup>38</sup>Timmerman RD. An overview of hypofractionation and introduction to this issue of seminars in radiation oncology. *Semin Radiat Oncol* 2008; 18:215-222.
- <sup>39</sup>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.
- <sup>40</sup>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.
- <sup>41</sup>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.
- <sup>42</sup>Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010; 76:S77-85.
- <sup>43</sup>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.
- <sup>44</sup>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.
- <sup>45</sup>Lagerwaard 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.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### PRINCIPLES OF RADIATION THERAPY - References (9 of 9)

<sup>46</sup>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.

<sup>47</sup>Timmerman 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.

<sup>48</sup>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.

<sup>49</sup>Xiao 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.

<sup>50</sup>Liu 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.

<sup>51</sup>Belderbos 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.

<sup>52</sup>Bradley 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.

<sup>53</sup>Sanuki-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.

<sup>54</sup>Sulman 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.

<sup>55</sup>Rosenzweig 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.

<sup>56</sup>Yuan 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.

<sup>57</sup>Perez 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.

<sup>58</sup>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.

<sup>59</sup>Rengan 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.

<sup>60</sup>Machta 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.

<sup>61</sup>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.

<sup>62</sup>Socinski 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.

<sup>63</sup>Stinchcombe 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.

<sup>64</sup>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.

<sup>65</sup>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 +/- cetuximab for stage III non-small cell lung cancer: results on radiation dose in RTOG 0617. *J Clin Oncol* 2013;31(suppl; abstr 7501).

<sup>66</sup>Maugen 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.

<sup>67</sup>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.

<sup>68</sup>Sonett JR, Suntharalingam M, Edelman MJ, 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.

<sup>69</sup>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.

<sup>70</sup>Suntharalingam 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.

<sup>71</sup>Kelsey 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.

<sup>72</sup>Spiegel 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.

<sup>73</sup>Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: a systematic review. *J Clin Oncol* 2007; 25:1423-1436.

<sup>74</sup>Lutz 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.

<sup>75</sup>Cross 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.

<sup>76</sup>Medical 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.

<sup>77</sup>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.

<sup>78</sup>Ung 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.

<sup>79</sup>Everitt S, Herschtal A, Callahan J, et al. High rates of tumor growth and disease progression detected on serial pretreatment fluorodeoxyglucose-positron emission tomography/computed tomography scans in radical radiotherapy candidates with nonsmall cell lung cancer. *Cancer* 2010;116:5030-5037.

<sup>80</sup>Mohammed 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.

<sup>81</sup>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.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- Cisplatin 50 mg/m<sup>2</sup> days 1 and 8; vinorelbine 25 mg/m<sup>2</sup> days 1, 8, 15, 22, every 28 days for 4 cycles<sup>a</sup>
- Cisplatin 100 mg/m<sup>2</sup> day 1; vinorelbine 30 mg/m<sup>2</sup> days 1, 8, 15, 22; every 28 days for 4 cycles<sup>b,c</sup>
- Cisplatin 75-80 mg/m<sup>2</sup> day 1; vinorelbine 25-30 mg/m<sup>2</sup> days 1 + 8, every 21 days for 4 cycles
- Cisplatin 100 mg/m<sup>2</sup> day 1; etoposide 100 mg/m<sup>2</sup> days 1-3, every 28 days for 4 cycles<sup>b</sup>
- Cisplatin 80 mg/m<sup>2</sup> days 1, 22, 43, 64; vinblastine 4 mg/m<sup>2</sup> days 1, 8, 15, 22, 29 then every 2 wks after day 43, every 21 days for 4 cycles<sup>b</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1; gemcitabine 1250 mg/m<sup>2</sup> days 1, 8, every 21 days for 4 cycles
- Cisplatin 75 mg/m<sup>2</sup> day 1; docetaxel 75 mg/m<sup>2</sup> day 1 every 21 days for 4 cycles<sup>d</sup>
- Cisplatin 75 mg/m<sup>2</sup> day 1, pemetrexed 500 mg/m<sup>2</sup> day 1 for nonsquamous (without specific histologic subtype) every 21 days for 4 cycles

#### Chemotherapy Regimens for patients with comorbidities or patients not able to tolerate cisplatin

Paclitaxel 200 mg/m<sup>2</sup> day 1, carboplatin AUC 6 day 1, every 21 days<sup>e</sup>

<sup>a</sup>Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-lung cancer. N Engl J Med 2005;352:2589-2597.

<sup>b</sup>Arriagada 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.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>Strauss 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.

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

#### Concurrent Chemotherapy/RT Regimens

- Cisplatin 50 mg/m<sup>2</sup> on days 1, 8, 29, and 36; etoposide 50 mg/m<sup>2</sup> days 1-5, 29-33; concurrent thoracic RT<sup>a</sup> (preferred)\*
- Cisplatin 100 mg/m<sup>2</sup> days 1 and 29; vinblastine 5 mg/m<sup>2</sup>/weekly x 5; concurrent thoracic RT<sup>b</sup> (preferred)
- Carboplatin AUC 5 on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 4 cycles; concurrent thoracic RT<sup>c</sup> (nonsquamous)
- Cisplatin 75 mg/m<sup>2</sup> on day 1, pemetrexed 500 mg/m<sup>2</sup> on day 1 every 21 days for 3 cycles; concurrent thoracic RT<sup>d</sup> (nonsquamous)

#### Sequential Chemotherapy/RT Regimens

- Cisplatin 100 mg/m<sup>2</sup> on days 1 and 29; vinblastine 5 mg/m<sup>2</sup>/weekly on days 1, 8, 15, 22, and 29; followed by RT<sup>b</sup>
- Paclitaxel 200 mg/m<sup>2</sup> 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<sup>e</sup>

#### Concurrent Chemotherapy/RT Followed by Chemotherapy

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

\*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.

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

<sup>b</sup>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.

<sup>c</sup>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.

<sup>d</sup>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.

<sup>e</sup>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.

**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.



# NCCN Guidelines Version 4.2014

## 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 of any age (performance status 3-4) do not benefit from cytotoxic treatment, except erlotinib for EGFR mutation-positive patients.

#### First-line therapy

- Bevacizumab + chemotherapy or chemotherapy alone is indicated in PS 0-1 patients with advanced or recurrent NSCLC. Bevacizumab should be given until disease progression.
- Cetuximab + vinorelbine/cisplatin is an option for patients with performance status 0-1 (category 2B).
- 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 select patients with sensitizing EGFR mutations.
- Crizotinib is indicated for select 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 or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- 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).

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

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

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





# NCCN Guidelines Version 4.2014

## 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 and cetuximab given in combination with chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials supporting their use.
  - ▶ Continuation of bevacizumab after 4-6 cycles of platinum-doublet chemotherapy and bevacizumab (category 1).
  - ▶ Continuation of cetuximab after 4-6 cycles of cisplatin, vinorelbine, and cetuximab (category 1).
  - ▶ Continuation of pemetrexed after 4-6 cycles of cisplatin and pemetrexed chemotherapy, for patients with histologies other than squamous cell carcinoma (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.

#### Second-line therapy

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

#### Third-line therapy

- If not already given, options for PS 0-2 include docetaxel, pemetrexed (nonsquamous), erlotinib, or gemcitabine (category 2B for all options).

#### 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 \(3 of 3\)](#)

**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.





# NCCN Guidelines Version 4.2014

## 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 therapy).

- |   |  |                                      |  |
|---|--|--------------------------------------|--|
| • <b>Cisplatin</b> <sup>1-9</sup>         | • <b>Gemcitabine</b> <sup>3,5,6,8,9,13</sup> | • <b>Ifosfamide</b> <sup>12</sup>    | • <b>Albumin-bound paclitaxel</b> <sup>19-21 †</sup> |
| • <b>Carboplatin</b> <sup>4,6-11</sup>    | • <b>Etoposide</b> <sup>4</sup>              | • <b>Pemetrexed</b> <sup>14,15</sup> | • <b>Crizotinib</b> <sup>22</sup>                    |
| • <b>Paclitaxel</b> <sup>1,4,6,8-11</sup> | • <b>Irinotecan</b> <sup>9</sup>             | • <b>Erlotinib</b> <sup>16</sup>     | • <b>Afatinib</b> <sup>23</sup>                      |
| • <b>Docetaxel</b> <sup>5,7,8,12,13</sup> | • <b>Vinblastine</b>                         | • <b>Bevacizumab</b> <sup>17</sup>   | • <b>Ceritinib</b> <sup>24</sup>                     |
| • <b>Vinorelbine</b> <sup>7,9,10</sup>    | • <b>Mitomycin</b>                           | • <b>Cetuximab</b> <sup>18</sup>     |  |

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

<sup>2</sup>Wozniak 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.

<sup>3</sup>Cardenal 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.

<sup>4</sup>Belani 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.

<sup>5</sup>Sandler 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.

<sup>6</sup>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.

<sup>7</sup>Fossella 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.

<sup>8</sup>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.

<sup>9</sup>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.

<sup>10</sup>Kelly 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.

<sup>11</sup>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.

<sup>12</sup>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.

<sup>13</sup>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.

<sup>14</sup>Hanna 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.

<sup>15</sup>Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543-3551.

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

<sup>17</sup>Sandler 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.

<sup>18</sup>Pirker R, Periera JR, Szczesna A, et al. Cetuximab plus chemotherapy in patients with advanced non-small-cell lung cancer (FLEX): an open label randomised phase III trial. *Lancet* 2009;373:1525-1531.

<sup>19</sup>Green 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.

<sup>20</sup>Rizvi 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.

<sup>21</sup>Socinski 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.

<sup>22</sup>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.

<sup>23</sup>Sequist LV, Yang JC-H, 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;published ahead of print on July 1, 2013.

<sup>24</sup>Shaw 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.

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

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

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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### CANCER SURVIVORSHIP CARE

#### NSCLC Long-term Follow-up Care

- **Cancer Surveillance**
    - ▶ H&P and a chest CT scan ± contrast every 6-12 months for 2 years, then H&P and a non-contrast-enhanced chest CT scan annually
    - ▶ Smoking status assessment at each visit; counseling and referral for cessation as needed.
  - **Immunizations**
    - ▶ Annual influenza vaccination
    - ▶ Herpes zoster vaccine
    - ▶ Pneumococcal vaccination with revaccination as appropriate
- #### Counseling Regarding Health Promotion and Wellness<sup>1</sup>
- 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<sup>2,3</sup>

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](#)

<sup>1</sup>ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention:

[http://www.cancer.org/docroot/PED/content/PED\\_3\\_2X\\_Diet\\_and\\_Activity\\_Factors\\_That\\_Affect\\_Risks.asp?sitearea=PED](http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED) (Accessed November 30, 2012)

<sup>2</sup>Memorial Sloan-Kettering Cancer Center Screening Guidelines: <http://www.mskcc.org/mskcc/html/65279.cfm> (Accessed November 30, 2012)

<sup>3</sup>American Cancer Society Guidelines for Early Detection of Cancer:

[http://www.cancer.org/docroot/PED/content/PED\\_2\\_3X\\_ACS\\_Cancer\\_Detection\\_Guidelines\\_36.asp?sitearea=PED](http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED) (Accessed November 30, 2012)

**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.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### TARGETED AGENTS FOR PATIENTS WITH GENETIC ALTERATIONS

Genetic Alteration (ie, Driver event)	Available Targeted Agents with Activity Against Driver Event in Lung Cancer
EGFR mutations	erlotinib, <sup>1</sup> gefitinib, <sup>2</sup> afatinib <sup>3</sup>
ALK rearrangements	crizotinib <sup>4</sup> , ceritinib <sup>5</sup>
HER2 mutations	trastuzumab, <sup>6</sup> afatinib <sup>7</sup>
BRAF mutations	vemurafenib, <sup>8</sup> dabrafenib <sup>9</sup>
MET amplification	crizotinib <sup>10</sup>
ROS1 rearrangements	crizotinib <sup>11</sup>
RET rearrangements	cabozantinib <sup>12</sup>

<sup>1</sup>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.

<sup>2</sup>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.

<sup>3</sup>Sequist LV, Yang JC-H, 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.

<sup>4</sup>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.

<sup>5</sup>Shaw 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.

<sup>6</sup>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.

<sup>7</sup>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.

<sup>8</sup>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.

<sup>9</sup>Planchard D, Mazieres J, Riely GJ, et al. Interim results of phase II study BR113928 of dabrafenib in BRAF V600E mutation-positive non-small cell lung cancer (NSCLC) patients [abstract]. *J Clin Oncol* 2013;31(Suppl 15): Abstract 8009.

<sup>10</sup>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.

<sup>11</sup>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.

<sup>12</sup>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.

