National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Non-Small Cell Lung Cancer

Version 3.2014

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NCCN Guidelines Panel Disclosures

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

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

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

See NCCN Categories of Evidence and Consensus.

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Updates in 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: reresection + chemotherapy or chemoradiation (sequential or concurrent).**
  - **R2 resection separated out with the following recommendations: reresection + 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 42 cycles of full-dose chemotherapy. (also applies to NSCL-6, NSCL-12)**

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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.**

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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, Bharma 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* ~~If ROS1 mutation status is known and positive~~, may treat with crizotinib. 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 "ll" 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-naive 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 "ll" 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.**

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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 adenocarcinomas*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*.**

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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.**

LUNG CANCER PREVENTION AND SCREENING

- **Lung cancer is a unique disease in that the major etiologic agent is an addictive product that is made and promoted by an industry. Approximately 85% to 90% of cases are caused by voluntary or involuntary (second-hand) cigarette smoking. Reduction of lung cancer mortality will require effective public health policies to prevent initiation of smoking, U.S. Food and Drug Administration (FDA) oversight of tobacco products, and other tobacco control measures.**
- **Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life, and reduced survival.**
- **Reports from the Surgeon General on both active smoking (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf) and second-hand smoke show that both cause lung cancer. The evidence shows a 20% to 30% increase in the risk 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/).**
- **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) to identify, counsel, and treat patients with nicotine habituation.**
- **Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.**
- **Lung cancer screening using low-dose CT (LDCT) is recommended in select high-risk smokers and former smokers (see the NCCN Guidelines for Lung Cancer Screening).**

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

CLINICAL PRESENTATION

Nodule suspicious for lung cancer

→

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

→

RISK ASSESSMENT[b]

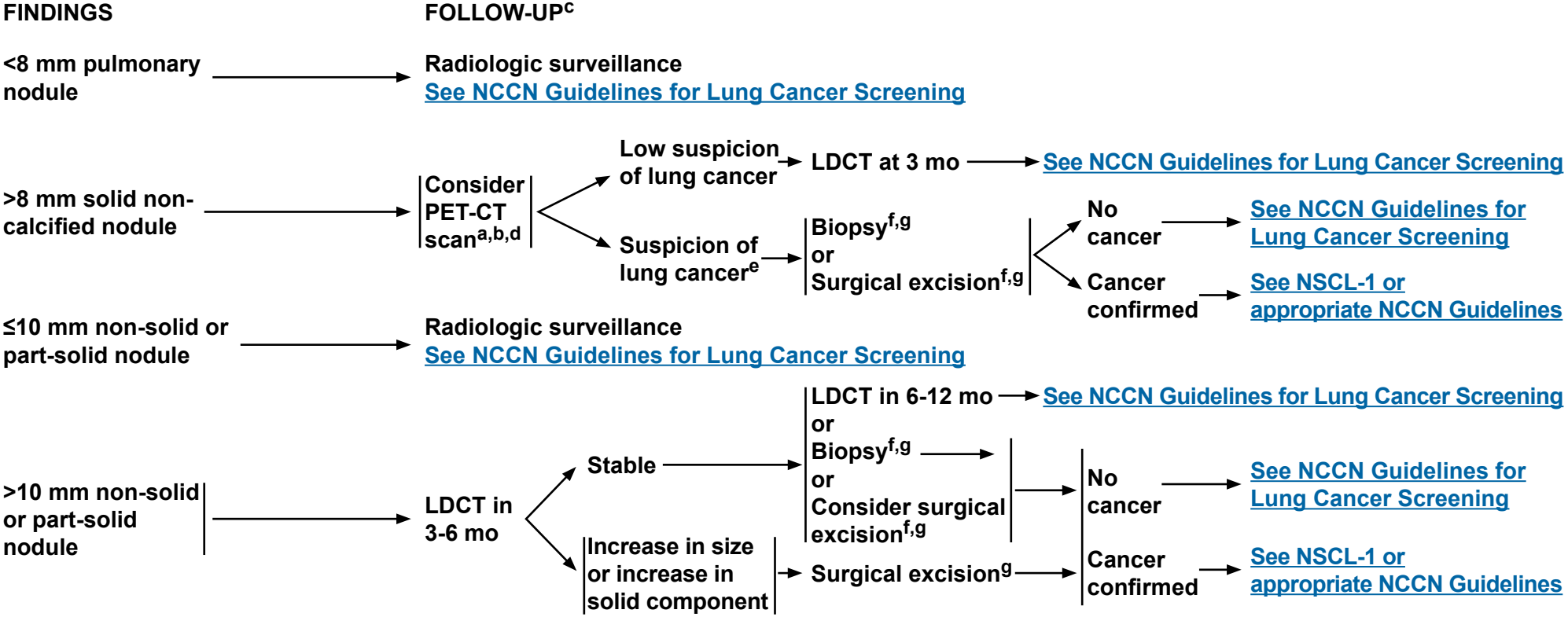
Patient factors
- **Age**
- **Smoking history**
- **Previous cancer history**
- **Family history**
- **Occupational exposures**
- **Other lung disease (chronic obstructive pulmonary disease [COPD], pulmonary fibrosis)**
- **Exposure to infectious agents (eg, endemic areas of fungal infections, tuberculosis)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

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

→ **See Findings and Follow-up (DIAG-2)**

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

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



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

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

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

[d]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).

[e]Patients with a suspicion of lung cancer after PET-CT require histologic confirmation before any nonsurgical therapy.

[f]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.

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

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

- **Patients with a strong clinical suspicion of stage I or II lung cancer (based on risk factors and radiologic appearance) do not require a biopsy before surgery.**
  - **A biopsy adds time, costs, and procedural risk and may not be needed for treatment decisions.**
  - **A preoperative biopsy may be appropriate if a non-lung cancer diagnosis is strongly suspected that can be diagnosed by 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.

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.

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PATHOLOGIC DIAGNOSIS OF NSCLC

Non-Small Cell Lung Cancer (NSCLC) →

INITIAL EVALUATION

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

CLINICAL STAGE

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

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

[b] 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.

[c] Based on the CT of the chest: Peripheral = outer third of lung. Central = inner two thirds of lung.

[d] T3, N0 related to size or satellite nodules.

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

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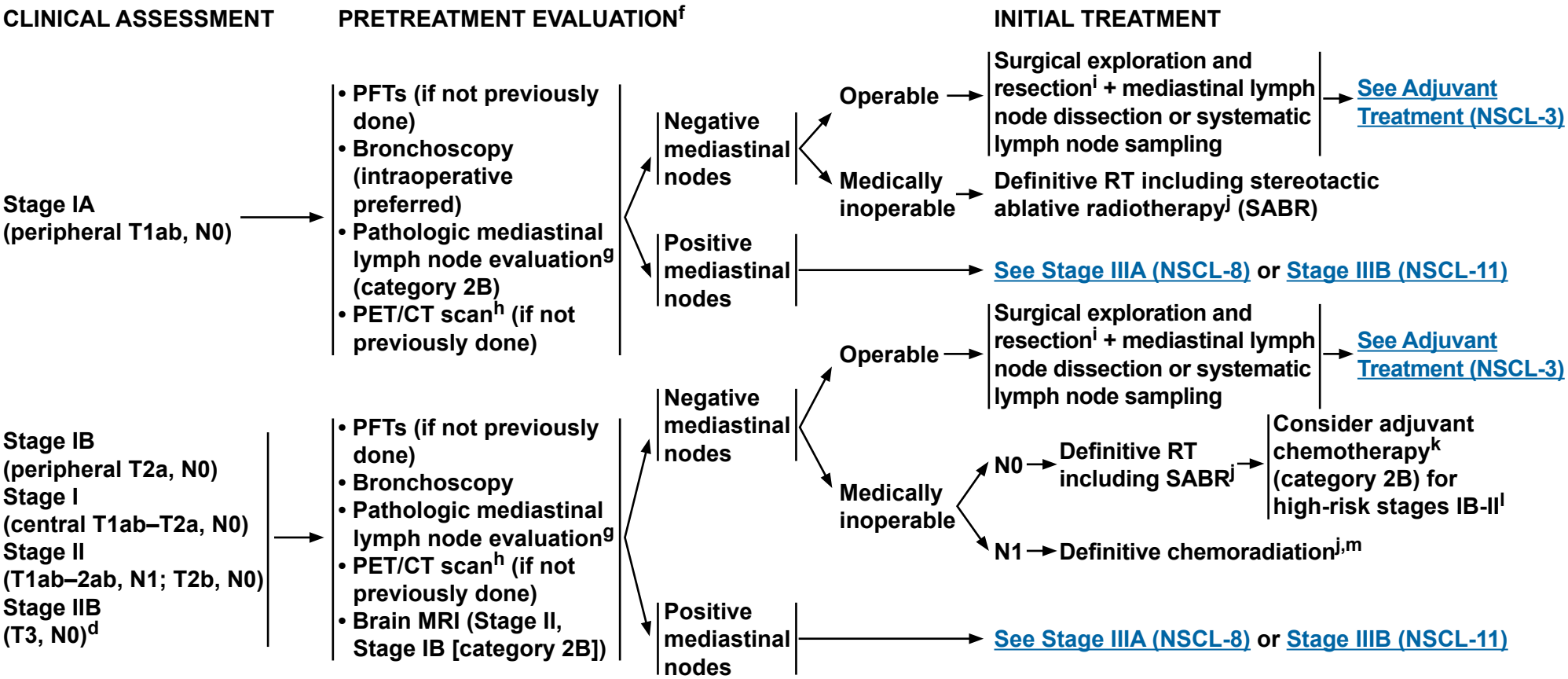

[d]T3, N0 related to size or satellite nodules.
[f]Testing is not listed in order of priority and is dependent upon clinical circumstances, institutional processes, and judicious use of resources.
[g]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h]Positive 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.
[i]See Principles of Surgical Therapy (NSCL-B).
[j]See Principles of Radiation Therapy (NSCL-C).
[k]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[l]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.
[m]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

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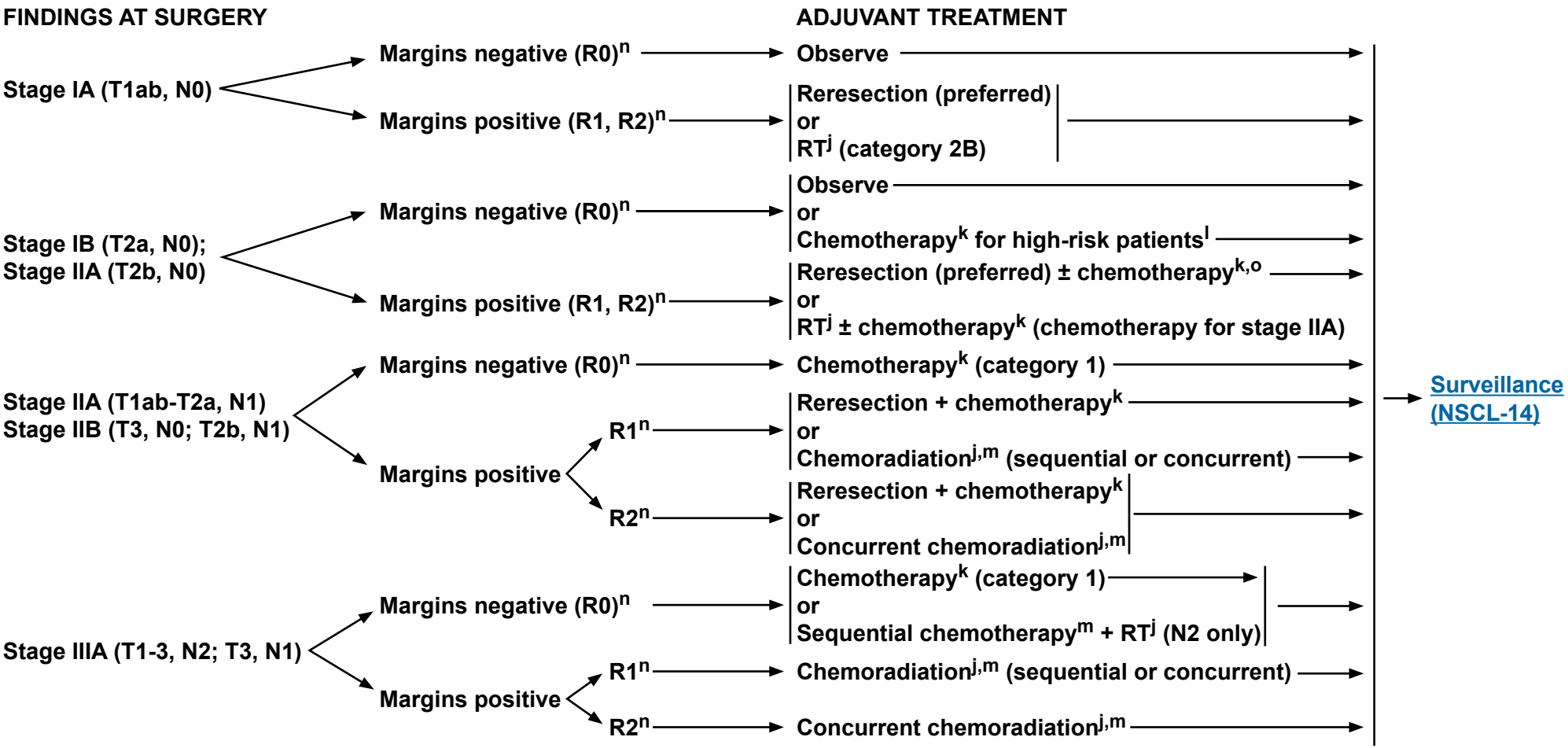

[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[l] Examples of high-risk factors may include poorly differentiated tumors (including lung neuroendocrine tumors [excluding well-differentiated neuroendocrine tumors]), vascular 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.
[m] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[n] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[o] Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.

