### NCCN Guidelines™ Version 3.2011 Panel Members

**Non-Small Cell Lung Cancer**

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**NCCN Guidelines™ Version 3.2011 Table of Contents**

**Non-Small Cell Lung Cancer**

**NCCN Non-Small Cell Lung Cancer Panel Members**

**Summary of Guidelines Updates**

**Lung Cancer Prevention and Screening (PREV-1)**

**Initial Evaluation and Clinical Stages (NSCL-1)**

**Evaluation and Treatment:**
- **Stage I (T1ab-2a, N0), Stage II (T1ab-2ab, N1; T2b, N0), and Stage IIIB (T3, N0)** (NSCL-2)
- **Stage IIIB (T3 invasion, N0) and Stage IIIA (T3-4, N1)** (NSCL-4)
- **Stage IIIA (T1-3, N2) and Separate Pulmonary Nodules (Stage IIIB, IIIA, IV)** (NSCL-6)
- **Stage IIIB (T1-3, N3)** (NSCL-9)
- **Stage IIIB (T4 extension, N2-3) and Stage IV (M1a) (pleural or pericardial effusion)** (NSCL-10)
- **Stage IV (M1b: solitary site)** (NSCL-11)

**Surveillance (NSCL-12)**

**Therapy for Recurrence and Metastasis (NSCL-12)**

- **Principles of Pathologic Review (NSCL-A)**
- **Principles of Surgical Therapy (NSCL-B)**
- **Principles of Radiation Therapy (NSCL-C)**
- **Chemotherapy Regimens for Adjuvant Therapy (NSCL-D)**
- **Chemotherapy Regimens Used with Radiation Therapy (NSCL-E)**
- **Systemic Therapy for Advanced or Metastatic Disease (NSCL-F)**
- **Cancer Survivorship Care (NSCL-G)**

**Staging (ST-1)**

The NCCN Guidelines™ are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient’s care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2010.
Summary of the changes in the 3.2011 version of the Non-Small Cell Lung Cancer guidelines from the 2.2011 version include:

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

Summary of the changes in the 2.2011 version of the Non-Small Cell Lung Cancer guidelines from the 1.2011 version include:

**NSCL-12**
- Denosumab was added as a treatment option for patients with bone metastases.

Summary of the changes in the 1.2011 version of the Non-Small Cell Lung Cancer guidelines from the 2.2010 version include:

**PREV-1**
- Bullet 1 - Percentage of cases changed from 90% to 85-90%.
- Bullet 2 added - Persistent smoking is associated with second primary cancers, treatment complications, drug interactions, other tobacco-related medical conditions, diminished quality of life and reduced survival.

**NSCL-1**
- Initial evaluation - “Smoking cessation counseling” changed to “Smoking cessation advice, counseling, and pharmacotherapy.” (also applies to the follow-up on NSCL-11)
- Footnote “c” is new to the page: “T3, N0 related to size or satellite nodules.” (also applies to NSCL-2)
- Footnote “e” is new to the page describing cytopathologic examinations of pleural and pericardial fluid.

**NSCL-2**
- Brain MRI added as a workup recommendation for Stage IB tumors with a category 2B designation.

**NSCL-3**
- Lymph node sampling clarified as “systematic.”
- Stage IA, margins positive - chemoradiation removed as an option for adjuvant treatment.
- Stage IB, IIA, margins positive - reresection listed as “preferred.” Chemoradiation + chemotherapy changed to RT + chemotherapy.
- Stage IIA, IIB, margins negative - adverse risk factors removed as a determinant for adjuvant therapy. Chemoradiation followed by chemotherapy removed as an option for adjuvant treatment. “± RT” added with a category 3 designation.
- Footnote “f” - “lung neuroendocrine tumors” added to the high risk criteria and “minimal margins” removed.
- Footnote “i” is new to the page - “Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.”

**NSCL-4**
- EBUS added as a workup recommendation.

**NSCL-5**
- Superior sulcus tumor (T4 extension, N0-1), unresectable - chemotherapy added as adjuvant therapy after Definitive chemoradiation.
- Footnote “r” is new to the page: “If full-dose chemotherapy not given concurrently with RT as initial treatment.” (also applies to NSCL-8, 9, 10)
- The footnote “It is sometimes difficult to distinguish between T3 and T4 superior sulcus tumors” was deleted.

**NSCL-6** and **NSCL-8**
- Separate pulmonary nodule, same lobe or ipsilateral lung - the T and N status added for clarification.
- Separate pulmonary nodules, contralateral lung changed to Stage IV (N0, M1a): Contralateral lung (solitary nodule).
- Reference to pleural effusions deleted from this page, as this is addressed on NSCL-10.

**NSCL-7**
- T1-3, N0-1: Thoracotomy changed to “Surgery.” Lymph node sampling clarified as “systematic.”

**NSCL-8**
- Stage IIIA (T4, N0-1), unresectable - chemotherapy listing after chemoradiation changed from a category 3 to a category 2A designation.

**NSCL-9**
- The term “consolidation” deleted and the category designation changed from 2B to category 2A.

**NSCL-10**
- T and N status added for clarification.
- The term “consolidation” deleted and the category designation changed from 2B to category 2A.
Summary of the changes in the 1.2011 version of the Non-Small Cell Lung Cancer guidelines from the 2.2010 version include:

**NSCL-11**
- Brain presentation - “Resect brain lesion ± WBRT (category 1) ± SRS (category 2B)” changed to “Surgical resection, followed by WBRT (category 1) or stereotactic radiosurgery (SRS).”
- Adrenal presentation - Category designation for local therapy changed from category 3 to category 2B.

**NSCL-12**
- Locoregional recurrence, SVC - Concurrent chemoradiation added as a treatment option, if not previously given.

**NSCL-13**
- The evaluation process for systemic therapy for patients with recurrent or metastatic disease has changed to first address histologic subtype and then recommend EGFR testing based on histologic subtype.
- EGFR testing is a category 1 recommendation for the following histologies: adenocarcinoma, large cell, and NSCLC NOS.
- EGFR testing is not recommended for squamous cell carcinoma.
- This page now addresses first-line systemic therapy for adenocarcinoma, large cell, NSCLC NOS, and squamous cell carcinoma with a positive EGFR mutation.
- Footnote “w” is new to the page, “The observed incidence 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 “y” is new to the page, clarifying that the erlotinib is for performance status 0-4.
- Footnote “z” is new to the page stating that gefitinib could be used in place of erlotinib in areas of the world where it is available. (also applies to NSCL-16)

**NSCL-14**
- This page now addresses first-line systemic therapy for adenocarcinoma, large cell, and NSCLC NOS with a negative or unknown EGFR mutation.
- Tumor response evaluation after the first cycle of chemotherapy was deleted.
- The category designation for pemetrexed as an option for switch maintenance was changed from a 2B to a 2A.
- NSCL-15
  - This page now addresses first-line systemic therapy for squamous cell carcinoma.
  - Tumor response evaluation after the first cycle of chemotherapy was deleted.
- NSCL-16
  - Performance status 0-2 - bevacizumab was added as a treatment option to the combination of a platinum doublet for patients who received erlotinib as first-line and the histology of adenocarcinoma.

**NSCL-A 2 of 3**
- Molecular Diagnostics:
  - Sub-bullets 5 through 7 under EGFR and KRAS are new to the page.
  - New section added for EML4-ALK.
  - Bullet 2: A new sentence was added: “In cases where stereotactic RT is considered for high-risk patients, a multidisciplinary evaluation including a radiation oncologist is recommended.”

**NSCL-B 2 of 4** through **NSCL-B 4 of 4**
- New pages added to discuss the controversial issue of surgery in the management of patients with Stage IIIA (N2) disease.

**NSCL-C**
- Revisions made throughout the Principles of Radiation Therapy section.
  - Table 2 - title changed from “Recommended Doses for Conventionally Fractionated Radiation Therapy” to “Commonly Used Doses for Conventionally Fractionated Radiation Therapy.”

**NSCL-C 6 of 7**
- Table 4 - title changed from “SBRT Regimens and Indications for Lung Tumors” to “Commonly Used SBRT Regimens.”

**NSCL-E**
- The consolidation regimen of docetaxel was removed as an option.
- Footnote “w” changed from “Randomized data support...” to “There are data to support...”
LUNG CANCER PREVENTION AND SCREENING

- Lung cancer is a unique disease in that the etiologic agent is an industry. Approximately 85-90% 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 (www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.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 and Quality (AHRQ) Guidelines (www.ahrq.gov/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Available data1-5 are conflicting and, thus, conclusive data from ongoing national trials are necessary to define the benefits and risks associated with screening for lung cancer with low dose CT. The panel recommends that high risk individuals participate in a clinical trial evaluating CT screening. If a trial is not available or the high risk individual is not eligible for participation in a trial, then the individual should go to a center of excellence with expertise (in radiology, pathology, cytology, thoracic surgery, and general expertise in lung cancer treatment) to discuss the potential risks and benefits before having a screening CT.2 If a screening strategy is used, then the I-ELCAP screening protocol should be followed. http://www.ielcap.org/professionals/docs/ielcap.pdf


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

**CLINICAL STAGE**

**Stage IA, peripheral\(^b\) (T1ab, N0)**
- Mediastinal CT negative (lymph nodes < 1 cm)

**Stage I, peripheral\(^b\) (T2a, N0); central\(^b\) (T1ab-T2a, N0); stage II (T1ab-T2ab, N1; T2b, N0); stage IIB (T3, N0)\(^c\)**
- Mediastinal CT negative (lymph nodes < 1 cm)

**Stage IIIB\(^d\) (T3 invasion, N0); Stage IIIA\(^d\) (T4 extension, N0-1; T3, N1)**

**Stage IIIA\(^d\) (T1-3, N2)**

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

**Stage IIIB\(^d\) (T1-3, N3) mediastinal CT positive**
- Contralateral (lymph nodes ≥ 1 cm) or palpable supraclavicular lymph nodes

**Stage IIIB\(^d\) (T4 extension, N2-3) on CT**

**Stage IV (M1a) (pleural or pericardial effusion)\(^e\)**

**Stage IV (M1b)**
- Solitary metastasis with resectable lung lesion

**Stage IV (M1b)**
- Disseminated metastases
  - Workup as clinically indicated

**See Pretreatment Evaluation (NSCL-2)**

**See Pretreatment Evaluation (NSCL-2)**

**See Pretreatment Evaluation (NSCL-4)**

**See Pretreatment Evaluation (NSCL-2)**

**See Pretreatment Evaluation (NSCL-4)**

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

\(^b\) Based on the CT of the chest:
- Peripheral = outer third of lung.
- Central = inner two thirds of lung.

\(^c\) T3, N0 related to size or satellite nodules.

\(^d\) 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.

\(^e\) Most pleural effusions associated with lung cancer are due to tumor. There are 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 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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**CLINICAL ASSESSMENT**

**PRETREATMENT EVALUATION**

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### Stage IA (Peripheral T1ab, N0)

- PFTs (if not previously done)
- Bronchoscopy (intraoperative preferred)
- Mediastinoscopy (category 2B)
- EBUS if appropriate (category 2B)
- PET/CT scan

#### Operable

- Negative mediastinal nodes

#### Medically Inoperable

- Positive mediastinal nodes

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### Stage IB (Peripheral T2a, N0)

- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy
- EBUS if appropriate (category 2B)
- PET/CT scan

- Brain MRI (Stage II, Stage IB [category 2B])

#### Operable

- Negative mediastinal nodes

#### Medically Inoperable

- Positive mediastinal nodes

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### Stage I (Central T1ab–T2a, N0)

#### Stage II (T1ab–2ab, N1; T2b, N0)

#### Stage IIB (T3, N0)

#### Stage IIIA (NSCL-7)

#### Stage IIIB (NSCL-9)

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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.

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*T3, N0 related to size or satellite nodules.

1Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

9See Principles of Surgical Therapy (NSCL-B).
INITIAL TREATMENT

FINDINGS AT SURGERY

ADJUVANT TREATMENT

Stage IA (T1ab, N0)

- Margins negative (R0)\(^h\)
- Margins positive (R1, R2)\(^h\)

Observe

Reresection (preferred) or RT\(^j\) (category 2B)

Stage IB (T2a, N0); Stage IIA (T2b, N0)

- Margins negative (R0)\(^h\)
- Margins positive (R1, R2)\(^h\)

Observe or Chemotherapy\(^k\) (category 2B) in high-risk patients\(^i\)

Reresection (preferred) ± chemotherapy\(^k, l\) or RT\(^j, m\) + chemotherapy

Stage IIA (T1ab-T2a, N1) Stage IIB (T3, N0; T2b, N1)

- Margins negative (R0)\(^h\)
- Margins positive (R1, R2)\(^h\)

Chemotherapy\(^k\) (category 1) ± RT\(^j\) (category 3 for RT)

Reresection + chemotherapy\(^k\) or Chemoradiation\(^j, m\) + chemotherapy

Stage IIIA (T1-3, N2)

- Margins negative (R0)\(^h\)
- Margins positive (R1, R2)\(^h\)

Chemotherapy\(^k\) (category 1) + RT\(^j\)

Chemoradiation\(^j, m\) + chemotherapy

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

\(^g\) See Principles of Surgical Therapy (NSCL-B).
\(^h\) R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
\(^i\) High-risk patients are defined by poorly differentiated tumors (including lung neuroendocrine tumors), vascular invasion, wedge resection, tumors > 4 cm, visceral pleural involvement, Nx.
\(^j\) See Principles of Radiation Therapy (NSCL-C).

\(^k\) See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).
\(^l\) Increasing size is an important variable when evaluating the need for adjuvant chemotherapy.
\(^m\) See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).
Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
### CLINICAL PRESENTATION

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Treatment</th>
<th>Adjuvant Treatment</th>
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<tbody>
<tr>
<td>Superior sulcus tumor (T3 invasion, N0-1)</td>
<td>Preoperative concurrent chemoradiation(^{j,m,n})</td>
<td>Surgery(^g) + chemotherapy(^k)</td>
</tr>
<tr>
<td>Superior sulcus tumor (T4 extension, N0-1)</td>
<td>Preoperative concurrent chemoradiation(^{j,m,n})</td>
<td>Surgery(^g) + chemotherapy(^k)</td>
</tr>
<tr>
<td>Marginal resectable(^g)</td>
<td>Surgical reevaluation(^o,q)</td>
<td>Complete definitive RT(^j) + chemotherapy(^k)</td>
</tr>
<tr>
<td>Unresectable(^g)</td>
<td></td>
<td>Chemotherapy(^m,r)</td>
</tr>
<tr>
<td>Margins negative (R0)(^h)</td>
<td>Margins positive (R1, R2)(^h)</td>
<td>Reresection + chemotherapy(^k) if not given as initial treatment</td>
</tr>
<tr>
<td>Margins positive (R1, R2)(^h)</td>
<td></td>
<td>Chemoradiation(^{j,m}) + chemotherapy if not given as initial treatment</td>
</tr>
</tbody>
</table>

\(^g\) See Principles of Surgical Therapy (NSCL-B).

\(^h\) R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.

\(^i\) See Principles of Radiation Therapy (NSCL-C).

\(^j\) See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).

\(^k\) See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

\(^l\) See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

\(^m\) In the preoperative chemoradiation setting, a total dose of 45-50 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease, although preoperative chemoradiotherapy should be avoided if a pneumonectomy is required to avoid post-operative pulmonary toxicity.

\(^n\) RT should continue to definitive dose without interruption if patient is not a surgical candidate.

\(^o\) In the definitive chemoradiation setting, a total dose of 60-70 Gy in 1.8 to 2 Gy fractions should be used to treat all volumes of gross disease.

\(^p\) If full-dose chemotherapy not given concurrently with RT as initial treatment.