**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.



# NCCN Guidelines Version 4.2014 Staging Non-Small Cell Lung Cancer

**Table 1. Definitions for T, N, M\***

<b>T</b>	<b>Primary Tumor</b>	<b>N</b>	<b>Regional Lymph Nodes</b>	<b>M</b>	<b>Distant Metastasis</b>
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) <sup>a</sup>	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 <sup>c</sup>
	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: <sup>b</sup>				
	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 <sup>a</sup> 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				

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

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

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

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



# NCCN Guidelines Version 4.2014 Staging Non-Small Cell Lung Cancer

**Table 2. Anatomic Stage and Prognostic Groups**

<b>Occult Carcinoma</b>	<b>TX</b>	<b>N0</b>	<b>M0</b>
<b>Stage 0</b>	<b>Tis</b>	<b>N0</b>	<b>M0</b>
<b>Stage IA</b>	<b>T1a</b>	<b>N0</b>	<b>M0</b>
	<b>T1b</b>	<b>N0</b>	<b>M0</b>
<b>Stage IB</b>	<b>T2a</b>	<b>N0</b>	<b>M0</b>
<b>Stage IIA</b>	<b>T2b</b>	<b>N0</b>	<b>M0</b>
	<b>T1a</b>	<b>N1</b>	<b>M0</b>
	<b>T1b</b>	<b>N1</b>	<b>M0</b>
	<b>T2a</b>	<b>N1</b>	<b>M0</b>
<b>Stage IIB</b>	<b>T2b</b>	<b>N1</b>	<b>M0</b>
	<b>T3</b>	<b>N0</b>	<b>M0</b>
<b>Stage IIIA</b>	<b>T1a</b>	<b>N2</b>	<b>M0</b>
	<b>T1b</b>	<b>N2</b>	<b>M0</b>
	<b>T2a</b>	<b>N2</b>	<b>M0</b>
	<b>T2b</b>	<b>N2</b>	<b>M0</b>
	<b>T3</b>	<b>N1</b>	<b>M0</b>
	<b>T3</b>	<b>N2</b>	<b>M0</b>
	<b>T4</b>	<b>N0</b>	<b>M0</b>
	<b>T4</b>	<b>N1</b>	<b>M0</b>
<b>Stage IIIB</b>	<b>T1a</b>	<b>N3</b>	<b>M0</b>
	<b>T1b</b>	<b>N3</b>	<b>M0</b>
	<b>T2a</b>	<b>N3</b>	<b>M0</b>
	<b>T2b</b>	<b>N3</b>	<b>M0</b>
	<b>T3</b>	<b>N3</b>	<b>M0</b>
	<b>T4</b>	<b>N2</b>	<b>M0</b>
	<b>T4</b>	<b>N3</b>	<b>M0</b>
<b>Stage IV</b>	<b>Any T</b>	<b>Any N</b>	<b>M1a</b>
	<b>Any T</b>	<b>Any N</b>	<b>M1b</b>

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



# NCCN Guidelines Version 4.2014 Staging Non-Small Cell Lung Cancer

**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	<b>IIA</b>	IIIA	IIIB
T2 (<5-7 cm)	T2b	<b>IIA</b>	IIB	IIIA	IIIB
T2 (>7 cm)	T3	<b>IIB</b>	<b>IIIA</b>	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		<b>IIB</b>	<b>IIIA</b>	<b>IIIA</b>	IIIB
T4 extension	T4	<b>IIIA</b>	<b>IIIA</b>	IIIB	IIIB
M1 (ipsilateral lung)		<b>IIIA</b>	<b>IIIA</b>	<b>IIIB</b>	<b>IIIB</b>
T4 (pleural effusion)	M1a	<b>IV</b>	<b>IV</b>	<b>IV</b>	<b>IV</b>
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.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

## Discussion

### NCCN Categories of Evidence and Consensus

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

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

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

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

**All recommendations are category 2A unless otherwise noted.**

## Table of Contents

Overview.....	MS-3
Risk Factors .....	MS-3
Prevention and Screening .....	MS-4
Classification and Prognostic Factors.....	MS-5
Diagnostic Evaluation of Lung Nodules.....	MS-5
Pathologic Evaluation of Lung Cancer .....	MS-6
Adenocarcinoma .....	MS-7
Immunohistochemical Staining .....	MS-7

Staging .....	MS-8
Predictive and Prognostic Biomarkers .....	MS-8
EGFR Mutations.....	MS-10
ALK Gene Rearrangements .....	MS-11
KRAS Mutations .....	MS-12
Treatment Approaches .....	MS-12
Surgery .....	MS-12
Lymph Node Dissection .....	MS-13
Stage IIIA N2 Disease.....	MS-14
Thorascopic Lobectomy.....	MS-14
Radiation Therapy .....	MS-15
General Principles .....	MS-15
Target Volumes, Prescription Doses, and Normal Tissue Dose Constraints .....	MS-16
Radiation Simulation, Planning, and Delivery.....	MS-16
Stereotactic Ablative Radiotherapy .....	MS-17
Radiofrequency Ablation.....	MS-17
Whole Brain RT and Stereotactic Radiosurgery .....	MS-17
Combined Modality Therapy.....	MS-18
Surgery Followed by Chemotherapy: Trial Data.....	MS-19
Neoadjuvant Chemotherapy Followed by Surgery: Trial Data ....	20



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Chemoradiation: Trial Data .....	MS-21	Stage IV Disease .....	MS-31
Chemotherapy: Trial Data .....	MS-21	<a href="#">Adjuvant Treatment .....</a>	<a href="#">MS-32</a>
Targeted Therapies .....	MS-22	Chemotherapy or Chemoradiation .....	MS-32
Bevacizumab .....	MS-22	Radiation Therapy .....	MS-34
Erlotinib .....	MS-23	<a href="#">Surveillance .....</a>	<a href="#">MS-35</a>
Afatinib .....	MS-24	<a href="#">Treatment of Recurrences and Distant Metastases .....</a>	<a href="#">MS-35</a>
Crizotinib .....	MS-24	Trial Data .....	MS-37
Ceritinib .....	MS-24	Number of Cycles of First-Line Systemic Therapy .....	MS-38
Cetuximab .....	MS-24	Maintenance Therapy .....	MS-39
Maintenance Therapy .....	MS-24	Continuation of Erlotinib, Gefitinib, or Afatinib After Progression ...	39
Continuation Maintenance Therapy .....	MS-25	Second-Line and Third-Line Systemic Therapy .....	MS-40
Switch Maintenance Therapy .....	MS-26	<a href="#">References .....</a>	<a href="#">MS-42</a>
<a href="#">Clinical Evaluation .....</a>	<a href="#">MS-26</a>		
Additional Pretreatment Evaluation .....	MS-27		
Mediastinoscopy .....	MS-27		
Other Imaging Studies .....	MS-27		
<a href="#">Initial Therapy .....</a>	<a href="#">MS-28</a>		
Stage I, Stage II, and Stage IIIA Disease .....	MS-28		
Multiple Lung Cancers .....	MS-30		
Stage IIIB Disease .....	MS-31		



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### Overview

Lung cancer is the leading cause of cancer death in the United States. In 2014, an estimated 224,210 new cases (116,000 in men and 108,210 in women) of lung and bronchial cancer will be diagnosed, and 159,260 deaths (86,930 in men and 72,330 in women) are estimated to occur because of the disease.<sup>1</sup> Only 16.6% of all lung cancer patients are alive 5 years or more after diagnosis

(<http://seer.cancer.gov/statfacts/html/lungb.html>).<sup>2</sup> However, much progress has been made in the last 10 years for lung cancer such as screening, minimally invasive techniques for diagnosis and treatment, and targeted therapies.<sup>3,4</sup> Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.<sup>5</sup>

The *Summary of the Guidelines Updates* describes the most recent revisions in the algorithms, which have been incorporated into this updated Discussion text (see the NCCN Guidelines for Non-Small Cell Lung Cancer). 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.

### Risk Factors

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths (<http://www.surgeongeneral.gov/library/smokingconsequences/>).<sup>6-11</sup>

Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).<sup>10,12</sup> 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).<sup>8,12-15</sup> Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.<sup>6,16-19</sup> The U.S. Environmental Protection Agency estimates that radon is the main cause of lung cancer in nonsmokers; however, secondhand smoke may also be a factor (<http://www.epa.gov/radon/healthrisks.html>).

Asbestos, a mineral compound that breaks into small airborne shards, 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.<sup>20</sup> In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (ie, bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, organic arsenic compounds).<sup>21,22</sup> 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.<sup>23,24</sup> Asbestos also causes malignant pleural mesothelioma (see the NCCN Guidelines for Malignant Pleural Mesothelioma).

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,<sup>25</sup> 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 non-small cell lung cancer (NSCLC) increased.<sup>25</sup>



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### Prevention and Screening

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.<sup>9</sup> Active smoking and secondhand smoke both cause lung cancer (see Reports of the Surgeon General, which are the next 2 links). 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

([http://www.cdc.gov/tobacco/data\\_statistics/sgr/2004/pdfs/executivesummary.pdf](http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf)). Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.<sup>26</sup> Those who live with someone who smokes have an increased risk for lung cancer (<http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf>). Further complicating this problem, cigarettes also contain nicotine, which is a highly addictive substance.

Oncologists should encourage smoking cessation, especially in patients with cancer (<http://www.smokefree.gov/>).<sup>27-29</sup> The 5 A's framework is a useful tool (that is, Ask, Advise, Assess, Assist, Arrange) (<http://www.ahrq.gov/clinic/tobacco/5steps.htm>). It is in the best interest of patients to quit smoking. Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival.<sup>30</sup> 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 (see *Treating Tobacco Use and Dependence: 2008 Update*, which is published by the Agency for Healthcare Research and Quality) (<http://www.ahrq.gov/professionals/clinicians-providers/guidelines-recommendations/tobacco/index.html>). The American Cancer Society has a Guide to Quitting Smoking

(<http://www.cancer.org/healthy/stayawayfromtobacco/guidetoquittingsmoking/index>). The E-Quit Study is using email to help smokers quit smoking

(<http://www.cancer.org/healthy/stayawayfromtobacco/acs-gwu-e-quit-study>).

Agents that can be used to promote smoking cessation include nicotine replacement (eg, gum, inhaler, lozenge, nasal spray, patch), bupropion sustained release, and varenicline. Studies have shown that varenicline is better than bupropion or nicotine patch for smoking cessation.<sup>31-33</sup>

However, almost 30% of patients had nausea while using varenicline.<sup>34</sup> The effectiveness of varenicline for preventing relapse has not been clearly established.<sup>35</sup> The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms

(<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm>). 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.<sup>36</sup> Bupropion may be also associated with similar serious neuropsychiatric symptoms

([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2012/020711s036lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020711s036lbl.pdf)). Nicotine replacement has fewer adverse effects than varenicline or bupropion.<sup>37</sup> However, in spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.<sup>37</sup>

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes.<sup>38,39</sup> Because localized cancer can be managed curatively and because the mortality rate in other solid tumors (eg, cervix, colon) seems to be decreased by screening and early detection, lung cancer



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

was an appropriate candidate for a population-based screening approach. Pilot trials of spiral (helical) low-dose CT in lung cancer screening were promising.<sup>40-42</sup>

The NLST (ACRIN Protocol A6654) was a randomized controlled study involving more than 53,000 current or former heavy smokers; this trial assessed the risks and benefits of low-dose helical CT scans compared with chest radiographs for detecting lung cancer.<sup>43</sup> Data from the NLST showed that screening individuals with high-risk factors using low-dose helical CT decreased the mortality rate from lung cancer by 20% when compared with chest radiograph.<sup>44</sup> Individuals with high-risk factors were either current or former smokers with a 30 or more pack-year smoking history (former smokers had quit 15 years ago), were 55 to 74 years of age, and had no evidence of lung cancer.<sup>43,45</sup> Additional information on NLST can be found at <http://www.cancer.gov/nlst>. NCCN, the American Cancer Society, the U.S. Preventive Services Task Force, and other organizations recommend lung cancer screening using low-dose helical CT for select high-risk current and former smokers (see the NCCN Guidelines for Lung Cancer Screening).<sup>46,47</sup>

### 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 cell type in nonsmokers. An international panel recently revised the classification of lung adenocarcinoma (see

the *Pathologic Evaluation of Lung Cancer* in this Discussion).<sup>48</sup> 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.<sup>49</sup>

### Diagnostic Evaluation of Lung Nodules

A section on evaluating suspicious lung nodules was recently added to the NCCN Guidelines for NSCLC (see *Principles of Diagnostic Evaluation* and corresponding algorithm pages).<sup>50</sup> This diagnostic section describes the evaluation of suspicious pulmonary nodules that are seen on low-dose helical CT scans. As previously described, low-dose CT has been shown to decrease the mortality rate from lung cancer and is a valuable tool for detecting lung cancer. Data from the NLST show that low-dose CT can be used to detect lung cancer at an early stage when it is still curable.<sup>44</sup> The NCCN Guidelines for Lung Cancer Screening recommend low-dose CT for select high-risk current and former smokers without symptoms of lung cancer (eg, those with a ≥30 pack-year smoking history). The diagnostic algorithm 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.

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*





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

**Assessment** in the NCCN Guidelines for Non-Small Cell Lung Cancer). It is important to note that false-positive results frequently occur with low-dose CT (eg, benign intrapulmonary lymph nodes, noncalcified granulomas) (see the NCCN Guidelines for Lung Cancer Screening).<sup>44</sup> A tissue diagnosis of lung cancer should be established before doing a lobectomy. An open procedure allows more diagnostic steps to confirm cancer before committing to a lobectomy, including a wedge resection or a Tru-Cut needle biopsy.

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 experience. 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 NCCN 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 NCCN 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.<sup>51</sup>

If pathology results from biopsy or surgical excision indicate a diagnosis of NSCLC, then further evaluation and staging need to be done so that the patient's health care team can determine the most appropriate and effective treatment plan (see *Pathologic Evaluation of Lung Cancer* and *Staging* in this Discussion and the NCCN Guidelines for Non-Small Cell Lung Cancer). Diagnosis, staging, and planned resection (eg,

lobectomy) are ideally one operative procedure for patients with early-stage disease (see the *Principles of Diagnostic Evaluation*).

