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<th>‡ Hematology/ oncology</th>
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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 IIB (T3, N0) (NSCL-2)
  - Stage II (T3 invasion, N0) and Stage IIIA (T3-4, N1) (NSCL-4)
  - Stage IIIA (T1-3, N2) and Separate Pulmonary Nodules (Stage IIB, IIIA, IV) (NSCL-6)
  - Stage IIB (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)
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Staging (ST-1)

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

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

See NCCN Categories of Evidence and Consensus

NCCN Guidelines for Patients™ available at www.nccn.com
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 “i” - “lung neuroendocrine tumors” added to the high risk criteria and “minimal margins” removed.
- Footnote “f” 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 “i” 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 clarifed 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.

**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.

NSCL-B 1 of 4
- 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.

NSCL-C 5 of 7
- 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 “*” 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 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. 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.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf](http://www.surgeongeneral.gov/library/secondhandsmoke/report/executivesummary.pdf).
- 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](http://www.ahrq.gov/path/tobacco.htm#Clinic) to identify, counsel, and treat patients with nicotine habituation.
- Patients who are current or former smokers have significant risk for the development of lung cancer; chemoprevention agents are not yet established for these patients. When possible, these patients should be encouraged to enroll in chemoprevention trials.
- At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Available data 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. If a screening strategy is used, then the I-ELCAP screening protocol should be followed. [http://www.ielcap.org/professionals/docs/ielcap.pdf](http://www.ielcap.org/professionals/docs/ielcap.pdf)

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PATHOLOGIC DIAGNOSIS OF NSCLC

INITIAL EVALUATION

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

Stage IIB\(^d\) (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-4)
See Pretreatment Evaluation (NSCL-6)
See Pretreatment Evaluation (NSCL-6)
See Pretreatment Evaluation (NSCL-9)
See Pretreatment Evaluation (NSCL-10)
See Pretreatment Evaluation (NSCL-10)
See Pretreatment Evaluation (NSCL-11)
See Systemic Therapy (NSCL-13)

Non-Small Cell Lung Cancer (NSCLC)

• 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

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

**PRETREATMENT EVALUATION**

<table>
<thead>
<tr>
<th>Stage IA (peripheral T1ab, N0)</th>
<th>Stage IB (peripheral T2a, N0)</th>
<th>Stage I (central T1ab–T2a, N0)</th>
<th>Stage II (T1ab–2ab, N1; T2b, N0)</th>
<th>Stage IIB (T3, N0)</th>
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</tbody>
</table>

- **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**

<table>
<thead>
<tr>
<th>Operable</th>
<th>Medically inoperable</th>
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<tr>
<td>See Initial Treatment and Adjuvant Treatment (NSCL-3)</td>
<td>See Definitive RT (see NSCL-C)</td>
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<tr>
<td>See Stage IIIA (NSCL-7) or Stage IIIB (NSCL-9)</td>
<td></td>
</tr>
</tbody>
</table>

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

\(^1\) 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.

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

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### INITIAL TREATMENT

#### FINDINGS AT SURGERY

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<tr>
<th>Stage IA (T1ab, N0)</th>
<th>Stage IB (T2a, N0); Stage IIA (T2b, N0)</th>
<th>Stage IIA (T1ab-T2a, N1) Stage IIB (T3, N0; T2b, N1)</th>
<th>Stage IIIA (T1-3, N2)</th>
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<tbody>
<tr>
<td>Margins negative (R0)(^h)</td>
<td>Margins positive (R1, R2)(^h)</td>
<td>Margins negative (R0)(^h)</td>
<td>Margins positive (R1, R2)(^h)</td>
</tr>
<tr>
<td>Margins positive (R1, R2)(^h)</td>
<td>Margins negative (R0)(^h)</td>
<td>Margins positive (R1, R2)(^h)</td>
<td>Margins positive (R1, R2)(^h)</td>
</tr>
</tbody>
</table>

### ADJUVANT TREATMENT

- **Margins negative (R0)**
  - Observe
  - Reresection (preferred) or RT\(^j\) (category 2B)
- **Margins positive (R1, R2)**
  - Observe or Chemotherapy\(^k\) (category 2B) in high-risk patients\(^i\)
  - Reresection (preferred) ± chemotherapy\(^k, l\) or RT\(^j, m\) + chemotherapy
  - Chemoradiation\(^j, m\) + chemotherapy
  - Chemotherapy\(^k\) (category 1) + RT\(^j\)

### SURVEILLANCE (NSCL-12)

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- **Margins positive (R1, R2)**
  - Observe
  - Reresection (preferred) ± chemotherapy\(^k, l\) or RT\(^j, m\) + chemotherapy
  - Chemoradiation\(^j, m\) + chemotherapy
  - Chemotherapy\(^k\) (category 1) + RT\(^j\)

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\(^g\) 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).