**Discussion**

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

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**CLINICAL ASSESSMENT**

**PRETREATMENT EVALUATION**

**MEDIASTINAL BIOPSY FINDINGS AND RESECTABILITY**

### Stage IIIA (T1–3, N2)
- PFTs (if not previously done)
- Bronchoscopy
- Pathologic mediastinal lymph node evaluation
- PET/CT scan
- Brain MRI

**N2, N3 nodes negative** → See Treatment T 1-3, N0-1 (NSCL-7)

**N2 nodes positive** → See Treatment (NSCL-7)

**N3 nodes positive** → See Stage IIIB (NSCL-9)

**Metastatic disease** → See Treatment for Metastasis solitary site (NSCL-11) or disseminated (NSCL-13)

### Separate pulmonary nodule(s) (Stage IIB, IIIA, IV)
- PFTs (if not previously done)
- Bronchoscopy
- Mediastinoscopy
- Brain MRI
- PET/CT scan

**Separate pulmonary nodule(s), same lobe (T3, N0) or ipsilateral lung (T4, N0)** → See Treatment (NSCL-8)

**Stage IV (N0, M1a): Contralateral lung (solitary nodule)** → See Treatment (NSCL-8)

**Unresectable** → See Treatment (NSCL-8)

**Metastatic disease** → See Treatment for Metastasis solitary site (NSCL-11) or disseminated (NSCL-13)

---

1 Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

*Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS and CT-guided biopsy.*

**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.
## MEDIASTINAL BIOPSY FINDINGS

<table>
<thead>
<tr>
<th>T1-3, N0-1 (including same lobe)</th>
<th>Resectable</th>
<th>Surgery&lt;sup&gt;g&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unresectable</td>
<td></td>
<td>See Treatment according to clinical stage (NSCL-1)</td>
</tr>
</tbody>
</table>

- **Resectable**
  - Surgical resection<sup>g</sup> + mediastinal lymph node dissection or systematic lymph node sampling
  - See NSCL-3 or NSCL-4

- **Unresectable**
  - Definitive concurrent chemoradiation<sup>j,m</sup> or induction chemotherapy ± RT<sup>j</sup>
  - See Principles of Radiation Therapy (NSCL-C).

### Negative for M1 disease

- **T1-2, T3 (≥ 7 cm), N2 nodes positive**
  - Brain MRI, PET/CT scan, if not previously done
  - No progression
  - Definitive concurrent chemoradiation<sup>j,m</sup> or induction chemotherapy ± RT<sup>j</sup>
  - See Principles of Surgical Therapy (NSCL-B).

- **T3 (invasion), N2 nodes positive**
  - Brain MRI, PET/CT scan, if not previously done
  - Definitive concurrent chemoradiation<sup>j,m</sup>
  - See Principles of Surgical Therapy (NSCL-B).

### Positive PET/CT scan findings need pathologic or other radiologic confirmation.

- Positive PET/CT scan findings need pathologic or other radiologic confirmation.
  - If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.
  - See Principles of Surgical Therapy (NSCL-B).

- N0–1
  - Margins negative (R0)<sup>h</sup>
  - Surgery<sup>g</sup> ± chemotherapy<sup>k</sup> (category 2B) ± RT<sup>j</sup> (if not given)

- N2
  - Margins positive (R1, R2)<sup>h</sup>
  - Chemoradiation<sup>j,m</sup> + chemotherapy

### Surveillance (NSCL-12)

- Local RT<sup>j</sup> (if not given) ± chemotherapy<sup>k</sup>
- Systemic
  - See Treatment for Metastasis solitary site (NSCL-11) or disseminated (NSCL-13)

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Non-Small Cell Lung Cancer

**CLINICAL PRESENTATION**

- Separate pulmonary nodule(s), same lobe (T3, N0) or ipsilateral lung (T4, N0)
  - Surgery\(^g\)
  - Surgery\(^g\)
  - Surgery\(^g\)
  - Surgery\(^g\)
  - See Principles of Surgical Therapy (NSCL-B).
  - R0 = no residual tumor, R1 = microscopic residual tumor, R2 = macroscopic residual tumor.
  - See Principles of Radiation Therapy (NSCL-C).

- Stage IV (N0, M1a) Contralateral lung (solitary nodule)
  - Treat as two primary lung tumors if both curable
  - See Evaluation (NSCL-1).

- Stage IIIA (T4, N0-1) Unresectable
  - Concurrent chemoradiation\(^j,m\)
  - Chemotherapy\(^k\)
  - See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).
  - See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).
  - If full-dose chemotherapy not given concurrently with RT as initial treatment.

**INITIAL TREATMENT**

- Margins negative (R0)\(^h\)
  - Chemotherapy\(^k\)
  - Surveillance (NSCL-12).

- Margins positive (R1, R2)\(^h\)
  - Concurrent chemoradiation\(^j,m\)
  - (if tolerated)
  - Surveillance (NSCL-12).

**ADJUVANT TREATMENT**

- Surveillance (NSCL-12).

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Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

If full-dose chemotherapy not given concurrently with RT as initial treatment.
**NCCN Guidelines™ Version 3.2011**

**Non-Small Cell Lung Cancer**

### Clinical Assessment

**Pretreatment Evaluation**

<table>
<thead>
<tr>
<th>Stage IIIB (T4 extension, N2–3)</th>
<th><strong>Contralateral, mediastinal node negative (T4, N0-1)</strong></th>
<th><strong>Ipsilateral, mediastinal node negative (T4, N0-1)</strong></th>
<th><strong>Concurrent chemoradiation (category 1)</strong></th>
<th><strong>Chemotherapy (category 1)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Ipsilateral, mediastinal node positive (T4, N2)</strong></td>
<td></td>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Concurrent chemoradiation (category 1)</strong></td>
<td></td>
<td><strong>Chemotherapy</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td><strong>See Treatment for Metastasis</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Stage IV, M1a: pleural or pericardial effusion**

<table>
<thead>
<tr>
<th>Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate</th>
<th><strong>Negative</strong></th>
<th><strong>Positive</strong></th>
<th><strong>See Treatment according to T, N, M stage NSCL-1</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Local therapy if necessary (e.g., pleurodesis, ambulatory small catheter drainage, pericardial window) + treatment as for stage IV disease (see NSCL-11)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

*See Principles of Radiation Therapy (NSCL-C).

*See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

*If full-dose chemotherapy not given concurrently with RT as initial treatment.

Most pleural effusions associated with lung cancer are due to tumor. There are 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 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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(e) Positive PET/CT scan findings need pathologic or other radiologic confirmation. If PET/CT scan positive in the mediastinum, lymph node status needs pathologic confirmation.

(m) See Principles of Radiation Therapy (NSCL-C).

(r) See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

(t) If full-dose chemotherapy not given concurrently with RT as initial treatment.
NCCN Guidelines™ Version 3.2011
Non-Small Cell Lung Cancer

**CLINICAL ASSESSMENT**

**PRETREATMENT EVALUATION**

**INITIAL TREATMENT**

---

### Stage IV, M1b: solitary site

- Mediastinoscopy
- Bronchoscopy
- Brain MRI
- PET/CT scan

#### Brain

- Surgical resection, followed by WBRT (category 1), or stereotactic radiosurgery (SRS) or SRS + WBRT or SRS alone

#### Adrenal

- Pathologic diagnosis by needle or resection

- Local therapy for adrenal lesion (if lung lesion curable, based on T and N stage) (category 2B) or See Systemic therapy (NSCL-13)

---

### T1-2, N0-1; T3, N0

- Surgical resection of lung lesion

### T1-2, N2; T3, N1-2; Any T, N3; T4, Any N

- Surgical resection of lung lesion

---

### Surveillance

- See Systemic Therapy (NSCL-13)

---

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Surveillance

NED, stages I-IV: v
- History & physical and a contrast-enhanced chest CT every 4-6 mo for 2 y (category 2B), then H&P and a non-contrast-enhanced chest CT annually (category 2B)
- Smoking cessation advice, counseling and pharmacotherapy
- PET or brain MRI is not indicated for routine follow-up

Therapy for Recurrence and Metastasis

- Laser/stent/other surgery
- Brachytherapy
- External-beam RT
- Photodynamic therapy
- Reresection
- External-beam RT

No evidence of disseminated disease
- Observation or Systemic chemotherapy (category 2B)

Evidence of disseminated disease
- See Therapy for Recurrence or Metastases (NSCL-13)

Locoregional recurrence

- Endobronchial obstruction
- Resectable recurrence
- Mediastinal lymph node recurrence
- Superior vena cava (SVC) obstruction
- Severe hemoptysis

Distant metastases

- Localized symptoms
- Diffuse brain metastases
- Bone metastasis
- Solitary metastasis
- Disseminated metastases

Regional symptoms

- Palliative external-beam RT
- Palliative external-beam RT
- Palliative external-beam RT + orthopedic stabilization, if risk of fracture
- Consider bisphosphonate therapy or denosumab

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THERAPY FOR RECURRENCE OR METASTASES

Establish histologic subtype

- Adenocarcinoma
- Large Cell
- NSCLC NOS

EGFR mutation testing (category 1)

- EGFR mutation negative or unknown
- EGFR mutation positive

Squamous cell carcinoma

EGFR mutation testing not recommended

FIRST-LINE THERAPY

- EGFR mutation discovered prior to first-line therapy
  - Erlotinib\(^y,z,aa\) → Progression → See Second-line Therapy (NSCL-16)

- EGFR mutation discovered during chemotherapy
  - Add erlotinib to current chemotherapy or Switch maintenance: erlotinib\(^bb\) → Progression → See Second-line Therapy (NSCL-16)

\(^x\)The observed incidence 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.


\(^z\)For performance status 0-4.

\(^aa\)In areas of the world where gefitinib is available, it may be used in place of erlotinib.


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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.
Bevacizumab should be given until progression. Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab. Criteria for treatment with bevacizumab + chemotherapy: non-squamous NSCLC, and no history of hemoptysis. Bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy.


Full-dose cisplatin for PS 2 patients should be given selectively.
SQUAMOUS CELL CARCINOMA

FIRST-LINE THERAPY

PS 0-2
- Chemotherapy (category 1 for PS 0-1) or Cetuximab/vinorelbine/cisplatin (category 2B)
- Tumor response evaluation
- Progression
- See Second-line Therapy (NSCL-16)

PS 3-4
- Best supportive care
- See NCCN Palliative Care Guidelines

RESPONSE EVALUATION

- Tumor response or stable disease
- 4-6 cycles (total)
- Tumor response evaluation

MAINTENANCE THERAPY

- Continuation of current regimen until disease progression or
- Continuation maintenance with cetuximab (category 1) or
- Switch maintenance with erlotinib (category 2B) or docetaxel (category 3) or
- Observation

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


Full-dose cisplatin for PS 2 patients should be given selectively.
### NSCLC Table of Contents

#### Discussion

- Performance status 0-2
  - Erlotinib or Pemetrexed (category 2B)
  - or Platinum doublet ± bevacizumab (if erlotinib given as first-line and adenocarcinoma)

- Performance status 3-4
  - Erlotinib or Best supportive care only (category 2B)

- Progression
  - Docetaxel or Pemetrexed (category 2B)
  - or Erlotinib or Platinum doublet ± bevacizumab (if erlotinib given as first-line and adenocarcinoma)

- Performance status 0-2
  - Erlotinib or Pemetrexed (category 2B)
  - or Platinum doublet ± bevacizumab (if erlotinib given as first-line and adenocarcinoma)

- Performance status 3, 4
  - Erlotinib or Best supportive care only (category 2B)

- Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

- In areas of the world where gefitinib is available, it may be used in place of erlotinib.

- Pemetrexed is not recommended for squamous histology.

- Erlotinib may be considered for PS 3 and 4 patients with EGFR mutation.

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Pathologic Evaluation

- The purpose of pathologic evaluation is to classify the lung cancer, determine the extent of invasion, establish the cancer involvement status of the surgical margins, and determine the molecular abnormalities of lung cancer that may be able to predict for sensitivity and resistance to epidermal growth factor receptor tyrosine-kinase inhibitors (EGFR-TKI).
- The World Health Organization (WHO) tumor classification system provides the foundation for tumor diagnosis, patient therapy and epidemiological and clinical studies.
- The surgical pathology report should include the histologic classification published by the WHO for carcinomas of the lung.

Bronchioloalveolar carcinoma (BAC)

- BAC includes tumors where neoplastic cells spread along pre-existing alveolar structures (lepidic spread).
- Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.
- BAC is divided into three subtypes: mucinous, non-mucinous, and a mixed mucinous and nonmucinous or indeterminate form.

- Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1), CK7 and lacks CK20. Mucinous BAC may have an aberrant immunophenotype, expressing CK20 and CK7, but reportedly lacking TTF-1 expression.

Immunohistochemical staining

- Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung, to distinguish adenocarcinoma from malignant mesothelioma and to determine the neuroendocrine status of tumors.
- Differentiation between primary pulmonary adenocarcinoma and metastatic adenocarcinoma
  - 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 is important in distinguishing primary from metastatic adenocarcinoma: the majority of primary lung carcinomas is positive for TTF-1 whereas metastatic adenocarcinoma to the lung is virtually always negative.
  - Pulmonary adenocarcinoma of the lung is usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum.
  - CDX-2 is a highly specific and sensitive marker for metastatic gastrointestinal malignancies, that could help distinguish from primary lung tumors. Prostate specific antigen, prostatic acid phosphatase and gross cystic disease fluid protein 15 may identify metastatic adenocarcinoma of prostate and breast origin, respectively.

- Determining neuroendocrine status of tumors
  - Chromogranin and synaptophysin are used to diagnose neuroendocrine tumors of the lung. All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin whereas small cell lung cancer is negative in 25% of cases.

- Distinguishing between malignant mesothelioma and lung adenocarcinoma
  - A panel of 4 markers, 2 positive in mesothelioma and 2 negative in mesothelioma (but positive in adenocarcinoma) is used routinely.
  - The stains negative in mesothelioma, but positive in adenocarcinoma are CEA, B72.3, Ber-EP4, MOC31, and TTF-1.
  - The stains sensitive and specific for mesothelioma are WT-1, calretinin, D2-40, and cytokeratin 5/6.
PRINCIPLES OF PATHOLOGIC REVIEW (2 of 3)

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 critical biological factors for proper patient selection.
  - There is a significant association between EGFR mutations — especially exon 19 deletion, exon 21 mutation (L861Q), and exon 18 (G719X) — and response to TKIs.⁹⁻¹²
  - EGFR and KRAS mutations are mutually exclusive in patients with lung cancer.¹³
  - 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.¹⁴
  - 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 tumors. KRAS mutations are most common in non-Asians, smokers, and in mucinous adenocarcinoma.¹⁵
  - 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 more common in non-mucinous lung adenocarcinoma with BAC features and in lung adenocarcinoma with papillary (and or micropapillary) features.
  - Resistance to TKI therapy is associated with KRAS mutation and specific acquired EGFR mutations, such as T790M.
  - Because EGFR gene mutations are the best predictor of a patient's response to EGFR TKI, various DNA mutational assays have been reported in the literature.¹⁶

- **EML4-ALK**
  - ALK-rearrangements in a subset of anaplastic large cell lymphomas (ALCL) have been recognized for over 15 years.¹⁷ The fusion between echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) has recently been identified in a subset of non-small cell lung cancers (NSCLCs). EML4-ALK NSCLC represents a unique subset of NSCLC patients for whom ALK inhibitors may represent a very effective therapeutic strategy.¹⁸
  - EML4-ALK NSCLC occurs most commonly in a unique clinical subgroup of NSCLC patients who share many of the clinical features of NSCLC patients likely to harbor EGFR mutations.¹⁹,²⁰ However, for the most part, EML4-ALK and EGFR mutations are mutually exclusive.¹⁹,²¹⁻²³ EML4-ALK translocations tend to occur in younger patients and those with more advanced NSCLC while this relationship has not been reported for EGFR mutant NSCLC.²¹,²⁴
  - There is currently no standard method for detecting EML4-ALK NSCLC. Several methods are currently being evaluated, including polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH). A big advantage of FISH is that a commercially available probe set, developed for the diagnosis of ALK-rearranged ALCLs, 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 the majority of ALK-rearranged lung adenocarcinomas.²⁵,²⁶ This is due to the lower level of ALK expression in ALK-rearranged NSCLCs compared with ALK-rearranged ALCLs.

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PRINCIPLES OF PATHOLOGIC REVIEW (3 of 3) - References

Determination of resectability should be performed by Board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice.

Resection, including wedge resection, is a preferred local treatment modality (other modalities include radiofrequency ablation, cryotherapy, stereotactic radiation). Thoracic surgical oncology consultation should be part of the evaluation of any patient being considered for curative local therapy. In cases where stereotactic RT is considered for high-risk patients, a multidisciplinary evaluation including a radiation oncologist is recommended.

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.

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 (e.g. multidisciplinary clinic and/or Tumor Board).

Anatomic pulmonary resection is preferred for the majority of patients with non-small cell lung cancer.