## 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).<sup>52</sup> 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).<sup>3,53-58</sup> Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.<sup>51,59</sup> Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC.<sup>60,61</sup> However, diagnosis may be more difficult when using small biopsies and cytology.<sup>62</sup> 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).<sup>63,64</sup>

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





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

should include the WHO histologic classification for carcinomas of the lung.<sup>65</sup> The classification for lung adenocarcinoma was recently revised by an international panel (see *Adenocarcinoma*).<sup>48</sup> The revised classification requires immunohistochemical, histochemical, and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>66</sup> 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 bronchioloalveolar carcinoma (BAC) or mixed subtype adenocarcinoma are no longer used.<sup>48</sup> If necessary, the term *former BAC* is used. The categories for adenocarcinoma include: 1) adenocarcinoma in situ (AIS) (formerly BAC), which is a preinvasive lesion; 2) minimally invasive adenocarcinoma (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 sensitizing 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.<sup>48</sup>

### 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 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.<sup>61,67</sup> 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.<sup>48,68</sup> Squamous cell carcinomas are often TTF-1 negative and p63 positive, whereas adenocarcinomas are usually TTF-1 positive.<sup>48</sup> These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.<sup>48,68</sup> Other markers (eg, p40) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.<sup>69,70</sup>

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma.<sup>71,72</sup> The stains that are positive for adenocarcinoma include CEA (carcinoembryonic antigen), B72.3, Ber-EP4, MOC-31, and TTF-1; these stains are negative for mesothelioma.<sup>73</sup> Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin antibody),<sup>74</sup> and cytokeratin 5/6.<sup>71,72</sup> 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).<sup>71,72,75</sup>

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.<sup>68</sup> However, TTF-1 is positive in tumors from



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

patients with thyroid cancer.<sup>76</sup> 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.<sup>51,68,77</sup> 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.<sup>78,79</sup> 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.<sup>80</sup> Data suggest that microRNA expression can be used to distinguish SCLC from NSCLC.<sup>81</sup>

### Staging

The NCCN Guidelines use the AJCC (7<sup>th</sup> edition) staging system for lung cancer.<sup>82</sup> The stage grouping is summarized in Table 2 of the 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)<sup>83,84</sup> and was adopted by the AJCC.<sup>85,86</sup> 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).<sup>87</sup>

From 2003 to 2009, the overall 5-year relative survival rate for lung cancer was 16.6% in the United States. 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% for regional, 3.9% for distant, and 7.8% for unstaged (<http://seer.cancer.gov/statfacts/html/lungb.html>). 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.<sup>88</sup> 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%.<sup>89</sup> 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

therapeutic efficacy; that is, 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; that is, the biomolecule is an indicator of the innate tumor aggressiveness (see end of this section).

Predictive biomarkers include EGFR and the ALK fusion oncogene (fusion between ALK and other genes [eg, echinoderm microtubule-associated protein-like 4]), and other biomarkers such as HER2 (also known as ERBB2) and BRAF mutations, ROS1 and RET gene rearrangements, and MET amplification (see *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitor (EGFR-TKI) therapy; therefore, these mutations are referred to as *sensitizing* EGFR mutations (see *EGFR Mutations* in this Discussion).<sup>90,91</sup> 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.<sup>92</sup> The ALK fusion oncogene (ie, ALK gene rearrangement) is a predictive biomarker that has been identified in a small subset of patients with NSCLC (see *ALK Gene Rearrangements* in this Discussion and *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer). Other gene rearrangements (ie, gene fusions) have recently been identified (such as ROS1, RET) that are susceptible to targeted therapies.<sup>93-96</sup>

Testing for sensitizing EGFR mutations and ALK gene rearrangements is recommended (category 1) in the NCCN Guidelines for NSCLC for select patients (eg, those with adenocarcinoma) so that patients with these genetic abnormalities can receive effective treatment (eg, erlotinib, afatinib, crizotinib, and ceritinib) (see *Targeted therapies* in this

Discussion).<sup>97</sup> Although rare, patients with EGFR mutations or ALK gene rearrangements can have mixed squamous cell histology.<sup>98,99</sup> Therefore, it is reasonable to test for EGFR mutations or ALK rearrangements in squamous cell histology if patients are never smokers, small biopsy specimens were used for testing, or mixed histology was reported.

Patients with NSCLC may have other genetic alterations (see *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>53,100,101</sup> 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 (<http://www.mycancergenome.org/content/disease/lung-cancer>).<sup>102</sup>

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.<sup>103-105</sup> Other driver mutations and gene rearrangements (ie, driver events) are being identified such as HER2 (also known as ERBB2) and BRAF mutations, ROS1 and RET gene rearrangements, and MET amplification.<sup>94,96,106-112</sup> Targeted agents are available for patients with NSCLC who have these genetic alterations, although they are FDA approved for other indications (see *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>103,113</sup> Thus, the NCCN Guidelines recommend testing for genetic alterations using multiplex/NGS to ensure that patients receive the most appropriate treatment; patients may be eligible for clinical trials for some of these



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

targeted agents. Several online resources are available that describe NSCLC driver events such as DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment)<sup>114</sup> and *My Cancer Genome* (<http://www.mycancergenome.org/content/disease/lung-cancer>).<sup>115</sup> 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).<sup>116</sup> KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.<sup>90,117,118</sup>

### 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 Agents* in this Discussion).<sup>119</sup> Thus, these mutations are referred to as sensitizing EGFR mutations. Erlotinib is commonly used in the United States in select 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 including EGFR and HER2.<sup>120,121</sup> The FDA recently approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.<sup>122,123</sup>

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.<sup>124</sup> Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).<sup>125</sup> Primary resistance to TKI therapy is

associated with KRAS mutations and ALK gene rearrangements. 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.<sup>126-129</sup> However, studies suggest the T790M mutation may also occur in patients who have not previously received TKI therapy.<sup>130</sup> 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).<sup>131,132</sup>

DNA mutational analysis is the preferred method to assess for EGFR status.<sup>133-135</sup> 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.<sup>124,134,136-138</sup> Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY system, SNaPshot Multiplex System) can detect more than 50 point mutations, including EGFR.<sup>102</sup> NGS can also be used to detect EGFR.<sup>104</sup>

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.<sup>119</sup> 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 an EGFR mutation.<sup>90</sup> A prospective study has shown that the objective response rate in North American patients with non-squamous NSCLC and EGFR mutations (53% Exon19del [LREA deletion], 26% L858R, 21% other mutations) is 55% with a median PFS of 9.2 months.<sup>91</sup> EGFR mutation testing is not usually recommended in patients with pure squamous cell carcinoma,





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

unless they are never smokers, if only a small biopsy specimen (ie, not a surgical resection) was used to assess histology, or if the histology is mixed.<sup>98</sup> Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.<sup>98</sup>

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 EGFR mutations documented before first-line therapy.<sup>123,139-144</sup> Data show that PFS is improved with use of EGFR TKI in patients with EGFR mutations when compared with standard chemotherapy, although overall survival is not statistically different.<sup>123,139</sup> Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.<sup>139,145</sup> In a recent phase III randomized trial, patients receiving afatinib had decreased cough, decreased dyspnea, and improved health-related quality of life when compared with those receiving cisplatin/pemetrexed.<sup>145</sup> However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.<sup>123</sup>

### ALK Gene Rearrangements

Estimates are that 2% to 7% of patients with NSCLC have ALK gene rearrangements, about 10,000 patients in the United States.<sup>58</sup> 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.<sup>101</sup> In these selected populations, estimates are that about 30% of patients will have ALK rearrangements.<sup>101,146</sup> ALK rearrangements are not routinely found in squamous cell carcinoma. Although rare, patients with ALK gene

rearrangements can have mixed squamous cell histology.<sup>99</sup> 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 are never smokers. 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.<sup>97,147-150</sup> NGS can also be used to assess whether ALK rearrangements are present.<sup>151,152</sup>

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) ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/202570s011lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202570s011lbl.pdf)).<sup>153-155</sup> Recently, crizotinib has been shown to yield very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements.<sup>58,156,157</sup> Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).<sup>156,158</sup> However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.<sup>153</sup> Patients have responded rapidly to crizotinib with improvement in symptoms (eg, cough, dyspnea, pain), although median time to progression on crizotinib is less than 1 year.<sup>159,160</sup> Randomized phase III trials are comparing crizotinib with standard second-line chemotherapy (PROFILE-1007) and with standard first-line therapy (PROFILE 1014).<sup>3,161</sup> Second-line therapy with crizotinib improved PFS and



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

response rate when compared with single-agent therapy (either docetaxel or pemetrexed).<sup>162</sup>

Newer ALK inhibitors are in development.<sup>163-169</sup> For example, 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.<sup>163</sup> 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

([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/205755s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/205755s000lbl.pdf)). In an interim 2014 update, the NCCN Panel now 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.<sup>163</sup>

EGFR sensitizing mutations and ALK rearrangements are generally mutually exclusive.<sup>170,171</sup> Thus, erlotinib (or gefitinib) or afatinib is not recommended as second-line therapy in patients with ALK rearrangements who relapse on crizotinib (see *Second-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>100,101</sup> Likewise, crizotinib or ceritinib is not recommended for patients with EGFR sensitizing mutations who relapse on erlotinib (or gefitinib) or afatinib. A new algorithm for second-line treatment for ALK-positive NSCLC was added for patients who progress on crizotinib (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>156,172,173</sup> In an interim 2014 update, this new algorithm for ALK-positive NSCLC was revised to include ceritinib (see *Second-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

### KRAS Mutations

Data suggest that approximately 25% of adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation.<sup>56,90,103,113,118</sup> KRAS mutation prevalence is associated with cigarette smoking.<sup>174</sup> In its mutated form, KRAS is constitutively active, able to transform immortalized cells, and able to promote cell proliferation and survival. KRAS mutational status is prognostic of survival. Patients with KRAS mutations appear to have a shorter survival than patients with wild-type KRAS.<sup>116,118,175</sup> KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.<sup>56,90,117</sup> EGFR and KRAS mutations appear to be mutually exclusive.<sup>176</sup> Targeted therapy is not currently available for patients with KRAS mutations, although MEK inhibitors are in clinical trials.<sup>113,177</sup>

### Treatment Approaches

Surgery, radiation therapy (RT), and chemotherapy are the 3 modalities commonly used to treat patients with NSCLC. They can be used either alone or in combination depending on the disease status. In the following sections, the clinical trials are described that have led to the standard treatments.

### Surgery

In general, for patients with stage I or II disease, surgery provides the best chance for cure.<sup>178</sup> 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





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

invasive surgery.<sup>178,179</sup> Patients with medically inoperable disease may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT). If SABR is considered for patients at high risk, a multidisciplinary evaluation is recommended.<sup>180</sup>

The *Principles of Surgical Therapy* are described in the 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).<sup>181</sup> 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.<sup>178,182,183</sup> Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the algorithm (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>184,185</sup> Resection (including wedge resection) is preferred over ablation.<sup>178,183</sup> Wide wedge resection may improve outcomes.<sup>186</sup> However, it is controversial whether lung-sparing surgeries, such as segmentectomy and wedge resection, are useful in

patients with severely reduced pulmonary function who are otherwise not candidates for surgery.<sup>178,183,187,188</sup> SABR may be more appropriate for these patients (see *Stereotactic Ablative Radiotherapy* in this Discussion).<sup>189</sup>

### **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.<sup>190-192</sup> 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.<sup>190</sup> 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.<sup>193</sup> 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

nodule 2 cm or less with very low-risk features. Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins that are: 1) 2 cm or more; or 2) the size of the nodule or more.

### **Stage IIIA N2 Disease**

The role of surgery in patients with pathologically documented stage IIIA (N2) disease is discussed in the 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).<sup>194,195</sup>

Randomized controlled trials suggest that surgery does not increase survival in these patients.<sup>196,197</sup> However, one of these trials (EORTC) only enrolled unresectable disease.<sup>197</sup> 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.<sup>198</sup> 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.<sup>199</sup> 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.<sup>200</sup> 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).<sup>194,201</sup> However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.<sup>196,201-207</sup> Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.<sup>201,208</sup>

### **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).<sup>209,210</sup> Published studies suggest that thorascopic lobectomy has several advantages over the standard thoracotomy (or pleurotomy).<sup>211-215</sup> Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.<sup>216,217</sup> Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.<sup>218-222</sup> Thorascopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.<sup>223-226</sup>

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.<sup>227-230</sup> Thorascopic lobectomy has also been shown to improve discharge independence in older populations and in patients at high risk.<sup>231,232</sup> Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.<sup>233,234</sup> Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy is recommended in the algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

standard principles of thoracic surgery are not compromised (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>235-238</sup> Robotic VATS seems to be more expensive with longer operating times than conventional VATS.<sup>239</sup>

### Radiation Therapy

#### General Principles

RT can be used as follows: 1) adjuvant therapy for patients with resectable NSCLC who have no contraindications for surgery; 2) the primary local treatment (ie, definitive RT or SABR for patients with medically inoperable or unresectable NSCLC); and/or 3) palliative therapy for patients with incurable NSCLC.<sup>180,240</sup> Treatment recommendations should be made by a multidisciplinary team. The goals of RT are to maximize tumor control and to minimize treatment toxicity. Advanced technologies such as 4D-conformal RT simulation, intensity-modulated radiotherapy/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.<sup>241-245</sup> CT-planned 3D-conformal RT is now considered to be the minimum standard.

The NCCN NSCLC algorithm contains the *Principles of RT*, which includes 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) radiation simulation, planning, and delivery.<sup>246-251</sup> 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 NCCN NSCLC algorithm (see Table 1 in *Principles of RT*). The American College of Radiology (ACR) Appropriateness

Criteria® may be useful (<http://www.acr.org/quality-safety/appropriateness-criteria>).