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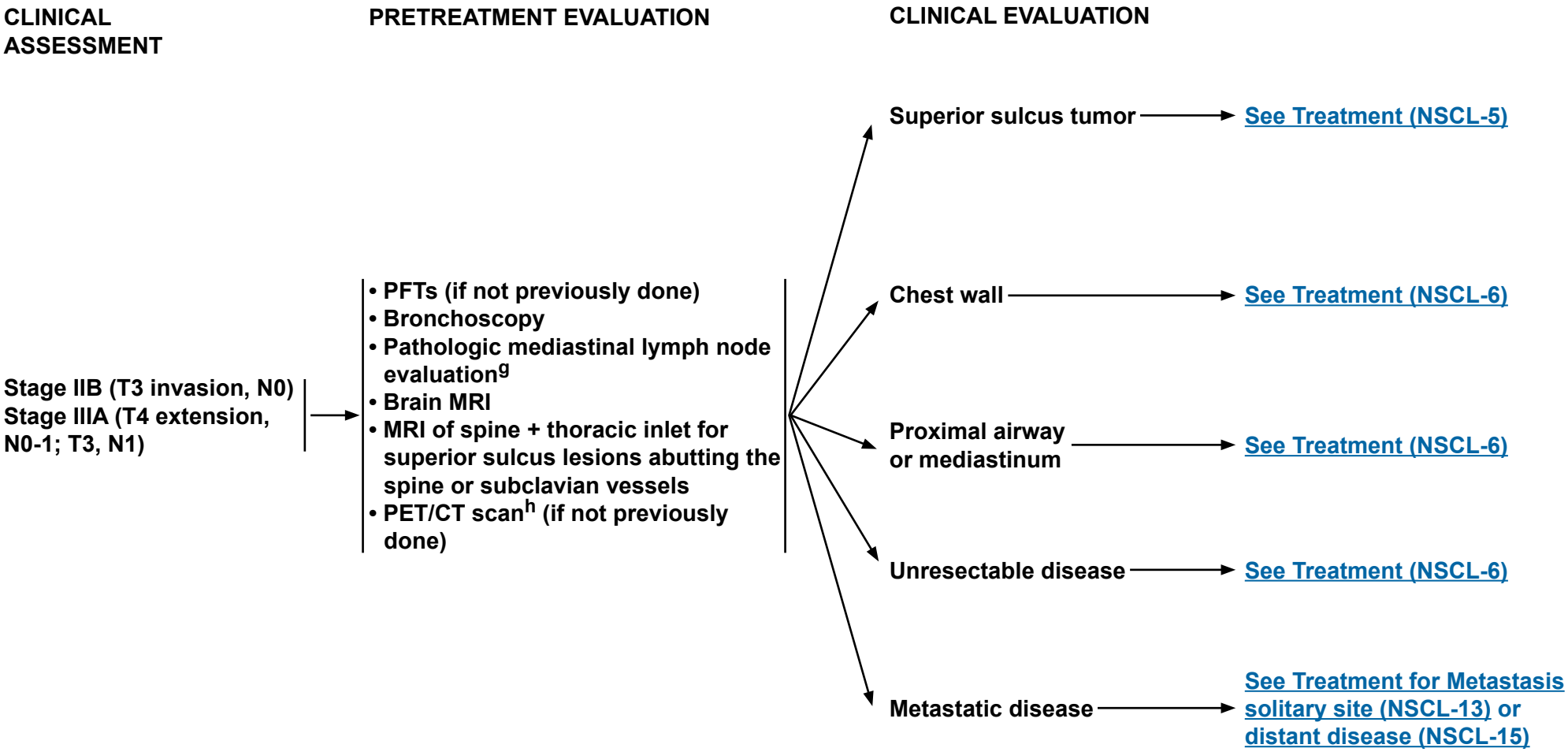

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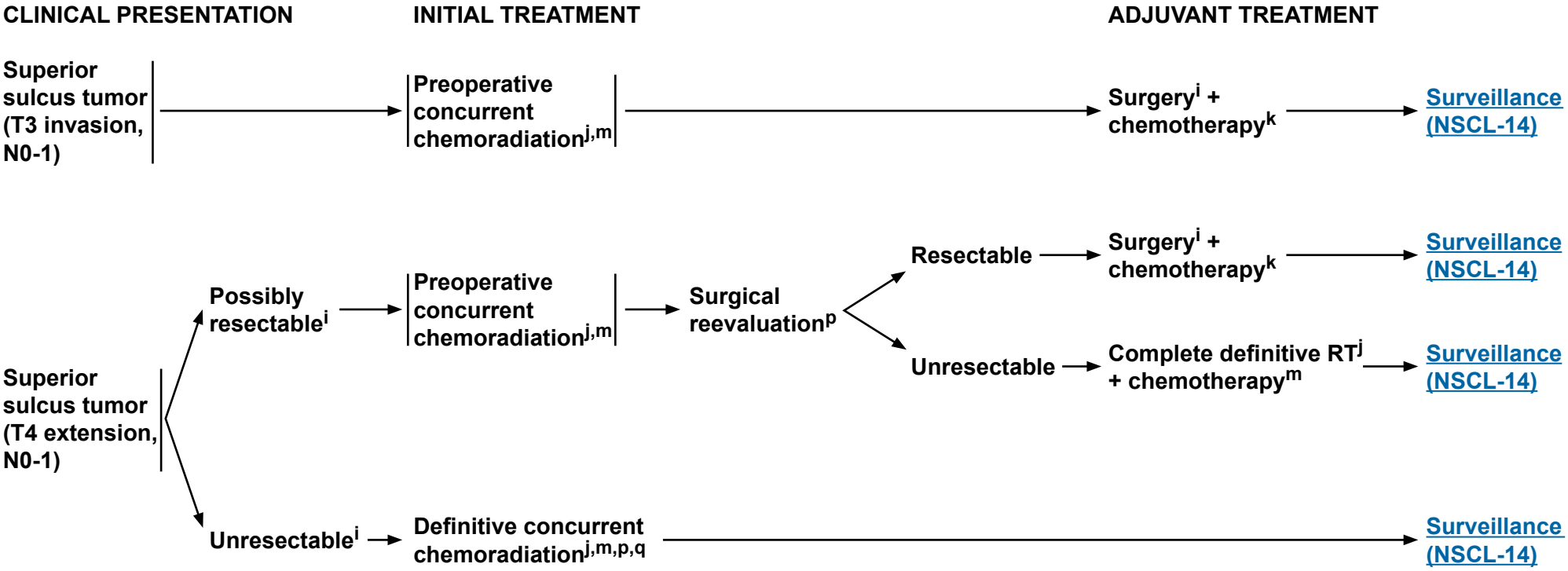

[i] See Principles of Surgical Therapy (NSCL-B).
[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[m] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).

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

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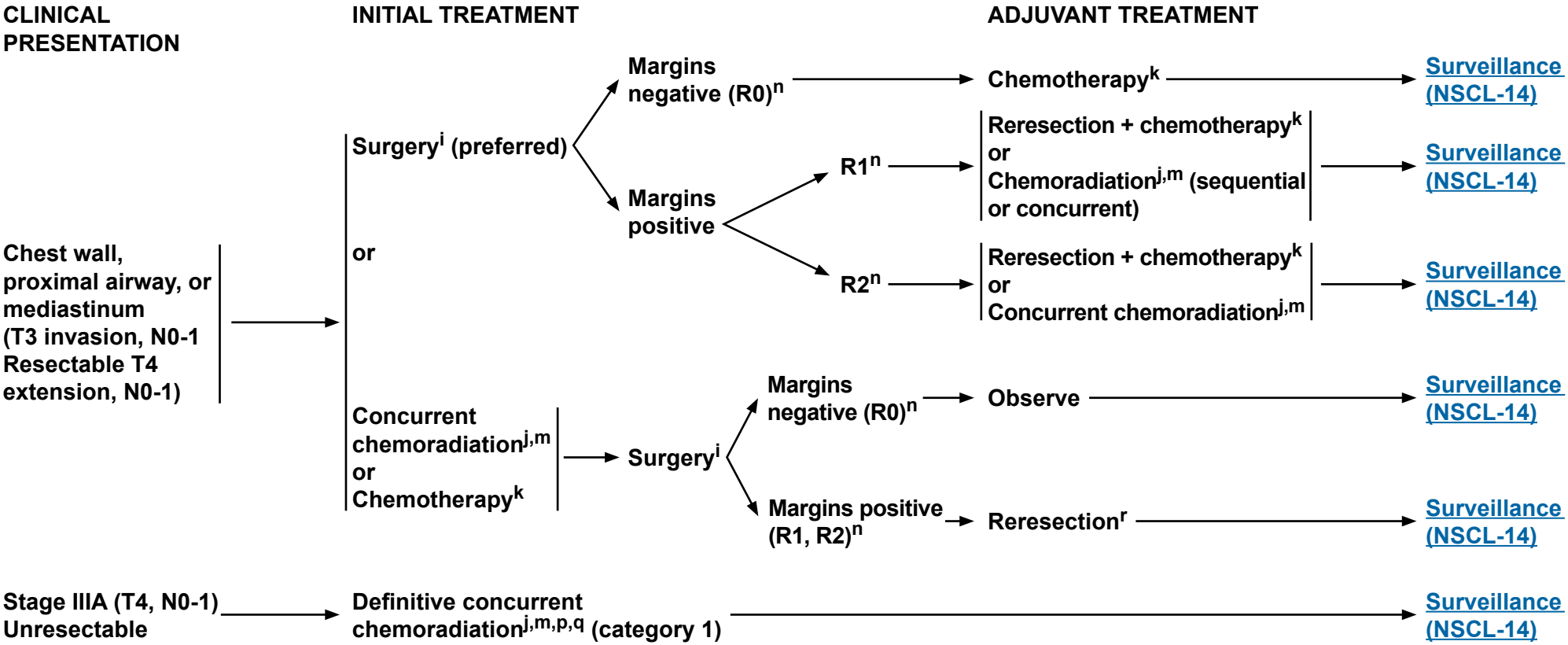

[i] See Principles of Surgical Therapy (NSCL-B).
[j] See Principles of Radiation Therapy (NSCL-C).
[k] See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[m] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[n] R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[p] RT should continue to definitive dose without interruption if patient is not a surgical candidate.
[q] If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.
[r] Consider RT boost if chemoradiation is given as initial treatment.

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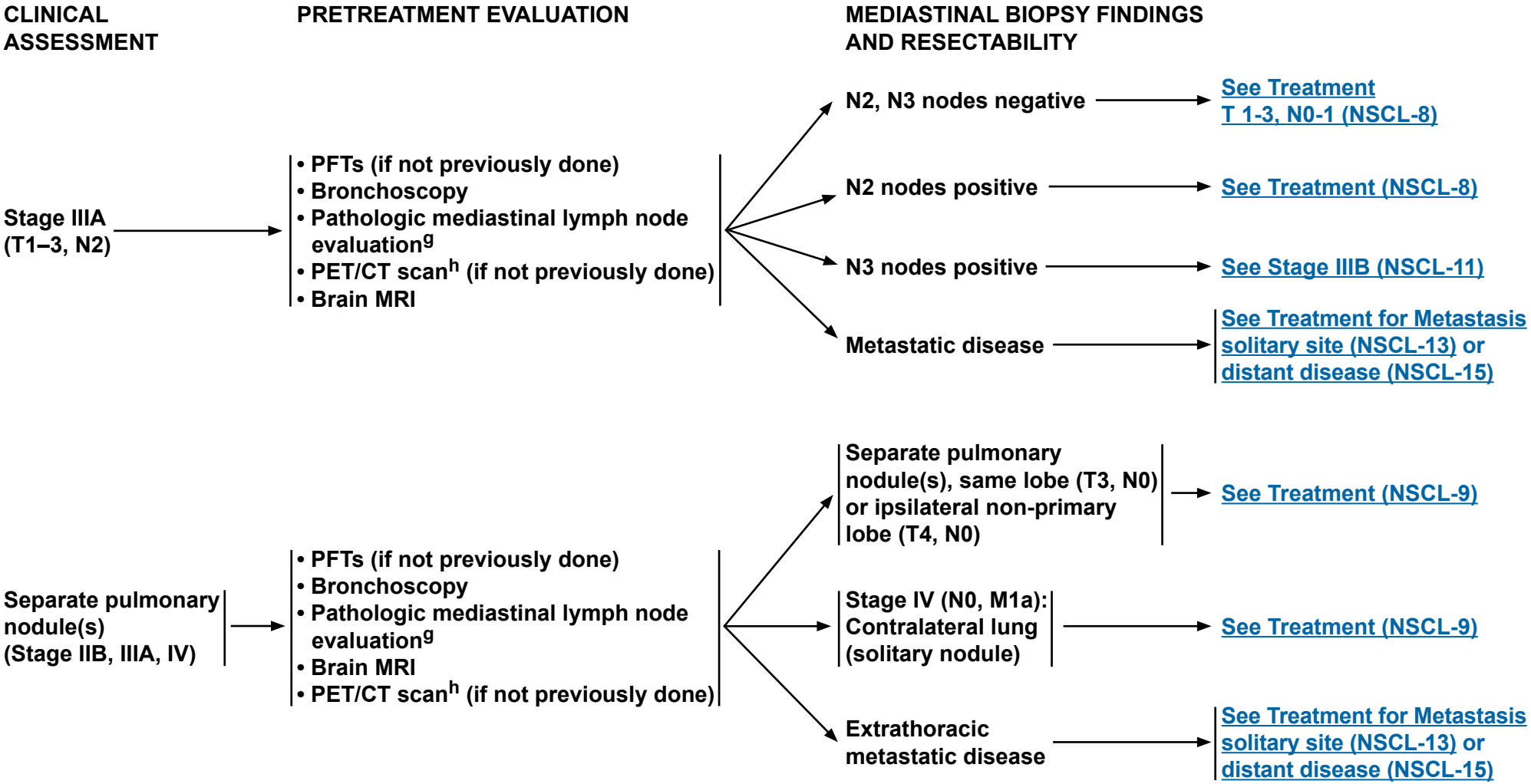

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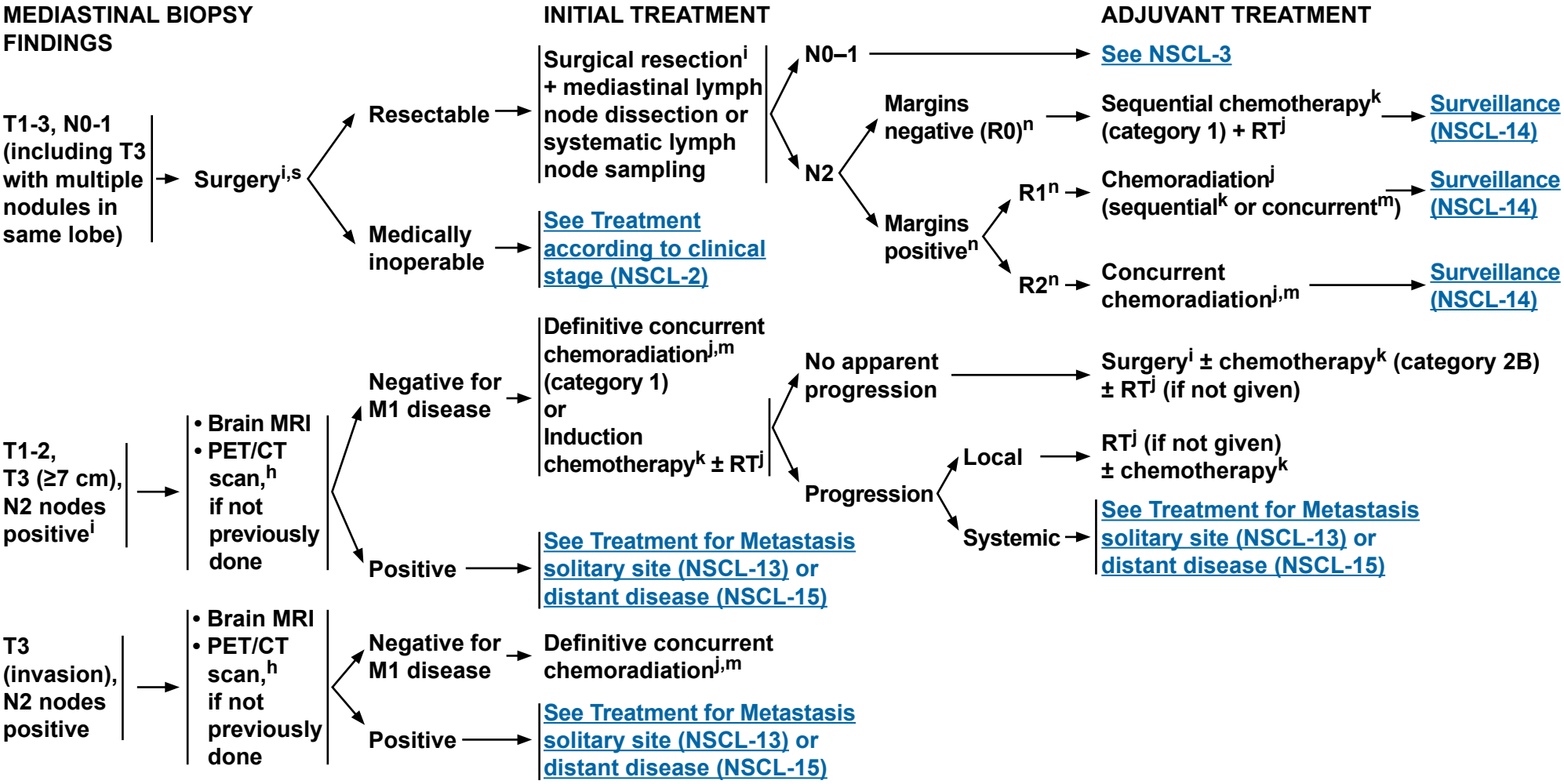

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[k]See Chemotherapy Regimens for Neoadjuvant and Adjuvant Therapy (NSCL-D).
[m]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[n]R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[s]Patients likely to receive adjuvant chemotherapy may be treated with induction chemotherapy as an alternative.