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 co-morbidity that contraindicates lobectomy
- Peripheral nodule ≤ 2 cm with at least one of the following:
  - Pure bronchioloalveolar carcinoma (BAC) histology (category 2B)
  - Nodule has ≥ 50% ground glass appearance on CT (category 2B)
  - Radiologic surveillance confirms a long doubling time (≥ 400 days) (category 2B)

- Video-assisted thoracic surgery (VATS) 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.

- Lung-sparing anatomic resection (sleeve lobectomy) preferred over pneumonectomy, if anatomically appropriate and margin-negative resection achieved.

- N1 and N2 node resection and mapping (ATS map) (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.
- Patients with pathologic stage II or greater should be referred to medical oncology for evaluation.
- Consider referral to medical oncologist for stage IB, and consider referral to radiation oncologist for stage IIIA.

Peripheral is defined as lying in the outer one third of the lung parenchyma.

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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.
The role of surgery in patients with pathologically documented N2 disease remains controversial. This population is heterogeneous. On one side of the spectrum we have a patient with negative pre-operative evaluation of the mediastinum, found to have involvement of a single station at the time of thoracotomy. On the other side we have patients with multiple pathologically proven malignant lymph node (LNs) greater than 3 cm. Most would consider the first patient a candidate for resection, while the majority would recommend definitive chemoradiotherapy, without surgery for the second. The goal of this text is to review concepts in the therapy of patients with stage IIIA (N2) NSCLC, based on the review of available evidence by the panel members of the NCCN guidelines committee. The panel recognizes that there are two randomized trials that evaluated the role of surgery in this population and that both did not show an overall survival benefit with the use of surgery. However, we believe that these trials do 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 LN dissection.
- The determination of the role of surgery in a patient with N2 positive LNs 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.
- The presence of N2 positive LNs substantially increases the likelihood of positive N3 LNs. Pathological evaluation of the mediastinum must include evaluation of the subcarinal station and contralateral lymph nodes. EBUS +/- EUS have provided additional techniques for pathologic mediastinal staging that are complementary, but do not replace 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 LN involvement prior to a final treatment decision.
- Patients with a single LN smaller than 3 cm can be considered for a multimodality approach that includes surgical resection.
- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.
- Radiographic methods have poor positive and negative predictive values in the evaluation of the mediastinum after neoadjuvant therapy. 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 pre-treatment evaluation and reserve mediastinoscopy for nodal restaging after neoadjuvant therapy.
The Role of Surgery in Patients with Stage IIIA (N2) NSCLC

- Neoadjuvant chemoradiotherapy is used in 50% of the NCCN institutions, while neoadjuvant chemotherapy is used in the other 50%. Overall survival appears similar provided RT is given postoperatively, if not given preoperatively. Neoadjuvant chemoradiotherapy is associated with higher rates of pathological complete response and negative mediastinal lymph nodes. 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 the ones considered standard definitive therapy, all efforts should be made to minimize any possible breaks in radiotherapy for surgical evaluation. 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 with the thoracic surgeon, is to complete definitive chemoradiotherapy prior to re-evaluation and consideration for surgery.

- Data from a large multi-institutional trial indicate that pneumonectomy after neoadjuvant chemoradiotherapy has unacceptable morbidity and mortality. 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.

We have submitted a questionnaire to the NCCN institutions regarding their approach to patients with N2 disease. Their responses are reported to give an idea to the readers of the patterns of practice when approaching this difficult clinical problem.

- Would consider surgery in patients with one N2 lymph node station involved by a LN smaller than 3cm: (90.5%).
- Would consider surgery with more than one N2 LN station involved, as long as no LN was bigger than 3cm: (47.6%).
- Uses EBUS (+/- EUS) in the initial evaluation of the mediastinum: (80%).
- Uses pathological evaluation of the mediastinum, after neoadjuvant therapy, to make a final decision before surgery: (40.5%).
- Would consider neoadjuvant therapy followed by surgery when a patient is likely, based on initial evaluation, to require a pneumonectomy: (54.8%).
PRINCIPLES OF SURGICAL THERAPY (4 of 4)

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


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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.
Treatment recommendations should be made after joint consultation and/or discussion by a multidisciplinary team including surgical oncologists, radiation oncologists, medical oncologists, pulmonologists, pathologists, and diagnostic radiologists. Radiation therapy can be offered as an adjunct for operable patients with resectable diseases, as the primary local treatment for patients with medically inoperable or unresectable diseases, and as an important palliative modality for patients with incurable diseases. The terminology and abbreviations for radiation therapy are summarized in Table 1. Commonly Used RT Abbreviations NSCL-C 5 of 7. For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy followed by postoperative radiotherapy is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established. For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiotherapy is recommended if the patient is medically fit. Radiation therapy should start earlier as local recurrence is the most common failure in this group of patients. Conformal radiation therapy with concurrent chemotherapy should be offered to patients with stage II and III NSCLC who are medically inoperable but of reasonable performance status and life expectancy. Modern technology is indicated when there is a need to deliver adequate dose to tumor without compromising normal tissue tolerance. In patients receiving radiation therapy or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (i.e. Grade 3 esophagitis or hematologic toxicities) should be minimized by conformal treatment planning and aggressive supportive care. Radiation therapy can be offered to primary or distant sites as palliative care for stage IV patients with extensive metastasis as indicated.
Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy

- Commonly used dose regimens for definitive and palliative radiation are summarized in Table 2. Commonly Used Doses for Conventionally Fractionated Radiation Therapy NSCL-C 5 of 7. Tissue heterogeneity correction is recommended in radiation treatment planning for all patients. When CT with IV contrast is used for planning, the area with a large amount of contrast may be treated as water density so that the impact of IV contrast is minimized.

- Preoperatively, a dose of 45-50 Gy in 1.8 to 2 Gy fraction size is recommended. Although it has been reported to be safe and achieved favorable survival outcome, doses > 50 Gy are not recommended unless with an experienced team.

- Postoperative radiation dose should be based on margin status. Lung tolerance to radiation after surgery seems to be remarkably smaller than those with the presence of both lungs. Every effort should be made to minimize the dose of radiation therapy. More conservative consideration is recommended for the dose constraints of normal lungs in the postoperative setting.

- For definitive radiation therapy, the commonly prescribed dose is 60-70 Gy. A retrospective study revealed that dose ≥ 74 Gy was significantly associated with better survival in patients treated with radiation alone or sequential chemoradiation. Radiation dose was also reported to be a significant factor for overall survival in stage I-II after radiation alone or stage III disease treated with concurrent chemoradiation. When radiation is given concurrently with chemotherapy, a dose up to 74 Gy may be delivered safely if the doses to normal structures are strictly limited to their tolerance (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7). The role of high dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).

- For treatment volume consideration, PTV should be defined per ICRU-62 guidelines, based on GTV, plus CTV margin for microscopic diseases, ITV margins for target motion, and margins for daily set-up errors. GTV should be confined to visible tumors (include both primary and nodal diseases) on CT and/or PET-CT.

- Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial and ENI should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. Involved field radiation without ENI is a common practice as it has been shown to allow higher dose radiation to tumor with acceptable toxicity and a low risk of isolated nodal relapse.

- In patients who receive postoperative radiotherapy, CTV may consist of the bronchial stump and high-risk draining lymph node stations.

- It is essential to evaluate the DVH of GTV, CTV, and PTV for target coverage and DVHs of critical structures and to limit the doses to the lungs, heart, esophagus, brachial plexus, and spinal cord (See Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT NSCL-C 5 of 7) to minimize normal tissue toxicity. These limits are largely empirical.

- For patients receiving postoperative radiation therapy, more strict DVH parameters should be considered for the lung. The exact limit is unknown for lobectomy cases. Based on data from pneumonectomy of mesothelioma cases, mean lung dose should be limited to ≤ 8.5 Gy in pneumonectomy patients.

See Radiation Simulation, Planning and Delivery (NSCL-C 3 of 7)
See Stereotactic Body Radiation Therapy (NSCL-C 4 of 7)
See Prophylactic Cranial Irradiation (NSCL-C 4 of 7)
**PRINCIPLES OF RADIATION THERAPY (3 of 7)**

**Radiation Simulation, Planning and Delivery**

- Treatment planning should be performed by CT scans obtained in the treatment position. IV contrast is recommended for better target delineation whenever possible, especially in patients with central tumors or with nodal disease. PET-CT is highly recommended for the treatment plan especially in cases with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improve the target accuracy.\(^{35}\) Since IV contrast interferes with dose heterogeneity correction, a separate scan without contrast can be used for planning.
- In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT prior to induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume, and the cone-down fields cover the post-chemotherapy tumor volume. However, in patients with compromised lung or cardiac function, large initial tumor or any other predicted high normal tissue toxicity, the post-chemotherapy volume can be used to avoid excessive normal tissue toxicity.
- Photon beam energy is to be individualized based on the anatomic location of the tumors and beam path. In general, photon beam energy between 4 to 10 MV is recommended for beams passing through low density lung tissue before entering the tumor. For large mediastinal tumors or tumors attached to chest wall, when there is no air gap before the beam entering the tumor, 15 MV or 18 MV energies can be considered for more optimal dose arrangement.
- In certain situations where there is a large volume of normal lung being irradiated or where tumors are located close to critical structures (i.e. spinal cord), intensity modulated radiotherapy (IMRT) can be considered for high-dose radiation to avoid overdose to normal tissues. Significantly lower risk of radiation pneumonitis and improved overall survival have been observed with IMRT compared to 3-D conformal radiation therapy for lung cancer.\(^{36}\) When IMRT is used, the NCI IMRT guideline ([http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf](http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf)) should be followed. Under strictly defined protocols, proton therapy may be allowed.\(^{37-41}\) When IMRT and proton therapy are used, daily image guidance at delivery is recommended for quality assurance. The modality of IGRT should be based on the institutional experience and the required treatment accuracy.
- The respiratory motion management needs to be considered for all patients with NSCLC when they receive radiation to the thorax for definitive purpose. Acceptable methods of accounting for tumor motion, per AAPM Task Group 76 guideline, include: 1) Motion-encompassing methods such as slow CT scanning, inhale and exhale breath-hold CT, four-dimensional (4-D) respiration-correlated CT, 2) Respiratory gating methods using an external respiration signal or using internal fiducial markers, 3) Breath-hold methods by deep-inspiration breath-hold, active-breathing control (ABC) device, self breath-hold without respiratory monitoring, 4) Forced shallow breathing with abdominal compression, and 5) Real-time tumor-tracking methods.

See Stereotactic Body Radiation Therapy (NSCL-C 4 of 7)

See Prophylactic Cranial Irradiation (NSCL-C 4 of 7)
Stereotactic Body Radiation Therapy (SBRT), also known as Stereotactic Ablative Radiotherapy (SABR) results in higher local control and possibly better long-term survival than 3DCRT in stage I NSCLC.\(^42\) SBRT is one of the well established treatments for inoperable stage I NSCLC patients with node negative peripheral lesions, although optimal dose fractionation needs to be determined (See Figure 1. **Schema of Central and Peripheral Locations NSCL-C 6 of 7**).

SBRT fractionation regimens vary widely in current practice, ranging from one single fraction\(^43\) to 3 fractions,\(^44,45\) 4 fractions,\(^46\) and 5 fractions\(^47,48\) (See Table 4. **Commonly Used SBRT Regimens NSCL-C 6 of 7**). While the optimal number of fractionation may be estimated based on the tumor size and total dose,\(^49\) an accumulative BED of \(\geq 100\) Gy is associated with better survival.\(^50\) Optimal dose and fractionation regimens for SBRT have not been fully characterized. RTOG 0915 is ongoing to compare the outcomes between one single fraction and 4 fractions.

While evidence is limited, conservative normal tissue constraints are recommended (See Table 5. **Normal Tissue Dose Volume Constraints for SBRT NSCL-C 6 of 7**).

**Prophylactic Cranial Irradiation (PCI)**

The benefit for the overall survival of prophylactic brain irradiation has not been proven for NSCLC. The recommendation of whole brain irradiation should be a decision after physician-patient discussion, weighing the potential benefit over the risk for each individual patient.
### PRINCIPLES OF RADIATION THERAPY (5 of 7)

#### Table 1. Commonly Used RT Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>3DCRT</td>
<td>3-D Conformal Radiation Therapy</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
</tr>
<tr>
<td>GTV¹</td>
<td>Gross Tumor Volume</td>
</tr>
<tr>
<td>CTV¹</td>
<td>Clinical Target Volume</td>
</tr>
<tr>
<td>PTV¹</td>
<td>Planning Target Volume</td>
</tr>
<tr>
<td>ITV¹</td>
<td>Internal Target Volume</td>
</tr>
<tr>
<td>BED</td>
<td>Biologically Effective Dose</td>
</tr>
<tr>
<td>OAR</td>
<td>Organ At Risk</td>
</tr>
<tr>
<td>V20</td>
<td>% Volume of an OAR Receiving ≥ 20 Gy</td>
</tr>
<tr>
<td>MLD</td>
<td>Mean Lung Dose</td>
</tr>
<tr>
<td>ABC</td>
<td>Active Breathing Control</td>
</tr>
<tr>
<td>IMRT</td>
<td>Intensity Modulated Radiation Therapy</td>
</tr>
<tr>
<td>OBI</td>
<td>On-Board Imaging</td>
</tr>
<tr>
<td>IGRT</td>
<td>Image Guided Radiation Therapy</td>
</tr>
<tr>
<td>SBRT</td>
<td>Stereotactic Body Radiation Therapy</td>
</tr>
<tr>
<td>SABR</td>
<td>Stereotactic Ablative Radiotherapy, aka SBRT</td>
</tr>
<tr>
<td>4DCT²</td>
<td>Four Dimensional Computerized Tomography</td>
</tr>
<tr>
<td>CBCT</td>
<td>Cone Beam Computerized Tomography</td>
</tr>
</tbody>
</table>

1 Please use ICRU62 for detailed target definitions.  
2 4DCT to assess respiratory motion.

#### Table 2. Commonly Used Doses for Conventionally Fractionated Radiation Therapy

<table>
<thead>
<tr>
<th>Treatment Type</th>
<th>Total Dose</th>
<th>Fraction Size</th>
<th>Treatment Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative</td>
<td>45-50 Gy</td>
<td>1.8-2 Gy</td>
<td>4-5 weeks</td>
</tr>
<tr>
<td>Postoperative</td>
<td>50-54 Gy</td>
<td>1.8-2 Gy</td>
<td>4-5 weeks</td>
</tr>
<tr>
<td>Negative margins</td>
<td>54-60 Gy</td>
<td>1.8-2 Gy</td>
<td>5-6 weeks</td>
</tr>
<tr>
<td>Extracapsular nodal extension or microscopic positive margins</td>
<td>60 to 70 Gy</td>
<td>1.8-2 Gy</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Gross residual tumors</td>
<td>60 to 70 Gy</td>
<td>1.8-2 Gy</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Definitive Radiation alone or sequential chemoradiation</td>
<td>60-74 Gy</td>
<td>2 Gy</td>
<td>6-7.5 weeks</td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td>60 to 70 Gy</td>
<td>2 Gy</td>
<td>6-7.5 weeks</td>
</tr>
<tr>
<td>Palliative Obstructive disease (SVC syndrome or obstructive pneumonia)</td>
<td>30-45 Gy</td>
<td>3 Gy</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Bone metastases with soft tissue mass</td>
<td>30 Gy</td>
<td>3 Gy</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Bone metastases without soft tissue mass</td>
<td>8 Gy</td>
<td>3 Gy</td>
<td>1 day</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td>8 Gy</td>
<td>See CNS Guidelines</td>
<td>See CNS Guidelines</td>
</tr>
</tbody>
</table>

#### Table 3. Normal Tissue Dose Volume Constraints for Conventionally Fractionated 3DCRT³,⁴

<table>
<thead>
<tr>
<th>Structures</th>
<th>Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal Cord</td>
<td>V20 &lt; 37% in 1.8-2 Gy</td>
</tr>
<tr>
<td>Lung</td>
<td>MLD &lt; 20 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V40 &lt; 100%</td>
</tr>
<tr>
<td></td>
<td>V45 &lt; 67%</td>
</tr>
<tr>
<td></td>
<td>V60 &lt; 33%</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Mean dose &lt; 34 Gy</td>
</tr>
<tr>
<td>Brachial Plexus</td>
<td>66 Gy in 1.8-2/Gy</td>
</tr>
</tbody>
</table>

³ The limits are consistent with those of the ongoing phase III trial RTOG 0617. Vxx refers to the percentage of whole organ receiving more or equal to xx Gy. Lung V20 refers to the percentage of both lungs with subtraction of overlapping CTV receiving ≥ 20 Gy, MLD=mean total lung dose.  