Definitive RT or SABR is recommended for patients with early-stage NSCLC (ie, stage I-II, N0) who are medically inoperable and those who refuse surgery (see *SABR* in this Discussion).<sup>180,240,252,253</sup> Adjuvant chemotherapy (category 2B) is an option after definitive RT or SABR in patients with high-risk factors (eg, poorly differentiated tumors). SABR is also an option for patients at high surgical risk who cannot tolerate a lobectomy (eg, age 75 years or older, poor lung function). However, resection is recommended for medically fit patients with early-stage NSCLC (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>254</sup> Definitive chemoradiation is recommended for patients with locally advanced (ie, stage II–III) disease who are medically inoperable.<sup>255</sup> For patients with advanced lung cancer (ie, stage IV) with extensive metastases, palliative RT can be used for primary or distant sites.<sup>240,256-258</sup> The RT recommendations for stages I to IV are described in the *Principles of RT* in the NCCN NSCLC algorithm.

The indications for using preoperative or postoperative chemoradiation or RT alone are described in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). For example, 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).<sup>248,259</sup> However, some suggest that preoperative chemotherapy alone is sufficient in patients with stage IIIA NSCLC;<sup>200</sup> this is also an option in the NCCN NSCLC algorithm, although definitive concurrent chemoradiation is category 1. NCCN Member Institutions are evenly split in their use of neoadjuvant chemotherapy



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.<sup>194</sup>

To avoid postoperative pulmonary toxicity, some clinicians feel that preoperative chemoradiotherapy should be avoided if pneumonectomy would be required; however, this is a controversial issue (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>194,196,206,260,261</sup> Surgery is difficult in a field that has had 60 Gy, because the landmarks disappear with high doses of radiation. Thus, surgeons are often wary of resection in areas that have previously received RT doses of more than 45 Gy, especially in patients who have received RT doses of more than 60 Gy (ie, patients who have received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. Soft tissue flap coverage can be considered in these patients.<sup>262,263</sup> RT should continue to definitive dose without interruption if the patient is not a surgical candidate.

### **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 RT* in the NCCN NSCLC algorithm (see Table 4).<sup>247,249,264-268</sup> After surgery, lung tolerance to RT is much less than for patients with intact lungs. Thus, every effort should be made to minimize the [postoperative] dose of RT. Although the dose volume constraints for normal lungs are a useful guide (see Table 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.<sup>269</sup> The use of higher RT doses is discussed in the *Principles of RT* in the NCCN NSCLC algorithm.<sup>270-275</sup> Results from a phase III randomized trial (RTOG 0617) show that

high-dose radiation (74 Gy) with concurrent chemotherapy does not improve survival when compared with standard-dose RT (60 Gy).<sup>275-278</sup>

For treatment volume consideration for 3D-conformal RT, planning target volume should be defined using the ICRU-50 and ICRU-62 (International Commission on Radiation Units and Measurements Reports 50 and 62) reports, based on gross tumor volume (GTV), plus clinical target volume margins for microscopic diseases, internal target volume margins for target motion, and margins for daily set-up errors (see Figure 1).<sup>279,280</sup> ICRU Report 83 is used for IMRT; the ACR-ASTRO guidelines are also useful

(<http://www.acr.org/~media/ACR/Documents/PGTS/guidelines/IMRT.pdf>).<sup>241,281,282</sup>

Additional volume considerations are described in the algorithm (see *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer). It is essential to evaluate the dose volume histogram (DVH) of critical structures and to limit the doses to the spinal cord, lungs, heart, esophagus, and brachial plexus to minimize normal tissue toxicity (see Table 5 in *Principles of Radiation Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>283</sup> These limits are mainly empirical.<sup>284-291</sup> 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 diseases. PET/CT is recommended for select patients (ie, those with significant atelectasis, when IV contrast is contraindicated). PET/CT can significantly improve the target accuracy.<sup>292</sup> In the *Principles of RT* of the NCCN NSCLC algorithm, recommendations are provided for patients receiving chemoradiation





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

(including those with compromised lung or cardiac function), photon beams, or IMRT (see *Simulation, Planning, and Delivery*).<sup>244,293-297</sup> Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the AAPM Task Group 76 guideline, are described in the *Principles of RT* of the NCCN NSCLC algorithm (see *Simulation, Planning, and Delivery* in the NCCN Guidelines for Non-Small Cell Lung Cancer)).<sup>298</sup>

### **Stereotactic Ablative Radiotherapy**

SABR (also known as SBRT) uses short courses of very high-dose RT that are precisely delivered to the target.<sup>299-301</sup> Studies have shown that SABR is very useful for patients with inoperable stage I NSCLC or for those who refuse surgery.<sup>180,302-304</sup> With conventional treatment, 3-year survival is only about 20% to 35% in these patients.<sup>253</sup> There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SABR.<sup>178,305,306</sup> Disease recurrence is infrequent after SABR.<sup>307</sup> In patients with stage I NSCLC, SABR provides a significantly longer survival than 3-D conformal RT.<sup>254,297,308</sup> SABR yields a median survival of 32 months and a 3-year overall survival of about 43% in patients with stage I disease; patients with T1 tumors survive longer than those with T2 tumors (39 vs. 25 months).<sup>309</sup> Thus, SABR is recommended in the NCCN Guidelines for patients with medically inoperable stage I and II NSCLC if they are node negative.<sup>178,304</sup>

SABR can also be used for patients with limited lung metastases and for palliative therapy.<sup>310,311</sup> Studies also suggest that SABR can be used for bone, liver, and brain metastases.<sup>299,304</sup> A recent study reported that SABR increased survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment.<sup>312</sup> SABR is discussed in the *Principles of RT* of the NCCN NSCLC algorithm; fractionation regimens and normal tissue constraints are also

provided (see Tables 2 and 3).<sup>303,309,313-319</sup> 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.<sup>320</sup> Although some suggest that SABR is more effective than RFA, they have not been compared in a randomized trial.<sup>178,180,308</sup>

### **Radiofrequency Ablation**

Data suggest that RFA may be an option for node-negative patients who either refuse surgery or cannot tolerate surgery because of poor PS, significant cardiovascular risk, poor pulmonary function, and/or comorbidities.<sup>180</sup> Optimal candidates for RFA include patients with an isolated peripheral lesion less than 3 cm; RFA can be used for previously irradiated tissue and for palliation.<sup>178,308,321</sup> RFA is not recommended for tumors near major pulmonary vessels.<sup>178,308</sup> A study with RFA in 33 patients with NSCLC yielded overall survival of 70% (95% CI, 51%–83%) at 1 year and 48% (95% CI, 30%–65%) at 2 years. A 2-year overall survival of 75% (95% CI, 45%–92%) was reported in patients with stage I NSCLC (n=13) who received RFA.<sup>322</sup> The procedure-specific 30-day mortality rate is reported to be 2.6%.<sup>323</sup> SABR and RFA are more effective than conventional RT for patients with medically inoperable disease.<sup>308</sup> Although there are more data to support the use of SABR, RFA may be a reasonable option in select patients as it only involves one treatment.<sup>178</sup>

### **Whole Brain RT and Stereotactic Radiosurgery**

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.<sup>324</sup> Surgery followed by whole brain RT is recommended (category 1) for select patients (those with good PS) with a single brain metastasis (see the NCCN Guidelines for Non-Small Cell Lung Cancer and Central Nervous System Cancers).<sup>325-328</sup> SRS is another option after surgical resection, although



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

there are only a few retrospective case series supporting this option.<sup>325</sup> Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with (or without) whole brain RT.<sup>324,329-331</sup> Data suggest that erlotinib may be useful to manage brain metastases.<sup>332-334</sup> 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.<sup>325,335-337</sup> Treatment should be individualized for patients with recurrent or progressive brain lesions.<sup>338</sup>

Some oncologists have been concerned that whole brain RT adversely affects neurocognition.<sup>339</sup> However, a study of 208 patients with brain metastases found that patients who responded (with tumor shrinkage) after whole brain radiation had improved neurocognitive function and that tumor progression affects neurocognition more than whole brain RT.<sup>340</sup> In 132 patients with 1 to 4 brain metastases who received SRS with (or without) whole brain RT, survival was similar in both groups.<sup>330</sup> In a subset of 92 of these patients who received SRS with (or without) whole brain RT, controlling the brain tumor with combined therapy was more important for stabilizing neurocognitive function.<sup>341</sup> However, a study in 58 patients found that patients who received SRS plus whole brain RT had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SRS alone.<sup>342</sup> Some have suggested that using resection with SRS (instead of resection with whole brain RT) will decrease neurocognitive problems.<sup>343,344</sup>

### Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or II disease who are medically fit and can tolerate surgery. However, SABR can be considered for patients with

unresectable stage I or II disease or those who refuse surgery if their disease is node negative (see *Stereotactic Ablative Radiotherapy* in this Discussion and see the NCCN Guidelines for Non-Small Cell Lung Cancer). In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.<sup>345-347</sup> 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).<sup>194,348-355</sup> However, a recent randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.<sup>356</sup> Neoadjuvant chemotherapy is also referred to as induction chemotherapy or preoperative chemotherapy. Concurrent chemoradiation is superior to sequential therapy for patients with unresectable stage III disease.<sup>357-360</sup>

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.<sup>361-366</sup> 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.<sup>367</sup> Patients should receive treatment for debilitating symptoms.<sup>5,368,369</sup> A recent study also suggests that social support, such as being married, is as effective as chemotherapy.<sup>370</sup> Surgery is rarely done for patients with stage IV disease. However, surgical resection of a solitary brain metastasis may improve survival in selected patients with stage IV disease and is recommended in the NCCN NSCLC algorithm (see also the NCCN Guidelines for Central Nervous System Cancers).<sup>371</sup> 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





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

settings (see *Stage IV, M1b: Solitary Site/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>181,304</sup> The trials supporting the recommendations for combined modality therapy are discussed in the following sections.

### ***Surgery Followed by Chemotherapy: Trial Data***

In the NCCN 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 NSCLC algorithm.

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.<sup>345</sup> 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.<sup>372</sup> Data show that adjuvant chemotherapy prevents recurrences.

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.<sup>346</sup> 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 stage II but not for stage IB patients.<sup>373</sup> In stage II patients receiving adjuvant chemotherapy, median survival is 6.8 versus 3.6 years in those who were only observed. Of note, patients receiving chemotherapy did not have an increased death rate.

In the 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.<sup>347</sup> 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.<sup>347</sup> 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.<sup>374</sup>

A meta-analysis of 4,584 patients (LACE) found that postoperative cisplatin-based chemotherapy increased survival over 5 years (absolute



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

benefit of 5.4%); there was no difference among the chemotherapy regimens (vinorelbine, etoposide, and others).<sup>375</sup> A subgroup analysis found that cisplatin/vinorelbine also increased survival.<sup>374</sup> 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.<sup>376</sup>

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;<sup>377</sup> updated results have been reported.<sup>378,379</sup> In this trial, 344 patients were randomly assigned either to paclitaxel and 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%,  $P = .02$ ).<sup>378,379</sup> The original results from CALGB suggested that the paclitaxel and carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors 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).<sup>380</sup> However, it is important to note that the CALGB trial was underpowered for patients with stage 1B disease.<sup>381</sup>

### **Neoadjuvant Chemotherapy Followed by Surgery: Trial Data**

Data from adjuvant clinical trials in patients with resected NSCLCs indicate that delivery of chemotherapy is an important problem. In the postoperative setting, significant comorbidities and incomplete recovery after surgery often make it difficult for patients to tolerate therapy. This problem was demonstrated in the NATCH phase III 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.<sup>353</sup> 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.<sup>356</sup> Postoperative chemotherapy is considered the standard of care for early-stage disease.<sup>178</sup>

Several trials suggest that neoadjuvant therapy is beneficial in patients with N2 disease.<sup>194,200,352</sup> Other trials suggest that neoadjuvant therapy is beneficial in patients with earlier stage disease.<sup>349,350,355</sup> 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.<sup>355</sup>

Scagliotti et al published a phase III 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).<sup>349</sup> 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

arm (HR, 0.84; 95% CI, 0.77–0.92;  $P = .0001$ ).<sup>348</sup> These results are similar to those recently reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98;  $P = .02$ ).<sup>349</sup> The benefit from neoadjuvant chemotherapy is similar to that attained with postoperative chemotherapy.<sup>349,356,375</sup>

### **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.<sup>382–386</sup> For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.<sup>382,383,385,386</sup> Concurrent chemoradiation is superior to sequential therapy.<sup>357–360</sup> However, concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. Patient selection affects not only the response to therapy but also how well the patient tolerates therapy.

Concurrent chemoradiation regimens that may be used for all histologies for initial treatment include cisplatin/etoposide (preferred) or cisplatin/vinblastine (preferred) (see *Chemotherapy Regimens Used with RT* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>357,359,387,388</sup> For non-squamous NSCLC, other concurrent chemoradiation regimens include carboplatin/pemetrexed and cisplatin/pemetrexed.<sup>389,390</sup> A randomized controlled trial in 203 unresectable patients with either stage IIIA or IIIB NSCLC assessed induction chemotherapy followed by either radiotherapy alone or chemoradiation using paclitaxel; median survival was 14.1 versus 18.7 months ( $P = .091$ ), respectively.<sup>391</sup>

### **Chemotherapy: Trial Data**

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.<sup>363,365,392</sup> 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.<sup>380,393–396</sup> 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.<sup>397,398</sup> Gemcitabine/cisplatin is used for patients with squamous cell carcinoma.<sup>396–399</sup> These regimens are commonly used based on phase III randomized trials (ie, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).<sup>396,400</sup>

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).<sup>396,401,402</sup> 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.<sup>402,403</sup> 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.<sup>402</sup> A retrospective cohort study suggests that



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

the addition of bevacizumab (to carboplatin/paclitaxel) does not increase survival in older patients (65 years or older) with advanced non-squamous NSCLC.<sup>404</sup> 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.<sup>405</sup> Single-agent chemotherapy includes vinorelbine, gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.<sup>406-408</sup> However, patients with a PS of 2 are often just treated with one chemotherapy agent because of concerns about toxicity.<sup>409</sup> 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.<sup>406,410</sup>

Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.<sup>411,412</sup> The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.<sup>399,413,414</sup> Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;<sup>393,415-417</sup> non-platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.<sup>418-421</sup> In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor.