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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.
### Clinical Presentation

<table>
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<tr>
<th>Superior sulcus tumor (T3 invasion, N0-1)</th>
<th>Preoperative concurrent chemoradiation, Surgery + chemotherapy</th>
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<tr>
<td>Marginally resectable</td>
<td>Preoperative concurrent chemoradiation or Surgical reevaluation</td>
</tr>
<tr>
<td>Unresectable</td>
<td>Definitive concurrent chemoradiation or Chemotherapy</td>
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</table>

#### Initial Treatment

<table>
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<tr>
<th>Superior sulcus tumor (T4 extension, N0-1)</th>
<th>Preoperative concurrent chemoradiation, Surgery (preferred) or Concurrent chemoradiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginally resectable</td>
<td>Surgery (preferred) or Concurrent chemoradiation</td>
</tr>
<tr>
<td>Unresectable</td>
<td>Surgery</td>
</tr>
</tbody>
</table>

#### Adjuvant Treatment

<table>
<thead>
<tr>
<th>Unresectable Complete definitive RT + chemotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical reevaluation</td>
</tr>
<tr>
<td>Resectable</td>
</tr>
</tbody>
</table>

#### Surveillance (NSCL-12)

- **Margins negative (R0)**: Chemotherapy if not given as initial treatment
- **Margins positive (R1, R2)**: Chemotherapy if not given as initial treatment

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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).

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

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

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.

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

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.


If full-dose chemotherapy not given concurrently with RT as initial treatment.
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), same lobe (T3, N0) or ipsilateral lung (T4, N0)

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)

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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.

2Methods for evaluation include mediastinoscopy, mediastinotomy, EBUS, EUS and CT-guided biopsy.
MEDIASTINAL BIOPSY FINDINGS

INITIAL TREATMENT

Negative for M1 disease

Resectable

Surgical resection\(^g\) + mediastinal lymph node dissection or systematic lymph node sampling

See Treatment according to clinical stage (NSCL-1)

T1-3, N0-1 (including same lobe) → Surgery\(^g\)

Unresectable

Definitive concurrent chemoradiation\(^{j,m}\)

See Treatment for Metastasis, solitary site (NSCL-11) or disseminated (NSCL-13)

T1-2, T3 (≥ 7 cm), N2 nodes positive

T1-3, N0-1 (including same lobe) → Surgery\(^g\)

T3 (invasion), N2 nodes positive

Brain MRI

PET/CT scan,\(^f\) if not previously done

Negative for M1 disease

No progression

Progression

See Treatment for Metastasis, solitary site (NSCL-11) or disseminated (NSCL-13)

Positive

Definitive concurrent chemoradiation\(^{j,m}\)

Surgery\(^g\) ± chemotherapy\(^k\) (category 2B) ± RT\(^j\) (if not given)

RT\(^j\) (if not given) ± chemotherapy\(^k\)

Surveillance (NSCL-12)

ADJUVANT TREATMENT

See NSCL-3 OR NSCL-4

Margins negative (R0)\(^h\)

Margins positive (R1, R2)\(^h\)

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

Chemoradiation\(^{j,m}\) + chemotherapy

\(^{f}\) Positive PET/CT scan findings need pathologic or other radiologic confirmation.

\(^{g}\) 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).

\(^{k}\) See Chemotherapy Regimens for Adjuvant Therapy (NSCL-D).

\(^{m}\) See Chemotherapy Regimens used with Radiation Therapy (NSCL-E).

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Separate pulmonary nodule(s), same lobe (T3, N0) or ipsilateral lung (T4, N0) → Surgery

Margins negative (R0) → Chemotherapy → Surveillance (NSCL-12)

Margins positive (R1, R2) → Concurrent chemoradiation (if tolerated) → Surveillance (NSCL-12)

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 (category 1) → Chemotherapy → Surveillance (NSCL-12)
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.

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.