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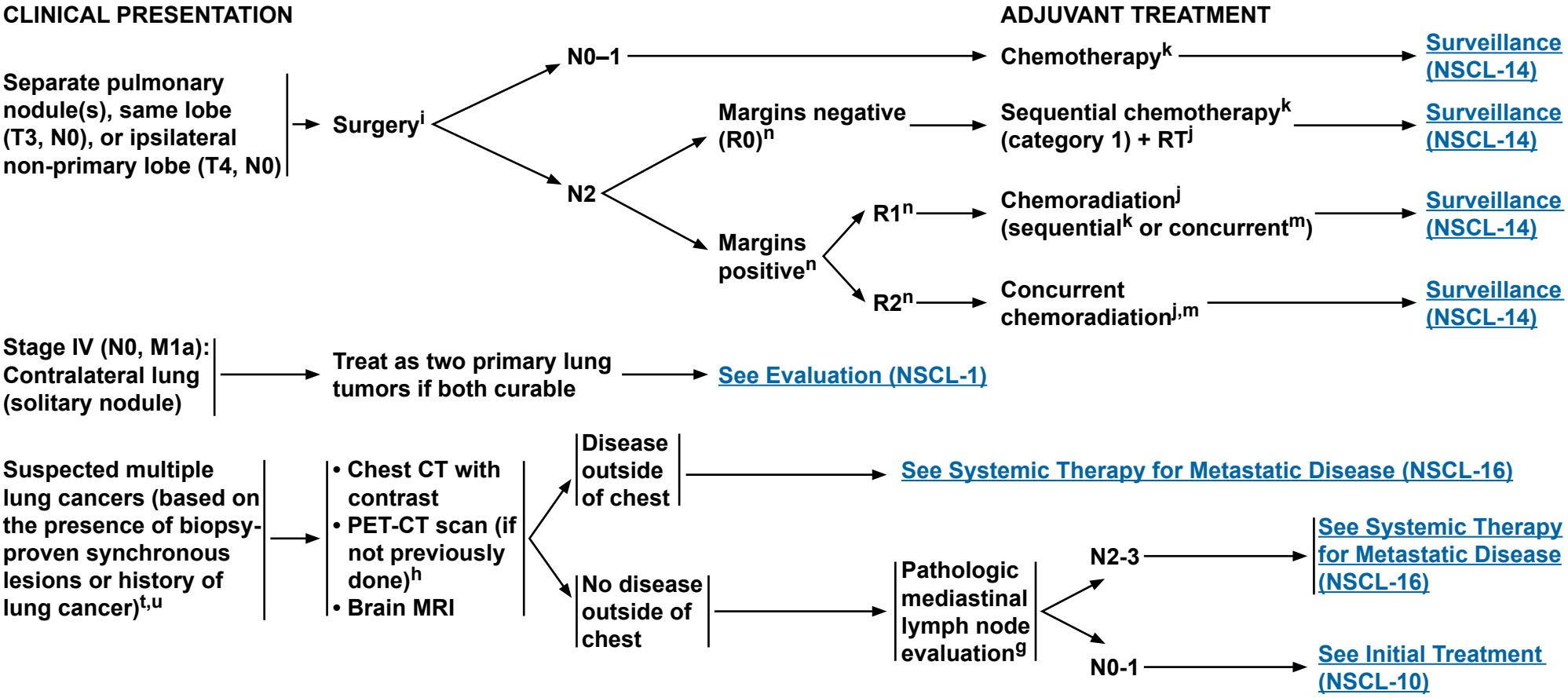

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[m]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[n]R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
[t]Lesions with different cell types (eg, squamous cell carcinoma, adenocarcinoma) may be different primary tumors. This analysis may be limited by small biopsy samples. However, lesions of the same cell type are not necessarily metastases.
[u]For guidance regarding the evaluation, workup, and management of subsolid pulmonary nodules, please see the diagnostic evaluation of a nodule suspicious for lung cancer (DIAG-1).

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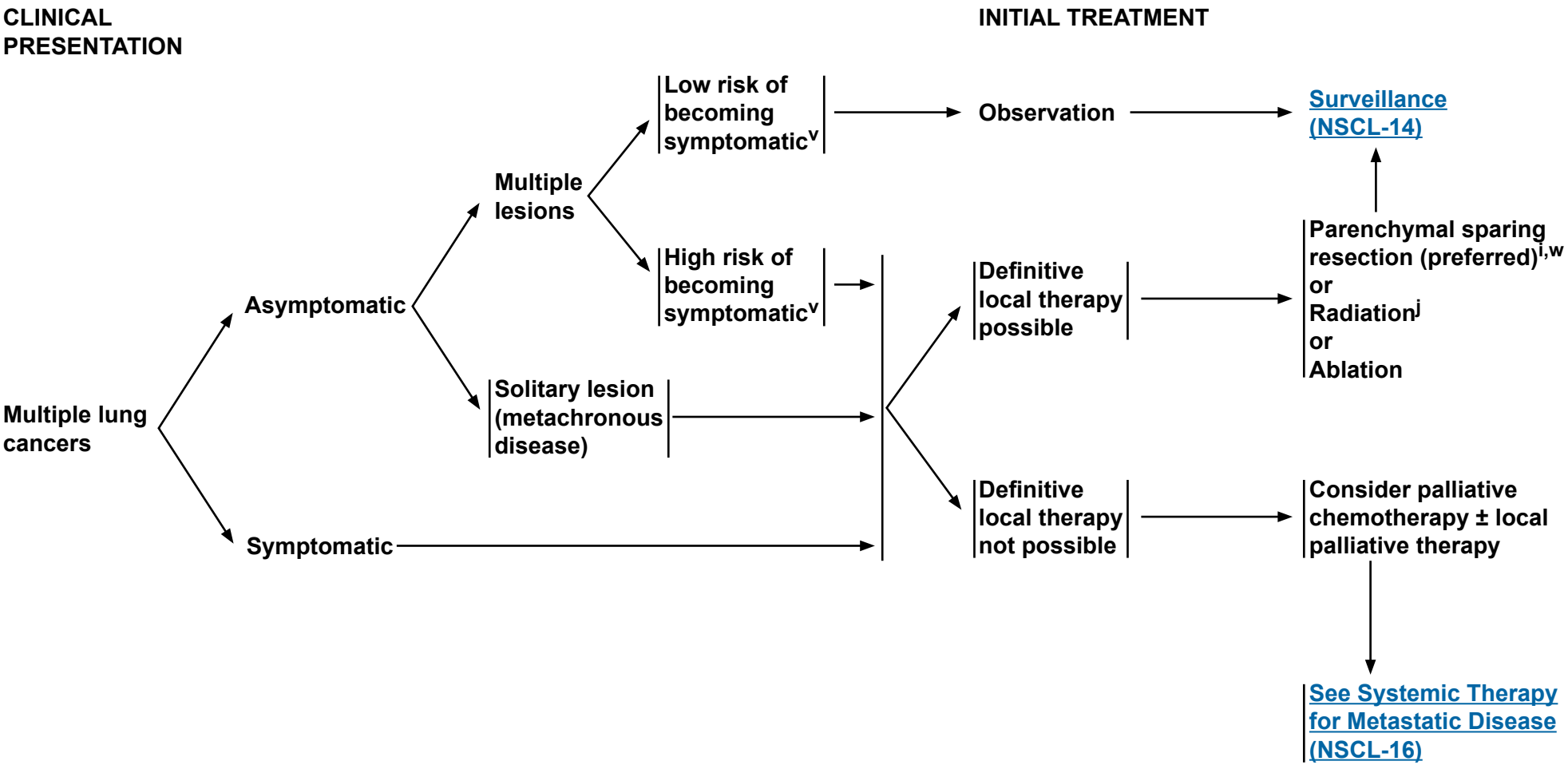

[i] See Principles of Surgical Therapy (NSCL-B).
[j] See Principles of Radiation Therapy (NSCL-C).
[v] Lesions at low risk of becoming symptomatic can be observed (eg, small subsolid nodules with slow growth). However, if the lesion(s) becomes symptomatic or becomes high risk for producing symptoms (eg,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

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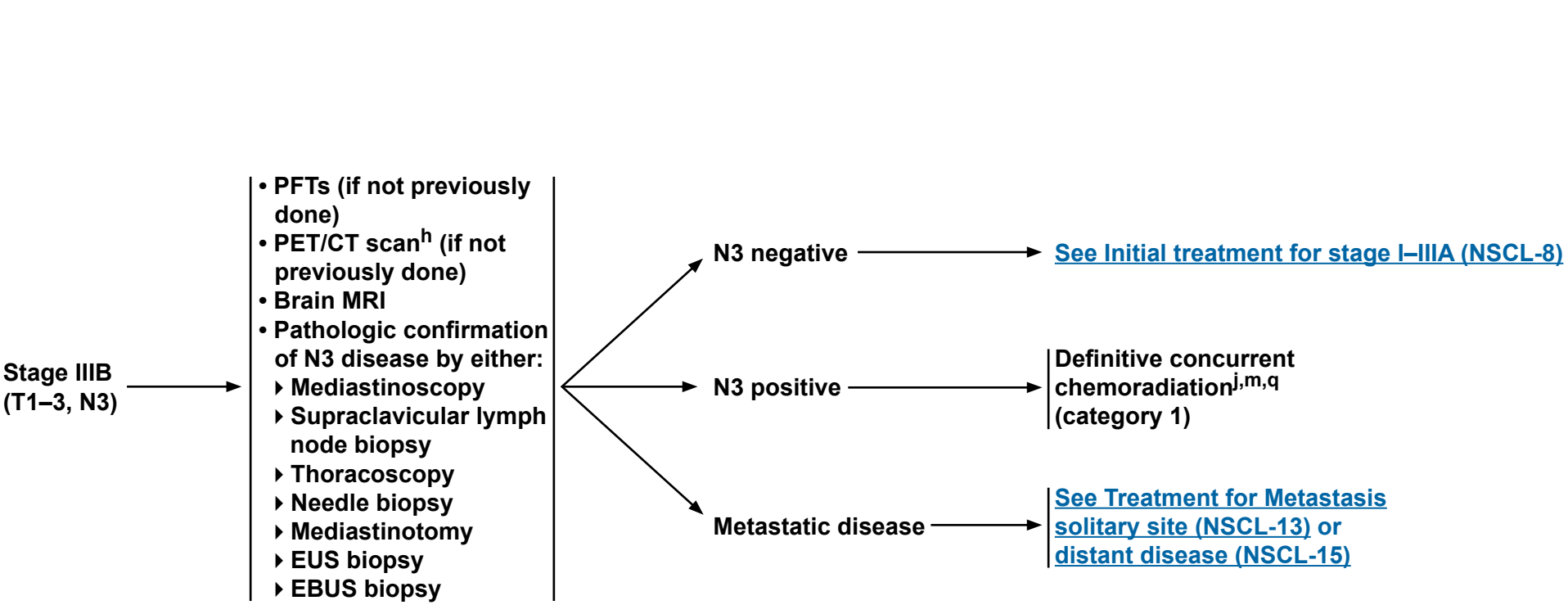

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[m]See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[q]If full-dose chemotherapy is not given concurrently with RT as initial treatment, give additional 2 cycles of full-dose chemotherapy.

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NCCN Guidelines Version 3.2014
Non-Small Cell Lung Cancer

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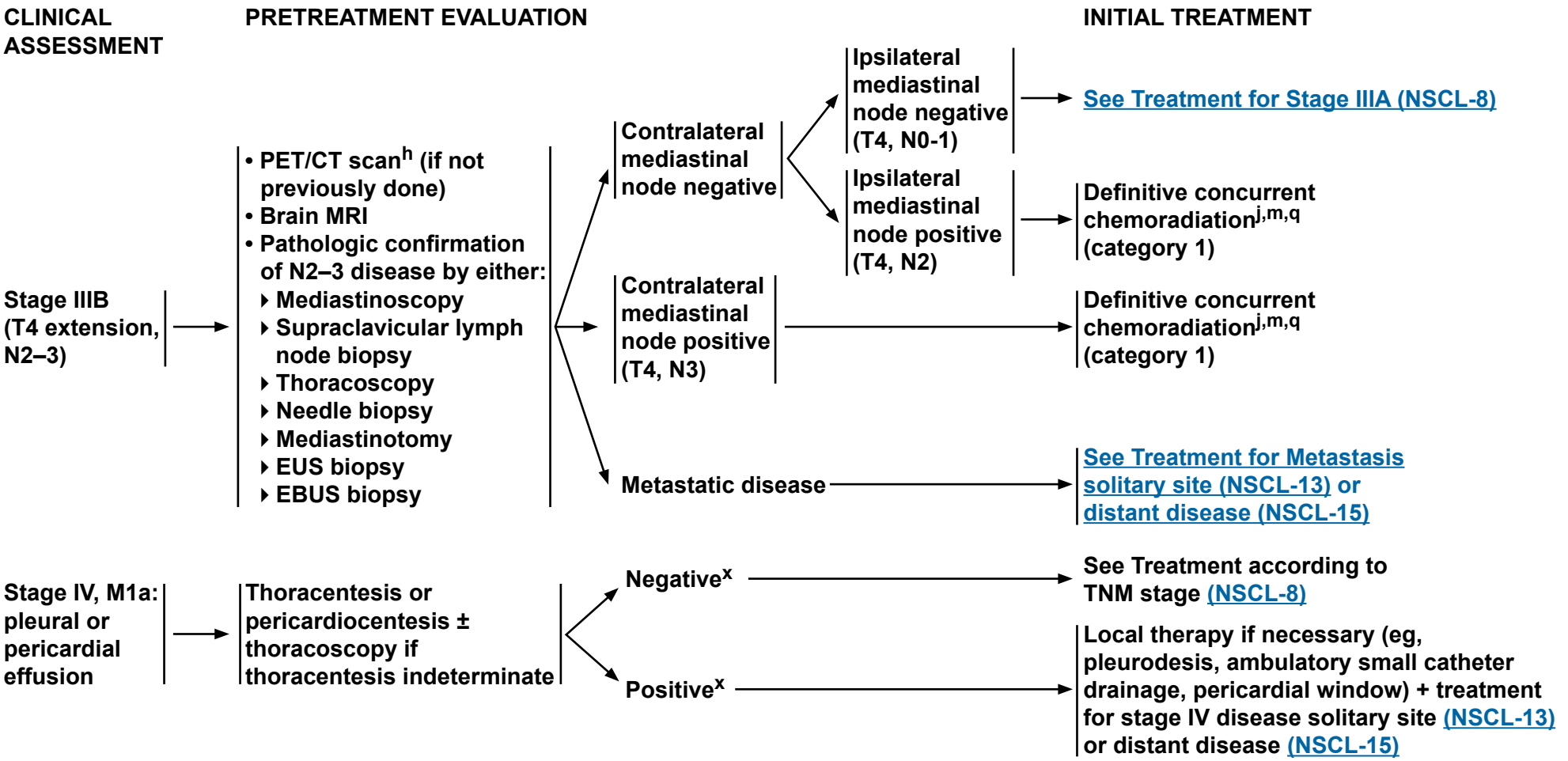

[h]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.