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 4. Commonly Used SBRT Regimens

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-34 Gy x 1</td>
<td>Peripheral small (&lt; 2 cm) tumors, &gt; 1 cm from chest wall</td>
</tr>
<tr>
<td>15-20 Gy x 3</td>
<td>Peripheral &lt; 5 cm tumors, &gt; 1 cm from chest wall</td>
</tr>
<tr>
<td>12-12.5 Gy x 4</td>
<td>Peripheral tumors, particularly those &lt; 1 cm from chest wall</td>
</tr>
<tr>
<td>10-11 Gy x 5</td>
<td>Peripheral tumors, particularly those &lt; 1 cm from chest wall</td>
</tr>
</tbody>
</table>

Table 5. Normal Tissue Dose Volume Constraints for SBRT*

<table>
<thead>
<tr>
<th>OAR</th>
<th>1 Fraction</th>
<th>3 Fractions</th>
<th>4 Fractions</th>
<th>5 Fractions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal cord</td>
<td>14 Gy</td>
<td>18 Gy (6 Gy/fx)</td>
<td>26 Gy (6.5 Gy/fx)</td>
<td>30 Gy (6 Gy/fx)</td>
</tr>
<tr>
<td>Esophagus</td>
<td>22 Gy</td>
<td>30 Gy (10 Gy/fx)</td>
<td>34 Gy (8.5 Gy/fx)</td>
<td>35 Gy (7 Gy/fx)</td>
</tr>
<tr>
<td>Heart/pericardium</td>
<td>37 Gy</td>
<td>39 Gy (13 Gy/fx)</td>
<td>49 Gy 12.25 Gy/fx</td>
<td>55 Gy 11 Gy/fx</td>
</tr>
<tr>
<td>Great vessels</td>
<td>20.2 Gy</td>
<td>30 Gy (10 Gy/fx)</td>
<td>34.8 Gy (8.7 Gy/fx)</td>
<td>40 Gy (8 Gy/fx)</td>
</tr>
<tr>
<td>Trachea/Large Bronchus</td>
<td>30 Gy</td>
<td>30 Gy (10 Gy/fx)</td>
<td>31.2 Gy (7.8 Gy/fx)</td>
<td>32.5 Gy (6.5 Gy/fx)</td>
</tr>
<tr>
<td>Rib</td>
<td>26 Gy</td>
<td>30 Gy (10 Gy/fx)</td>
<td>36 Gy (9 Gy/fx)</td>
<td>40 Gy 8 Gy/fx</td>
</tr>
<tr>
<td>Skin</td>
<td>12.4 Gy</td>
<td>27 Gy (9 Gy/fx)</td>
<td>30 Gy (7.5 Gy/fx)</td>
<td>35 Gy 7 Gy/fx</td>
</tr>
</tbody>
</table>

*The limits are based on a combined consideration of recommendations from ongoing multicenter trials (RTOG 0617, RTOG 0618, RTOG 0813 and RTOG 0915).


Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
PRINCIPLES OF RADIATION THERAPY - References (7 of 7)


### CHEMOTHERAPY REGIMENS FOR ADJUVANT THERAPY

<table>
<thead>
<tr>
<th>Published Chemotherapy Regimens</th>
<th>Schedule</th>
<th>Other Acceptable Cisplatin-based Regimens</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 50 mg/m² days 1 and 8 Vinorelbine 25 mg/m² days 1, 8, 15, 22</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cisplatin 75 mg/m² on day 1 Gemcitabine 1250 mg/m² on days 1, 8</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² on day 1 Vinorelbine 30 mg/m² days 1, 8, 15, 22</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Cisplatin 75 mg/m² Docetaxel 75 mg/m²</td>
<td>Every 21 days&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cisplatin 75-80 mg/m² day 1; Vinorelbine 25-30 mg/m² days 1 + 8</td>
<td>Every 21 days for 4 cycles</td>
<td>Pemetrexed 500 mg/m² on day 1 Cisplatin 75 mg/m² on day 1 for adenocarcinoma and large cell carcinoma and NSCLC NOS (without specific histologic subtype)</td>
<td>Every 21 days for 4 cycles</td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² on day 1 Etoposide 100 mg/m² days 1-3</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 80 mg/m² on day 1, 22, 43, 64 Vinblastine 4 mg/m² days 1, 8, 15, 22 then every 2 wks after day 43</td>
<td>Every 21 days for 4 cycles&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel 200 mg/m² on day 1 Carboplatin AUC 6 on day 1</td>
</tr>
</tbody>
</table>


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

**Clinical Trials:** NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
## CHEMOTHERAPY REGIMENS USED WITH RADIATION THERAPY

### Concurrent Chemotherapy/RT Regimens*

<table>
<thead>
<tr>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 50 mg/m² on day 1, 8, 29, and 36</td>
</tr>
<tr>
<td>Etoposide 50 mg/m² days 1-5, 29-33</td>
</tr>
<tr>
<td>Concurrent thoracic RT&lt;sup&gt;a&lt;/sup&gt; (preferred)</td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² day 1, 29</td>
</tr>
<tr>
<td>Vinblastine 5 mg/m&lt;sup&gt;2&lt;/sup&gt;/weekly x 5</td>
</tr>
<tr>
<td>Concurrent thoracic RT&lt;sup&gt;b&lt;/sup&gt; (preferred)</td>
</tr>
<tr>
<td>Paclitaxel 45-50 mg/m² weekly over 1 hour</td>
</tr>
<tr>
<td>Carboplatin AUC = 2 mg/mL/min over 30 min weekly</td>
</tr>
<tr>
<td>Concurrent thoracic RT&lt;sup&gt;c&lt;/sup&gt; (category 2B)</td>
</tr>
</tbody>
</table>

### Sequential Chemotherapy/RT Regimens

<table>
<thead>
<tr>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 100 mg/m² on day 1, 29</td>
</tr>
<tr>
<td>Vinblastine 5 mg/m&lt;sup&gt;2&lt;/sup&gt;/weekly on days 1, 8, 15, 22, 29 followed by RT&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel 200 mg/m² every 3 weeks over 3 hours, 2 cycles</td>
</tr>
<tr>
<td>Carboplatin AUC 6, 2 cycles followed by thoracic RT&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

*There are data that support full-dose cisplatin over carboplatin-based regimens. Carboplatin regimens have not been adequately tested.

### Concurrent Chemotherapy/RT Followed by Chemotherapy

<table>
<thead>
<tr>
<th>Regimen Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin 50 mg/m² on day 1, 8, 29, 36</td>
</tr>
<tr>
<td>Etoposide 50 mg/m² days 1-5, 29-33</td>
</tr>
<tr>
<td>Concurrent thoracic RT followed by cisplatin 50 mg/m&lt;sup&gt;2&lt;/sup&gt; and etoposide 50 mg/m&lt;sup&gt;2&lt;/sup&gt; x 2 additional cycles (category 2B)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paclitaxel 45-50 mg/m&lt;sup&gt;2&lt;/sup&gt; weekly</td>
</tr>
<tr>
<td>Carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m&lt;sup&gt;2&lt;/sup&gt; and carboplatin AUC 6&lt;sup&gt;c&lt;/sup&gt; (category 2B)</td>
</tr>
</tbody>
</table>

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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.
ADVANCED DISEASE:

- Baseline prognostic variables (stage, weight loss, PS, 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 y survival rate (30-40%) and 2 y survival rate (10-15%) in fit patients.
- No specific platinum-based cytotoxic combination is clearly superior.
- 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 indicated in PS 0-2 patients with advanced or recurrent NSCLC.
- Erlotinib is indicated for EGFR mutation positive patients.
- There is evidence of superior efficacy and reduced toxicity for cisplatin/pemetrexed in patients with nonsquamous histology, in comparison to cisplatin/gemcitabine.
- Two drug regimens are preferred; a third cytotoxic drug does not increase survival, with the exception of bevacizumab or cetuximab in treatment-naïve PS 0-1 NSCLC.
- Single agent therapy or platinum-based combinations are a reasonable alternative in PS 2 patients or the elderly.
- Systemic chemotherapy is not indicated in PS 3 or 4 patients.
- In locally advanced NSCLC, chemoradiation is superior to radiation alone: concurrent chemoradiation appears to be better than sequential chemoradiation.
- Cisplatin-based combinations have been proven superior to best supportive care in advanced, incurable disease, with improvement in median survival of 6-12 wks, and a doubling of one-year survival rates (absolute 10-15% improvement).
- Cisplatin or carboplatin have been proven effective in combination with any of the following agents: paclitaxel, docetaxel, gemcitabine, vinorelbine, irinotecan, etoposide, vinblastine, pemetrexed.
- New agent/non-platinum combinations are reasonable alternatives if available data show activity and tolerable toxicity (eg, gemcitabine/docetaxel).
- If patient has a known KRAS mutation, therapy other than erlotinib should be considered first.
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:** Biologic agents given in combination with conventional chemotherapy should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. There are no randomized data supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.
  - 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 2B).

- **Switch Maintenance:** Two recent 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.
  - 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 (category 3).
  - Close follow-up of patients without therapy is a reasonable alternative to switch 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 has been proven superior to BSC, vinorelbine, or ifosfamide with improved survival/QOL.
  - Pemetrexed has been shown to be superior to docetaxel with less toxicity in patients with adenocarcinoma and large cell carcinoma.
  - Erlotinib has proven superior to BSC with significantly improved survival and delayed time to symptom deterioration.

Third-line therapy
- Erlotinib has proven statistically superior to BSC with respect to survival.

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

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

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

NSCLC long term follow-up care

- Cancer Surveillance
  - History and Physical and a contrast-enhanced chest CT scan every 4-6 months for 2 years (category 2B), then H&P and a non-contrast-enhanced chest CT scan annually (category 2B)
  - Smoking status assessment at each visit, counseling and referral for cessation as needed.
- Immunizations
  - Annual Influenza vaccination
  - Pneumococcal vaccination with revaccination as appropriate
- Counseling Regarding Health Promotion and Wellness
  - 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
  

Cancer Screening Recommendations

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

- Colorectal Cancer: For men and women, Colonoscopy every 10 years (preferred) or fecal occult blood test (FOBT) annually and flexible sigmoidoscopy every 5 years, beginning at age 50. See NCCN Colorectal Cancer Screening Guidelines
- Prostate Cancer: For men-annual prostate specific antigen (PSA) testing beginning at age 50; for African American males and those with family history of prostate cancer, PSA testing beginning at age 40. See NCCN Prostate Cancer Early Detection Guidelines
- Breast Cancer: For women-monthly self breast exam (SBE) beginning at age 20 (optional); annual clinical breast exam (CBE) beginning at age 25; annual mammogram beginning at age 40. See NCCN Breast Cancer Screening Guidelines
- Cervical Cancer: Annual cervical cytology testing for women up to age 30; after age 30, annual cervical cytology testing or cervical cytology testing every 2-3 years (if 3 negative/satisfactory annual cervical cytology tests) or cervical cytology and HPV-DNA testing. If both negative, testing every 3 years. See NCCN Cervical Cancer Screening Guidelines

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 6. Definitions for T, N, M*

<table>
<thead>
<tr>
<th>T</th>
<th>Primary Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>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</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumor</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>T1</td>
<td>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)</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumor ≤ 2 cm in greatest dimension</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumor &gt; 2 cm but ≤ 3 cm in greatest dimension</td>
</tr>
<tr>
<td>T2</td>
<td>Tumor &gt; 3 cm but ≤ 7 cm or tumor with any of the following features:</td>
</tr>
<tr>
<td>T2a</td>
<td>Involves main bronchus, ≥ 2 cm distal to the carina</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt; 3 cm but ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T3</td>
<td>Tumor &gt; 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 &lt; 2 cm distal to the carina 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</td>
</tr>
<tr>
<td>T4</td>
<td>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</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>M</th>
<th>Distant Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>MX</td>
<td>Distant metastasis cannot be assessed</td>
</tr>
<tr>
<td>M0</td>
<td>No distant metastasis</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule(s) in a contralateral lobe; tumor with pleural nodules or malignant pleural (or pericardial) effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

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

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

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

### Table 7. Descriptors, T and M Categories, and Stage Grouping*

<table>
<thead>
<tr>
<th>Sixth Edition T/M Descriptor</th>
<th>7th Edition T/M</th>
<th>N0</th>
<th>N1</th>
<th>N2</th>
<th>N3</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 (less than or equal to 2 cm)</td>
<td>T1a</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1 (&gt;2–3 cm)</td>
<td>T1b</td>
<td>IA</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (less than or equal to 5 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>IIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt;5–7 cm)</td>
<td>T2b</td>
<td>IIA</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt; 7 cm)</td>
<td>T3</td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3 invasion</td>
<td></td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td></td>
<td>IIIB</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td></td>
<td>IIIA</td>
<td>IIIA</td>
<td>IIIB</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (pleural effusion)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td></td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
</tbody>
</table>

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

Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Overview

Lung cancer is the leading cause of cancer death in the United States. An estimated 222,500 new cases (116,750 in men and 105,770 in women) of lung and bronchial cancer will be diagnosed in 2010, and 157,300 deaths (86,200 in men, 71,100 in women) are estimated to occur due to the disease. Only 15.8% of all lung cancer patients are alive 5 years or more after diagnosis (http://seer.cancer.gov/statfacts/html/lungb.html). Common symptoms of lung cancer include cough, dyspnea, weight loss, and chest pain; symptomatic patients are more likely to have chronic obstructive pulmonary disease.

The primary risk factor for lung cancer is smoking, which accounts for more than 85%-90% of all lung cancer-related deaths. The risk of lung cancer increases with the number of cigarettes smoked per day and with the number of years spent smoking. Exposed nonsmokers also have an increased relative risk of developing lung cancer from “secondhand smoke”. Radon gas, a radioactive gas that is produced by the decay of radium 226, is the second leading cause of lung cancer. The U.S. Environmental Protection Agency (EPA) estimates that radon is the main cause of lung cancer in nonsmokers; however, secondhand smoke is also a major factor (http://www.epa.gov/radon/healthrisks.html). The decay of radon leads to the production of substances that emit alpha-particles, which may cause cell damage and, therefore, increase the potential for malignant transformation. Data suggest that postmenopausal women who smoke or are former smokers should not receive hormone replacement therapy, because it increases the risk of death from non-small cell lung cancer (NSCLC).

Asbestos, a mineral compound that breaks into small airborne shards, is a known carcinogen that increases the risk of 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. In addition, other possible risk factors include recurring lung inflammation, lung scarring secondary to tuberculosis, family history, and exposure to other carcinogens (i.e., bis(chloromethyl)ether, polycyclic aromatic hydrocarbons, chromium, nickel, and organic arsenic compounds).

Prevention and Screening

Approximately 85%-90% of cases of lung cancer are caused by voluntary or involuntary secondhand cigarette smoking. Active smoking and secondhand smoke both cause lung cancer (see Reports from the
Surgeon General, which are the next 2 links). There is a causal relationship between active smoking and lung cancer and also with other cancers, such as esophageal, oral cavity, laryngeal, pharyngeal, bladder, pancreatic, gastric, kidney, and cervical cancers as well as other diseases and conditions (http://www.cdc.gov/tobacco/data_statistics/sgr/2004/pdfs/executivesummary.pdf). Smoking harms nearly every organ in the body. Those who live with someone who smokes have a 20% to 30% 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/). Persistent smoking is associated with second primary cancers, treatment complications, and decreased survival. Programs using behavioral counseling combined with medications that promote smoking cessation (approved by the FDA [Food and Drug Administration]) can be very useful (see Treating Tobacco Use and Dependence: 2008 Update, which is published by the Agency for Healthcare Research and Quality [AHRQ]) (http://www.surgeongeneral.gov/tobacco/treating_tobacco_use08.pdf).

Agents that can be used to promote smoking cessation include nicotine replacement (e.g., gum, inhaler, nasal spray, patch), bupropion, and varenicline. Studies have shown that varenicline is better than bupropion for smoking cessation.\(^9, 10\) However, almost 30% of patients had nausea while using varenicline.\(^11\) The effectiveness of varenicline for preventing relapse has not been clearly established.\(^12\) The FDA has issued an alert for varenicline regarding neuropsychiatric symptoms (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm106540.htm).