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

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**NCCN Guidelines™ Version 2.2011**  
Non-Small Cell Lung Cancer

### CLINICAL ASSESSMENT

#### PRETREATMENT EVALUATION

| Stage IIIB  
(T4 extension, N2–3) | • PET/CT scan  
• Pathologic confirmation of T4, N2–3 disease by either:  
  - Mediastinoscopy  
  - Supraclavicular lymph node biopsy  
  - Thoracoscopy  
  - Needle biopsy  
  - Mediastinotomy  
  - EUS biopsy  
  - EBUS biopsy |
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Concurrent chemoradiation (category 1)</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Chemotherapy</strong></td>
</tr>
<tr>
<td>Ipsilateral, mediastinal node negative (T4, N0-1)</td>
<td><strong>See Treatment for Stage IIIA (NSCL-6)</strong></td>
</tr>
<tr>
<td>Ipsilateral, mediastinal node positive (T4, N2)</td>
<td><strong>See Treatment for Metastasis solitary site (NSCL-11) or disseminated (NSCL-13)</strong></td>
</tr>
<tr>
<td>Ipsilateral, mediastinal node positive (T4, N3)</td>
<td><strong>See Treatment according to T, N, M stage NSCL-1</strong></td>
</tr>
<tr>
<td>Contralateral, mediastinal node negative</td>
<td>Metastatic disease</td>
</tr>
<tr>
<td>Contralateral, mediastinal node positive (T4, N2)</td>
<td></td>
</tr>
</tbody>
</table>

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

- Thoracentesis or pericardiocentesis ± thoracoscopy if thoracentesis indeterminate

  - **Negative**
  - **Positive**

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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.

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*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.*
**Clinical Assessment**

**Pretreatment Evaluation**

- **Brain**
- **Adrenal**

**Initial Treatment**

- **Stage IV, M1b: solitary site**
  - Mediastinoscopy
  - Bronchoscopy
  - Brain MRI
  - PET/CT scan

- **Pathologic diagnosis by needle or resection**

- **Local therapy for adrenal lesion (if lung lesion curable, based on T and N stage)**
  - (category 2B)

- **See Systemic Therapy (NSCL-13)**

- **Surgical resection of lung lesion**
  - Chemotherapy (category 2B)
  - Stereotactic body radiation therapy (SBRT) (category 2B)

- **Surgical resection of lung lesion** (category 2B)

---

**Notes**

- 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).

- See NCCN CNS Guidelines.

- Surveillance (NSCL-12)

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**SURVEILLANCE**

- **NED, stages I-IV:**
  - 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

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

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

**THERAPY FOR RECURRENTNESS AND METASTASIS**

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

- **Evidence of disseminated disease**
  - Concurrent chemoradiation (if RT not previously given)
    - External-beam RT
    - Stent
    - Concurrent chemoradiation (if not previously given)
    - Brachytherapy
    - Laser
    - Photodynamic therapy
    - Embolization
    - Surgery

- **Distant recurrence**
  - Laser/stent/other surgery
  - Brachytherapy
  - External-beam RT
  - Photodynamic therapy

- **Locoregional recurrence**
  - Reresection
  - External-beam RT

- **Localized symptoms**
  - Palliative external-beam RT

- **Diffuse brain metastases**
  - Palliative external-beam RT

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

- **Solitary metastasis**
  - See pathway for Stage IV, M1b, solitary site (NSCL-11)

- **Distant metastases**
  - See Systemic Therapy (NSCL-13)

---

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Establish histologic subtype

- Adenocarcinoma
- Large Cell
- NSCLC NOS

THERAPY FOR RECURRENCE OR METASTASES

**EGFR mutation testing not recommended**

Squamous cell carcinoma

**EGFR mutation testing (category 1)**

Adenocarcinoma, Large Cell, NSCLC NOS

**EGFR mutation negative or unknown**

**EGFR mutation discovered prior to first-line therapy**

**EGFR mutation positive**

**EGFR mutation discovered during chemotherapy**

**Add erlotinib to current chemotherapy or Switch maintenance: erlotinib**

**Progression**

**See Second-line Therapy (NSCL-16)**

**See First-Line Therapy (NSCL-15)**

**FIRST-LINE THERAPY**

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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.


For performance status 0-4.