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel for patients 1) who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication; or 2) in whom the standard premedications (ie, dexamethasone, H2

blockers, H1 blockers) to prevent hypersensitivity are contraindicated.<sup>422,423</sup> A recent phase III 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.<sup>424</sup> 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 ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021660s03/8lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021660s03/8lbl.pdf)). 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 *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>425,426</sup> 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. Cetuximab is a monoclonal antibody that targets EGFR.

### Bevacizumab

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic non-squamous NSCLC. ECOG recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced non-squamous NSCLC based on the results of phase II to III clinical trials (ECOG 4599).<sup>400</sup> To receive treatment with bevacizumab and chemotherapy, patients must





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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 and PS 0 to 1 who are negative for either EGFR mutations or ALK gene rearrangements, bevacizumab in combination with chemotherapy is one of the recommended options (see *Adenocarcinoma, Large Cell, NSCLC NOS: EGFR Mutation and ALK Negative/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 failure of at least one prior chemotherapy regimen. Erlotinib is also recommended (category 1) 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 *Adenocarcinoma, Large Cell, NSCLC NOS: EGFR Mutation or ALK Positive* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>56,427-429</sup> This recommendation is based on the results of a phase III randomized trial (IPASS) in which patients with 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).<sup>428</sup> Updated results from the IPASS study show that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of EGFR mutation status.<sup>430</sup> 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 EGFR mutations. TKIs are recommended in patients with 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 EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.<sup>431</sup> The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced non-squamous NSCLC.<sup>432</sup> Survival was increased in patients with wild-type EGFR who received first-line chemotherapy compared with those who received erlotinib first followed by second-line chemotherapy (11.6 vs. 8.7 months). The OPTIMAL trial found that PFS was increased in patients with EGFR mutations who received erlotinib.<sup>142,143</sup> ASCO recommends that patients be tested for EGFR mutations.<sup>433</sup> However, the NCCN and ESMO Guidelines specify that only patients with non-squamous NSCLC (eg, adenocarcinoma) be assessed for sensitizing EGFR mutations.<sup>405</sup> Patients with pure squamous cell carcinoma are unlikely to have EGFR mutations; however, those with adenosquamous carcinoma may have mutations.<sup>98</sup>

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.<sup>434,435</sup> The data showed that erlotinib alone was associated with fewer side effects in patients with EGFR mutations when compared with erlotinib/chemotherapy. Thus, it is appropriate to switch to erlotinib therapy in patients found to have 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 plus chemotherapy as a category 2B recommendation.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

### *Afatinib*

A recent randomized phase III 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,  $P = .001$ ).<sup>123</sup> The FDA recently approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.<sup>122,436</sup> Based on this phase III 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).<sup>120,123,173</sup> Afatinib is also recommended for second-line therapy based on data showing efficacy in patients who have progressed after first-line chemotherapy (see *Second-Line and Third-Line Systemic Therapy* in this Discussion).<sup>119</sup>

### *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 II trial that showed dramatic response rates (>80%) to crizotinib in patients who had previously progressed.<sup>153,154</sup> Patients receiving crizotinib reported clinically significant improvements in pain, dyspnea, and cough. Recently, crizotinib was shown to be effective as second-line therapy when compared with chemotherapy for patients with ALK rearrangements.<sup>162</sup>

### *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.<sup>163</sup> Some patients with CNS lesions responded to ceritinib.

### *Cetuximab*

A large phase III randomized trial (FLEX) assessed cisplatin/vinorelbine with (or without) cetuximab for patients with advanced NSCLC (most patients had stage IV disease).<sup>437</sup> Adding cetuximab slightly increased overall survival (11.3 vs. 10.1 months,  $P = .04$ ).

Cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC without EGFR mutations or ALK rearrangements, regardless of histology (see *First-Line Therapy for Adenocarcinoma or Squamous Cell Carcinoma* in the NCCN Guidelines for Non-Small Cell Lung Cancer). However, the cetuximab/cisplatin/vinorelbine regimen has a category 2B recommendation in the NCCN Guidelines because the benefits are very slight, it is a difficult regimen to administer, and patients have poorer tolerance for this regimen when compared with other regimens (eg, almost 40% of patients have grade 4 neutropenia). Patients may also have comorbid conditions that prevent them from receiving cisplatin (eg, poor kidney function). Some clinicians feel that although the FLEX trial results were statistically significant they were not clinically significant.

### **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.<sup>438</sup> However, patients are only candidates for maintenance therapy if they have responded to their previous treatment (ie, tumor response) or have stable disease and their tumors have not progressed. *Continuation maintenance* therapy refers to the use of at least one of the agents that was given in the first-line regimen. *Switch maintenance* 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





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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).<sup>439</sup>

### *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 EGFR mutations or ALK rearrangements.<sup>400,440,441</sup> Single-agent pemetrexed (category 1) may also be given as continuation maintenance therapy in patients with non-squamous NSCLC (who are negative for EGFR mutations or ALK rearrangements).<sup>440,442</sup> A recent phase III randomized trial (PARAMOUNT) found that continuation maintenance therapy with pemetrexed slightly increased PFS when compared with placebo (4.1 vs. 2.8 months).<sup>442,443</sup> Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).<sup>444,445</sup> 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 EGFR mutations or ALK rearrangements. Single-agent cetuximab (category 1) may be continued beyond 4 to 6 cycles of initial therapy (ie, cisplatin, vinorelbine, and cetuximab therapy) in patients with non-squamous NSCLC (who are negative for EGFR mutations or ALK rearrangements) or those with squamous histology.<sup>437</sup>

Continuation maintenance therapy using bevacizumab/pemetrexed is also an option in patients with non-squamous NSCLC (who are negative for EGFR mutations or ALK rearrangements); 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.<sup>402,403</sup> 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.<sup>446,447</sup>

A recent phase III randomized trial compared using maintenance therapy with either gemcitabine or erlotinib after first-line therapy with cisplatin-gemcitabine. Data show that continuation maintenance therapy with 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).<sup>448,449</sup> Another phase III randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.<sup>450</sup> 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 EGFR mutations or ALK rearrangements.

Use of continuation maintenance therapy depends on several factors such as whether the patient had minimal toxicity during treatment. A



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

drug vacation may be more appropriate for some patients.<sup>401</sup> 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.<sup>401,451</sup> In addition, maintenance therapy has not been shown to be superior to second-line therapy, which is initiated at disease progression. Data from a phase III 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).<sup>451,452</sup>

### *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.<sup>401,453</sup> Therefore, switch maintenance therapy is a category 2B recommendation in the NCCN Guidelines. Two phase III 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.<sup>454,455</sup> Switch maintenance therapy with pemetrexed may be initiated in patients with histologies other than squamous cell carcinoma who are negative for EGFR mutations or ALK rearrangements.<sup>455</sup> The FDA has approved maintenance therapy with pemetrexed ([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2013/021462s04/5lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021462s04/5lbl.pdf)).<sup>456</sup> Likewise, switch maintenance therapy with erlotinib may be initiated in patients 1) without EGFR mutations or gene rearrangements; or 2) with squamous cell carcinoma.<sup>449,454</sup> Both erlotinib and pemetrexed have a category 2B recommendation for switch maintenance therapy in the NCCN NSCLC algorithm, although pemetrexed is not recommended for squamous cell carcinoma. The FDA has approved maintenance

therapy with erlotinib

([http://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021743s01/9lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021743s01/9lbl.pdf)).<sup>457</sup>

A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.<sup>458</sup> 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 NCCN algorithm (see *Diagnostic Evaluation of Lung Nodules* in this Discussion and see *Principles of Diagnostic Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).

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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

provided to patients (<http://www.smokefree.gov/expert.aspx>). Based on the initial evaluation, the clinical stage is determined and the patient is assigned to one of the pathways that are defined by the stage, specific subdivision of the particular stage, and location of the tumor.

### Additional Pretreatment Evaluation

#### ***Mediastinoscopy***

As previously noted, evaluation of the mediastinal nodes is a key step in the further staging of the patient. Although PET/CT scans can be used as an initial assessment of the hilar and mediastinal nodes (ie, the presence of N1, N2, or N3, which are key determinants of stage II and stage III disease), CT scans have known limitations for evaluating the extent of lymph node involvement in lung cancer (see *Mediastinoscopy* and *Other Imaging Studies* in this Discussion).<sup>459-462</sup> 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,<sup>463</sup> some NCCN Member Institutions do not use routine mediastinoscopy in these patients (category 2B). However, in patients with peripheral T2a, central T1ab, or T2 lesions with negative PET/CT scans, the risk for mediastinal lymph node involvement is higher and mediastinoscopy and/or endoscopic ultrasound–guided FNA (EUS-FNA) and EBUS–guided transbronchial needle aspiration (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.<sup>464</sup> 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.<sup>465</sup>

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.<sup>460</sup> PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN Panel reviewed the diagnostic performance of CT and PET scans. The NCCN Panel



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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.<sup>459,466,467</sup> However, PET/CT is even more sensitive and is recommended by NCCN.<sup>468–470</sup>

The NCCN Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.<sup>471</sup> Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.<sup>472</sup> 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.<sup>473</sup> 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%.<sup>474</sup> Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.<sup>475,476</sup> 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.<sup>477,478</sup>

When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.<sup>468</sup> 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.<sup>459,479</sup> 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.<sup>480–483</sup> 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.<sup>484</sup> In patients with positive

nodes on CT or PET, EBUS-TBNA can be used to clarify the results.<sup>485,486</sup> However, in patients with negative findings on EBUS-TBNA, conventional mediastinoscopy can be done to confirm the results.<sup>481,486–488</sup> 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.<sup>489</sup> For patients with stage IB NSCLC, brain MRI only has a category 2B recommendation because they are less likely to have brain metastases. 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 RT* recommends doses for RT (see the NCCN Guidelines for Non-Small Cell Lung Cancer). In addition, the NCCN NSCLC algorithm also recommends 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*).

### 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





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

dissection. 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 NSCLC algorithm 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 (ie, the superior sulcus, chest wall, proximal airway, or mediastinum). For each location, a thoracic surgeon needs to determine whether the tumor is resectable (see *Principles of Surgical Therapy* in the NCCN 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 the NCCN Guidelines for Non-Small Cell Lung Cancer). Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has shown 2-year survival in the 50% to 70% range.<sup>181,265,267,490–493</sup> The overall 5-year survival rate is approximately 40%.<sup>265</sup> 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.<sup>388,494</sup>

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.<sup>196,357</sup> 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).<sup>196,357,388</sup> For patients with stage IIIA disease and positive mediastinal nodes (T1–3, N2), treatment is based on the findings of pathologic mediastinal lymph node evaluation (see the NCCN Guidelines for Non-Small Cell Lung Cancer). Patients with negative mediastinal biopsy findings are candidates for surgery, with additional assessment of resectability at the time of thoracotomy. For those patients with resectable lesions, mediastinal lymph node dissection or lymph node sampling should be performed during the surgery. Those individuals who are medically inoperable should be treated according to pathologic 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).<sup>358</sup> Induction chemotherapy with (or without) RT is another option for patients with T1–3, N2 disease.<sup>197</sup> Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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).<sup>495</sup> Patients with separate pulmonary nodule(s) in the same lobe or ipsilateral non-primary lobe without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.<sup>496</sup> Intrapulmonary metastases have been downstaged in the TNM staging (ie, AJCC 7<sup>th</sup> edition).<sup>86,496,497</sup> 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. 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 guidelines 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).<sup>498</sup>

### Multiple Lung Cancers

Multiple lung cancers may be suspected or detected in various ways. 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).<sup>499,500</sup> 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.<sup>48,181,501,502</sup> 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).<sup>503,504</sup> Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.<sup>504-507</sup> 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.<sup>507</sup>

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).<sup>501,508-510</sup> In patients who are eligible for definitive local therapy, parenchymal-sparing resection is preferred (see the *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>500,501</sup> VATS or SABR may be useful in select patients.<sup>511</sup>

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).<sup>512</sup> The Fleischner Society has recommendations for patients with solid nodules and has recently developed recommendations for those with subsolid nodules.<sup>513,514</sup> *Subsolid* nodules include pure ground glass nodules and part-solid ground glass nodules.<sup>513</sup> Ground glass nodules are also known as nonsolid nodules or ground glass opacities.<sup>515</sup> Solid nodules are more





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

likely to be malignant than part-solid nodules, but ground glass nodules are the least malignant, which is reflected in the NCCN Guidelines for Lung Cancer Screening.<sup>514,516</sup>

### Stage IIIB Disease

Stage IIIB tumors comprise 2 groups, including: 1) T1–3, N3 tumors; and 2) T4 extension and 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 guidelines recommend pathologic confirmation of nodal status (see *Pretreatment Evaluation* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>517,518</sup> 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.<sup>196,357,388,519,520</sup> For metastatic disease that is confirmed by PET/CT scan and brain MRI, treatment is described in the NCCN NSCLC algorithm.