Lung cancer is still the leading cause of cancer death worldwide, and late diagnosis is a fundamental obstacle to improving lung cancer outcomes.\(^13, 14\) Because localized cancer can be managed curatively and because survival in other solid tumors (e.g., breast, cervix, colon, and prostate) appears to be increased by screening and early detection, lung cancer would be an appropriate candidate for a population-based screening approach. Pilot trials of spiral computed tomography (CT) in lung cancer screening are promising with a frequency of stage I detectable lung cancer in more than 80% of newly diagnosed cases.\(^15-17\)

The National Lung Screening Trial (NLST, ACRIN Protocol A6654) is a randomized, controlled study involving more than 53,000 current or former heavy smokers; this trial assessed the risks and benefits of low-dose spiral CT scans compared with chest x-rays for detecting lung cancer.\(^18\) A press release from the NLST (November 4, 2010) suggests that screening high-risk patients with low-dose spiral CT decreases the mortality rate from lung cancer by 20% when compared with chest x-ray (http://www.cancer.gov/newscenter/pressreleases/NLSTresultsRelease). High-risk patients were either current or former smokers with a 30-pack year smoking history (former smokers had quit 15 years ago), were 55-74 years old, and had no evidence of lung cancer.\(^19, 20\) However, the complete data from the NLST have not been published yet in a peer-reviewed journal. Additional information on NLST can be found at http://www.cancer.gov/nlst.

The International Early Lung Cancer Action Program (I-ELCAP) has been assessing whether annual screening by spiral 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. Additional information on I-ELCAP can be found at http://www.ielcap.org/index.htm. Screening can increase the diagnosis of early-stage lung cancers and yields excellent survival data. A recent press release from the NLST suggests that screening decreases the mortality rate.

The NCCN NSCLC panel met in July 2010 to update the guidelines for 2011. At that time, the recent results from the NLST (about lung cancer screening with low-dose CT) were not available. In addition, the complete data regarding screening for lung cancer from the NLST have not been published yet in a peer-reviewed journal. Previously, the NCCN NSCLC panel did not recommend (category 3) the routine use of screening for lung cancer with low-dose CT, although there was major disagreement among panel members and some believe that screening is appropriate. An NCCN panel is currently assessing lung cancer screening.

Previous published data about screening are conflicting, thus, conclusive data from ongoing trials are necessary to define the benefits and risks associated with screening for lung cancer with low-dose CT (see also the NCCN 2011 NSCLC algorithm). Patients should discuss the risks and benefits with an expert at a center of excellence before having a screening CT. Data show that a CT screening clinic detected a malignant tumor in 3% of patients; many patients (45%) did not complete followup.

### Classification and Prognostic Factors

The World Health Organization (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 NCCN Small Cell Lung Cancer Guideline). 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, 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. Gene expression profiling (using DNA microarrays) has identified subtypes of lung adenocarcinomas (i.e., bronchioid, squamoid, magnoid), which correlate with stage-specific survival and metastatic pattern. Bronchioid tumors were associated with increased survival in early-stage disease, whereas, squamoid tumors were associated with increased survival in advanced disease.

Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status ([PS] Eastern Cooperative Oncology Group 0, 1, or 2), no significant weight loss (not more than 5%), and female gender. Age and histologic subtype have little prognostic significance. Biologic prognostic factors, including mutations of the tumor suppressor gene (p53), the activation of proto-oncogene Kirsten-Rous sarcoma virus (K-ras), and other biologic markers, may have significant value in predicting a poor prognosis. Patients with stage I lung adenocarcinoma who have specific genetic abnormalities, such as k-ras oncogene activation, have a poor prognosis and disease-free survival.
Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed to classify 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 (i.e., positive or negative margins), and do molecular diagnostic studies to determine whether certain gene mutations are present (e.g., epidermal growth factor receptor [EGFR] mutations). Data show that targeted therapy is potentially very effective in patients with specific gene mutations (see sections on “EGFR Mutations” and “EML4-ALK Mutations”). Preoperative evaluations include examination of one of the following specimens: bronchial brushings, bronchial washings, fine-needle aspiration (FNA) biopsy, core needle biopsy, endobronchial biopsy, and transbronchial biopsy. In addition, the mediastinal lymph nodes are systematically sampled to assess the staging and therapeutic options.

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 histologic classification published by the WHO for carcinomas of the lung. Note that the “Principles of Pathologic Review” are listed in the 2011 NSCLC algorithm.

Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important type of pulmonary adenocarcinoma, because reports suggest that EGFR mutations are common in patients with nonmucinous BAC, which is one of 3 subtypes of BAC. EGFR inhibitors, such as gefitinib and erlotinib, are useful for patients with BAC. However, mucinous BAC typically are negative for EGFR mutations and positive for K-ras mutations. The different subtypes of BAC and methods for distinguishing the subtypes are described in the 2011 NSCLC algorithm (see “Principles of Pathologic Review”).

Immunohistochemical Staining

Immunostains are used to differentiate primary pulmonary adenocarcinoma from metastatic adenocarcinoma to the lung (e.g., breast and prostate), to distinguish adenocarcinoma from malignant mesothelioma, and to determine the neuroendocrine status of tumors. Immunohistochemical staining is described in the 2011 NSCLC algorithm (see “Principles of Pathologic Review”). Immunohistochemistry is most valuable in distinguishing between malignant mesothelioma and lung adenocarcinoma. The stains that are positive for adenocarcinoma, include CEA (carcinoembryonic antigen), B72.3, Ber-EP4, MOC31, and TTF-1; these stains are negative for mesothelioma. Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40, and cytokeratin 5/6. 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 WT1), CEA, and MOC-31 (or B72.3, Ber-EP4, or BG-8).

TTF-1 is a transcription factor that regulates tissue-specific expression of surfactant apoprotein A (SPA), surfactant apoprotein B (SPB), surfactant apoprotein C (SPC), Clara cell antigen, and T1α. TTF-1 is very important in distinguishing primary from metastatic adenocarcinoma, because most primary carcinomas are TTF-1 positive. However, TTF-1 is positive in tumors from patients with thyroid...
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+. CDX-2 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 small cell lung carcinoma is negative in 25% of the cases.

Most SCLCs are immunoreactive for keratin, epithelial membrane antigen, and TTF-1. Many SCLCs also stain positively for markers of neuroendocrine differentiation, including chromogranin A, neuron-specific enolase, neural cell adhesion molecule (NCAM), 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. Recent data suggest that microRNAs (miRNA) expression can be used to distinguish SCLC from NSCLC.

**Staging**

The international staging system for lung cancer has been revised and adopted by the American Joint Committee on Cancer (AJCC) and by the Union Internationale Contre le Cancer. Recently, the lung cancer staging system was revised by the International Association of the Study of Lung Cancer (IASLC). This new revised staging is available from the AJCC (7th edition). These NCCN guidelines use the revised AJCC (7th edition) staging. The revised stage grouping is summarized in Table 6 of the staging tables. The descriptors of the TNM classification scheme are summarized in Table 7 (note that the cells in bold indicate a change from the 6th edition for a particular TNM category).

The TNM staging revisions (AJCC 7th edition) became effective for all new cases diagnosed after January 1, 2010. With the new staging, locally advanced disease is now stage III; advanced disease is now stage IV. The revised AJCC staging for 2010 includes upstaging and downstaging: for example, 1) T2bN0M0 is upstaged from stage IB to stage IIA; 2) T2aN1M0 is downstaged from stage IIIB to stage IIA; 3) T4N0-N1M0 is downstaged from stage IIIB to stage IIIA; and 4) wet IIIB (i.e., malignant pleural effusions) is upstaged to stage IV. These new changes reflect the prognosis of patients with these different tumors.

Pathologic staging uses both clinical staging information (which is noninvasive and includes medical history, physical examination, imaging) and other invasive staging procedures (i.e., thoracotomy, examination of lymph nodes using mediastinoscopy).

For 1999-2006, the overall 5-year relative survival rate for lung cancer was 15.8% (from 17 SEER [Surveillance, Epidemiology, and End Results] geographic areas 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; 56% were diagnosed after the cancer had already metastasized (distant stage); and for the remaining 8%, the staging information was unknown. The corresponding 5-year relative survival rates were: 52.9% for localized, 24% for regional, 3.5% for distant, and 8.7% for unstaged (http://seer.cancer.gov/statfacts/html/lungb.html). However, these data include small cell lung cancer, 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. 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%. Of stage I patients who refused surgery (although it was recommended), 78% died of lung cancer within 5 years.

Prognostic and Predictive Biomarkers

Several biomarkers have emerged as prognostic and predictive markers for NSCLC. Among these biomarkers, the evidence is strongest for epidermal growth factor receptor (EGFR), the 5’ endonuclease of the nucleotide excision repair complex (ERCC1), the k-ras oncogene, the regulatory subunit of ribonucleotide reductase (RRM1), and the EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]). 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. A **predictive** biomarker is a biomolecule that is indicative of therapeutic efficacy; that is, there is an interaction between the biomolecule and therapy on patients’ outcome.

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. However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR tyrosine kinase inhibitors (EGFR-TKI) therapy. High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy. High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy. The presence of K-ras mutations is prognostic of poor survival for patients with NSCLC when compared to absence of K-ras mutations, independent of therapy. K-ras mutations are also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy. High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression, independent of therapy. High levels of RRM1 expression are also predictive of poor response to gemcitabine-based chemotherapy.

The EML4-ALK fusion oncogene (fusion between echinoderm microtubule-associated protein-like 4 [EML4] and anaplastic lymphoma kinase [ALK]) is a new predictive biomarker that has been identified in a small subset of patients with NSCLC (see the section on “EML4-ALK Mutations” and the 2011 NSCLC algorithm).

**EGFR Mutations**

EGFR is a transmembrane receptor. When EGF binds to the extracellular domain, receptor dimers are formed with activation of the intracellular tyrosine kinase domain. This results in autophosphorylation and in phosphorylation of downstream molecules with activation of multiple cellular functions including proliferation and survival. EGFR is detectable in approximately 80%-85% of patients with NSCLC, and the levels of expression vary widely on a continual scale.

The most commonly found EGFR mutations in patients with NSCLC are deletions in exon 19 (E19del [LREA deletion] 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, erlotinib and gefitinib. These drug-sensitive mutations are found in approximately 10% of Caucasian
patients with NSCLC and up to 50% of Asian patients. Other drug-sensitive mutations include point mutations at exon 21 (L861Q) and exon 18 (G719X). The T790M mutation is associated with resistance to TKI therapy and has been reported in about 50% of patients with disease progression.

DNA mutational analysis is the preferred method to assess for EGFR status, although fluorescence in situ hybridization ([FISH] to determine gene copy number) and immunohistochemistry (to determine level of expression) have been used. Various DNA mutation detection assays can be used to determine the EGFR mutation status in tumor cells. Direct sequencing of DNA corresponding to exons 18-21 (or just testing for exons 19 and 21) is a reasonable approach; however, more sensitive methods are available. It may be better to assess EGFR mutation status on the primary tumor before therapy and not on the metastasis, although no consensus has been reached.

The prognostic effect of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—is not clear, because most reports are limited to patients receiving active therapy. Tsao and colleagues determined mutations in 177 patients who participated in a randomized trial of second-line gefitinib versus placebo. Mutations were found in 40 patients, and 20 had E19del (LREA deletions) or L858R. They did not find a correlation between mutational status and gene copy number or expression by standard immunohistochemistry. In the placebo-treated group, 19 patients had any EGFR mutation, and their overall survival was apparently not different from the 44 patients without mutations. A retrospective study of patients treated with first-line chemotherapy with or without erlotinib found that the median overall survival for all patients with mutations (N=11) was significantly better (>20 months, \(P<.001\)) than overall survival for patients without mutations (N=45, 10 months). It has been reported that in patients with EGFR mutations who receive TKIs, those with E19del (LREA deletion) have increased survival when compared with L858R mutations; those with wild-type EGFR have poorer outcomes.

The predictive effects of the drug-sensitive EGFR mutations—E19del (LREA deletion) and L858R—are well defined. Patients with these mutations have a significantly better response to erlotinib or gefitinib. The initial retrospective reports suggested that approximately 90% of patients with a tumor response to these drugs had mutations, whereas unresponsive patients did not have mutations. Subsequent retrospective studies have demonstrated an objective response rate of approximately 80% with a median progression-free survival of 13 months to single-agent therapy in patients with a bronchioloalveolar variant of adenocarcinoma and an EGFR mutation. A prospective study has demonstrated that the objective response rate in North American patients with non-squamous cell histology and EGFR mutations (53% E19del [LREA deletion], 26% L858R, 21% other mutations) is 55% with a median progression-free survival of 9.2 months. In patients treated with first-line chemotherapy with or without erlotinib, EGFR mutations were predictive of a better response in patients receiving erlotinib (53% in patients with mutations versus 18% in those without mutations). The response rates in the group of patients receiving only chemotherapy were 21% for those with mutations and 27% for those without mutations.

EML4-ALK Mutations

Estimates are that 2%-7% of patients have EML4-ALK mutations, about 10,000 patients in the United States. These patients are resistant to EGFR TKIs but are otherwise similar to those with EGFR mutations (i.e., adenocarcinoma, nonsmokers or light smokers). In these selected populations, estimates are that about 30% of patients will have EML4-ALK mutations. Mutations for EGFR and EML4-ALK are
generally mutually exclusive.\(^8\) Currently, no standard method is available for detecting EML4-ALK mutations, although a FISH probe set (for ALK-rearranged anaplastic large cell lymphomas) appears to be better than immunohistochemistry tests (see the 2011 NSCLC algorithm).\(^8\),\(^9\)

PF-02341066 (crizotinib) is an inhibitor of ALK and MET tyrosine kinases.\(^9\) Recently, crizotinib has been shown to yield very high disease control rates (about 90\%) when used in patients with advanced NSCLC who have EML4-ALK mutations and have progressed on previous therapy.\(^3\)\(^6\) Crizotinib is orally active with few side effects (5\% of patients had elevations in aminotransferases). Patients have responded rapidly to crizotinib. Some patients have developed resistance to crizotinib;\(^9\) however, other EMLK4-ALK inhibitors are in development.\(^9\),\(^4\) A randomized phase III trial (PROFILE-1007) is comparing crizotinib with standard second-line chemotherapy.

**ERCC1 Level of Expression**

ERCC1 is the 5’ endonuclease of the nucleotide excision repair complex. It is found in all tumor cells, and its level of expression varies widely. In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, ERCC1 mRNA levels were prognostic of survival. Patients whose tumors had high levels (N=26, relative ERCC1 expression above the cohort median of 50) lived significantly longer than patients whose tumors had low levels (N=25, relative expression below 50).\(^6\)\(^5\) These results were independently confirmed in a similar cohort of patients (N=372) using standard immunohistochemistry. Patients with high tumoral ERCC1 expression had a median overall survival of 55 months compared to 42 months for patients with low ERCC1 expression.\(^6\)

Multiple translational investigations have provided evidence for the predictive use of ERCC1 levels to assess the efficacy of platinum-based chemotherapies in NSCLC; high levels are associated with resistance, while low levels are associated with sensitivity. Olaussen and colleagues found that ERCC1 protein expression, as determined by standard immunohistochemistry, was predictive of benefit from adjuvant cisplatin-based therapy in a large group of patients with surgically resected NSCLC who participated in the International Adjuvant Lung Trial (IALT).\(^6\) In this study, only patients with low tumoral ERCC1 protein levels benefited from adjuvant chemotherapy (adjusted hazard ratio for death, 0.65; 95\% CI, 0.50 to 0.86; \(P=.002\)). In a community-based randomized phase III clinical trial, Bepler and colleagues reported that in situ ERCC1 protein levels (in tumor specimens collected prospectively) were significantly and inversely correlated with disease response to carboplatin/gemcitabine or gemcitabine alone (\(P=.003\), \(r=-0.39\)); that is, response was better in patients with low levels of ERCC1 expression.\(^7\),\(^2\)

**K-ras Mutations**

K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, K-ras is constitutively active, able to transform immortalized cells, and promote cell proliferation and survival. Initially, K-ras was described as mutated in codon 12 in 5/10 adenocarcinomas, 0/15 squamous, and 0/10 large cell carcinomas.\(^9\)\(^5\) Current data suggest that approximately 25\% of adenocarcinomas in a North American population have K-ras mutations.\(^3\),\(^4\),\(^0\),\(^6\) K-ras mutation prevalence is associated with cigarette smoking.\(^9\)\(^6\)

K-ras mutational status is prognostic of survival. Patients with K-ras mutations have a shorter survival than patients with wild-type K-ras. Slebos and colleagues determined K-ras codon 12 mutations in 69 patients with completely resected adenocarcinomas who did not
receive additional therapy. They found that disease-free and overall survival were significantly ($P=.038$ and $P=.002$, respectively) shorter in the 19 patients with mutations compared to the 50 patients without mutations. These data were independently confirmed in a cohort of 66 patients (11 with K-ras codon 12 mutations; $P=.03$ for overall survival difference) by Mitsudomi and colleagues. However, Tsao and colleagues did not find a significant difference ($P=.40$) in survival by ras mutational status on the observation arm of the Canadian adjuvant chemotherapy trial (JBR10). In this report, the authors investigated codons 12, 13, and 61 of all 3 ras genes and categorized patients as ras mutated if any mutation was detected.