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

ADENOCARCINOMA, LARGE CELL, NSCLC NOS: EGFR MUTATION NEGATIVE OR UNKNOWN

FIRST-LINE THERAPY

<table>
<thead>
<tr>
<th>PS 0-1</th>
<th>PS 2</th>
<th>PS 3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy^w (category 1) or Bevacizumab + chemotherapy^w,cc,dd (if criteria met)^ee</td>
<td>Cisplatin/pemetrexed (category 1) (if criteria met)^ff or Cetuximab/vinorelbine/cisplatin^gg (category 2B)</td>
<td>Best supportive care only (See NCCN Palliative Care Guidelines)</td>
</tr>
</tbody>
</table>

RESPONSE EVALUATION

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

MAINTENANCE THERAPY

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

^w See Systemic Therapy for Advanced or Metastatic Disease (NSCL-F).
^cc Bevacizumab should be given until progression.
^dd Any regimen with a high risk of thrombocytopenia and the potential risk of bleeding should be used with caution in combination with bevacizumab.
^ee 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.
^hh 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) |
| PS 3-4 | Best supportive care |

**RESPONSE EVALUATION**

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

- Progression: Tumor response or stable disease
  - Continuation of current regimen until disease progression or Continuation maintenance of cetuximab (category 1) or Switch maintenance of erlotinib (category 2B) or docetaxel (category 3) or Observation

**MAINTENANCE THERAPY**

See Second-line Therapy (NSCL-16)

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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.
**Second-line Therapy**

<table>
<thead>
<tr>
<th>Performance status 0-2</th>
<th>Docetaxel or Pemetrexed or Erlotinib or Platinum doublet ± bevacizumab (if erlotinib given as first-line and adenocarcinoma) (category 2B)</th>
</tr>
</thead>
</table>

| Performance status 3-4 | Erlotinib or Best supportive care only (See NCCN Palliative Care Guidelines) |

**Third-line Therapy**

<table>
<thead>
<tr>
<th>Performance status 0-2</th>
<th>Erlotinib → Progression</th>
</tr>
</thead>
</table>

| Performance status 3, 4 | Erlotinib or Best supportive care only (See NCCN Palliative Care 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.

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

**Best supportive care (See NCCN Palliative Care Guidelines) or Clinical trial**
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.
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.
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.

1 Peripheral is defined as lying in the outer one third of the lung parenchyma.
The Role of Surgery in Patients with Stage IIIA (N2) NSCLC

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. ¹ On the other side we have patients with multiple pathologically proven malignant lymph node (LN)s 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.²,³ 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.⁴

- 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.¹,⁵,⁶

- Patients with negative mediastinum after neoadjuvant therapy have a better prognosis.⁶,⁷

- Radiographic methods have poor positive and negative predictive values in the evaluation of the mediastinum after neoadjuvant therapy.⁸ 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.⁹
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 indicates 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.

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

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

**General Principles**

- 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.\(^1\text{-}^3\)
- For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiotherapy is recommended if the patient is medically fit.\(^4\text{-}^5\) Radiation therapy should start earlier as local recurrence is the most common failure in this group of patients.\(^6\)
- 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.

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See Dose, Volume and Normal Tissue Constraints for Conventionally Fractionated Radiation Therapy (NSCL-C 2 of 7)

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)
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)

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.
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. 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. When IMRT is used, the NCI IMRT guideline should be followed. Under strictly defined protocols, proton therapy may be allowed. 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)
- 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.
### 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>

¹Please use ICRU62 for detailed target definitions. ²4DCT 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>Extracapsular nodal extension or microscopic positive margins</td>
<td>54-60 Gy</td>
<td>1.8-2 Gy</td>
<td>5-6 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</td>
<td>60-74 Gy</td>
<td>2 Gy</td>
<td>6-7.5 weeks</td>
</tr>
<tr>
<td>Radiation alone or sequential chemoradiation</td>
<td>60 to 70 Gy</td>
<td>2 Gy</td>
<td>6-7 weeks</td>
</tr>
<tr>
<td>Concurrent chemotherapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Palliative</td>
<td>30-45 Gy</td>
<td>3 Gy</td>
<td>2-3 weeks</td>
</tr>
<tr>
<td>Obstructive disease (SVC syndrome or obstructive pneumonia)</td>
<td>30 Gy</td>
<td>3 Gy</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Bone metastases with soft tissue mass</td>
<td>8 Gy</td>
<td>8 Gy</td>
<td>1 day</td>
</tr>
<tr>
<td>Bone metastases without soft tissue mass</td>
<td>See CNS Guidelines</td>
<td>See CNS Guidelines</td>
<td>See CNS Guidelines</td>
</tr>
<tr>
<td>Brain metastasis</td>
<td></td>
<td></td>
<td></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 ≤ 50 Gy in 1.8-2 Gy</td>
</tr>
<tr>
<td>Lung</td>
<td>V20 &lt; 37% MLD &lt; 20 Gy</td>
</tr>
<tr>
<td>Heart</td>
<td>V40 &lt; 100% V45 &lt; 67% 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>

³The 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. ⁴Please also consider dose limit recommendations from Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76:S10-19.