For patients with T4 extension, N2–3 disease (stage IIIB), surgical resection is not generally recommended. The initial 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).<sup>196,357,388,519-521</sup>

### Stage IV Disease

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).<sup>86</sup> 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 unresectable disease in 95% of cases.<sup>522</sup> 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).<sup>523</sup>

The NCCN NSCLC algorithm for patients with distant metastasis in a solitary site (ie, stage IV, M1b) depends on the location of the metastasis—a solitary nodule 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,



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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 a solitary brain metastasis may benefit from surgical resection (see *Whole Brain RT and Stereotactic Radiosurgery* in this Discussion, and the NCCN Guidelines for Central Nervous System Cancers and for Non-Small Cell Lung Cancer).<sup>181,324,325</sup> The 5-year survival rates with such an approach range from 10% to 20%;<sup>524</sup> median survival is about 40 weeks.<sup>328</sup> Follow-up whole brain RT (category 1) or SRS may be used.<sup>326,340,525</sup> SRS alone or followed by whole brain radiation are additional treatment options.<sup>329,330</sup> Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.<sup>526</sup> After their brain or adrenal lesions are treated, further treatment options for these patients—with T1–2, N0–1 NSCLC or for those with T3, N0—then include: 1) surgical resection of the lung lesion followed by chemotherapy; 2) SABR of the lung lesion; or 3) additional chemotherapy followed by surgical resection or SABR of the lung lesion. Systemic therapy is an option after surgery for patients with higher stage NSCLC. 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).<sup>527–529</sup> 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).<sup>379,530</sup> 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).<sup>248,379</sup>

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.<sup>375,531</sup> 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, N2 or T3, N1 disease (discovered only at surgical exploration and



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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). Patients with negative margins may be treated with either 1) chemotherapy (category 1); or 2) sequential chemotherapy plus RT (for N2 only).<sup>375</sup>

NCCN Panel Members do not recommend chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.<sup>247</sup> In this trial, no difference in survival rates was observed between stage II and stage IIIA patients who had a surgical resection and received either adjuvant radiotherapy alone (median survival = 39 months) or radiotherapy given with concurrent chemotherapy (median survival = 38 months).

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). In the case of possibly resectable superior sulcus tumors (T4 extension, N0–1), if the lesion converts to a resectable status following concurrent chemoradiation, resection followed by chemotherapy is recommended (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If the lesion does not convert (ie, it remains unresectable), the full course of definitive RT followed by chemotherapy is administered as an adjuvant treatment. Among patients with chest wall lesions with T3 invasion–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. 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 or ipsilateral non-primary lobe, surgery is recommended (see the NCCN Guidelines for Non-Small Cell Lung Cancer). If the margins are negative for N2 disease, sequential chemoradiation is recommended. If the resection margins are positive for N2 disease, concurrent chemoradiation is recommended for an R2 resection and sometimes for an R1 resection.

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

On the basis of clinical studies on neoadjuvant and adjuvant chemotherapy for NSCLC,<sup>345–347</sup> the NCCN Panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

combined with gemcitabine, pemetrexed, or docetaxel (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>380,393,396</sup> For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel is an option.<sup>380,532</sup> A recent phase III 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).<sup>533</sup> However, data are conflicting regarding whether bevacizumab benefits elderly patients.<sup>404,534</sup> A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.<sup>535-537</sup>

Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.<sup>352,538-540</sup> 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.<sup>539,540</sup> All 3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase III 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

NCCN Panel Members disagreed (category 2B) about using postoperative RT alone as adjuvant treatment for T1ab, N0 tumors with

positive margins based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).<sup>541</sup> This study showed that postoperative radiotherapy is detrimental to patients with early-stage, completely resected NSCLC and should not be given routinely to such patients. However, the NCCN Panel found several flaws in the meta-analysis, including:

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

An assessment of postoperative radiation in 7,465 patients with resected stage II or III NSCLC found that postoperative radiation increased survival in patients with N2 disease but not in those with N1 or N0 disease.<sup>259</sup> Therefore, guidelines from some cancer organizations recommend that postoperative RT should only be given to those with N2 disease.<sup>542</sup> The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.<sup>248</sup> Postoperative adjuvant sequential chemotherapy with RT is recommended for T1–3, N2 patients with 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.<sup>531</sup> In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemo/RT. Regimens included





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide. The ACR Appropriateness Criteria® provide specific recommendations for postoperative adjuvant therapy.<sup>543,544</sup>

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. Cisplatin/etoposide is the preferred concurrent neoadjuvant chemoradiation regimen recommended by the NCCN Panel.<sup>387</sup> 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.<sup>249,250,357,358,388-390</sup>

### Surveillance

The surveillance guidelines for patients with no clinical or radiographic evidence of disease are as follows (see 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; a non-contrast-enhanced chest CT is recommended annually thereafter.<sup>40,545-548</sup> 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 (<http://www.smokefree.gov/>). 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.<sup>44</sup> However, use of low-dose CT for surveillance is not

currently recommended by the NCCN Panel for patients who have been previously treated for lung cancer.

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.<sup>549</sup>

### 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 NSCLC algorithm (see *Therapy for Recurrence and Metastasis*).<sup>5</sup> 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.<sup>550</sup> After the treatment for the locoregional recurrence, observation or systemic chemotherapy (category 2B for chemotherapy) is recommended if disseminated disease is not evident. However, for observed disseminated disease, systemic therapy is recommended. The type of systemic therapy depends on the histologic type, whether any genetic alterations are present, and PS (see the NCCN Guidelines for Non-Small Cell Lung Cancer).

Management of distant metastases (eg, localized symptoms; bone, solitary, diffuse brain, or disseminated metastases) is described in the NCCN NSCLC algorithm (see *Therapy for Recurrence and Metastasis*).





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Palliation of symptoms can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis.<sup>264,551</sup> Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis.<sup>552-554</sup> 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).<sup>555</sup> Denosumab 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 in patients with bone metastases from solid tumors.<sup>556</sup>

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 *Histologic Subtype* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>396</sup> 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. A new section was recently added to the algorithm showing recommended therapy for patients with certain genetic alterations (see *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer). The following targeted agents are now recommended for patients with specific genetic alterations: afatinib, cabozantinib, ceritinib, crizotinib, dabrafenib, erlotinib, gefitinib, trastuzumab, and vemurafenib.<sup>53,58,93,94,103,108,111,112,121,123,427,557-561</sup>

EGFR mutation testing (category 1) is recommended in patients with non-squamous NSCLC (ie, adenocarcinoma, large cell carcinoma) or in

NSCLC not otherwise specified (NOS), because erlotinib or afatinib (category 1 for both) is recommended for patients who are positive for EGFR mutations (see *EGFR Mutation Positive/First-Line Therapy* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>56,119,141,428,562</sup> 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.<sup>97,563</sup> Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification (see *Targeted Agents for Patients with Genetic Alterations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>94,111,564</sup> Ceritinib is recommended for patients with ALK-positive metastatic NSCLC who have progressed on crizotinib or are intolerant to crizotinib.<sup>163</sup> 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.<sup>103-105</sup>

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.<sup>48</sup> Patients with pure squamous cell carcinoma do not seem to have EGFR mutations or ALK rearrangements; therefore, routine testing is not recommended in these patients.<sup>98,565-567</sup> However, testing for EGFR mutations and ALK rearrangements in squamous cell carcinomas can be considered in never smokers and those whose histology was determined using small biopsy specimens or mixed histology specimens.<sup>98</sup> Treatment recommendations and eligibility criteria for patients with non-squamous NSCLC (or NSCLC NOS) who are negative for EGFR mutations or ALK rearrangements are described in the NCCN NSCLC algorithm. Treatment recommendations and eligibility criteria for patients with squamous cell carcinoma are also



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

described in the NCCN NSCLC algorithm. 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 can also be added to the 2-drug regimen (eg, the addition of bevacizumab to carboplatin/paclitaxel). Single-agent targeted therapy may also be recommended for select patients with EGFR mutations, ALK rearrangements, or other driver mutations (see *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 EGFR mutations or ALK rearrangements 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.<sup>396</sup>

Bevacizumab/chemotherapy is another option for patients with non-squamous NSCLC who are negative for EGFR mutations or ALK rearrangements if eligibility criteria are met.<sup>568</sup> 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.<sup>569</sup> Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on histology, PS, and other factors (see *Trial Data* in this Discussion, *Systemic Therapy for Advanced or Metastatic Disease* in the NCCN Guidelines for Non-Small Cell Lung Cancer, and the NCCN Drugs &

Biologics Compendium [NCCN Compendium®]). NCCN Panel Members disagree (category 2B) about using cetuximab with cisplatin and vinorelbine, because data only show a slight improvement in survival with the addition of cetuximab (11.3 vs. 10.1 months,  $P = .04$ ), and this regimen is generally not used in the United States because of concerns about toxicity with cisplatin.<sup>361,437</sup>

Cisplatin/gemcitabine (category 1) is an option for patients with squamous cell carcinoma.<sup>396</sup> Carboplatin/paclitaxel, cisplatin/vinorelbine (category 1 for both), and other regimens listed in the 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). Another option is cetuximab with cisplatin and vinorelbine, although this is a category 2B recommendation.<sup>437</sup> 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.<sup>3,53,105,570,571</sup>

### Trial Data

In a phase II/III trial (ECOG 4599), 878 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.<sup>400,572</sup> 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.<sup>400</sup> 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.<sup>400</sup> However, more significant toxicities were observed with



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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 adenocarcinoma histology was associated with improved survival in patients receiving bevacizumab/paclitaxel/carboplatin compared with chemotherapy alone (14.2 vs. 10.3 months).<sup>568</sup> However, a trial (AVAiL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.<sup>573,574</sup>

A noninferiority trial in 1725 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine compared with cisplatin plus pemetrexed.<sup>396</sup> 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 plus pemetrexed, 9 patients [1.0%]; cisplatin plus 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, second-line, and maintenance therapy.<sup>575</sup>

In the FLEX trial, 1125 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) were randomly assigned to either 1) cetuximab in combination with vinorelbine and cisplatin; or 2) vinorelbine and cisplatin alone.<sup>437</sup> The response rate was increased with cetuximab (36% vs. 29%,  $P = .01$ ); there was no difference in PFS. Overall survival was slightly better in patients receiving cetuximab (11.3 vs. 10.1 months,  $P = .04$ ). However, 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. Treatment-related deaths were similar in both groups (3% vs. 2%).

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.<sup>380,393-396,415,416,424</sup> Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives because data show they are active and less toxic than platinum-based regimens.<sup>418-421,576</sup>

### 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; second-line 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.<sup>362,452,577</sup> Currently, the NCCN Guidelines do not recommend continuing chemotherapy beyond 4 to 6 cycles.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Recent data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;<sup>442</sup> 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.<sup>401</sup> 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.<sup>578</sup> A phase III 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.<sup>451,452</sup> In this phase III trial, taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.<sup>452</sup>

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.<sup>401</sup> 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 dropped out because of neurotoxicity.<sup>440,452</sup>

### 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 EGFR mutations or ALK rearrangements, continuation maintenance therapy regimens include bevacizumab (category 1), cetuximab

(category 1), pemetrexed (category 1), bevacizumab/pemetrexed, or gemcitabine (category 2B) (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>400,402,437,442,443,447-449</sup> Switch maintenance therapy regimens for these patients include pemetrexed or erlotinib (both are category 2B).<sup>448,449,454,455</sup> A phase III 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.<sup>455</sup> 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, cetuximab (category 1) or gemcitabine (category 2B) can be used as continuation maintenance therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>449,454</sup> Switch maintenance therapy for these patients includes erlotinib or docetaxel (category 2B for both). Close observation is another option. A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.<sup>458</sup> 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.<sup>579</sup>

### Continuation of Erlotinib, Gefitinib, or Afatinib After Progression

Erlotinib is commonly used in the United States in select patients with 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;





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).<sup>580</sup> 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.<sup>581</sup> Data support the continued use of erlotinib in patients with lung adenocarcinoma with *EGFR* mutations after development of acquired resistance to erlotinib. The NCCN Panel recommends continuing either erlotinib or afatinib in patients with asymptomatic progression; however, treatment varies for patients with symptomatic progression (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>558,582,583</sup> In most cases, erlotinib or afatinib is continued for these patients; however, additional therapy may be added (eg, whole brain RT, local therapy, systemic therapy).

Accumulating data suggest how cancers become resistant to EGFR inhibitors.<sup>584</sup> The most common known mechanism is the acquisition of a secondary mutation in EGFR—T790M—that renders the kinase resistant to erlotinib and gefitinib.<sup>585,586</sup> 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.<sup>580,587</sup> Thus, continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.

### Second-Line and Third-Line Systemic Therapy

Although many new active drugs are available for lung cancer, the reported response rates to second-line systemic therapy have generally been less than 10%. For all histologic subtypes, docetaxel, erlotinib, or gemcitabine are recommended if not already given as second-line systemic therapy regimens for patients with PS of 0 to 2 and who have experienced disease progression during or after first-line therapy (see the NCCN Guidelines for Non-Small Cell Lung Cancer).<sup>588-597</sup> For non-squamous NSCLC without sensitizing EGFR mutations, pemetrexed is recommended as second-line therapy. For non-squamous NSCLC with sensitizing EGFR mutations or ALK-positive disease, algorithms are provided for second-line therapy based on whether or not patients have symptoms.

Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life.<sup>594,595</sup> When compared with docetaxel, pemetrexed has similar median survival but less toxicity.<sup>596,598</sup> Pemetrexed is recommended in patients with adenocarcinoma or large cell carcinoma (ie, non-squamous NSCLC).<sup>455</sup> Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.<sup>597</sup> In patients with PS of 3 to 4 who have the EGFR mutation, erlotinib is recommended for second-line therapy for progressive disease (see the NCCN Guidelines for Non-Small Cell Lung Cancer). A platinum doublet with (or without) bevacizumab and/or with (or without) erlotinib is an option for patients with non-squamous NSCLC who have progressed with symptomatic systemic multiple lesions after therapy with erlotinib, afatinib, crizotinib, or ceritinib.<sup>400</sup> Afatinib is recommended as second-line therapy in patients with sensitizing EGFR mutations who have progressed after first-line therapy based on several studies.<sup>119,558,582,583</sup> Ceritinib is recommended as





## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

second-line therapy in patients with ALK-positive NSCLC who have progressed after first-line therapy with crizotinib or are intolerant to crizotinib.<sup>163</sup>

In a randomized, placebo-controlled, double-blind trial (NCIC CTG trial), 731 patients (stage IIIB or IV, PS 0–3) were randomly assigned (2:1) to receive either erlotinib or placebo, following failure of first- or second-line chemotherapy.<sup>597</sup> 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, adjusted for stratification categories;  $P < .001$ ). However, 5% of patients discontinued erlotinib because of toxic side effects. This trial confirms that erlotinib can prolong survival in patients after failure of first- or second-line systemic therapy. A randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel.<sup>599</sup> Pemetrexed (non-squamous only), docetaxel, gemcitabine, or erlotinib are recommended for third-line therapy in patients with advanced NSCLC if these agents have not already been given.<sup>589,600,601</sup> If disease progression occurs after third-line chemotherapy, patients with PS of 0 to 2 may be treated with best supportive care or be enrolled in a clinical trial (see the NCCN Guidelines for Palliative Care).<sup>5,368,369</sup> Patients often have a limited response to third-line chemotherapy, although it may serve a useful palliative role.<sup>602</sup>



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

### References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer Statistics, 2014. CA Cancer J Clin 2014;64:9-29. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24399786>.
2. Howlader N, Noone A, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2009 (Vintage 2009 Populations) based on November 2011 SEER data submission. Bethesda, MD: National Cancer Institute; 2012. Available at: [http://seer.cancer.gov/csr/1975\\_2009\\_pops09/](http://seer.cancer.gov/csr/1975_2009_pops09/).
3. 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>.
4. 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>.
5. 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>.
6. 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>.
7. Alberg AJ, Ford JG, Samet JM. Epidemiology of lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition). Chest 2007;132:29S-55S. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17873159>.
8. 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>.
9. 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.
10. 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>.
11. 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>.
12. 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>.
13. 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.
14. 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>.
15. Wald NJ, Nanchahal K, Thompson SG, Cuckle HS. Does breathing other people's tobacco smoke cause lung cancer? Br Med J (Clin Res Ed) 1986;293:1217-1222. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/3096439>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

16. 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>.

17. 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>.

18. 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>.

19. 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.

20. 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>.

21. 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>.

22. 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>.

23. 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>.

24. 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>.

25. 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>.

26. 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>.

27. 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>.

28. 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>.

29. 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>.

30. 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>.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

31. 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>.
32. 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>.
33. 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>.
34. 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>.
35. 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>.
36. 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>.
37. 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>.
38. 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>.
39. 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>.
40. 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>.
41. Henschke CI, Naidich DP, Yankelevitz DF, et al. Early Lung Cancer Action Project: initial findings on repeat screenings. *Cancer* 2001;92:153-159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11443621>.
42. Kaneko M, Kusumoto M, Kobayashi T, et al. Computed tomography screening for lung carcinoma in Japan. *Cancer* 2000;89:2485-2488. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11147632>.
43. The national lung screening trial: overview and study design. *Radiology* 2011;258:243-253. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21045183>.
44. Aberle DR, Adams AM, Berg CD, 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>.
45. Aberle DR, Adams AM, Berg CD, 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>.
46. 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*





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

2013;63:88-105. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/23378235>.

47. Moyer VA. Screening for Lung Cancer: U.S. Preventive Services Task Force Recommendation Statement. Ann Intern Med 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24378917>.

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

49. 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>.

50. 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>.

51. 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>.

52. 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>.

53. 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>.

54. 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>.

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

56. 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>.

57. 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>.

58. 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>.

59. 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>.

60. Cameron SE, Andrade RS, Pambuccian SE. Endobronchial ultrasound-guided transbronchial needle aspiration cytology: a state of





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

the art review. *Cytopathology* 2010;21:6-26. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20015257>.

61. 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>.

62. 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>.

63. 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>.

64. 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>.

65. 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.

66. 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>.

67. 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>.

68. 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>.

69. 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>.

70. 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>.

71. 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>.

72. 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>.

73. 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>.

74. Ordonez NG. D2-40 and podoplanin are highly specific and sensitive immunohistochemical markers of epithelioid malignant



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

mesothelioma. Hum Pathol 2005;36:372-380. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/15891998>.

75. 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>.

76. 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>.

77. Rivera MP, Mehta AC. 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>.

78. 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>.

79. 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>.

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

81. 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>.

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

83. 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>.

84. Dettterbeck 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>.

85. 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>.

86. 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>.

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

88. 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>.

89. 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>.

90. 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

2008;26:1472-1478. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18349398>.

91. 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>.

92. 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>.

93. 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>.

94. 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>.

95. 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>.

96. 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>.

97. 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>.

98. 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>.

99. 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>.

100. 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>.

101. 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>.

102. 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>.

103. 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>.

104. 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>.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

105. 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>.

106. 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>.

107. 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>.

108. 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>.

109. 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>.

110. 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>.

111. 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>.

112. 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>.

113. 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>.

114. 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>.

115. 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>.

116. 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>.

117. 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>.

118. 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>.

119. 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>.

120. Nelson V, Ziehr J, Agulnik M, Johnson M. Afatinib: emerging next-generation tyrosine kinase inhibitor for NSCLC. Onco Targets Ther





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

2013;6:135-143. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23493883>.

121. 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>.

122. Dungo RT, Keating GM. Afatinib: first global approval. *Drugs* 2013;73:1503-1515. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23982599>.

123. 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>.

124. 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>.

125. 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>.

126. 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>.

127. 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>.

128. 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>.

129. Onitsuka T, Uramoto H, Nose N, et al. Acquired resistance to gefitinib: the contribution of mechanisms other than the T790M, MET, and HGF status. *Lung Cancer* 2010;68:198-203. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19589612>.

130. 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>.

131. 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>.

132. 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>.

133. 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>.

134. Dacic S. EGFR assays in lung cancer. *Adv Anat Pathol* 2008;15:241-247. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18580100>.

135. 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*





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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

136. Eberhard DA, Giaccone G, Johnson BE. 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>.

137. 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>.

138. 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>.

139. 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>.

140. 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>.

141. 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>.

142. 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>.

143. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7520).

144. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7503).

145. 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>.

146. Sun JM, Lira M, Pandya K, et al. Clinical characteristics associated with ALK rearrangements in never-smokers with pulmonary adenocarcinoma. Lung Cancer 2013. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24300132>.

147. 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>.



## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

148. 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>.

149. 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>.

150. 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>.

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

152. 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>.

153. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7514).

154. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/2501).

155. 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>.

156. 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>.

157. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/15_suppl/7507).

158. 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* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24258622>.

159. 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>.

160. 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>.

161. Frampton JE. Crizotinib: a review of its use in the treatment of anaplastic lymphoma kinase-positive, advanced non-small cell lung



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

cancer. *Drugs* 2013;73:2031-2051. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/24288180>.

162. 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>.

163. 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>.

164. Solomon B, Wilner KD, Shaw AT. Current status of targeted therapy for anaplastic lymphoma kinase-rearranged non-small cell lung cancer. *Clin Pharmacol Ther* 2013;95:15-23. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24091716>.

165. 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:S579-S592. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163750>.

166. 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>.

167. 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>.

168. 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.

169. 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>.

170. 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>.

171. 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>.

172. 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>.

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

174. 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>.

175. Mitsudomi T, Steinberg SM, Oie HK, et al. ras gene mutations in non-small cell lung cancers are associated with shortened survival irrespective of treatment intent. *Cancer Res* 1991;51:4999-5002. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1654209>.

176. Febbo PG, Ladanyi M, Aldape KD, et al. NCCN Task Force report: Evaluating the clinical utility of tumor markers in oncology. *J Natl Compr*



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

Canc Netw 2011;9 Suppl 5:S1-32; quiz S33. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22138009>.

177. 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>.

178. 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>.

179. 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>.

180. 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>.

181. Kozower BD, Larner 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>.

182. 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>.

183. 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>.

184. 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>.

185. 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>.

186. 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>.

187. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg* 1995;60:615-622; discussion 622-613. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/7677489>.

188. Koike T, Yamato Y, Yoshiya K, et al. Intentional limited pulmonary resection for peripheral T1 N0 M0 small-sized lung cancer. *J Thorac Cardiovasc Surg* 2003;125:924-928. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/12698157>.

189. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

cancer. J Clin Oncol 2010;28:928-935. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20065181>.

190. 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>.

191. 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>.

192. 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](http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7555).

193. 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>.

194. 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>.

195. 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>.

196. 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 2009;374:379-386. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19632716>

197. 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>.

198. 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>.

199. 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>.

200. 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>.

201. 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>.

202. 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





National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

Oncol Biol Phys 2010;78:969-974. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20813465>.

203. 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>.

204. 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>.

205. 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>.

206. 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>.

207. 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>.

208. 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>.

209. 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>.

210. 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>.

211. 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>.

212. 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: Technology and Techniques in Cardiothoracic and Vascular Surgery 2007;2:261-292. 210.1097/IMI.1090b1013e3181662c3181666a. Available at: [http://journals.lww.com/innovjournal/Fulltext/2007/11000/Video\\_Assisted\\_Thoracic\\_Surgery\\_in\\_Lung\\_Cancer.1.aspx](http://journals.lww.com/innovjournal/Fulltext/2007/11000/Video_Assisted_Thoracic_Surgery_in_Lung_Cancer.1.aspx).

213. 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>.

214. 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>.

215. 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>.

216. 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;



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

discussion 981-973. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/20172539>.

217. 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>.

218. 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>.

219. 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>.

220. 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>.

221. 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>.

222. 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>.

223. 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* 2012;16:244-249. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23169877>.

224. 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>.

225. Villamizar NR, Darrabie MD, Burfeind WR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. *J Thorac Cardiovasc Surg* 2009;138:419-425. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/19619789>.

226. 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>.

227. 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>.

228. 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>.

229. 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>.

230. 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>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

231. 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>.

232. 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>.

233. 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>.

234. 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>.

235. 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:S182-S189. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24040521>.

236. Yan TD, Cao C, D'Amico TA, et al. Video-assisted thoracoscopic surgery lobectomy at 20 years: a consensus statement. *Eur J Cardiothorac Surg* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24130372>.

237. 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>.

238. 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*

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

239. 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* 2013. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24210834>.

240. 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>.

241. 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>.

242. 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>.

243. 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>.

244. 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>.

245. 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>.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

246. 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>.

247. 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>.

248. 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>.

249. 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>.

250. 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>.

251. 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>.

252. 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>.

253. 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>.

254. 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>.

255. 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>.

256. 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>.

257. 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>.

258. 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>.





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

259. 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>.

260. 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>.

261. Albain KS, Swann RS, Rusch VR, et al. Phase III study of concurrent chemotherapy and radiotherapy (CT/RT) vs CT/RT followed by surgical resection for stage IIIA(pN2) non-small cell lung cancer (NSCLC): Outcomes update of North American Intergroup 0139 (RTOG 9309) [abstract]. *J Clin Oncol* 2005;23 (Suppl 16):Abstract 7014. Available at:

[http://meeting.ascopubs.org/cgi/content/abstract/23/16\\_suppl/7014](http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/7014).

262. Bosc R, Lepage C, Hamou C, et al. Management of chest wall reconstruction after resection for cancer: a retrospective study of 22 consecutive patients. *Ann Plast Surg* 2011;67:263-268. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/21407062>.

263. Skoracki RJ, Chang DW. Reconstruction of the chestwall and thorax. *J Surg Oncol* 2006;94:455-465. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/17061266>.

264. Lutz ST, Lo SS, Chang EL, et al. ACR Appropriateness Criteria® non-spine bone metastases. *J Palliat Med* 2012;15:521-526. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22536988>.

265. 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>.

266. 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>.

267. 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>.

268. 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>.

269. 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>.

270. 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>.

271. 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*





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Oncol Biol Phys 2007;68:103-110. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17363189>.

272. 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>.

273. 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>.

274. 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>.

275. 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>.

276. 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](http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/7501).

277. 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/IIIb 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.

278. 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>.

279. ICRU. ICRU Report 50. Prescribing, Recording and Reporting Photon Beam Therapy. Bethesda, MD: International Commission on Radiation Units and Measurements; 1993.

280. ICRU. Prescribing, Recording and Reporting Photon Beam Therapy (Report 62) (Supplement to ICRU Report 50). Bethesda, MD: ICRU; 1999.

281. 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>.

282. Holmes T, Das R, Low D, 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>.

283. 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 Oncol Biol Phys 2011;81:1442-1457. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20934273>.

284. Kong FM, Pan C, Eisbruch A, Ten Haken RK. Physical models and simpler dosimetric descriptors of radiation late toxicity. Semin Radiat



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Oncol 2007;17:108-120. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17395041>.

285. 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>.

286. 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>.

287. 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>.

288. 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>.

289. 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>.

290. 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>.

291. 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>.

292. 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>.

293. Chang JY, Zhang X, Wang X, et al. Significant reduction of normal tissue dose by proton radiotherapy compared with three-dimensional 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>.

294. Cox JD, Sejal S, Komaki R, et al. Proton therapy with concurrent chemotherapy can reduce toxicity and allow higher radiation doses in advanced non-small cell lung cancer. J Thorac Oncol 2008;3:S303-S304. Available at: <http://journals.lww.com/jto/toc/2008/11001>.

295. 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>.

296. 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>.

297. 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>.