K-ras mutational status is also predictive of therapeutic efficacy from EGFR-TKIs; however, it does not appear to affect chemotherapeutic efficacy. In a retrospective study of 101 patients with a bronchioloalveolar variant of adenocarcinoma, K-ras codon 12 and 13 mutations were found in 23% (18/80) of patients. All patients had been treated with first-line single-agent erlotinib. None of the patients with K-ras mutations responded (0/18), while 20 without K-ras mutations responded (20/62, 32%). This difference was statistically significant ($P<.01$). In patients treated with first-line chemotherapy plus erlotinib or chemotherapy plus placebo (the TRIBUTE trial), K-ras codon 12 and 13 mutations were present in 51/264 and 4/264 patients respectively. Patients with K-ras mutations had a response rate of 8% in the chemotherapy plus erlotinib arm (2/25) and 23% in the chemotherapy only arm (7/30). Patients without K-ras mutations had a response rate of 26% in the chemotherapy plus erlotinib arm (27/104) and 26% in the chemotherapy only arm (27/103). In this report, time-to-progression and overall survival were also shortest in the group of patients with K-ras mutations receiving chemotherapy plus erlotinib, which suggests that the addition of erlotinib to chemotherapy in patients with K-ras mutations may adversely interfere with chemotherapeutic efficacy.

Tsao and colleagues identified 88 patients with and 333 without any ras mutation (codons 12, 13, and 61 of K-ras, N-ras, H-ras) in the Canadian adjuvant chemotherapy trial (JBR10). They found that patients with ras mutations did not derive benefit from adjuvant cisplatin/vinorelbine (hazard ratio of death for chemotherapy versus observation 0.95, CI, 0.53-1.71; $P=.87$), while those without ras mutations (N=333) benefited significantly (hazard ratio of death for chemotherapy versus observation 0.69, CI, 0.49-0.97; $P=.03$) from adjuvant therapy. However, when taking both the treatment arm and the ras mutational status into account (i.e., when testing for interaction), the $P$-value did not reach statistical significance ($P=.29$).

RRM1 Level of Expression

*RRM1* is the gene that encodes the regulatory subunit of ribonucleotide reductase, and it is crucial for production of deoxynucleotides from nucleotides. RRM1 is found in all tumor cells, and its level of expression varies widely over a continuous range.

In patients with completely resected NSCLC who did not receive perioperative chemotherapy or radiation, *RRM1* mRNA levels were prognostic of survival. Patients whose tumors had high levels (N=39, relative *RRM1* expression above the cohort median of 12.2) lived significantly longer than patients whose tumors had low levels (N=38, relative expression below 12.2). These results were independently confirmed in a cohort of 187 patients with stage I disease. Patients with high tumoral RRM1 expression had a median overall survival of greater than 120 months compared to 60.2 months for patients with low RRM1 expression.
In a community-based randomized phase III clinical trial, Bepler and colleagues reported that in situ RRM1 protein levels (in tumor specimens collected prospectively) were significantly and inversely correlated with disease response to gemcitabine or carboplatin/gemcitabine \((P=0.001, r=-0.41)\); that is, response was better in patients with low levels of RRM1 expression.\(^71,72\)

**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 stage II disease, surgery provides the best chance for cure. 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.

The “Principles of Surgical Therapy” are described in the 2011 NSCLC algorithm and are summarized here. 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. Patients with pathologic stage II or greater disease should be referred to medical oncology for evaluation. For patients with stage IB, consider referral to medical oncologist. For stage IIIA, consider referral to radiation oncologist. If stereotactic body RT (SBRT) is considered for high-risk patients, a multidisciplinary evaluation is recommended (including 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; otherwise, lobectomy or pneumonectomy should be done if physiologically feasible.\(^100,101\) Sublobular resection, either segmentectomy (preferred) or wedge resection, is appropriate in select patients; the parenchymal resection margins are defined in the 2011 NSCLC algorithm (see “Principles of Surgical Therapy”).\(^102,103\) Resection (including wedge resection) is preferred over ablation.\(^101\) 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.\(^101,104,105\) SBRT may be more appropriate for these patients.\(^106\)

**Lymph Node Dissection**

The American College of Surgeons Oncology Group randomized trial (ACOSOG Z0030) compared 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. This study is evaluating whether complete mediastinal lymph node dissection results in better overall survival when compared to mediastinal lymph node sampling in the patient undergoing resection for N0 or non-hilar N1 NSCLC. Initial results indicate that morbidity is not increased with complete lymphadenectomy.\(^107,108\) Recent data from this study indicate
that 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. Data on survival are not available yet.

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. Note that the IASCL (International Association for the Study of Lung Cancer) has proposed a new lymph node map. 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 the 2011 NSCLC algorithm): 1) those who are not eligible for lobectomy; and 2) those with a peripheral nodule 2 cm or less with very low-risk features (category 2B for low-risk features). Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins either 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 2011 NSCLC algorithm (see the “Principles of Surgical Therapy”) and is summarized here; note that this is a new section for the NCCN NSCLC guidelines. Before treatment, it is essential to carefully evaluate for N2 disease using radiologic and invasive staging (i.e., endobronchial ultrasound-guided procedures, mediastinoscopy, thoroscopic procedures) and to discuss whether surgery is appropriate in a multidisciplinary team (which should include a board-certified thoracic surgeon). Randomized controlled trials suggest that surgery does not increase survival in these patients. However, one of these trials (EORTC) only enrolled unresectable patients.

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. Neoadjuvant therapy is recommended for select patients. In N2 patients, 50% of the NCCN institutions use neoadjuvant chemoradiotherapy whereas 50% use neoadjuvant chemotherapy. 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 the 2011 NSCLC algorithm). However, it is controversial whether pneumonectomy after neoadjuvant chemoradiotherapy is appropriate. Patients with resectable N2 disease should not be excluded from surgery, because some of them may have long-term survival or may be cured.

**Thorascopic Lobectomy**

Video-assisted thoracic surgery (VATS), which is also referred to as thorascopic lobectomy, is a minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer. Published studies suggest that thorascopic lobectomy has several advantages over the standard thoracotomy (or pleurotomy).
and chronic pain associated with thorascopic lobectomy is minimal; thus, this procedure requires shorter length of hospitalization.\textsuperscript{130} Thorascopic lobectomy is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.\textsuperscript{131-135} Recent analyses show that thorascopic lobectomy is associated with less morbidity than lobectomy by thoracotomy.\textsuperscript{136, 137}

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.\textsuperscript{138-140} Thorascopic lobectomy has also been shown to improve discharge independence in older populations and in high-risk patients as well.\textsuperscript{141, 142} Data show that thorascopic lobectomy improves the ability of patients to complete postoperative chemotherapy regimens.\textsuperscript{143, 144} Based on its favorable effects on postoperative recovery and morbidity, thorascopic lobectomy is included in the 2011 NSCLC algorithm as an acceptable approach for patients who are surgically resectable (and have no anatomic or surgical contraindications) as long as standard principles of thoracic surgery are not compromised (see “Principles of Surgical Therapy”).

**Radiation Therapy**

**General Principles**

Radiation therapy can be used as 1) adjuvant therapy for patients with resectable NSCLC who have no contraindications for surgery; 2) the primary local treatment (i.e., definitive RT for patients with medically inoperable or unresectable NSCLC; and/or 3) palliative therapy for patients with incurable NSCLC. Treatment recommendations should be made by a multidisciplinary team. The 2011 NSCLC algorithm contains a “Principles of RT” section, which includes the following: 1) general principles; 2) dose, volume and normal tissue constraints for conventionally fractionated RT; 3) radiation simulation, planning and delivery; 4) SBRT; and 5) prophylactic cranial irradiation (PCI).\textsuperscript{145-150} These RT principles are summarized in this section. Whole brain RT and stereotactic radiosurgery for brain metastases are also discussed in this section. The terminology and abbreviations for RT are described in the 2011 NSCLC algorithm (see Table 1).

For stage IV patients with extensive metastases, palliative RT can be used for primary or distant sites. Definitive chemoradiation is recommended for patients with stage II-III disease who are medically inoperable. For patients with pN2 and positive or negative resection margins, the RT recommendations are described in “Principles of RT” section in the 2011 NSCLC algorithm (see “General Principles”). To avoid postoperative pulmonary toxicity, preoperative chemoradiotherapy should be avoided if at all possible, if pneumonectomy is required.\textsuperscript{151, 152} Surgery in a field that has had 60 Gy is difficult, 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 patients who have received RT doses of more than 60 Gy (i.e., patients who have received definitive concurrent chemoradiation). Therefore, the radiation dose should be carefully considered if patients might be eligible for surgery. Radiation therapy should continue to definitive dose without interruption if the patient is not a surgical candidate.

**Dose, Volume and Normal Tissue Constraints for Conventionally Fractionated RT**

The dose recommendations for preoperative, postoperative, definitive, and palliative RT are described in “Principles of RT” section in the 2011 NSCLC algorithm (see “Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy” and see also Table
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 3), more conservative constraints should be used for postoperative RT. For definitive RT, the commonly prescribed dose is 60-70 Gy. The use of higher RT doses is discussed in “Principles of RT” section in the 2011 NSCLC algorithm (see “Dose, Volume, and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy”). The role of high-dose radiation with concurrent chemotherapy is currently being tested in a phase III randomized trial (RTOG 0617).

For treatment volume consideration, planning target volume (PTV) should be defined using the ICRU-62 (International Commission on Radiation Units and Measurements Report 62) guidelines, based on gross tumor volume (GTV), plus clinical target volume (CTV) margins for microscopic diseases, internal target volume (ITV) margins for target motion, and margins for daily set-up errors. Additional volume considerations are described in the 2011 NSCLC algorithm.

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 3). These limits are mainly empirical. For patients receiving postoperative RT, more strict DVH parameters should be considered for lung. The exact limit is unknown for lobectomy cases; the mean lung dose should be limited to 8.5 Gy or less in pneumonectomy patients.

**Radiation Simulation, Planning and Delivery**

Treatment planning should be based on CT scans obtained in the treatment position. IV 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 (i.e., those with significant atelectases, when IV contrast is contraindicated). PET-CT can significantly improve the target accuracy. In the “Principles of RT” section of the 2011 NSCLC algorithm, recommendations are provided for patients receiving chemoradiation (including those with compromised lung or cardiac function), photon beams, or intensity modulated radiotherapy (IMRT).

Stereotactic Body Radiation Therapy (SBRT)

SBRT, which is also known as stereotactic ablative radiotherapy (SABR), uses short courses of very high dose RT that are precisely delivered to the target. Studies have shown that SBRT is very useful for patients with inoperable stage I NSCLC. With conventional treatment, 3-year survival is only about 20%-35% in these patients. However, local control is increased after SBRT. In patients with stage I NSCLC, SBRT provides a significantly longer 5-year survival than 3-D conformal RT. SBRT yields median survival of 32 months and 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 versus 25 months).

SBRT can also be used for patients with limited lung metastases and for palliative therapy. A recent study suggests that SBRT...
increases survival in elderly patients (75 years or older) with stage I NSCLC who otherwise would not have received treatment. SBRT is discussed in the “Principles of RT” section of the 2011 NSCLC algorithm; fractionation regimens and normal tissue constraints are also provided (see Tables 4 and 5; Figure 1; “Stereotactic Body Radiation Therapy”). Decisions about whether to recommend SBRT should be based on multidisciplinary discussion.

**Radiofrequency Ablation**

Studies suggest that radiofrequency ablation (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. 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. A study with RFA in 33 patients with NSCLC yielded overall survival of 70% (95% CI, 51%–83%) at 1 year and 48% (30%–65%) at 2 years. A 2-year overall survival of 75% (45%–92%) was reported in patients with stage I NSCLC (n=13) who received RFA. The procedure specific 30-day mortality rate is reported to be 2.6%.

**Whole Brain RT and Stereotactic Radiosurgery**

Many patients with NSCLC have brain metastases (30%-50%), which substantially affect their quality of life. Surgery followed by whole brain RT is recommended (category 1) for select patients (those with good PS) with a single brain metastasis (see the 2011 NSCLC algorithm). Stereotactic radiosurgery (SRS) is another option after surgical resection, although there are only a few retrospective case series supporting this option. Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with SRS with or without whole brain RT. Note that recent data suggest that erlotinib may be useful to manage brain metastases.

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. Treatment should be individualized for patients with recurrent or progressive brain lesions.

There have been concerns that whole brain RT adversely affects neurocognition. However, a study in 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 radiation. In 132 patients with 1-4 brain metastases who received SRS with or without whole brain RA, survival was similar in both groups. 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. However, a study in 58 patients found that patients who received SRS plus whole brain radiation had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SRS alone. Some have suggested that using resection with SRS (instead of resection with WBRT) will decrease neurocognitive problems.

**Prophylactic Cranial Irradiation**

Prophylactic cranial irradiation (PCI) does not appear to improve survival in patients with NSCLC. Although it closed early because of poor accrual, a randomized phase III trial (RTOG 0214) of PCI for patients with stage III NSCLC showed that the incidence of brain metastases was decreased in patients who received PCI (18% versus 7.7%); however, overall survival was not improved. Impaired memory (immediate and delayed recall) was reported in these patients receiving PCI.
Combined Modality Therapy

As previously mentioned, surgery provides the best chance for cure for patients with stage I or stage II disease who are medically fit and can tolerate surgery. In patients with completely resected NSCLC, adjuvant chemotherapy has been shown to improve survival in patients with early-stage disease.\textsuperscript{226-228} Currently, concurrent chemoradiation appears superior to sequential therapy for patients with unresectable stage III disease.\textsuperscript{229-231}

For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.\textsuperscript{232-235} Of interest, recent 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.\textsuperscript{236} 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 2011 NSCLC algorithm (see also the NCCN CNS guidelines).\textsuperscript{237} Surgical resection of a solitary metastasis located in sites other than the brain remains controversial. The trials supporting the recommendations for combined modality therapy are discussed in this section.

Surgery Followed by Chemotherapy: Trial Data

In the NCCN guidelines for stage IA disease, adjuvant chemotherapy is not recommended based on the following trials. Adjuvant chemotherapy is only recommended for high-risk margin-negative stage IB disease (see the 2011 NSCLC algorithm). Recommended chemotherapy regimens for adjuvant therapy are provided in the 2011 NSCLC algorithm (see “Chemotherapy Regimens for Adjuvant Therapy”).

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.\textsuperscript{226} 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 (44.5\% versus 40.4\% at 5 years; hazard ratio for death, 0.86; 95\% confidence interval [CI], 0.76 to 0.98; \textit{P}<.03) and disease-free survival rate (39.4\% versus 34.3\% at 5 years; hazard ratio, 0.83; 95\% CI, 0.74 to 0.94; \textit{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 followup, there were more deaths in the chemotherapy group and the benefit of chemotherapy decreased over time.\textsuperscript{236} But, data show that adjuvant chemotherapy prevents recurrences.

The NCIC CTG JBR.10 trial and the ANITA (Adjuvant Navelbine International Trialist Association) 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 (242 patients) or to observation (240 patients).\textsuperscript{227} The median age was 61 years in both groups. Chemotherapy was not excessively toxic. Adjuvant chemotherapy significantly prolonged overall survival (94 versus 73 months, hazard ratio for death, 0.69, \textit{P}=.04) and relapse-free survival (not reached versus 46.7 months, hazard ratio for recurrence, 0.60; \textit{P}<.001) when compared with observation alone. The 5-year survival rates were 69\% and 54\%, respectively (\textit{P}=.03).
However, recent updated data from JBR.10 after 9 years of followup show that when compared with observation alone, adjuvant chemotherapy is beneficial for stage II but not for stage IB patients.\textsuperscript{239} 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 2010 NCCN update, some chemotherapy options for early-stage disease were deleted.