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>15.4 Gy</td>
<td>30 Gy (10 Gy/fx)</td>
<td>30 Gy (7.5 Gy/fx)</td>
<td>32.5 Gy (6.5 Gy/fx)</td>
</tr>
<tr>
<td>Brachial plexus</td>
<td>17.5 Gy</td>
<td>21 Gy (7 Gy/fx)</td>
<td>27.2 Gy (6.8 Gy/fx)</td>
<td>30 Gy (6 Gy/fx)</td>
</tr>
<tr>
<td>Heart/ pericardium</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>Great vessels</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>Trachea/ Large Bronchus</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>Rib</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>Skin</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>Stomach</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.

---

### 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</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cisplatin 75 mg/m² on day 1</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>Vinorelbine 25 mg/m² days 1, 8, 15, 22</td>
<td></td>
<td>Gemcitabine 1250 mg/m² on days 1, 8</td>
<td></td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² on day 1</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>Cisplatin 75 mg/m²</td>
<td>Every 21 days&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vinorelbine 30 mg/m² days 1, 8, 15, 22</td>
<td></td>
<td>Docetaxel 75 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Cisplatin 75-80 mg/m² day 1;</td>
<td>Every 21 days for 4 cycles</td>
<td>Pemetrexed 500 mg/m² on day 1</td>
<td>Every 21 days for 4 cycles</td>
</tr>
<tr>
<td>Vinorelbine 25-30 mg/m² days 1 + 8</td>
<td></td>
<td>Cisplatin 75 mg/m² on day 1</td>
<td></td>
</tr>
<tr>
<td>Cisplatin 100 mg/m² on day 1</td>
<td>Every 28 days for 4 cycles&lt;sup&gt;b&lt;/sup&gt;</td>
<td>for adenocarcinoma and large cell carcinoma and NSCLC NOS&lt;sup&gt;c&lt;/sup&gt; (without specific histologic subtype)</td>
<td></td>
</tr>
<tr>
<td>Etoposide 100 mg/m² 1-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cisplatin 80 mg/m² on day 1, 22, 43, 64</td>
<td>Every 21 days for 4 cycles&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinblastine 4 mg/m² days 1, 8, 15, 22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>then every 2 wks after day 43</td>
<td></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</td>
</tr>
<tr>
<td>Carboplatin AUC 6 on day 1</td>
</tr>
</tbody>
</table>


**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

<table>
<thead>
<tr>
<th>Concurrent Chemotherapy/RT Regimens*</th>
<th>Sequential Chemotherapy/RT Regimens</th>
</tr>
</thead>
</table>
| Cisplatin 50 mg/m² on day 1, 8, 29, and 36  
Etoposide 50 mg/m² days 1-5, 29-33  
Concurrent thoracic RT<sup>a</sup> (preferred) | Cisplatin 100 mg/m² on day 1, 29  
Vinblastine 5 mg/m² weekly x 5  
Concurrent thoracic RT<sup>b</sup> (preferred) |
| Cisplatin 100 mg/m² day 1, 29  
Vinblastine 5 mg/m² weekly x 5  
Concurrent thoracic RT<sup>b</sup> (preferred) | Paclitaxel 200 mg/m² every 3 weeks over 3 hours, 2 cycles  
Carboplatin AUC 6, 2 cycles followed by thoracic RT<sup>c</sup> |
| Paclitaxel 45-50 mg/m² weekly over 1 hour  
Carboplatin AUC = 2 mg/mL/min over 30 min weekly  
Concurrent thoracic RT<sup>c</sup> (category 2B) | |

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

#### Concurrent Chemotherapy/RT Followed by Chemotherapy

| Cisplatin 50 mg/m² on day 1, 8, 29, 36  
Etoposide 50 mg/m² days 1-5, 29-33  
Concurrent thoracic RT followed by cisplatin 50 mg/m² and etoposide 50 mg/m² x 2 additional cycles (category 2B)<sup>a</sup> | Paclitaxel 45-50 mg/m² weekly  
Carboplatin AUC 2, concurrent thoracic RT followed by 2 cycles of paclitaxel 200 mg/m² and carboplatin AUC 6<sup>c</sup> (category 2B) |


**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.

See Maintenance Chemotherapy, Second- and Third-line therapy NSCL-F (2 of 3)
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (2 OF 3)

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

- **Continuation Maintenance:** 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.