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

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

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

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

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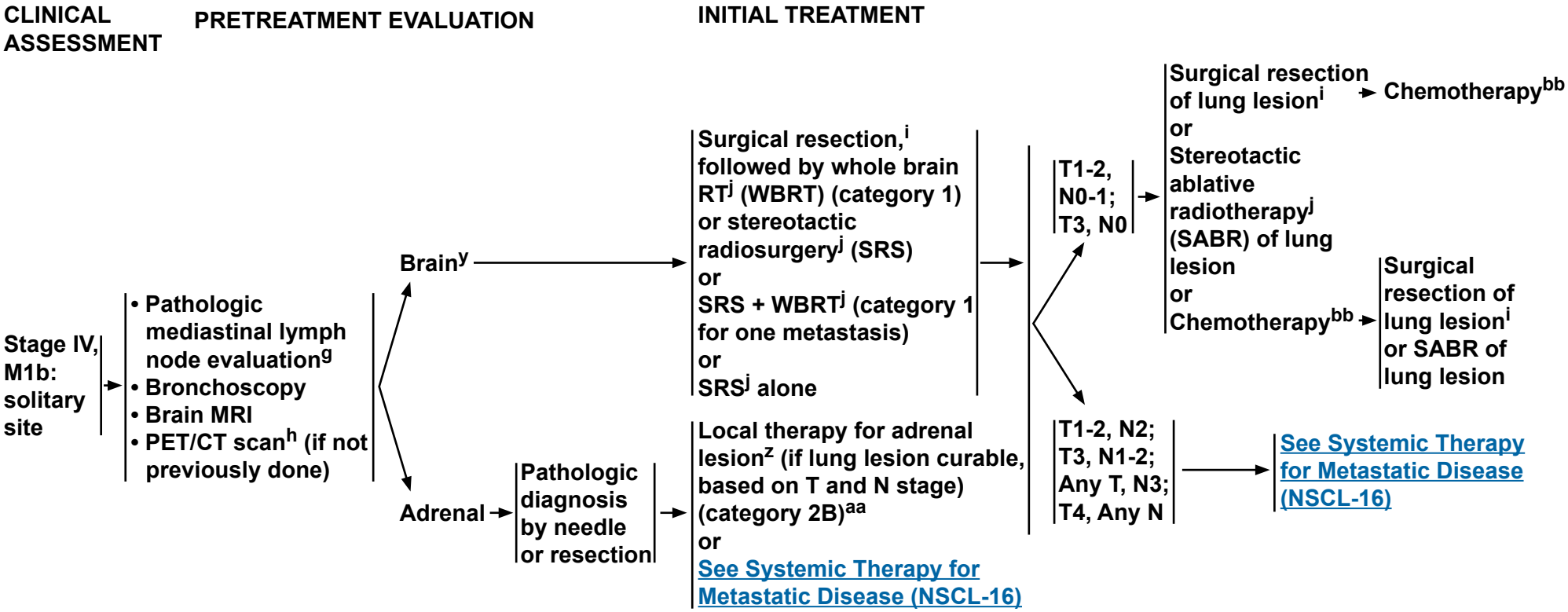

[g]Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS, and CT-guided biopsy.
[h]Positive PET/CT scan findings for distant disease need pathologic or other radiologic confirmation. If PET/CT scan is positive in the mediastinum, lymph node status needs pathologic confirmation.
[i]See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

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SURVEILLANCE

No evidence of clinical/radiographic disease, stages I-IV:
- **H&P and chest CT ± contrast every 6-12 mo for 2 y, then H&P and a 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).**

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

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

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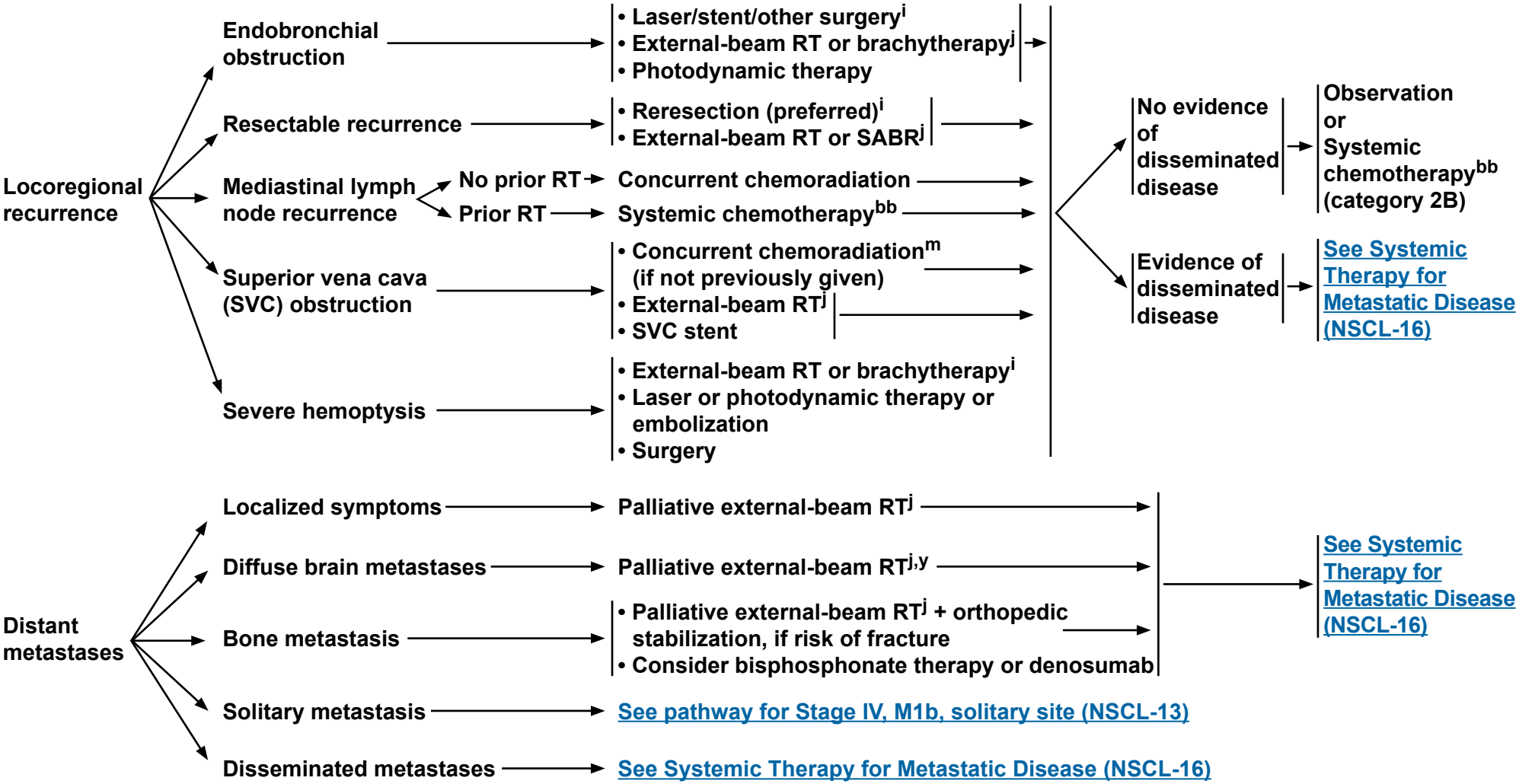
THERAPY FOR RECURRENCE AND METASTASIS



[i] See Principles of Surgical Therapy (NSCL-B).
[j] See Principles of Radiation Therapy (NSCL-C).
[m] See Chemotherapy Regimens Used with Radiation Therapy (NSCL-E).
[y] See NCCN Guidelines for Central Nervous System Cancers.
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).

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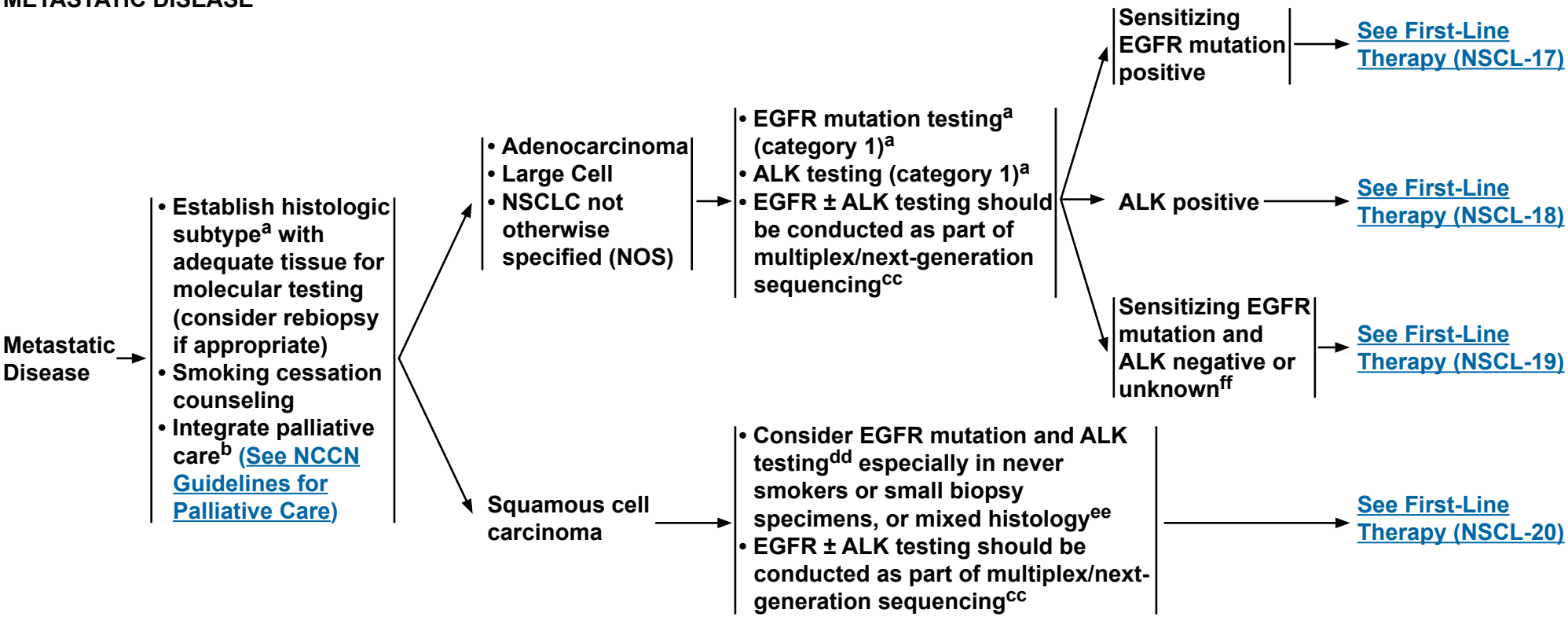
SYSTEMIC THERAPY FOR METASTATIC DISEASE

HISTOLOGIC SUBTYPE



[a] See Principles of Pathologic Review (NSCL-A).
[b] 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.
[cc] See Targeted Agents for Patients with Other Genetic Alterations (NSCL-H).
[dd] In patients with squamous cell carcinoma, the observed incidence of EGFR mutations is 2.7% with a confidence that the true incidence of mutations is less than 3.6%. This frequency of EGFR mutations does not justify routine testing of all tumor specimens. Forbes SA, Bharma G, Bamford S, et al. The catalogue of somatic mutations in cancer (COSMIS). Curr Protoc Hum Genet 2008;chapter 10:unit 10.11.
[ee] 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.
[ff] 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.

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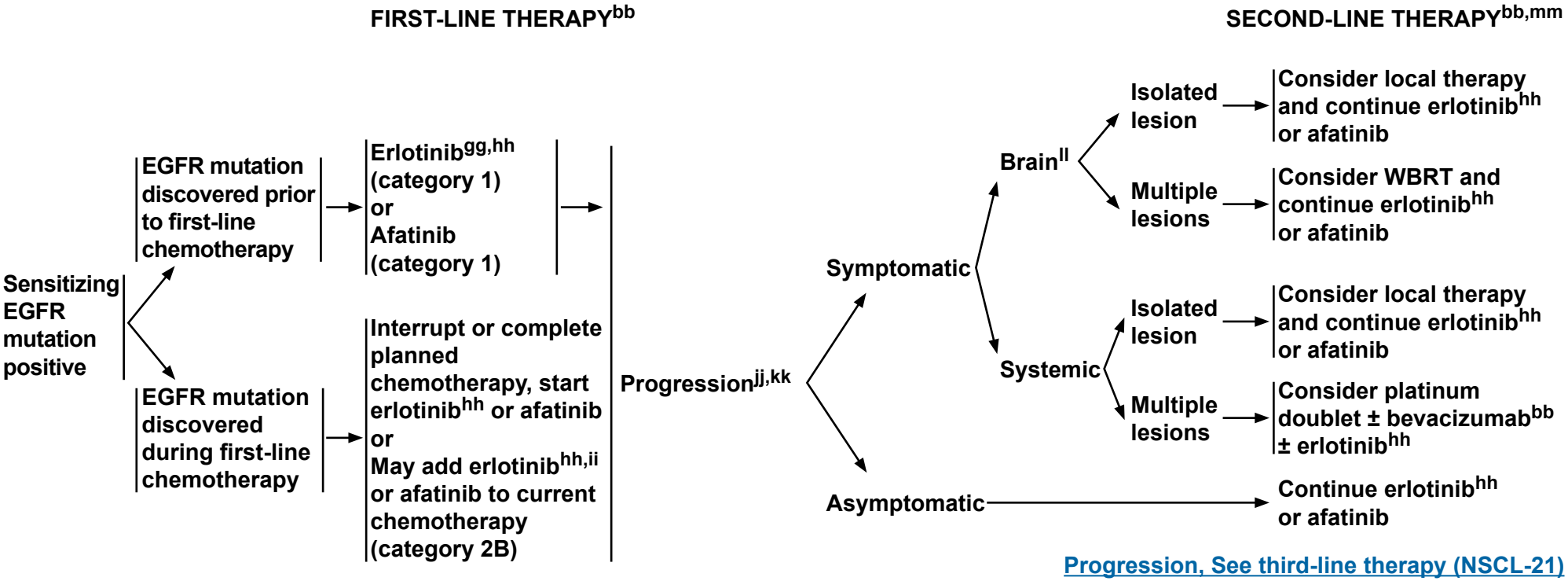
ADENOCARCINOMA, LARGE CELL, NSCLC NOS: SENSITIZING EGFR MUTATION POSITIVE[a]



Progression, See third-line therapy (NSCL-21)

[a] See Principles of Pathologic Review (NSCL-A).
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[gg] For performance status 0-4.
[hh] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ii] 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.
[jj] Biopsy on progression to determine mechanism of acquired resistance, because proportion of patients will transform to SCLC at progression.
[kk] Beware of flare phenomenon in subset of patients who discontinue EGFR TKI. If disease flare occurs, restart EGFR TKI.
[ll] Consider pulse erlotinib for carcinomatosis meningitis.
[mm] Afatinib appears to have some efficacy in patients who progressed on EGFR therapy. Miller VA, Hirsh V, Cadrenal J, et al. Afatinib versus placebo for patients with advanced, metastatic non-small-cell lung cancer after failure of erlotinib, gefitinib, or both, and one or two lines of chemotherapy (LUX-Lung 1): a phase 2b/3 randomised trial. Lancet Oncol 2012;13:528-38.