In the ANITA trial, 840 patients (median age, 59 years) with stage IB (T2, N0), II, or IIIA NSCLC were randomly assigned either to adjuvant vinorelbine plus cisplatin or to observation.\textsuperscript{228} Grade 3/4 toxicities were manageable in the chemotherapy group; however, 7 toxic deaths were reported. After median follow-up of 76 months, median survival was 65.7 months in the chemotherapy group and 43.7 months in the observation group.\textsuperscript{228} Adjuvant chemotherapy significantly improved 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.

A meta-analysis in 4,584 patients (the Lung Adjuvant Cisplatin Evaluation) 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, others).\textsuperscript{240} The benefit was greater in patients with stage II and III disease and good PS.

The CALGB 9633 trial assessed paclitaxel and carboplatin in patients with T2, N0, M0, stage IB lung cancer;\textsuperscript{241} updated results have been reported.\textsuperscript{242, 243} In this trial, 344 patients (34-81 years) were randomly assigned either to paclitaxel and carboplatin or to observation within 4-8 weeks of resection with a median follow-up duration of 54 months. Adjuvant chemotherapy was well tolerated with no chemotherapy-related toxic deaths. Overall survival at 4 years was not significantly different, although 3-year survival was significant (79% versus 70%, \(P=.045\)).\textsuperscript{242, 243} The original results from CALGB suggested that the paclitaxel and carboplatin regimen improved survival in patients with stage I disease; however, the updated results did not show improved survival (although a subset analysis showed a benefit for tumors greater than 4 cm). Thus, the carboplatin/paclitaxel regimen is only recommended if patients cannot tolerate cisplatin (see the 2011 NSCLC algorithm).\textsuperscript{244}

**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 the “Principles of Surgery” section in the 2011 NSCLC algorithm ). 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.\textsuperscript{245-249} For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone.\textsuperscript{245, 246, 248, 249} However, concurrent chemoradiation appears to be superior to sequential therapy.\textsuperscript{229-231} 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 used for initial treatment include cisplatin/etoposide (preferred), cisplatin/vinblastine (preferred), and carboplatin/paclitaxel (category 2B) (see “Chemotherapy Regimens Used with Radiation Therapy” in the 2011 NSCLC algorithm ).\textsuperscript{230, 250, 251}
Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.\(^{252}\)

A phase II trial from SWOG (9504) assessed concurrent chemoradiation (using cisplatin/etoposide) followed by consolidation docetaxel in 83 patients with unresectable stage IIIB NSCLC.\(^{253}\) Results from SWOG 9504 have shown a median survival of 26 months and a 5-year survival rate of 29%.\(^{254}\) However, results from a phase III trial in patients with unresectable stage III NSCLC assessing consolidation docetaxel after cisplatin/etoposide with concurrent chemoradiation did not show improved survival with docetaxel and did show increased toxicity.\(^{255},^{256}\) 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 months versus 18.7 months \((P=.091)\), respectively.\(^{257}\)

**Chemotherapy: Trial Data**

Patients with stage IV disease who have a good PS, benefit from chemotherapy, usually with a platinum-based regimen.\(^{232-234}\) Many drugs are useful for stage IV NSCLC. These drugs include platinum agents (cisplatin, carboplatin), taxanes (paclitaxel, docetaxel), vinorelbine, etoposide, pemetrexed, the camptothecin analogs (irinotecan), and gemcitabine (see the 2011 NCCN algorithm). 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.\(^{244,258-261}\) Phase III randomized trials have shown that many of the platinum-doublet combinations yield similar objective response rates and survival.\(^{262,263}\) The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin, and pemetrexed/carboplatin;\(^{258,264-266}\) gemcitabine/docetaxel is another option.\(^{267}\) 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 (i.e., dexamethasone, H2 blockers, H1 blockers) to prevent hypersensitivity are contraindicated.\(^{268,269}\)

**Targeted Therapies**

Specific targeted therapies have been developed for the treatment of advanced lung cancer.\(^{270,271}\) Bevacizumab is a recombinant monoclonal antibody that blocks the vascular endothelial growth factor (VEGF). Erlotinib is a small molecule inhibitor of EGFR. Cetuximab is a monoclonal antibody that targets EGFR.

In 2006, the FDA approved bevacizumab for patients with unresectable, locally advanced, recurrent, or metastatic nonsquamous NSCLC. The Eastern Cooperative Oncology Group (ECOG) recommends bevacizumab in combination with paclitaxel and carboplatin for select patients with advanced nonsquamous NSCLC based on the results of phase II-III clinical trials (ECOG 4599).\(^{272}\) To receive treatment with bevacizumab and chemotherapy, patients must meet the following criteria: nonsquamous NSCLC and no 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 nonsquamous NSCLC and PS 0-1 who are EGFR mutation negative or unknown, bevacizumab in combination
with chemotherapy is one of the recommended options (see the 2011 NSCLC algorithm).

Erlotinib was approved by the FDA in 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen. However, erlotinib is also recommended as first-line therapy in patients with advanced, recurrent, or metastatic nonsquamous NSCLC who have known active EGFR mutation or gene amplification regardless of their PS (see the 2011 NSCLC algorithm). This recommendation is based on the results of a phase III randomized trial (Iressa Pan-Asia study [IPASS]) in which patients with EGFR mutations who received gefitinib had increased progression-free survival (25% versus 7%), response rate (71%), and quality of life and fewer side effects (e.g., neutropenia) when compared with those receiving chemotherapy (carboplatin/paclitaxel).

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. The recent TORCH trial suggests that EGFR mutation testing should be done in patients with advanced nonsquamous NSCLC. Survival was increased in patients with wild type EGFR who received first-line chemotherapy compared with those who receive erlotinib first followed by second-line chemotherapy (10.8 versus 7.7 months). Erlotinib is an orally active agent that is very well tolerated by most patients.

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). Adding cetuximab slightly increased overall survival (11.3 versus 10.1 months, \( P = .04 \)). Cetuximab/cisplatin/vinorelbine is an option for patients with advanced NSCLC, regardless of histology (see the 2011 NSCLC algorithm). However, because the benefits are very slight, the cetuximab/cisplatin/vinorelbine regimen has a category 2B recommendation in the NCCN guidelines.

**Maintenance Therapy**

Maintenance therapy may be given after 4-6 cycles of chemotherapy for patients with tumor response or stable disease who have not progressed. Continuation maintenance refers to the use of at least one of the agents given in first line. Switch maintenance refers to the initiation of a different agent, not included as part of the first-line regimen.

For continuation maintenance therapy, targeted agents (which were initially given in combination with conventional chemotheraphy) should be continued until evidence of disease progression or unacceptable toxicity, as per the design of the clinical trials that led to their approval. Bevacizumab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., platinum-doublet chemotherapy given with bevacizumab) in patients with nonsquamous histology. Cetuximab (category 1) may be continued beyond 4-6 cycles of initial therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown) or those with squamous histology (i.e., cisplatin, vinorelbine, and cetuximab therapy). Pemetrexed (category 2B) may also be given as continuation maintenance therapy in patients with nonsquamous histology (who are EGFR mutation negative or unknown). There are no randomized trials supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.

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 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). However, currently, there is no evidence that continuation maintenance therapy improves overall survival or quality of life.279, 281, 282

For switch maintenance therapy, 2 recent studies have shown a benefit in progression-free survival and overall survival with the initiation of pemetrexed or erlotinib after first-line chemotherapy (4-6 cycles) in patients without disease progression.283, 284 Pemetrexed may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy, in patients with histologies other than squamous cell carcinoma who are EGFR mutation negative (or with unknown mutation status).284 The FDA has approved maintenance therapy with pemetrexed (http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021462s021lbl.pdf). Likewise, erlotinib (category 2B) or docetaxel (category 3) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy in this same patient population.283

Recently, an updated study (CALGB 30406) compared erlotinib alone versus erlotinib/carboplatin/paclitaxel in patients with advanced NSCLC.285 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 maintenance therapy with erlotinib in patients found to have EGFR mutations during chemotherapy (see the 2011 NSCLC algorithm). The FDA has approved maintenance therapy with erlotinib (http://www.osip.com/pdf/Tarceva_PI_042010.pdf).

Initial Clinical Evaluation

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC (see the 2011 NSCLC algorithm). The clinical stage is initially determined from disease history (i.e., cough, dyspnea, chest pain, weight loss) and physical examination together with a limited battery of tests (see the 2011 NSCLC algorithm). The panel also recommends that smoking cessation counseling be made available 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 (i.e., 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.286-288

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-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, some
NCCN 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 is recommended (see the 2011 NSCLC algorithm).

Dillemans and colleagues have reported a selective mediastinoscopy strategy, proceeding straight to thoracotomy without mediastinoscopy for T1 peripheral tumors without enlarged mediastinal lymph nodes on preoperative CT. 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% versus 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 and colleagues specifically examined lung cancer metastases to normal size mediastinal lymph nodes in 90 patients and found an incidence of 16% false-negative chest CT scans with histologic identification of occult N2 or N3 disease.

Bronchoscopy is used in diagnosis and local staging of both central and peripheral lung lesions and is recommended for pretreatment evaluation of stage I, stage II, and stage 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. PET scans have been used to help evaluate the extent of disease and to provide more accurate staging. The NCCN guideline panel reviewed the diagnostic performance of CT and PET scans. Panel members assessed studies that examined the sensitivity and specificity of chest CT scans for mediastinal lymph node staging. Depending on the clinical scenario, a sensitivity of 40% to 65% and a specificity of 45% to 90% were reported. Seely and coworkers reported on the number of metastatic lymph nodes discovered on routine mediastinoscopy and chest CT scan in patients with the most favorable tumors (i.e., T1 cancer). This study revealed a 21% incidence of identifying N2 or N3 nodes in patients who clinically appeared to have stage IA tumors. The positive predictive value of chest CT scan was only 43% per patient, and the negative predictive value was 92%.

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. Chin and colleagues found that PET, when used to stage the mediastinal nodes, was 78% sensitive and 81% specific with a negative predictive value of 89%. Kernstine and coworkers compared PET scan to CT scan for identifying N2 and N3 disease in NSCLC. The PET scan was found to be more sensitive than the CT scan in identifying mediastinal node disease (70% versus 65%). PET/CT has been shown to be useful in restaging patients after adjuvant therapy.

The NCCN panel believes that PET scans can play a role in the evaluation and more accurate staging of NSCLC, for example,
Identifying stage I (peripheral and central T1-2, N0), stage II, stage III, and stage IV diseases. However, PET/CT is even more sensitive and is now recommended by NCCN. When patients with early-stage disease are accurately staged using PET/CT, inappropriate surgery is avoided. However, positive PET/CT scans findings need pathologic or other radiologic confirmation (e.g., MRI of bone). If the PET/CT scan is positive in the mediastinum, the lymph node status needs pathologic confirmation. Precisely how PET/CT scans will fit into the overall staging and surveillance of NSCLC will become clearer as newer studies mature.

Transesophageal endoscopic ultrasound–guided fine-needle aspiration (EUS-FNA) and endobronchial ultrasound–guided transbronchial needle aspiration (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. 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. In patients with positive nodes on CT or PET, EBUS-TNBA can be used to clarify the results. However, in patients with negative findings on EBUS-TNBA, conventional mediastinoscopy can be done to confirm the results.

The routine use of magnetic resonance imaging (MRI) (to rule out asymptomatic brain metastases) and of bone scans (to exclude bone metastases) are not recommended. Brain MRI is recommended for patients with stage II, III, and IV disease to rule out metastatic disease if aggressive combined-modality therapy is being considered.

Initial Therapy

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 2011 NSCLC algorithm).

Stage I, Stage IIA, and Stage II (T1-2, N1) 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 node mapping. 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 (i.e., inclusion of mediastinal lymph node dissection) must be modified accordingly. Therefore, the 2011 NSCLC algorithm includes 2 different tracks for T1–3, N2 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.

Stage IIB (T3, N0), Stage IIIA, and Stage IIIB 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 should be performed. For the subsets of stage IIB (T3, N0) and stage IIIA (T3-4, N1) tumors, treatment options are organized according to the location of the tumor (i.e., the superior sulcus, chest wall, and 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 2011 NSCLC algorithm).

For patients with resectable tumors (T3 invasion, N0-1) in the superior sulcus, the panel suggests concurrent chemoradiation therapy followed by surgical resection and chemotherapy (see the 2011 NSCLC...
algorithm). Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range.\textsuperscript{153, 155, 311-314} The overall 5-year survival rate is approximately 40%.\textsuperscript{153} Patients with marginally resectable superior sulcus tumors should undergo concurrent chemoradiation before surgical re-evaluation. For patients with unresectable tumors (T4 extension, N0-1) in the superior sulcus, definitive RT with chemotherapy (i.e., definitive concurrent chemoradiation) is recommended if full-dose chemotherapy was not given initially.\textsuperscript{251, 253} Note that “Principles of RT” is in the 2011 NSCLC algorithm. In addition, the 2011 NSCLC algorithm also provides recommendations for chemotherapy (see “Chemotherapy Regimens for Adjuvant Therapy,” “Chemotherapy Regimens Used with Radiation Therapy,” and “Systemic Therapy for Advanced or Metastatic Disease”).

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 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 2011 NSCLC algorithm). 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 found to have unresectable lesions should be treated according to pathologic stage (see the 2011 NSCLC algorithm). For patients with (T1-2 or T3) node-positive disease, an additional brain MRI and PET/CT scan (if not done previously) are recommended to search for distant metastases. When distant metastases are not present, the panel recommends that the patient be treated with definitive concurrent chemoradiation therapy (see the 2011 NSCLC algorithm).\textsuperscript{229} Induction chemotherapy with (or without) RT is another option for patients with T1-3, N2 disease.\textsuperscript{113} Recommended therapy for metastatic disease is described in the 2011 NSCLC algorithm.

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. Although uncommon, patients with lung metastases but without systemic metastases have a better prognosis and are candidates for surgery.\textsuperscript{315} Patients with separate pulmonary nodule(s) in the same lobe or ipsilateral lung without other systemic metastases are potentially curable by surgery; 5-year survival rates are about 30%.\textsuperscript{316} Intrapulmonary metastases have been downstaged in the recent TNM revised staging (i.e., AJCC 7th edition).\textsuperscript{60, 316, 317} After surgery, concurrent chemoradiation (if tolerated) is recommended for those with positive margins and chemotherapy is recommended for those with negative margins (see the 2011 NSCLC algorithm).

For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy (category 3) (see the 2011 NSCLC algorithm).\textsuperscript{254-256} In patients with synchronous nodules (contralateral lung), the guidelines suggest treating them as 2 primary lung tumors if both are curable, even if the histology of the 2 tumors is similar (see the 2011 NSCLC algorithm).

Stage IIIB tumors comprise 2 groups including 1) tumors with contralateral mediastinal nodes (T1-3, N3); and 2) tumors with T4
extension and N2-3 disease, which are unresectable. 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 the 2011 NSCLC algorithm). In addition, PET/CT scans 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 2011 NSCLC algorithm). If N3 disease is confirmed, concurrent chemoradiation (category 1) is recommended followed by chemotherapy if full-dose chemotherapy was not given initially. For metastatic disease that is confirmed by PET/CT scan and brain MRI, treatment is described in the 2011 NSCLC algorithm.

For patients with T4 extension, N2-3 disease (stage III B), surgical resection is not generally recommended. The initial work-up 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 2011 NSCLC algorithm). If either the contralateral or ipsilateral mediastinal node is positive, concurrent chemoradiation therapy is recommended (category 1) followed by chemotherapy if full-dose chemotherapy was not given initially (see the 2011 NSCLC algorithm).

Stage IV Disease

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised AJCC staging (7th edition), T4 with effusion has been reclassified as stage IV, M1a (see ST-2). 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 (e.g., obstructive pneumonia), an exudate or sanguineous effusion is considered malignant no matter what the results of cytologic examination. If the pleural effusion is considered negative, the 2011 NSCLC algorithm tracks back to the confirmed T and N stage (see the 2011 NSCLC algorithm). However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases. In patients with effusions that are positive for malignancy, the tumor is treated as M1a with local therapy (i.e., ambulatory small catheter drainage, pleurodesis, and pericardial window) in addition to treatment as for stage IV disease (see the 2011 NSCLC algorithm).