298. Keall PJ, Mageras GS, Balter JM, et al. The management of respiratory motion in radiation oncology report of AAPM Task Group 76.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

Med Phys 2006;33:3874-3900. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/17089851>.

299. 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>.

300. 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>.

301. 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>.

302. 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>.

303. 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>.

304. 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>.

305. 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>.

306. 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>.

307. Senthil 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>.

308. 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>.

309. 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>.

310. 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>.

311. 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>.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

312. 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* 2010;28:5153-5159. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21041709>.

313. 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>.

314. 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>.

315. 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>.

316. 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>.

317. 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>.

318. 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>.

319. 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>.

320. 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>.

321. Decker RH, Tanoue LT, Colasanto JM, et al. Evaluation and definitive management of medically inoperable early stage non-small-cell lung cancer. Part 2: newer treatment modalities. *Oncology (Williston Park)* 2006;20:899-905; discussion 905-898, 913. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16922260>.

322. Lencioni R, Crocetti L, Cioni R, et al. Response to radiofrequency ablation of pulmonary tumours: a prospective, intention-to-treat, multicentre clinical trial (the RAPTURE study). *Lancet Oncol* 2008;9:621-628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18565793>.

323. Simon CJ, Dupuy DE, DiPetrillo TA, et al. Pulmonary radiofrequency ablation: long-term safety and efficacy in 153 patients. *Radiology* 2007;243:268-275. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17392258>.

324. 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>.

325. 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>.





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

326. 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>.

327. 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>.

328. 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* 1990;322:494-500. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2405271>.

329. 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>.

330. 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>.

331. 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>.

332. Kim JE, Lee DH, Choi Y, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. *Lung Cancer* 2009;65:351-354. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19157632>.

333. Olson JJ, Paleologos NA, Gaspar LE, et al. The role of emerging and investigational therapies for metastatic brain tumors: a systematic review and evidence-based clinical practice guideline of selected topics. *J Neurooncol* 2010;96:115-142. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19957013>.

334. Welsh JW, Komaki R, Amini A, et al. Phase II trial of erlotinib plus concurrent whole-brain radiation therapy for patients with brain metastases from non-small-cell lung cancer. *J Clin Oncol* 2013;31:895-902. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/23341526>.

335. 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>.

336. 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>.

337. 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>.

338. 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>.

339. 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>.





## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

340. 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>.

341. 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>.

342. 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>.

343. 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>.

344. 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>.

345. 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>.

346. 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>.

347. 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>.

348. 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>.

349. 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>.

350. 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>.

351. Rosell R, Gomez-Codina J, Camps C, et al. Preresectional chemotherapy in stage IIIA non-small-cell lung cancer: a 7-year assessment of a randomized controlled trial. *Lung Cancer* 1999;26:7-14. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/10574676>.

352. 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>.

353. Felip E, Rosell R, Maestre JA, et al. Preoperative chemotherapy plus surgery versus surgery plus adjuvant chemotherapy versus surgery



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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>.

354. 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:

355. 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>.

356. 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>.

357. 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>.

358. 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>.

359. 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>.

360. 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>.

361. 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>.

362. 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>.

363. Azzoli CG, Baker S, Jr., Temin S, et al. American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy 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>.

364. NSCLC Meta-Analyses Collaborative Group. 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://jco.ascopubs.org/cgi/content/abstract/26/28/4617>.

365. 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>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

366. 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>.

367. 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>.

368. Yates P, Schofield P, Zhao I, Currow D. Supportive and palliative care for lung cancer patients. *J Thorac Dis* 2013;5:S623-S628. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24163753>.

369. 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>.

370. 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>.

371. 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>.

372. 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>.

373. 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>.

374. 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>.

375. 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>.

376. 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>.

377. 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](http://meeting.ascopubs.org/cgi/content/abstract/22/14_suppl/7019).

378. 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](http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7007).

379. 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-5051. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/18809614>.

380. 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>.

381. 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>.

382. 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>.

383. 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>.

384. 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>.

385. 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:

386. 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>.

387. 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>.

388. 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>.

389. 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>.

390. 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>.

391. Huber RM, Flentje M, Schmidt M, et al. Simultaneous chemoradiotherapy compared with radiotherapy alone after induction chemotherapy in inoperable stage IIIA or IIIB non-small-cell lung cancer: study CTRT99/97 by the Bronchial Carcinoma Therapy Group. J Clin Oncol 2006;24:4397-4404. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16983107>.





## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

392. 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>.

393. 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>.

394. 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>.

395. 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>.

396. 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>.

397. 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>.

398. 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>.

399. Leighl NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. *Curr Oncol* 2012;19:S52-S58. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22787411>.

400. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542-2550. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17167137>.

401. 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>.

402. 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>.

403. 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>.

404. Zhu J, Sharma DB, Gray SW, et al. Carboplatin and paclitaxel with vs without bevacizumab in older patients with advanced non-small cell





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

lung cancer. JAMA 2012;307:1593-1601. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22511687>.

405. 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>.

406. 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](http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/7506).

407. 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>.

408. Lilenbaum R, Villaflor 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>.

409. 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>.

410. 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>.

411. Kelly K, Crowley J, Bunn PA, Jr., 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/11432888>.

412. 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>.

413. 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>.

414. 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>.

415. 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>.

416. 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>.



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

417. 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>.

418. 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>.

419. 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>.

420. 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>.

421. 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>.

422. 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>.

423. 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>.

424. Socinski 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22547591>.

425. 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>.

426. 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>.

427. 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>.

428. 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>.

429. 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>.

430. 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



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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>.

431. 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>.

432. 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>.

433. 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>.

434. 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>.

435. 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](http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7503).

436. FDA approves afatinib for advanced lung cancer. Oncology (Williston Park) 2013;27:813-814. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24133833>.

437. 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>.

438. 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>.

439. 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>.

440. 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>.

441. 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>.

442. 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.



## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

Lancet Oncol 2012;13:247-255. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22341744>.

443. 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](http://meeting.ascopubs.org/cgi/content/abstract/29/18_suppl/CRA7510).

444. 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>.

445. 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](http://meeting.ascopubs.org/cgi/content/abstract/30/18_suppl/LBA7507).

446. 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>.

447. 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/](http://new.ecco-org.eu/ecco_content/2011StockholmLateBreakingflipbook/index.html#/20/).

448. 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>.

449. 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](http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/7507).

450. 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>.

451. 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>.

452. 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>.

453. Gerber DE, Schiller JH. Maintenance chemotherapy for advanced non-small-cell lung cancer: new life for an old idea. J Clin Oncol





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

2013;31:1009-1020. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/23401441>.

454. 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>.

455. 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>.

456. 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>.

457. 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>.

458. 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>.

459. 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>.

460. 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>.

461. 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>.

462. 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>.

463. 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>.

464. 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>.

465. 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>.

466. Pieterman RM, van Putten JW, Meuzelaar JJ, et al. Preoperative staging of non-small-cell lung cancer with positron-emission





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

tomography. N Engl J Med 2000;343:254-261. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/10911007>.

467. 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](http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/17525).

468. Maziak DE, Darling GE, Inculet 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>.

469. 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>.

470. 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>.

471. 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>.

472. 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>.

473. 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>.

474. 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>.

475. Kernstine KH, Trapp JF, Croft DR, al e. 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:

476. 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>.

477. 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>.

478. 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>.

479. 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>.

480. Yasufuku K, Pierre A, Darling G, et al. A prospective controlled trial of endobronchial ultrasound-guided transbronchial needle aspiration



# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

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>.

481. 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>.

482. 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>.

483. 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>.

484. 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>.

485. 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>.

486. 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>.

487. 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>.

488. 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>.

489. 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>.

490. 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](http://www.asco.org/ascov2/Meetings/Abstracts?&vmview=abst_detail_view&confID=23&abstractID=103854).

491. 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>.

492. 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>.

493. 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



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

2008;33:829-836. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18367406>.

494. 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>.

495. 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>.

496. Lee JG, Lee CY, Kim DJ, et al. Non-small cell lung cancer with ipsilateral pulmonary metastases: prognosis analysis and staging assessment. *Eur J Cardiothorac Surg* 2008;33:480-484. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/18249000>.

497. 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>.

498. 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>.

499. 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>.

500. Adebonojo 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>.

501. 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>.

502. 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>.

503. Allen MS. Multiple benign lung tumors. *Semin Thorac Cardiovasc Surg* 2003;15:310-314. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/12973710>.

504. 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>.

505. 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>.

506. 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>.

507. 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>.

508. 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>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

509. 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>.

510. 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>.

511. 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>.

512. 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>.

513. 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>.

514. 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>.

515. 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>.

516. Mario S, Nicola S, Carmelinda M, et al. Long-term surveillance of ground-glass nodules: evidence from the MILD trial. *J Thorac Oncol* 2012;7:1541-1546. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22968185>.

517. 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>.

518. Rice TW. Thoracoscopy in the staging of thoracic malignancies. In: Kaiser LR, Daniel TM, eds. *Thoracoscopic Surgery*. Philadelphia: Lippincott Williams & Wilkins; 1993:153-162.

519. 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>.

520. 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](http://meeting.ascopubs.org/cgi/content/abstract/26/15_suppl/7519).

521. 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](http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7512).

522. 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>.

523. Demmy TL, Gu L, Burkhalter JE, et al. Optimal management of malignant pleural effusions (results of CALGB 30102). *J Natl Compr*





# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

Canc Netw 2012;10:975-982. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/22878823>.

524. Burt M, Wronski M, Arbit E, Galicich JH. Resection of brain metastases from non-small-cell lung carcinoma. Results of therapy. Memorial Sloan-Kettering Cancer Center Thoracic Surgical Staff. J Thorac Cardiovasc Surg 1992;103:399-410; discussion 410-391. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/1312184>.

525. Mehta MP, Tsao MN, Whelan TJ, et al. The American Society for Therapeutic Radiology and Oncology (ASTRO) evidence-based review of the role of radiosurgery for brain metastases. Int J Radiat Oncol Biol Phys 2005;63:37-46. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/16111570>.

526. Alexander E, 3rd, Moriarty TM, Davis RB, et al. Stereotactic radiosurgery for the definitive, noninvasive treatment of brain metastases. J Natl Cancer Inst 1995;87:34-40. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/7666461>.

527. 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>.

528. 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>.

529. 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>.

530. 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>.

531. Arriagada R, Auperin A, Burdett S, 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>.

532. 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>.

533. 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>.

534. 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](http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8073).

535. 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>.

536. 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:

537. Rusch VW, Albain KS, Crowley JJ, et al. Surgical resection of stage IIIA and stage IIIB non-small-cell lung cancer after concurrent





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

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>.

538. 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>.

539. 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](http://meeting.ascopubs.org/cgi/content/abstract/23/16_suppl/LBA7012).

540. 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](http://meeting.ascopubs.org/cgi/content/abstract/25/18_suppl/7520).

541. 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>.

542. Pisters KM, Evans WK, Azzoli CG, et al. Cancer Care Ontario and American Society of Clinical Oncology adjuvant chemotherapy and adjuvant radiation therapy for stages I-IIIa resectable non small-cell lung cancer guideline. J Clin Oncol 2007;25:5506-5518. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/17954710>.

543. Decker RH, Langer CJ, Rosenzweig KE, et al. ACR Appropriateness Criteria® 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>.

544. 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>.

545. 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>.

546. 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>.

547. 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>.

548. 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>.

549. 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>.



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

550. 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>.

551. 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>.

552. 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>.

553. Rosen LS, Gordon D, Tchekmedyan 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>.

554. 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](http://meeting.ascopubs.org/cgi/content/abstract/28/15_suppl/9133).

555. 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>.

556. 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>.

557. 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>.

558. 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>.

559. 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>.

560. 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>.

561. 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](http://meeting.ascopubs.org/cgi/content/abstract/31/15_suppl/8009).

562. 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>.

563. Shaw AT, Yeap BY, Solomon BJ, et al. Effect of crizotinib on overall survival in patients with advanced non-small-cell lung cancer



National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

harbouring ALK gene rearrangement: a retrospective analysis. *Lancet Oncol* 2011;12:1004-1012. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/21933749>.

564. 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>.

565. 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>.

566. 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>.

567. 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>.

568. 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 Thorac Oncol* 2010;5:1416-1423. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/20686429>.

569. 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>.

570. 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>.

571. 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>.

572. 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>.

573. 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>.

574. 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 (Supl 15):Abstract e19001. Available at:  
<http://meeting.ascopubs.org/cgi/content/abstract/27/15S/e19001>.

575. 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>.

576. 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>.



National  
Comprehensive  
Cancer  
Network®

# NCCN Guidelines Version 4.2014

## Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

577. 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>.

578. 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>.

579. 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>.

580. 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>.

581. 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 international group 03-05 study. *J Clin Oncol* 2009;27:1999-2006. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19289619>.

582. 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>.

583. 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>.

584. 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>.

585. 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>.

586. 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>.

587. 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>.

588. 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>.

589. 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>.

590. 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.





National  
Comprehensive  
Cancer  
Network®

## NCCN Guidelines Version 4.2014 Non-Small Cell Lung Cancer

[NCCN Guidelines Index](#)  
[NSCLC Table of Contents](#)  
[Discussion](#)

Lung Cancer 2001;33:289-298. Available at:  
<http://www.ncbi.nlm.nih.gov/pubmed/11551424>.

591. 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>.

592. 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>.

593. 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>.

594. 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>.

595. 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>.

596. 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>.

597. 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>.

598. 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](http://meeting.ascopubs.org/cgi/content/abstract/24/18_suppl/7133).

599. 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>.

600. 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 2012;39:252-260. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22703830>.

601. Noble J, Ellis PM, Mackay JA, Evans WK. 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>.

602. 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>.