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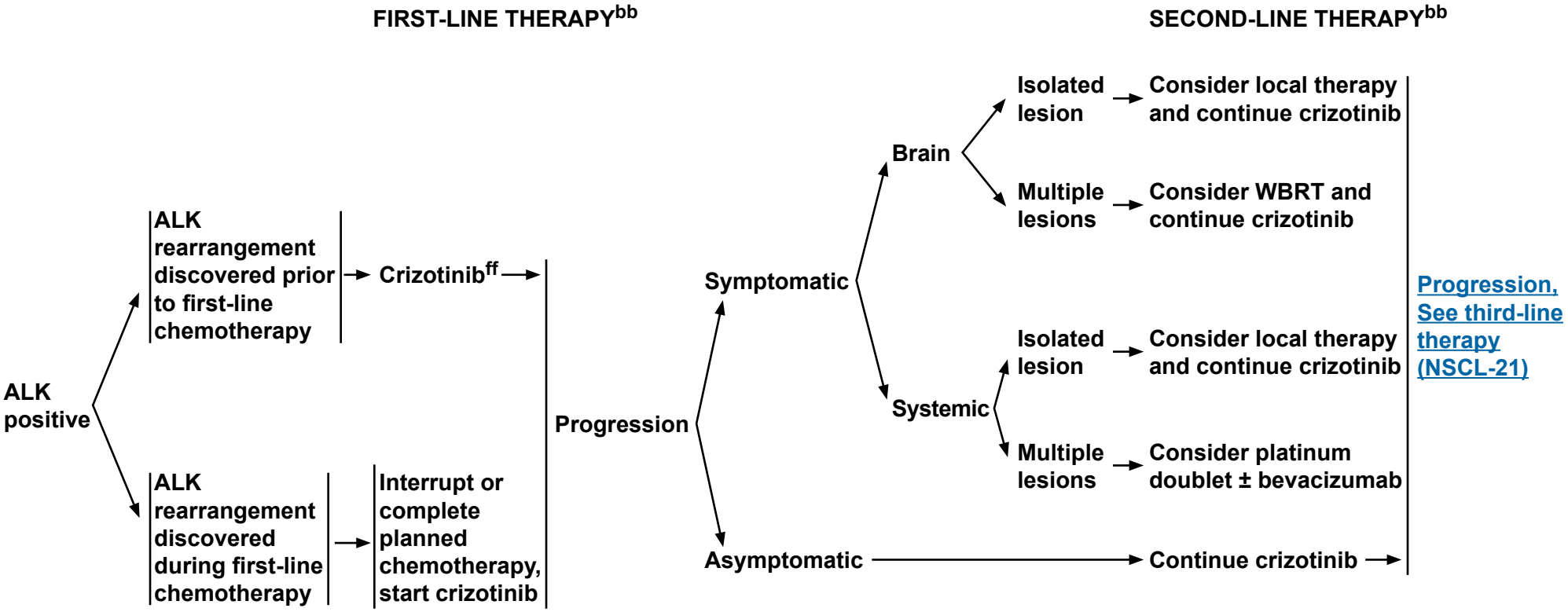
ADENOCARCINOMA, LARGE CELL, NSCLC NOS: ALK POSITIVE[a]



[a] See Principles of Pathologic Review (NSCL-A).
[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[ff] 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.

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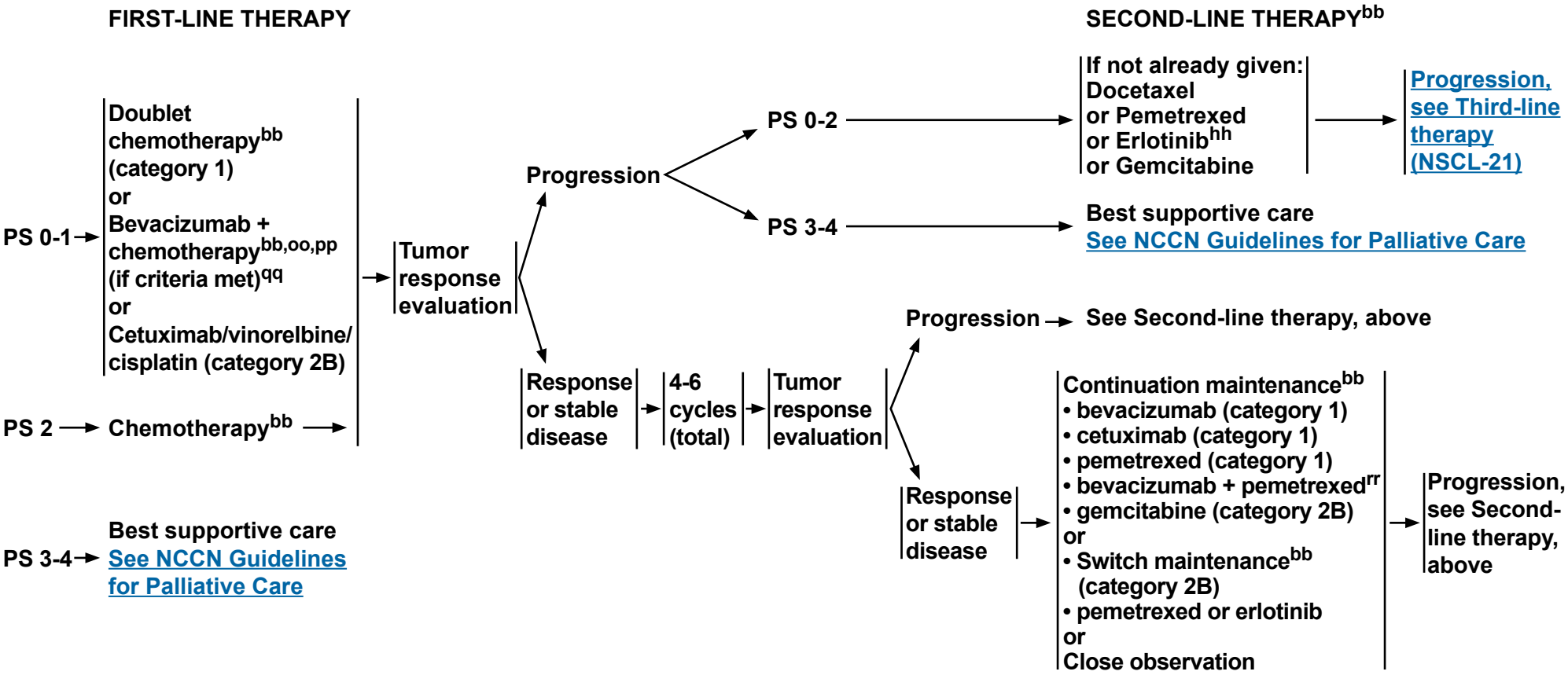
ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION AND ALK NEGATIVE OR UNKNOWN[nn]



[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[hh] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[nn] Consider additional mutational testing if only EGFR and ALK were performed. See Targeted Agents for Patients with Other Genetic Alterations (NSCL-H).
[oo] Bevacizumab should be given until progression.
[pp] Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
[qq] 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.
[rr] If bevacizumab was used with a first-line pemetrexed/platinum chemotherapy regimen.

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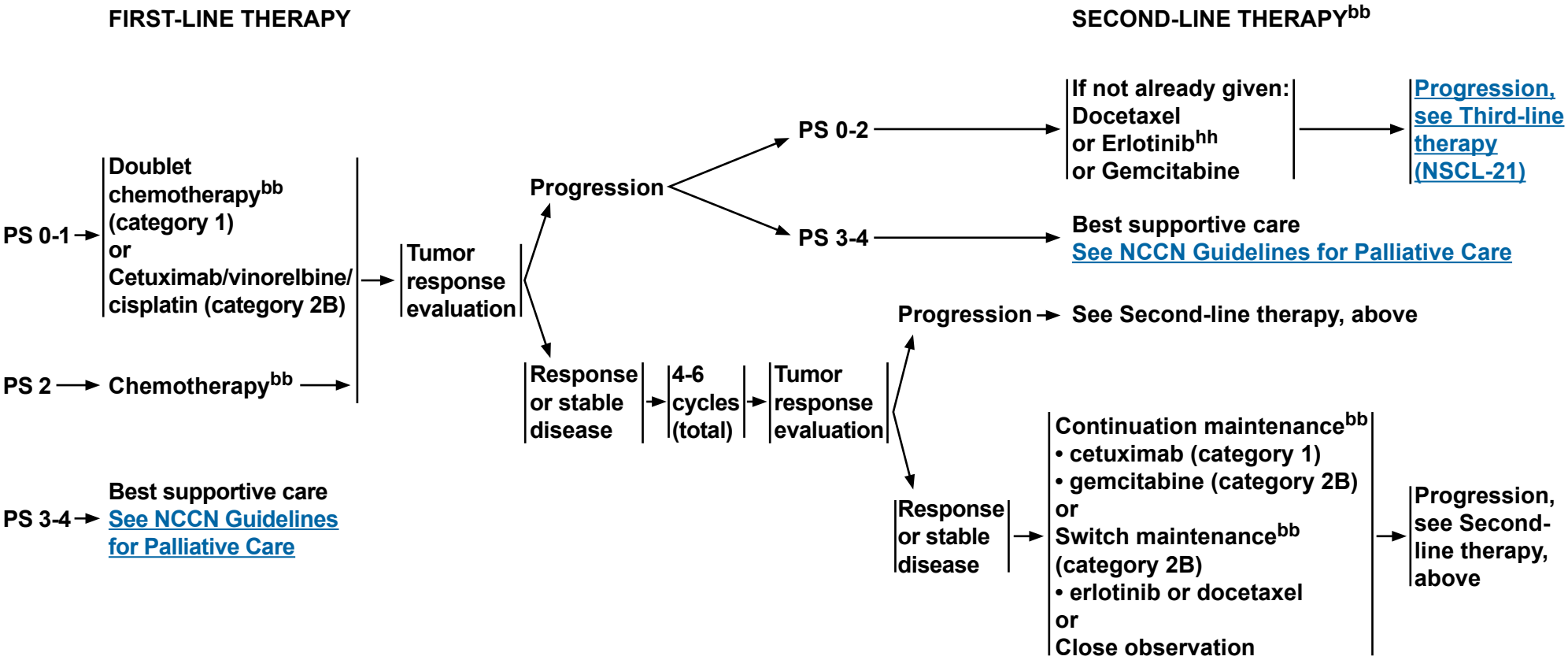
SQUAMOUS CELL CARCINOMA



[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[hh] 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.
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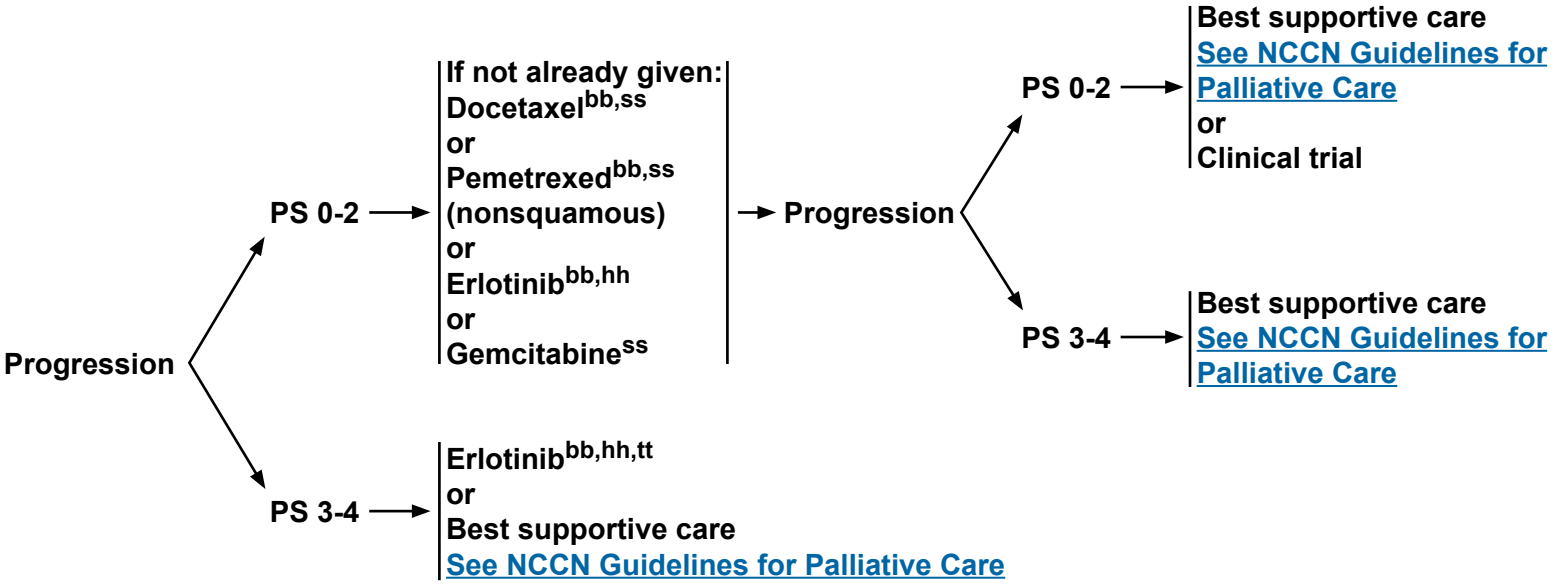
ADENOCARCINOMA, LARGE CELL, NSCLC NOS, or SQUAMOUS CELL CARCINOMA

THIRD-LINE THERAPY



[bb] See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
[hh] In areas of the world where gefitinib is available, it may be used in place of erlotinib.
[ss] Pemetrexed, docetaxel, and gemcitabine are category 2B if patient did not receive erlotinib or crizotinib in first- or second-line therapy.
[tt] Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

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

PRINCIPLES OF PATHOLOGIC REVIEW (1 of 4)

Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the histologic type of lung cancer and to determine all staging parameters as recommended by the AJCC,[1] including tumor size, the extent of invasion (pleural and bronchial), adequacy of surgical margins, and presence or absence of lymph node metastasis.[2,3] Further, determination of the specific molecular abnormalities of the tumor is critical for predicting sensitivity or resistance to an increasing number of drugable targets, primarily tyrosine kinase inhibitors (TKIs) (see *Molecular Diagnostic Studies* in this section).[4,5]
- The WHO tumor classification system has historically provided the foundation for the classification of lung tumors, including histologic types, clinical features, staging considerations, and the molecular, genetic, and epidemiologic aspects of lung cancer.[6,7]
- The pathology diagnostic report should include the histologic classification as described by the WHO for carcinomas of the lung 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.[8] Use of bronchioloalveolar carcinoma (BAC) terminology is strongly discouraged.
- The generic term "non-small cell lung cancer (NSCLC)" should be avoided as a single diagnostic term. In small biopsies of poorly differentiated carcinomas where immunohistochemistry (IHC) is used, the following terms are acceptable: "NSCLC favor adenocarcinoma" or "NSCLC favor squamous cell carcinoma."[8] Mutational testing (eg, epidermal growth factor receptor [EGFR]) 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.[8]

Adenocarcinoma Classification[8]

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

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

PRINCIPLES OF 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.[9-11]
- Primary pulmonary adenocarcinoma
  - An appropriate panel of immunohistochemical stains is recommended to exclude metastatic carcinoma to the lung.[12]
  - TTF-1 is a homeodomain-containing nuclear transcription protein of the Nkx2 gene family that is expressed in epithelial cells of the embryonal and mature lung and thyroid. TTF-1 immunoreactivity is seen in primary pulmonary adenocarcinoma in the majority (70%-100%) of non-mucinous adenocarcinomas subtypes.[13] Metastatic adenocarcinoma to the lung is virtually always negative for TTF-1 except in metastatic thyroid malignancies, in which case thyroglobulin is also positive.
  - Napsin A—an aspartic proteinase expressed in normal type II pneumocytes and in proximal and distal renal tubules—appears to be expressed in >80% of lung adenocarcinomas and may be a useful adjunct to TTF-1.[12]
  - The panel of TTF-1 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).[8]
- Neuroendocrine differentiation
  - CD56, chromogranin, and synaptophysin are used to identify neuroendocrine tumors.
- Malignant mesothelioma versus pulmonary adenocarcinoma
  - The distinction between pulmonary adenocarcinoma and malignant mesothelioma (epithelial type) is made by using a panel of markers, including 2 with known immunopositivity in mesothelioma (but negative in adenocarcinoma) and 2 with known positivity in adenocarcinoma (but negative in mesothelioma).[11]
    - ◊ Immunostains relatively sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, HMBE-1, and cytokeratin 5/6 (negative in adenocarcinoma).[14,15]
  - Antibodies immunoreactive in adenocarcinoma include CEA, B72.3, Ber-EP4, MOC31, CD15, and TTF-1 (negative in mesothelioma).[8,11]

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 4)