The 2011 NSCLC algorithm for patients with distant metastases (i.e., stage IV, M1b) depends on the location of the metastases—a solitary nodule in the brain or adrenal—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 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 solitary brain metastases may benefit from surgical resection (see 2011 NSCLC algorithm). The 5-year survival rates with such an approach range from 10% to 20%, median survival is about 40 weeks. Follow-up whole brain RT (category 1) or SRS may be used. SRS alone or followed by whole brain radiation are additional treatment options. Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions. After their brain 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 (category 2B for chemotherapy); 2) SBRT (category 2B); or 3) additional chemotherapy followed by surgical resection of the lung lesion (category 2B). Systemic therapy is an option after surgery for patients with higher stage NSCLC.

Adrenal metastases 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. If an adrenal metastasis is found and if the lung lesion is curable, the resection of the adrenal lesion has produced some long-term survivors (category 2B) (see the 2011 NSCLC algorithm). Some panel members feel that resection of adrenal metastases only makes sense if the synchronous lung disease is stage I or maybe stage II (i.e., resectable). Systemic therapy is another treatment option for adrenal metastasis.

**Adjuvant Treatment**

**Chemotherapy or Chemoradiation**

Treatment options for patients with stage IA (T1ab, N0 disease) and with positive surgical margins (R1, R2) include 1) re-resection (preferred); or 2) 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; chemotherapy (category 2B) is recommended as adjuvant treatment for patients with high-risk features, such as poorly differentiated tumor, vascular invasion, wedge resection, minimal margins, tumors greater than 4 cm, visceral pleural involvement, and Nx (see the 2011 NSCLC algorithm). If the surgical margins are positive in patients with T2ab, N0 tumors, these patients should have either 1) re-resection with or without chemotherapy; or 2) RT and chemotherapy.

Note that in the 2011 update for the NCCN NSCLC guidelines, the postoperative chemoradiation recommendation was deleted for stage IA margin-positive disease because there are no data to support this recommendation (see the UPDATES pages in the 2011 NSCLC algorithm). Likewise, the postoperative chemoradiation plus chemotherapy recommendations were also removed from the guidelines for stage IB and IIA (T2b,N0) margin-positive disease and for stage IIA and IIB margin-negative disease based on the lack of data.

The panel recommends chemotherapy (category 1) with or without RT (category 3 for RT) for patients with negative surgical margins and stage II disease 1) T1ab-2a, N1; 2) T2b, N1; or 3) T3, N0 disease. If surgical margins are positive in these patients, options include: 1) re-resection and chemotherapy; or 2) chemoradiation and chemotherapy.

Patients with T1-3, N2 disease (discovered only at surgical exploration and mediastinal lymph node dissection) and positive margins may be treated with chemoradiation and chemotherapy (see the 2011 NSCLC algorithm). Patients with negative margins may be treated with chemotherapy (category 1) and RT.

Panel members disagreed about the use of chemoradiation for stage II disease with negative margins based on the results of the Intergroup E3590 trial. 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). Because the 5-year survival rate is less than
90%, some NCCN panel members feel that survival rates may increase with newer chemotherapeutic agents and with higher doses of radiation. For example, a phase II trial (RTOG 9705) (n = 88) using concurrent paclitaxel/carboplatin yielded a median survival of 56.3 months with 3-year survival of 61% in patients with resected stage II and IIIA disease. A phase II trial in 42 patients had similar results (5-year survival, 68%) except those with adenocarcinoma had poorer survival (only 28%).

As with stage IB and stage II surgically resected disease, cisplatin-based doublet adjuvant chemotherapy can be used in stage III NSCLC patients who have had surgery (see the 2011 NSCLC algorithm). In the case of marginally 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 2011 NSCLC algorithm). If the lesion does not convert (i.e., 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-4 extension, N0-1 disease, those that 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 chemoradiation and chemotherapy or 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 IIIB disease and positive mediastinal nodes (T1-3, N2), if there is no disease progression after initial treatment, recommended treatment includes surgery with (or without) chemotherapy (category 2B) (see the 2011 NSCLC algorithm). In addition, postoperative RT should be given if not used preoperatively. 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 2011 NSCLC algorithm).

In patients with separate pulmonary nodules in the same lobe or ipsilateral lung, surgery is recommended (see the 2011 NSCLC algorithm). If the margins are negative, adjuvant chemotherapy is recommended. If the resection margins are positive, concurrent chemoradiation is recommended (if tolerated).

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, with no one clear preference. 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 adjuvant chemotherapy for NSCLC, the 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 2011 NSCLC algorithm). A recent phase III randomized trial in elderly (70-89 years) patients 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 (10.4 versus 6.2 months).

A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by...
Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC.\textsuperscript{330-333} The S9900 trial, a SWOG (Southwest Oncology Group) 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). Progression-free survival and overall survival were in favor of preoperative chemotherapy.\textsuperscript{332, 333} All 3 studies showed a survival advantage for patients who received neoadjuvant chemotherapy. The 2 earlier phase III studies had 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 RT alone as adjuvant treatment for T1ab, N0 tumors based on a 1998 published report (PORT Meta-analysis Trialists Group, 1998).\textsuperscript{334} 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 guideline panelists 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.\textsuperscript{335} The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.\textsuperscript{147} Adjuvant chemotherapy (category 1) with RT is recommended for T1-3, N2 patients with negative margins (see the 2011 NSCLC algorithm).

**Surveillance and Treatment of Recurrences and Metastases**

**Surveillance**

The surveillance guidelines are described in the 2011 NSCLC algorithm. A spiral contrast-enhanced chest CT scan is recommended every 4 to 6 months postoperatively for 2 years (category 2B); a non-contrast-enhanced chest CT is recommended annually thereafter (category 2B), although the panel disagreed about these recommendations for spiral chest CT scans.\textsuperscript{15} Information about smoking cessation (e.g., advice, counseling, and 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/).

The 2011 NSCLC guidelines include an algorithm for long-term followup care of NSCLC survivors (see “Cancer Survivorship Care”). These recommendations include guidelines for routine cancer surveillance, immunizations, health monitoring, counseling for wellness and health promotion, and cancer screening.
Treatment of Recurrences and Distant Metastases

Recurrences are subdivided into locoregional recurrences and distant metastases. Management of locoregional recurrences (e.g., endobronchial obstruction, mediastinal lymph node recurrence, superior vena cava obstructions, severe hemoptysis) is described in the 2011 NSCLC algorithm. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life. 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 chemotherapy or best supportive care are recommended. The type of systemic therapy depends on the histologic type, EGFR mutation status, and PS (see the 2011 NSCLC algorithm).

Management of distant metastases (e.g., localized symptoms; diffuse brain, bone, solitary, or disseminated metastases) is described in the 2011 NSCLC algorithm. For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT. Bisphosphonate therapy or denosumab can be considered in patients with bone metastasis. Note that denosumab can be associated with severe hypocalcemia; patients with hypoparathyroidism and vitamin D deficiency are at increased risk for hypocalcemia. The FDA recently approved the use of denosumab in patients with bone metastases from solid tumors.

For patients with recurrent and metastatic disease, the 2011 NSCLC guidelines now recommend that histologic subtype should be determined before therapy so that the best treatment can be selected (see the 2011 NSCLC algorithm). EGFR mutation testing is recommended in patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell, or NSCLC not otherwise specified), because erlotinib is recommended for patients who are positive for EGFR mutations (see section on “EGFR Mutations”). However, very few patients with squamous cell carcinoma have EGFR mutations (<4%); therefore, routine testing is not recommended in these patients.

Treatment recommendations and eligibility criteria for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) are described in the 2011 NSCLC algorithm. Treatment recommendations and eligibility criteria for patients with squamous histology are described in the 2011 NSCLC algorithm. These recommendations are briefly summarized in the following paragraph. Data supporting these recommendations are described in the following section (see “Trial Data”).

Cisplatin/pemetrexed is recommended (category 1) for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met. Bevacizumab/chemotherapy is another option for patients with nonsquamous NSCLC who are EGFR mutation negative (or with unknown mutation status) if eligibility criteria are met. 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. Other chemotherapy options are also recommended, although some regimens may be more appropriate for certain patients, depending on PS and other factors (see next section “Trial Data”). Panel members disagreed (category 2B) about using cetuximab with cisplatin and vinorelbine, because data only showed a slight improvement in survival with the addition of cetuximab.
versus 10.1 months, \( P = .04 \).\(^{277}\) Note that full-dose cisplatin may not be appropriate for some PS 2 patients.

Cisplatin/gemcitabine is an option for patients with squamous cell carcinoma.\(^{261}\) Another option is cetuximab with cisplatin and vinorelbine, although this is a category 2B recommendation.\(^{277}\)

**Trial Data**

In a phase II/III trial (ECOG 4599), 842 patients were randomly assigned to either 1) bevacizumab in combination with paclitaxel and carboplatin; or 2) paclitaxel and carboplatin alone.\(^{272, 345}\) Both regimens were well tolerated with selected toxicities. Patients receiving bevacizumab/paclitaxel/carboplatin demonstrated an improved response rate (27% versus 10%, \( P < .0001 \)), progression-free survival (6.4 versus 4.5 months, \( P < .0001 \)), and median survival (12.5 versus 10.2 months, \( P = .0075 \)) when compared to patients receiving paclitaxel and carboplatin alone. The overall 1-year and 2-year survival was 51.9% versus 43.7% and 22.1% versus 16.9%, respectively, in favor of the bevacizumab/paclitaxel/carboplatin arm.\(^{272}\) However, more significant toxicities were observed with bevacizumab/paclitaxel/carboplatin compared to paclitaxel and carboplatin (grade 4 neutropenia: 24% versus 16.4%, grade 3/4 hemorrhage: 4.5% versus 0.7%, hemoptysis: 1.9% versus 0.2%, and hypertension: 6.0% versus 0.7%). Treatment-related deaths were more common with bevacizumab/paclitaxel/carboplatin (9 patients) than with paclitaxel and carboplatin (2 patients).

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 versus 10 months).\(^{343}\) Of interest, a trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab.\(^{346, 347}\) A noninferiority trial in 1745 patients with advanced NSCLC (either stage IIIB or IV; most were stage IV) assessed cisplatin plus gemcitabine compared with cisplatin plus pemetrexed.\(^{261}\) Patients with either adenocarcinoma or large cell histology (i.e., nonsquamous) had improved survival with cisplatin/pemetrexed (adenocarcinoma: 12.6 versus 10.9 months). Patients with squamous cell histology had improved survival with the cisplatin/gemcitabine regimen (10.8 versus 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%]).

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.\(^{277}\) The response rate was increased with cetuximab (36% versus 29%, \( P = .012 \)); there was no difference in progression-free survival. Overall survival was slightly better in patients receiving cetuximab (11.3 versus 10.1 months, \( P = .04 \)). However, there was increased grade 3 or 4 febrile neutropenia in patients receiving cetuximab (22% versus 15%, \( P < .05 \)); patients also had grade 2 acne-like rash. Treatment-related deaths were similar in both groups (3% versus 2%).

Data show that cisplatin-based combination therapy is superior to best supportive care for patients with advanced, incurable disease. Patients receiving cisplatin-based therapy had an improvement in median survival of 6-12 weeks and a doubling of 1-year survival rates (10%-15% improvement). Cisplatin or carboplatin have been proven
effective in combination with any of the following agents: docetaxel, etoposide, gemcitabine, irinotecan, paclitaxel, pemetrexed, vinblastine, and vinorelbine. New agent/non-platinum regimens are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel). As yet, there is no evidence that one platinum-based regimen is better than any other. A recent meta-analysis reported that the objective response rate is higher with cisplatin therapy when compared with carboplatin therapy (30% versus 24%). For patients with advanced, incurable NSCLC, many clinicians prefer to give carboplatin-based regimens because they are better tolerated.

**Maintenance Therapy**

Patients receiving therapy should be evaluated for tumor response with a CT scan. Approximately 25% of patients demonstrate disease progression after the initial cycle of chemotherapy. Patients with responsive or stable disease can continue to receive a total of 4 to 6 cycles of chemotherapy or until the disease progresses. A meta-analysis suggests that continuing the initial regimen beyond 4-6 cycles is associated with increased PFS; however, patients have more adverse events. Another review suggests that there is no benefit to continuing chemotherapy beyond 4-6 cycles; however, it is important to note that many patients assigned to longer duration of therapy did not receive the planned number of cycles.

For patients with nonsquamous NSCLC who are EGFR mutation negative (or unknown mutation status), continuation maintenance therapy regimens include bevacizumab (category 1), cetuximab (category 1), or pemetrexed (category 2B) (see the 2011 NSCLC algorithm). Switch maintenance therapy regimens for these patients include pemetrexed, erlotinib (category 2B), or docetaxel (category 3). Observation is another option.

For patients with squamous cell histology, cetuximab (category 1) can be used as a continuation maintenance therapy regimen (see the 2011 NSCLC algorithm). Switch maintenance therapy for these patients includes erlotinib (category 2B) or docetaxel (category 3). Observation is another option.

A phase III randomized trial (n = 663) assessed the effect of best supportive care with or without maintenance pemetrexed in patients with advanced NSCLC who had received platinum-based chemotherapy but had not progressed. In patients with nonsquamous NSCLC, overall survival was increased with pemetrexed when compared with placebo (13.4 versus 10.6 months, \( P = .012 \)).

**Continuation of Erlotinib or Gefitinib After Progression: Has Its Time Come?**

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). 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. Data support the continued use of erlotinib or gefitinib in patients with lung adenocarcinoma with EGFR mutations after development of acquired resistance to erlotinib or gefitinib when conventional chemotherapy is initiated.

There is accumulating data about how cancers become resistant to EGFR inhibitors. The most common known mechanism is the acquisition of a secondary mutation in EGFR, T790M, that renders the...
kinase resistant to erlotinib and gefitinib. Amplification of the MET oncogene is another validated resistance mechanism. Activation of the IGF-1R pathway has been observed in laboratory models. To overcome all 3 types of resistance, EGFR must still be inhibited. In the case of MET amplification and IGF-1R activation, new inhibitors must be added to the EGFR inhibitor; however, EGFR inhibition is still required to induce remission. Furthermore, data by Riely and colleagues demonstrate that when cancers that were once sensitive to EGFR inhibitors start to progress, discontinuation of the EGFR TKI can lead to a much more accelerated progression of the cancer. In total, it is likely that continuing EGFR TKIs is beneficial in many patients even after they develop resistance to EGFR TKIs.

Second-Line Chemotherapy

Although many new active drugs are available for lung cancer, the reported response rates to second-line chemotherapy have generally been less than 10%. Docetaxel, pemetrexed, and erlotinib are recommended as single-agent second-line chemotherapy regimens for patients with PS of 0-2 and who have experienced disease progression during or after first-line therapy (see the 2011 NSCLC algorithm). Docetaxel has been proven superior to best supportive care, vinorelbine, or ifosfamide with improved survival and quality of life. When compared with docetaxel, pemetrexed has similar median survival but less toxicity. Pemetrexed is recommended in patients with adenocarcinoma or large cell histology (i.e., nonsquamous NSCLC). Erlotinib has been proven superior to best supportive care with significantly improved survival and delayed time to symptom deterioration. Erlotinib is recommended for second- or third-line therapy for progressive disease in patients with PS of 3-4 who have the EGFR mutation (see the 2011 NSCLC algorithm). A platinum doublet with or without bevacizumab is an option (category 2B) for patients with nonsquamous NSCLC (i.e., adenocarcinoma, large cell, NSCLC NOS) who have progressed after first-line therapy with erlotinib.

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. Median age was 61.4 years. The response rate was 8.9% in the erlotinib group and less than 1% in the placebo group ($P<0.001$). Patients treated with erlotinib showed an overall survival of 6.7 versus 4.7 months for placebo (hazard ratio, 0.70; $P<0.001$). Progression-free survival was 2.2 months for the erlotinib group versus 1.8 months for placebo (hazard ratio, 0.61, adjusted for stratification categories; $P<0.001$). 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 chemotherapy. A randomized phase III trial in 829 patients found that oral topotecan was not inferior to docetaxel.

If disease progression occurs after second- or third-line chemotherapy, patients with PS of 0-2 may be treated with best supportive care or be enrolled in a clinical trial. Best supportive care only should be provided to patients with PS of 3-4 and progressive disease during any stage of the treatment (see the NCCN Palliative Care Guidelines).
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