Molecular Diagnostic Studies in Lung Cancer

- **EGFR and KRAS**
  - EGFR is normally found on the surface of epithelial cells and is often overexpressed in a variety of human malignancies. Presence of EGFR-activating mutations represents a critical biological determinant for proper therapy selection in patients with lung cancer.
  - There is a significant association between EGFR mutations—especially exon 19 deletion and exon 21 (L858R, L861) and exon 18 (G719X, G719) mutations—and sensitivity to TKIs.[16-19]
  - The exon 20 insertion mutation may predict resistance to clinically achievable levels of TKIs.[20,21]
  - EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.[22]
  - 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.[23]
  - The prevalence of EGFR mutations in adenocarcinomas is 10% of Western and up to 50% of Asian patients, with higher EGFR mutation frequency in non-smokers, women, and non-mucinous cancers. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.[24] The most common EGFR mutations result in an arginine for leucine substitution at amino acid 858 in exon 21 (L858R) and in frame deletions at exon 19. Mutations are more common in non-mucinous lung adenocarcinoma with lepidic pattern (former BAC pattern) and in lung adenocarcinoma with papillary (and or micropapillary) pattern.
  - Primary resistance to TKI therapy is associated with KRAS mutation. Acquired resistance is associated with second-site mutations within the EGFR kinase domain (such as T790M), amplification of alternative kinases (such as MET), histologic transformation from NSCLC to SCLC, and epithelial to mesenchymal transition (EMT).
- **ALK**
  - Anaplastic lymphoma kinase (ALK) gene rearrangements represent the fusion between ALK and various partner genes, including echinoderm microtubule-associated protein-like 4 (EML4).[25] ALK fusions have been identified in a subset of patients with NSCLC and represent a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.[26] Crizotinib 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.[27,28] However, for the most part, ALK translocations and EGFR mutations are mutually exclusive.[27, 29-31]
  - The current standard method for detecting ALK NSCLC is fluorescence in situ hybridization (FISH), although other methods are currently being evaluated, including polymerase chain reaction (PCR) and IHC. A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged anaplastic large cell lymphomas (ALCL), is applicable for the diagnosis of ALK-rearranged lung adenocarcinomas. The IHC tests used to diagnose ALK-rearranged ALCLs in clinical laboratories worldwide are inadequate for the detection of most ALK-rearranged lung cancer.[32,33] This inadequacy is because of the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs. A molecular diagnostic test that uses FISH was recently approved by the FDA to determine which patients have ALK-positive lung cancer.

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PRINCIPLES OF PATHOLOGIC REVIEW (4 of 4) - References

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PRINCIPLES OF SURGICAL THERAPY (1 of 4)

Evaluation

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

Resection

- Anatomic pulmonary resection is preferred for the majority of patients with NSCLC.
- Sublobar resection - Segmentectomy and wedge resection should achieve parenchymal resection margins ≥2 cm or ≥ the size of the nodule.
- Sublobar resection should also sample appropriate N1 and N2 lymph node stations unless not technically feasible without substantially increasing the surgical risk.
- Segmentectomy (preferred) or wedge resection is appropriate in selected patients for the following reasons:
  - Poor pulmonary reserve or other major comorbidity that contraindicates lobectomy
  - Peripheral nodule[1] ≤2 cm with at least one of the following:
    - Pure AIS histology
    - Nodule has ≥50% ground-glass appearance on CT
    - Radiologic surveillance confirms a long doubling time (≥400 days)
- VATS or minimally invasive surgery 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)

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

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

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PRINCIPLES OF SURGICAL THERAPY (2 of 4)

Margins and Nodal Assessment

- Surgical pathologic correlation is critical to assess apparent close or positive margins, as these may not represent true margins or may not truly represent areas of risk for local recurrence (eg, medial surface of mainstem or bronchus intermedius when separate subcarinal lymph node dissection has been performed, 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.[1] Two randomized trials evaluated the role of surgery in this population, but neither showed an overall survival benefit with the use of surgery.[2,3] However, this population is heterogeneous and the panel believes that these trials did not sufficiently evaluate the nuances present with the heterogeneity of N2 disease and the likely oncologic benefit of surgery in specific clinical situations.

- The presence or absence of N2 disease should be vigorously determined by both radiologic and invasive staging prior to the initiation of therapy since the presence of mediastinal nodal disease has a profound impact on prognosis and treatment decisions. (NSCL-1, NSCL-2, and NSCL-6)
- Patients with occult-positive N2 nodes discovered at the time of pulmonary resection should continue with the planned resection along with formal mediastinal lymph node dissection. If N2 disease is noted in patients undergoing VATS, the surgeon may consider stopping the procedure so that induction therapy can be administered before surgery; however, continuing the procedure is also an option.
- The determination of the role of surgery in a patient with N2-positive lymph nodes should be made prior to the initiation of any therapy by a multidisciplinary team, including a board-certified thoracic surgeon who has a major part of his/her practice dedicated to thoracic oncology.[4]
- The presence of N2-positive lymph nodes substantially increases the likelihood of positive N3 lymph nodes. Pathologic evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS are additional techniques for minimally invasive pathologic mediastinal staging that are complementary to mediastinoscopy. Even when these modalities are employed it is important to have an adequate evaluation of the number of stations involved and biopsy and documentation of negative contralateral lymph node involvement prior to a final treatment decision.

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

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PRINCIPLES OF SURGICAL THERAPY (3 of 4)

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

- Repeat mediastinoscopy, while possible, is technically difficult and has a lower accuracy compared to primary mediastinoscopy. One possible strategy is to perform EBUS (± EUS) in the initial pretreatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.[5]
- Patients with a single lymph node smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.[1,6,7]
- Restaging after induction therapy is difficult to interpret, but CT +/- PET should be performed to exclude disease progression or interval development of metastatic disease.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.[7,8]
- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN Member Institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively.[5,9] Neoadjuvant chemoradiotherapy is associated with higher rates of pathologic complete response and negative mediastinal lymph nodes.[10] However, that is achieved at the expense of higher rates of acute toxicity and increased cost.
- When neoadjuvant chemoradiotherapy is used with doses lower than those used for standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. Treatment breaks of more than 1 week are considered unacceptable.
- When timely surgical evaluation is not available, the strategy of neoadjuvant chemoradiotherapy should not be used. Another option in individual cases, and with the agreement of the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.[11,12] If a surgeon or center is uncertain about the feasibility or safety of resection after definitive doses of radiation, consider obtaining an additional surgical opinion from a high-volume specialized center. These operations may also benefit from additional considerations of soft tissue flap coverage in the radiation field resection.
- Data from a large multi-institutional trial indicate that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality.[2] However, it is not clear if this is also true with neoadjuvant chemotherapy alone. Further, many groups have challenged that cooperative group finding with single-institution experiences demonstrating safety of pneumonectomy after induction therapy.[13-16] In addition, there is no evidence that adding RT to induction regimens for patients with operable stage IIIA (N2) disease improves outcomes compared to induction chemotherapy.[17]

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

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

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PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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

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PRINCIPLES OF RADIATION THERAPY (1 of 9)

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

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

Early-Stage NSCLC (Stage I)

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

Locally Advanced NSCLC (Stagew II-III)

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

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PRINCIPLES OF RADIATION THERAPY (2 of 9)

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

- Accelerated RT regimens may be beneficial, particularly if not concurrent with chemotherapy (ie, in a sequential or RT-only approach).[20,21]
- RT has a role before or after surgery.
  http://www.acr.org/~/media/ACR/Documents/AppCriteria/Oncology/InductionAndAdjuvantTherapyForN2NSCLC.pdf
  - Preoperative concurrent chemoRT is an option for patients with resectable stage IIIA (minimal N2 and treatable with lobectomy)[22] and is recommended for resectable superior sulcus tumors.[23-24]
  - Preoperative chemotherapy and postoperative RT is an alternative for patients with resectable stage IIIA.[25,26]
  - The determination of resectability in trimodality therapy should be made prior to initiation of all treatment.
  - In patients with clinical stage I/II upstaged surgically to N2+, PORT appears to improve survival significantly as an adjunct to postoperative chemotherapy in non-randomized analyses.[27,28] Although the optimal sequence is not established, PORT is generally administered after postoperative chemotherapy. PORT with concurrent chemotherapy can be administered safely in medically fit patients[29-31] and is recommended for positive resection margins.
  - PORT is not recommended for patients with pathologic stage N0-1 disease, because it has been associated with increased mortality, at least when using older RT techniques.[32]

Advanced/Metastatic NSCLC (Stage IV)

- RT is recommended for local palliation or prevention of symptoms (such as pain, bleeding, or obstruction).
- Definitive local therapy to isolated or limited metastatic sites (oligometastases) (including but not limited to brain, lung, and adrenal gland) achieves prolonged survival in a small proportion of well-selected patients with good performance status who have also received radical therapy to the intrathoracic disease. Definitive RT to oligometastases, particularly SABR, is an appropriate option in such cases if it can be delivered safely to the involved sites.[33-35]
- 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.[37,38] Useful references include the recent reviews of normal organ dose responses from the QUANTEC project.[39-43]

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PRINCIPLES OF RADIATION THERAPY (3 of 9)

Node-Negative Early-Stage SABR

- The high-dose intensity and conformity of SABR require minimizing the PTV.
- For SABR, intensive regimens of BED ≥100 Gy are associated with significantly better local control and survival than less intensive regimens.[44] In the United States, only regimens of ≤5 fractions meet the arbitrary billing code definition of SBRT, but slightly more protracted regimens are appropriate as well.[44,45] 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,[45,46] while 54 to 60 Gy in 3 fractions is unsafe and should be avoided.[47] 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.[48]
- 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.[49,50] 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.[51-55] One randomized trial found improved survival for IFI versus ENI, possibly because it enabled dose escalation.[56] 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.[57] Dose escalation in RT alone,[58] sequential chemoRT,[59] or concurrent chemoRT[60] 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.[61-64] 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.[65] A meta-analysis demonstrated improved survival with accelerated fractionation RT regimens,[66] 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,[67-70] 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.[71] Standard doses after complete resection are 50 to 54 Gy in 1.8 to 2 Gy fractions, but a boost may be administered to high-risk regions including areas of nodal extracapsular extension or microscopic positive margins.[29,30] Lung dose constraints should be more conservative as tolerance appears to be reduced after surgery. The ongoing European LungART trial provides useful guidelines for PORT technique.[72]

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PRINCIPLES OF RADIATION THERAPY (4 of 9)

Advanced Stage/Palliative RT

- The dose and fractionation of palliative RT should be individualized based on goals of care, symptoms, performance status, and logistical considerations. Shorter courses of RT provide similar pain relief as longer courses, but with a higher potential need for retreatment,[73-76] 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,[77] especially for patients with significant atelectasis and when IV CT contrast is contraindicated. A randomized trial of PET/CT versus CT-only RT planning demonstrated improved preemption of futile radical RT, decreased recurrences, and a trend toward improved overall survival with PET/CT RT planning.[77] Given the potential for rapid progression of NSCLC,[79,80] 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.[50]
- 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.[81]
- IGRT—including (but not limited to) orthogonal pair planar imaging and volumetric imaging (such as CBCT or CT on rails)—is recommended when using SABR and 3D-CRT/IMRT with steep dose gradients around the target, when OARs are in close proximity to high-dose regions, and when using complex motion management techniques.

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PRINCIPLES OF RADIATION THERAPY (5 of 9)

Table 1. Commonly Used Abbreviations in Radiation Therapy

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

*Refer to ICRU Report 83 for detailed definitions.

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Table 2. Commonly Used Doses for SABR

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

Table 3. Maximum Dose Constraints for SABR*

OAR/Regimen	1 Fraction	3 Fractions	4 Fractions	5 Fractions
Spinal Cord	14 Gy	18 Gy (6 Gy/fx)	26 Gy (6.5 Gy/fx)	30 Gy (6 Gy/fx)
Esophagus	15.4 Gy	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).

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

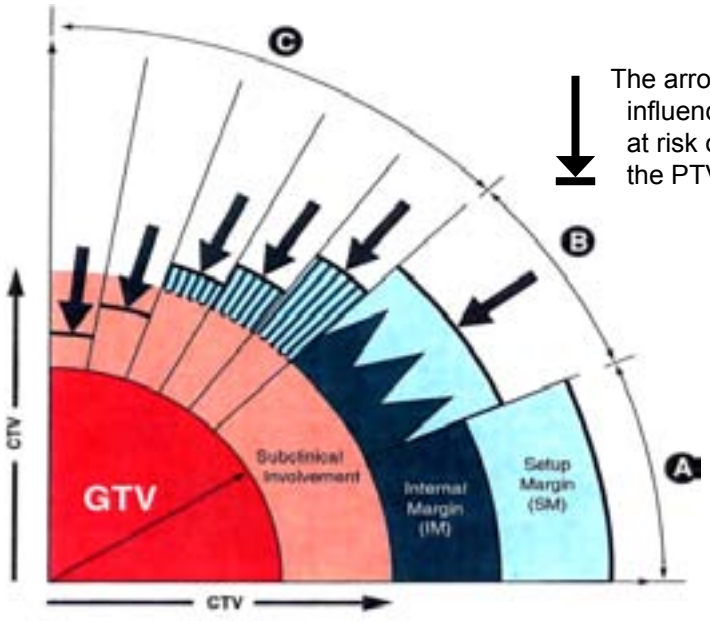
Treatment Type	Total Dose	Fraction Size	Treatment Duration
Definitive RT with or without chemotherapy	60-74 Gy	2 Gy	6-7.5 weeks
Preoperative RT	45-50 Gy	1.8-2 Gy	5 weeks
Postoperative RT			
• Negative margins	50-54 Gy	1.8-2 Gy	5-6 weeks
• Extracapsular nodal extension or microscopic positive margins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

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



The arrow illustrates the influence of the organs at risk on delineation of the PTV (thick, full line)

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CHEMOTHERAPY REGIMENS FOR NEOADJUVANT AND ADJUVANT THERAPY

- **Cisplatin 50 mg/m² days 1 and 8; vinorelbine 25 mg/m² days 1, 8, 15, 22, every 28 days for 4 cycles[a]**
- **Cisplatin 100 mg/m² day 1; vinorelbine 30 mg/m² days 1, 8, 15, 22; every 28 days for 4 cycles[b,c]**
- **Cisplatin 75-80 mg/m² day 1; vinorelbine 25-30 mg/m² days 1 + 8, every 21 days for 4 cycles**
- **Cisplatin 100 mg/m² day 1; etoposide 100 mg/m² days 1-3, every 28 days for 4 cycles[b]**
- **Cisplatin 80 mg/m² days 1, 22, 43, 64; vinblastine 4 mg/m² days 1, 8, 15, 22, 29 then every 2 wks after day 43, every 21 days for 4 cycles[b]**
- **Cisplatin 75 mg/m² day 1; gemcitabine 1250 mg/m² days 1, 8, every 21 days for 4 cycles**
- **Cisplatin 75 mg/m² day 1; docetaxel 75 mg/m² day 1 every 21 days for 4 cycles[d]**
- **Cisplatin 75 mg/m² day 1, pemetrexed 500 mg/m² day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype) every 21 days for 4 cycles**

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

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

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CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

Concurrent Chemotherapy/RT Regimens

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

Sequential Chemotherapy/RT Regimens

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

Concurrent Chemotherapy/RT Followed by Chemotherapy

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

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

[a]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.
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SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (1 OF 3)

ADVANCED DISEASE:

- **The drug regimen with the highest likelihood of benefit with toxicity deemed acceptable to both the physician and the patient should be given as initial therapy for advanced lung cancer.**
- **Stage, weight loss, performance status, and gender predict survival.**
- **Platinum-based chemotherapy prolongs survival, improves symptom control, and yields superior quality of life compared to best supportive care.**
- **Histology of NSCLC is important in the selection of systemic therapy.**
- **New agent/platinum combinations have generated a plateau in overall response rate (≈ 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)

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

Maintenance Therapy

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

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

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) in patients with EGFR sensitizing mutations or ALK rearrangements who have experienced objective regressions with targeted therapy, no agent should be continued after disease progression has been documented except in selected situations. (refer to discussion section)**

See Specific Systemic Agents on page NSCL-F (3 of 3)

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

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

- **Cisplatin**[1-9]
- **Carboplatin**[4,6-11]
- **Paclitaxel**[1,4,6,8-11]
- **Docetaxel**[5,7,8,12,13]
- **Vinorelbine**[7,9,10]
- **Gemcitabine**[3,5,6,8,9,13]
- **Etoposide**[4]
- **Irinotecan**[9]
- **Vinblastine**
- **Mitomycin**
- **Ifosfamide**[12]
- **Pemetrexed**[14,15]
- **Erlotinib**[16]
- **Bevacizumab**[17]
- **Cetuximab**[18]
- **Albumin-bound paclitaxel**[19-21] †
- **Crizotinib**[22]
- **Afatinib**[23]

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†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.

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CANCER SURVIVORSHIP CARE

NSCLC Long-term Follow-up Care

- Cancer Surveillance
  - H&P and a chest CT scan ± contrast every 6-12 months for 2 years, then H&P and a non-contrast-enhanced chest CT scan annually
  - Smoking status assessment at each visit; counseling and referral for cessation as needed.
- Immunizations
  - Annual influenza vaccination, herpes zoster vaccine
  - Pneumococcal vaccination with revaccination as appropriate

Counseling Regarding Health Promotion and Wellness[1]

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

Additional Health Monitoring

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

Resources

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

Cancer Screening Recommendations[2,3]

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

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

[1]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 (Accessed November 30, 2012)
[2]Memorial Sloan-Kettering Cancer Center Screening Guidelines: http://www.mskcc.org/mskcc/html/65279.cfm (Accessed November 30, 2012)
[3]American Cancer Society Guidelines for Early Detection of Cancer: http://www.cancer.org/docroot/PED/content/PED_2_3X_ACS_Cancer_Detection_Guidelines_36.asp?sitearea=PED (Accessed November 30, 2012)

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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,[1] gefitinib,[2] afatinib[3]
ALK rearrangements	crizotinib[4]
HER2 mutations	trastuzumab,[5] afatinib[6]
BRAF mutations	vemurafenib,[7] dabrafenib[8]
MET amplification	crizotinib[9]
ROS1 rearrangements	crizotinib[10]
RET rearrangements	cabozantinib[11]

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

Table 1. Definitions for T, N, M*

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

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

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

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

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

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

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

Table 2. Anatomic Stage and Prognostic Groups

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

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

6th Edition T/M Descriptor	7th Edition T/M	N0	N1	N2	N3
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (<2-3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (<5-7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion		IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)		**IIB**	**IIIA**	**IIIA**	IIIB
T4 extension	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)		**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)		IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

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

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

Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Table of Contents

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.[1] Only 16.6% of all lung cancer patients are alive 5 years or more after diagnosis (http://seer.cancer.gov/statfacts/html/lungb.html).[2] 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 therapy.[3,4] Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.[5]

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/).[6-11] Cigarette smoke contains many carcinogenic chemicals (eg, nitrosamines, benzo(a)pyrene diol epoxide).[10,12] 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).[8,12-15] Radon gas, a radioactive gas that is produced by the decay of radium 226, also seems to cause lung cancer.[6,16-19] 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.[20] 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).[21,22] 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.[23,24] 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,[25] no increase in the incidence of lung cancer was found among postmenopausal women treated with estrogen plus progestin HRT; however, the risk of death from non-small cell lung cancer (NSCLC) increased.[25]

Prevention and Screening

Approximately 85% to 90% of cases of lung cancer are caused by cigarette smoking.[9] 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). Smoking harms nearly every organ in the body; smokers have increased mortality compared with nonsmokers.[26] Those who live with someone who smokes have an increased risk for lung cancer (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/).[27-29] 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.[30] 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/resources/tobacco/treating-tobacco-use.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.[31-33] However, almost 30% of patients had nausea while using varenicline.[34] The effectiveness of varenicline for preventing relapse has not been clearly established.[35] 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.[36] Bupropion is also associated with similar serious neuropsychiatric symptoms (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020711s036lbl.pdf). Nicotine replacement has fewer adverse effects than varenicline or bupropion.[37] However, in spite of the potential adverse effects, it is probably more beneficial for motivated patients to use agents to promote smoking cessation.[37]

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a major obstacle to improving lung cancer outcomes.[38,39] 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

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

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.[43] Data from the NLST showed that screening high-risk patients with low-dose helical CT decreased the mortality rate from lung cancer by 20% when compared with chest radiograph.[44] High-risk patients 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.[43,45] 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).[46,47]

The I-ELCAP has been assessing whether annual screening by low-dose helical CT scan increases the detection of early-stage lung cancer in patients at risk for cancer. Data from I-ELCAP showed that stage I lung cancer can be detected using annual low-dose CT screening. The 10-year survival rate was 92% for stage I patients whose cancers were promptly removed; however, all stage I patients who chose not to be treated died within 5 years.[48] Additional information on I-ELCAP can be found at http://www.ielcap.org/. Screening can increase the diagnosis of early-stage lung cancers. Data from the NLST show that screening decreases the mortality rate.[44]

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).[49] 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.[50]

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).[51] 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 presumably it is still curable.[44] 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 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).[44] 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.[52]

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).[53] 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).[3,54-59] Preoperative evaluations include examination of the following: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy.[52,60] Minimally invasive techniques can be used to obtain specimens in patients with advanced unresectable NSCLC.[61,62] However, diagnosis may be more

difficult when using small biopsies and cytology.[63] 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).[64,65]

Lobectomy or pneumonectomy specimens are evaluated intraoperatively to determine the surgical resection margin status, diagnose incidental nodules discovered at the time of surgery, or evaluate the regional lymph nodes. Postoperative evaluation provides the pathology characteristics necessary for the classification of tumor type, staging, and prognostic factors. The surgical pathology report should include the WHO histologic classification for carcinomas of the lung.[66] The classification for lung adenocarcinoma was recently revised by an international panel (see *Adenocarcinoma*).[49] The revised classification requires immunohistochemical, histochemical, and molecular studies (see *Principles of Pathologic Review* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[67] 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.[49] 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. The terms *AIS*, *MIA*, and *large cell carcinoma* should not be used for small samples because of challenges with cytology specimens.[49]

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.[62,68] 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.[49,69] Squamous cell carcinomas are often TTF-1 negative and p63 positive, whereas adenocarcinomas are usually TTF-1 positive.[49] These 2 markers may be sufficient to distinguish adenocarcinomas from squamous cell carcinomas.[49,69] Other markers (eg, p40) may also be useful in distinguishing adenocarcinoma from squamous cell carcinoma.[70,71]

Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma.[72,73] 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.[74] Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40 (podoplanin antibody),[75] and cytokeratin 5/6.[72,73] 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).[72,73,76]

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.[69] However, TTF-1 is positive in tumors from patients with thyroid cancer.[77] 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.[52,69,78] 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.[79,80] 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.[81] Data suggest that microRNA expression can be used to distinguish SCLC from NSCLC.[82]

Staging

The NCCN Guidelines use the AJCC (7th edition) staging system for lung cancer.[83] 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)[84,85] and was adopted by the AJCC.[86,87] 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).[88]

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 (localized stage); 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 (distant stage); 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.[89] Another study in stage I patients (n=19,702) found that 82% had surgical resection and their 5-year overall survival was 54%; however, for untreated stage I NSCLC, 5-year overall survival was only 6%.[90] Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Predictive and Prognostic Biomarkers

Several biomarkers have emerged as predictive and prognostic markers for NSCLC. A *predictive* biomarker is a biomolecule that is indicative of therapeutic efficacy; 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).[91,92] 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.[93] 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 therapy.[94-97]

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) (see *Targeted Therapies* in this Discussion).[98] Although rare, patients with EGFR mutations or ALK gene rearrangements can have mixed squamous cell histology.[99,100] 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)).[54,101,102] 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).[103] 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.[104-106] 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.[95,97,107-113] 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)).[104,114] 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 targeted agents. Several online resources are available that describe NSCLC driver events such as DIRECT (DNA-mutation Inventory to Refine and Enhance Cancer Treatment)[115] and *My Cancer Genome* (http://www.mycancergenome.org/content/disease/lung-cancer).[116]

Prognostic biomarkers include the KRAS oncogene and 5′ endonuclease of the nucleotide excision repair complex (ERCC1). 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).[117] KRAS mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.[91,118,119] High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.[120,121]

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).[122] 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.[123,124] The FDA recently approved afatinib for first-line treatment of patients with metastatic non-squamous NSCLC who have sensitizing EGFR mutations.[125,126]

These sensitizing EGFR mutations are found in approximately 10% of Caucasian patients with NSCLC and up to 50% of Asian patients.[127] Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X).[128] 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.[129-132] However, studies suggest the T790M mutation may also occur in patients who have not previously received TKI therapy.[133] Acquired resistance is also 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).[134,135]

DNA mutational analysis is the preferred method to assess for EGFR status.[136-138] 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.[127,137,139-141] Mutation screening assays using multiplex PCR (eg, Sequenom's MassARRAY system, SNaPshot Multiplex System) can detect more than 50 point mutations, including EGFR.[103] NGS can also be used to detect EGFR.[105]

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.[122] 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.[91] 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.[92] EGFR mutation testing is not usually recommended in patients with pure squamous cell carcinoma, 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.[99] Data suggest that EGFR mutations can occur in patients with adenosquamous carcinoma, which is harder to discriminate from squamous cell carcinoma in small specimens.[99]

Recent data suggest that erlotinib 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.[126,142-147] 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.[126,142] Patients receiving erlotinib have fewer treatment-related severe side effects and deaths when compared with those receiving chemotherapy.[142,148] 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.[148] However, afatinib was potentially associated with 4 treatment-related deaths, whereas there were none in the chemotherapy group.[126]

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.[59] 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.[102] In these selected populations, estimates are that about 30% of patients will have ALK rearrangements.[102,149] ALK rearrangements are not routinely found in squamous cell carcinoma. Although rare, patients with ALK gene rearrangements can have mixed squamous cell histology.[100] 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.[98,150-153] NGS can also be used to assess whether ALK rearrangements are present.[154,155]

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) (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202570s006lbl.pdf).[156-158] Recently, crizotinib has been shown to yield very high response rates (>60%) when used in patients with advanced NSCLC who have ALK rearrangements.[59,159,160] Crizotinib has relatively few side effects (eg, eye disorders, edema, transient changes in renal function).[159,161] However, a few patients have had life-threatening pneumonitis; crizotinib should be discontinued in these patients.[156] 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.[162,163] Newer ALK inhibitors are in development.[164-169] Randomized phase III trials are comparing crizotinib with standard second-line chemotherapy (PROFILE-1007) and with standard first-line therapy (PROFILE 1014).[3,170] Second-line therapy with crizotinib improved PFS and response rate when compared with single-agent therapy (either docetaxel or pemetrexed).[171]

EGFR mutations and ALK rearrangements are generally mutually exclusive.[172,173] 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).[101,102] A new algorithm for second-line treatment was added for patients who progress on crizotinib (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[159,174,175]

KRAS Mutations

Data suggest that approximately 25% of adenocarcinomas in a North American population have KRAS mutations; KRAS is the most common mutation.[57,91,104,114,119] KRAS mutation prevalence is associated with cigarette smoking.[176] 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.[117,119,177] KRAS mutational status is also predictive of lack of therapeutic efficacy with EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy.[57,91,118] EGFR and KRAS mutations appear to be mutually exclusive.[178] Targeted therapy is not currently available for patients with KRAS mutations, although MEK inhibitors are in clinical trials.[114,179]

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.[180] However, thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. The overall plan of treatment and the necessary imaging studies should be determined before any nonemergency treatment is initiated. It is essential to determine whether patients can tolerate surgery or whether they are medically inoperable; some patients deemed inoperable may be able to tolerate minimally invasive surgery.[180,181] Medically inoperable patients may be candidates for stereotactic ablative radiotherapy (SABR), also known as stereotactic body RT (SBRT). If SABR is considered for high-risk

patients, a multidisciplinary evaluation is recommended (including a radiation oncologist).[182]

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 lung cancer patients. 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).[183] 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.[180,184,185] 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).[186,187] Resection (including wedge resection) is preferred over ablation.[180,185] Wide wedge resection may improve outcomes.[188] 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.[180,185,189,190] SABR may be more appropriate for these patients (see *Stereotactic Ablative Radiotherapy* in this Discussion).[191]

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.[192-194] 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.[192] 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.[195] Formal ipsilateral mediastinal lymph node dissection is indicated for patients undergoing resection for stage IIIA (N2) disease. For patients undergoing sublobular resection, the appropriate N1 and N2 lymph node stations should be sampled unless not technically feasible because it would substantially increase the surgical risk.

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

(preferred) or wedge resection should achieve parenchymal resection margins that are: 1) 2 cm or more; or 2) the size of the nodule or more.

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).[196,197] Randomized controlled trials suggest that surgery does not increase survival in these patients.[198,199] However, one of these trials (EORTC) only enrolled unresectable patients.[199] 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.[200] Neoadjuvant therapy is recommended for select patients. In N2 patients, 50% of the NCCN Member Institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy.[201] 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.[202] 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).[196,203] However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate.[198,203-209] Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.[203,210]

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).[211,212] Published studies suggest that thorascopic lobectomy has several advantages over the standard thoracotomy (or pleurotomy).[213-217] Acute and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires a shorter length of hospitalization.[218,219] Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.[220-224] Thoracoscopic lobectomy is associated with less morbidity, fewer complications, and more rapid return to function than lobectomy by thoracotomy.[225-228]

In stage I NSCLC patients who had thorascopic lobectomy with lymph node dissection, the 5-year survival rate, long-term survival, and local recurrence were comparable to those achieved by routine open lung resection.[229-232] Thorascopic lobectomy has also been shown to improve discharge independence in older populations and in high-risk patients.[233,234] Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.[235,236] 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 standard principles of thoracic surgery are not compromised (see *Principles of Surgical Therapy* in the NCCN Guidelines for Non-Small Cell Lung

Cancer).[237-240] Robotic VATS seems to be more expensive with longer operating times than conventional VATS.[241]

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.[182,242] 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.[243-247] 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.[248-253] 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/Oncology/Lung).

Definitive RT or SABR is recommended for early-stage NSCLC patients (ie, stage I-II, N0) who are medically inoperable and those who refuse surgery (see *SABR* in this Discussion).[182,242,254,255] 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 high surgical risk patients 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).[256] Definitive chemoradiation is recommended for patients with locally advanced (ie, stage II–III) disease who are medically inoperable.[257] For patients with advanced lung cancer (ie, stage IV) with extensive metastases, palliative RT can be used for primary or distant sites.[242,258-260] 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).[250,261] However, some suggest that preoperative chemotherapy alone is sufficient in patients with stage IIIA NSCLC;[202] 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

versus neoadjuvant chemoradiation in patients with stage IIIA N2 NSCLC.[196]

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).[196,198,208,262,263] 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.[264,265] 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).[249,251,266-270] 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.[271] The use of higher RT doses is discussed in the *Principles of RT* in the NCCN NSCLC algorithm.[272-277] 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).[277-280]

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).[281,282] 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).[243,283,284] 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).[285] These limits are mainly empirical.[286-293] 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.[294] In the *Principles of RT* of the NCCN NSCLC algorithm, recommendations are provided for patients receiving chemoradiation

(including those with compromised lung or cardiac function), photon beams, or IMRT (see *Simulation, Planning, and Delivery*).[246,295-299] 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)).[300]

Stereotactic Ablative Radiotherapy

SABR (also known as SBRT) uses short courses of very high-dose RT that are precisely delivered to the target.[301-303] Studies have shown that SABR is very useful for patients with inoperable stage I NSCLC or for those who refuse surgery.[182,304-306] With conventional treatment, 3-year survival is only about 20% to 35% in these patients.[255] There is a high rate of local failure in patients receiving conventional RT. However, local control is increased after SABR.[180,307,308] Disease recurrence is infrequent after SABR.[309] In patients with stage I NSCLC, SABR provides a significantly longer survival than 3-D conformal RT.[256,299,310] 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).[311] Thus, SABR is recommended in the NCCN Guidelines for patients with medically inoperable stage I and II NSCLC if they are node negative.[180,306]

SABR can also be used for patients with limited lung metastases and for palliative therapy.[312,313] Studies also suggest that SABR can be used for bone, liver, and brain metastases.[301,306] 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.[314] 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).[305,311,315-321] 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.[322] Although some suggest that SABR is more effective than RFA, they have not been compared in a randomized trial.[180,182,310]

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.[182] 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.[180,310,323] RFA is not recommended for tumors near major pulmonary vessels.[180,310] 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.[324] The procedure-specific 30-day mortality rate is reported to be 2.6%.[325] SABR and RFA are more effective than conventional RT for medically inoperable patients.[310] 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.[180]

Whole Brain RT and Stereotactic Radiosurgery

Many patients with NSCLC have brain metastases (30%–50%), which substantially affect their quality of life.[326] 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).[327-330] SRS is another option after surgical resection, although

there are only a few retrospective case series supporting this option.[327] Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with (or without) whole brain RT.[326,331-333] Data suggest that erlotinib may be useful to manage brain metastases.[334-336] 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.[327,337-339] Treatment should be individualized for patients with recurrent or progressive brain lesions.[340]

Some oncologists have been concerned that whole brain RT adversely affects neurocognition.[341] 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.[342] In 132 patients with 1 to 4 brain metastases who received SRS with (or without) whole brain RT, survival was similar in both groups.[332] 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.[343] 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.[344] Some have suggested that using resection with SRS (instead of resection with whole brain RT) will decrease neurocognitive problems.[345,346]

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 stage I or II disease who are unresectable or refuse surgery if they are 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.[347-349] 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).[196,350-357] However, a recent randomized trial found no difference in survival with preoperative versus postoperative chemotherapy.[358] 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.[359-362]

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.[363-368] 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.[369] Patients should receive treatment for debilitating symptoms.[5,370,371] A recent study also suggests that social support, such as being married, is as effective as chemotherapy.[372] 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).[373] Local therapy of a solitary metastasis located in sites other than the brain remains controversial and thus is a category 2B recommendation; however, SRS or SABR may be useful in these

settings (see *Stage IV, M1b: Solitary Site/Initial Treatment* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[183,306] 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 is only recommended 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.[347] 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.[374] 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.[348] 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.[375] 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.[349] 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.[349] 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.[376]

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

benefit of 5.4%); there was no difference among the chemotherapy regimens (vinorelbine, etoposide, and others).[377] A subgroup analysis found that cisplatin/vinorelbine also increased survival.[376] 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.[378]

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;[379] updated results have been reported.[380,381] 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).[380,381] The original results from CALBG 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).[382] However, it is important to note that the CALGB trial was underpowered for stage 1B patients.[383]

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.[355] 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.[358] Postoperative chemotherapy is considered the standard of care for early-stage disease.[180]

Several trials suggest that neoadjuvant therapy is beneficial in patients with N2 disease.[196,202,354] Other trials suggest that neoadjuvant therapy is beneficial in patients with earlier stage disease.[351,352,357] 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.[357]

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).[351] Song et al published a meta-analysis of all available randomized clinical trials evaluating preoperative chemotherapy in resectable NSCLCs. This meta-analysis evaluated 13 randomized trials and found improvement in overall survival in the neoadjuvant chemotherapy arm when compared with the surgery alone arm (HR, 0.84; 95% CI, 0.77–0.92; *P* = .0001).[350] These results are

similar to those recently reported in another meta-analysis (HR, 0.89; 95% CI, 0.81–0.98; *P* = .02).[351] The benefit from neoadjuvant chemotherapy is similar to that attained with postoperative chemotherapy.[351,358,377]

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.[384-388] For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.[384,385,387,388] Concurrent chemoradiation is superior to sequential therapy.[359-362] 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).[359,361,389,390] For non-squamous NSCLC, other concurrent chemoradiation regimens include carboplatin/pemetrexed and cisplatin/pemetrexed.[391,392] 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.[393]

Chemotherapy: Trial Data

Patients with stage IV disease who have a good PS benefit from chemotherapy, usually with a platinum-based regimen.[365,367,394] Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (eg, cisplatin, carboplatin), taxanes (eg, paclitaxel, albumin-bound paclitaxel, 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.[382,395-398] 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.[399,400] Gemcitabine/cisplatin is used for patients with squamous cell carcinoma.[398-401] These regimens are commonly used based on phase III randomized trials (ie, cisplatin/pemetrexed, carboplatin/paclitaxel [with or without bevacizumab], gemcitabine/cisplatin).[398,402]

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).[398,403,404] 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.[404,405] 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.[404] A retrospective cohort study suggests that

the addition of bevacizumab (to carboplatin/paclitaxel) does not increase survival in older patients (65 years or older) with advanced non-squamous NSCLC.[406] 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.[407] Single-agent chemotherapy includes vinorelbine, gemcitabine, pemetrexed, or taxanes; combination chemotherapy regimens include carboplatin/paclitaxel or carboplatin/pemetrexed.[408-410] However, patients with a PS of 2 are often just treated with one chemotherapy agent because of concerns about toxicity.[411] 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.[408,412]

Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.[413,414] The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients.[401,415,416] Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;[395,417-419] non–platinum-based regimens such as gemcitabine/vinorelbine and gemcitabine/docetaxel are also options.[420-423] 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.[424,425] 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.[426] 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/2013/021660s038lbl.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).[427,428] 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. Erlotinib, afatinib, crizotinib, 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).[402] To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: non-squamous NSCLC and no recent history

of hemoptysis. Any regimen with a high risk for thrombocytopenia—and, therefore, possible bleeding—should be used with caution when combined with bevacizumab. For patients with non-squamous NSCLC 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).[57,429-431] 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).[430] Updated results from the IPASS study show that overall survival was similar in patients receiving gefitinib or chemotherapy regardless of EGFR mutation status.[432] 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 mainly Western patients (n = 223) with advanced NSCLC (stage IIIB or IV) found that patients with EGFR mutations who received TKIs had a 67% response rate and an overall survival of about 24 months.[433] The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced non-squamous NSCLC.[434] 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.[145,146] ASCO recommends that patients be tested for EGFR mutations.[435] However, the NCCN and ESMO Guidelines specify that only patients with non-squamous NSCLC (eg, adenocarcinoma) be assessed for sensitizing EGFR mutations.[407] Patients with pure squamous cell carcinoma are unlikely to have EGFR mutations; however, those with adenosquamous carcinoma may have mutations.[99]

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients (mainly Caucasian) with advanced NSCLC.[436,437] 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.

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).[126] The FDA recently approved afatinib for first-line treatment of patients with metastatic NSCLC who have sensitizing EGFR mutations.[125,438] 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).[123,126,175] 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).[122]

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%) in patients who had previously progressed.[156,157] 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.[171]

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).[439] 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.[440] 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 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).[441]

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.[402,442,443] 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).[442,444] 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).[444,445] Results show that continuation maintenance therapy with pemetrexed also improves overall survival (13.9 vs. 11.0 months).[446,447] 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.[439]

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.[404,405] 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.[448,449]

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).[450,451] Another phase III randomized trial assessed continuation maintenance therapy with gemcitabine versus best supportive care after an initial regimen of cisplatin/gemcitabine.[452] 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 drug vacation may be more appropriate for some patients.[403] 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.[403,453] 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).[453,454]

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.[403,455] 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.[456,457] 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.[457] The FDA has approved maintenance therapy with pemetrexed (http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021462s045lbl.pdf).[458] Likewise, switch maintenance therapy with erlotinib may be initiated in patients 1) without EGFR mutations or gene rearrangements; or 2) with squamous cell carcinoma.[451,456] 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/2013/021743s018lbl.pdf).[459]

A phase III trial assessed switch maintenance therapy with docetaxel given either immediately after chemotherapy or delayed until progression.[460] 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 symptomatic patients, 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 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).[461-464] 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,[465] 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.[466] 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.[467]

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.[462] PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN Panel reviewed the diagnostic performance of CT and PET scans. The NCCN Panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, for example, in identifying stage I (peripheral and central T1–2, N0), stage II, stage III, and stage IV diseases.[461,468,469] However, PET/CT is even more sensitive and is recommended by NCCN.[470-472]

The NCCN Panel assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging.[473] Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported.[474] 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.[475] 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%.[476] Kernstine et al compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC.[477,478] 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.[479,480]

When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided.[470] 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.[461,481] 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.[482-485] 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.[486] In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results.[487,488] However, in patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.[483,488-490] 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.[491] 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 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.[183,267,269,492-495] The overall 5-year survival rate is approximately 40%.[267] 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.[390,496]

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.[198,359] 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).[198,359,390] 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).[360] Induction chemotherapy with (or without) RT is another option for patients with T1–3, N2 disease.[199] Recommended therapy for metastatic disease depends on whether disease is in a solitary site or is widespread (see the NCCN Guidelines for Non-Small Cell Lung Cancer).

When a lung metastasis is present, it usually occurs in patients with other systemic metastases; the prognosis is poor. Therefore, many of these patients are not candidates for surgery; however, systemic therapy is recommended. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery (see *Multiple Lung Cancers* in this Discussion).[497] 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%.[498] Intrapulmonary metastases have been downstaged in the TNM staging (ie, AJCC 7th edition).[87,498,499] 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).[500]

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).[501,502] 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.[49,183,503,504] 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).[505,506] Although criteria have been established for diagnosing multiple lung cancers, no definitive method has been established before treatment.[506-509] 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.[509]

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).[503,510-512] 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).[502,503] VATS or SABR may be useful in select patients.[513]

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).[514] The Fleischner Society has recommendations for patients with solid nodules and has recently developed recommendations for those with subsolid nodules.[515,516] *Subsolid* nodules include pure ground glass nodules and part-solid ground glass nodules.[515] Ground glass nodules are also known as nonsolid nodules or ground glass opacities.[517] Solid nodules are more 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.[516,518]

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).[519,520] 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.[198,359,390,521,522] 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).[198,359,390,521-523]

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).[87] 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.[524] 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).[525]

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, 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).[183,326,327] The 5-year survival rates with such an approach range from 10% to 20%;[526] median survival is about 40 weeks.[330] Follow-up whole brain RT (category 1) or SRS may be used.[328,342,527] SRS alone or followed by whole brain radiation are additional treatment options.[331,332] Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.[528] 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).[529-531] 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).[381,532] 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).[250,381]

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.[377,533] 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 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).[377]

NCCN Panel Members do not recommend chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial.[249] 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 stage III NSCLC patients 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,[347-349] the NCCN Panel has included cisplatin combined with vinorelbine, vinblastine, or etoposide for adjuvant chemotherapy in the guidelines; other options include cisplatin combined with gemcitabine, pemetrexed, or docetaxel (see the NCCN Guidelines for Non-Small Cell Lung Cancer).[382,395,398] For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel is an option.[382,534] 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).[535,536] However, data are conflicting regarding whether bevacizumab benefits elderly patients.[406,537] A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with (or without) RT, followed by surgery.[538-540]

Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.[354,541-543] 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.[542,543] 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).[544] 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.[261] Therefore, guidelines from some cancer organizations recommend that postoperative RT should only be given to those with N2 disease.[545] The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.[250] 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.[533] In this meta-analysis, 70% of the eligible trials used adjuvant chemotherapy before RT; 30% used concurrent chemo/RT. Regimens included cisplatin/vinorelbine followed by RT or concurrent cisplatin/etoposide. The ACR Appropriateness Criteria® provide specific recommendations for postoperative adjuvant therapy.[546,547]

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.[389] 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.[251,252,359,360,390-392]

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.[40,548-551] 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.[44] 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.[552]

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*).[5] For patients with endobronchial obstruction, relieving airway obstruction may increase survival, especially in severely compromised patients, and may improve the quality of life.[553] 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*). Palliation of symptoms can be achieved with external-beam RT for distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis.[266,554] Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis.[555-557] 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).[558] 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.[559]

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).[398] 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 Alternations* 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, crizotinib, dabrafenib, erlotinib, gefitinib, trastuzumab, and vemurafenib.[54,59,94,95,104,109,112,113,124,126,429,560-564]

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).[57,122,144,430,565] 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.[98,566] Crizotinib is also recommended for patients who are positive for ROS1 rearrangements and MET amplification (see *Targeted Agents for Patients with Genetic Alternations* in the NCCN Guidelines for Non-Small Cell Lung Cancer).[95,112,567] 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.[104-106]

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.[49] 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.[99,568-570] 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.[99] 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 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 Therapy 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.[398] 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.[571] 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.[572] 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.[363,439]

Cisplatin/gemcitabine (category 1) is an option for patients with squamous cell carcinoma.[398] 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.[439] 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.[3,54,106,573,574]

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.[402,575] 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.[402] 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.[402] However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 25.5% vs. 16.8%, grade 5 hemoptysis: 1.2% vs. 0% and grade 3 hypertension: 6.8% vs. 0.5%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (15 patients) than with paclitaxel and carboplatin (2 patients) (P =.001).

A recent analysis of ECOG 4599 found that adenocarcinoma histology was associated with improved survival in patients receiving

bevacizumab/paclitaxel/carboplatin compared with chemotherapy alone (14.2 vs. 10.3 months).[571] However, a trial (AVAiL) comparing cisplatin/gemcitabine with (or without) bevacizumab did not show an increase in survival with the addition of bevacizumab.[576,577]

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.[398] 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.[578]

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.[439] 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.[382,395-398,417,418,426] Non-platinum regimens (eg, gemcitabine/docetaxel, gemcitabine/vinorelbine) are reasonable alternatives because data show they are active and less toxic than platinum-based regimens.[420-423,579]

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.[364,454,580] Currently, the NCCN Guidelines do not recommend continuing chemotherapy beyond 4 to 6 cycles.

Recent data from the PARAMOUNT trial suggest that 4 cycles of platinum-based therapy is not optimal;[444] 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.[403] 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.[581] 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.[453,454] In this phase III trial,

taxane-based regimens were used and patients had increasing neurotoxicity as more cycles were used.[454]

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.[403] 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.[442,454]

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).[402,404,439,444,445,449-451] Switch maintenance therapy regimens for these patients include pemetrexed or erlotinib (both are category 2B).[450,451,456,457] 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.[457] 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).[451,456] 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.[460] 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.[582]

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; discontinuation of erlotinib or gefitinib leads to more rapid progression of disease (symptoms, tumor size, and FDG-avidity on PET scan).[583] 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.[584] 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).[561,585,586] 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.[587] The most common known mechanism is the acquisition of a secondary mutation in EGFR—T790M—that renders the kinase resistant to erlotinib and gefitinib.[588,589] 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.[583,590] 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).[591-600] 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.[597,598] When compared with docetaxel, pemetrexed has similar median survival but less toxicity.[599,601] Pemetrexed is recommended in patients with adenocarcinoma or large cell carcinoma (ie, non-squamous NSCLC).[457] Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration.[600] 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 first-line therapy with erlotinib, afatinib, or crizotinib.[402] Afatinib is recommended as second-line therapy in patients with sensitizing EGFR mutations who have progressed after first-line therapy based on several studies.[122,561,585,586]

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.[600] 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.[602] 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.[592,603,604] 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).[5,370,371] Patients often have a limited response to third-line chemotherapy, although it may serve a useful palliative role.[605]

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