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

Note: All recommendations are category 2A unless otherwise indicated. Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
SYSTEMIC THERAPY FOR ADVANCED OR METASTATIC DISEASE (3 OF 3)

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

- Cisplatin
- Carboplatin
- Paclitaxel
- Docetaxel
- Vinorelbine
- Gemcitabine
- Etoposide
- Irinotecan
- Vinblastine
- Mitomycin
- Ifosfamide
- Pemetrexed
- Erlotinib
- Bevacizumab
- Albumin-bound paclitaxel

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

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.

1. ACS Guidelines on Nutrition and Physical Activity for Cancer Prevention
   http://www.cancer.org/docroot/PED/content/PED_3_2X_Diet_and_Activity_Factors_That_Affect_Risks.asp?sitearea=PED (Accessed November 18, 2009)
3. American Cancer Society Guidelines for Early Detection of Cancer:
# 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)(^a)</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:(^b)</td>
</tr>
<tr>
<td></td>
<td>Involves main bronchus, ≥ 2 cm distal to the carina</td>
</tr>
<tr>
<td></td>
<td>Invades visceral pleura</td>
</tr>
<tr>
<td></td>
<td>Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumor &gt; 3 cm but ≤ 5 cm in greatest dimension</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumor &gt; 5 cm but ≤ 7 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(^b) 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(^c)</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>

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

\(^b\)T2 tumors with these features are classified T2a if ≤ 5 cm or if size cannot be determined, and T2b if > 5 cm but ≤ 7 cm 

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

### 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>II A</td>
<td>III A</td>
<td>IIIB</td>
</tr>
<tr>
<td>T1 (&gt;2–3 cm)</td>
<td>T1b</td>
<td>IA</td>
<td>II A</td>
<td>III A</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (less than or equal to 5 cm)</td>
<td>T2a</td>
<td>IB</td>
<td>II A</td>
<td>III A</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt;5–7 cm)</td>
<td>T2b</td>
<td>II A</td>
<td>II B</td>
<td>III A</td>
<td>IIIB</td>
</tr>
<tr>
<td>T2 (&gt;7 cm)</td>
<td>T3</td>
<td>II B</td>
<td>III A</td>
<td>III A</td>
<td>IIIB</td>
</tr>
<tr>
<td>T3 invasion</td>
<td>T4</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (same lobe nodules)</td>
<td>T4</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>IIIB</td>
</tr>
<tr>
<td>T4 (extension)</td>
<td>T4</td>
<td>III A</td>
<td>III A</td>
<td>III B</td>
<td>IIIB</td>
</tr>
<tr>
<td>M1 (ipsilateral lung)</td>
<td>M1a</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>T4 (pleural effusion)</td>
<td>M1b</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (contralateral lung)</td>
<td>M1c</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
<td>IV</td>
</tr>
<tr>
<td>M1 (distant)</td>
<td>M1d</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.

The primary risk factor for lung cancer is smoking, which accounts for more than 85% 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. In addition to the hazard of first-hand smoke, exposed nonsmokers have an increased relative risk of developing lung cancer. Radon gas, a radioactive gas that is produced by the decay of radium 226, is the second leading cause of lung cancer. The decay of this isotope 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
Lung cancer is a unique disease, because the etiologic agent is an industry and more than 85% of cases are caused by voluntary or involuntary “second-hand” cigarette smoking. Active smoking and second-hand 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, laryngeal, pharyngeal, and...

Further complicating this problem, cigarettes also contain the highly addictive substance nicotine. Oncologists should encourage smoking cessation, especially in patients with cancer (http://www.smokefree.gov/). 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).

Varenicline is a new class of drug for smoking cessation; other drugs include nicotine replacement (e.g., gum, inhaler, nasal spray, patch) and bupropion. 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 50,000 current or former smokers; this trial is assessing the risks and benefits of spiral CT scans compared with chest x-rays for detecting lung cancer. The NSLT is now closed; results are expected by 2011. 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.18 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. However, whether mortality is decreased by screening has not yet been conclusively demonstrated and is expected to be answered by the NLST.

At the present time, the NCCN panel does not recommend the routine use of screening CT as standard clinical practice (category 3). Available data18-21 are conflicting,22, 23 thus, conclusive data from ongoing 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 if the high-risk individual is not eligible for 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. If a screening strategy is used, then the I-ELCAP screening protocol should be followed (http://www.ielcap.org/professionals/docs/ielcap.pdf). Data show that a CT screening clinic detected a malignant tumor in 3% of patients; many patients (45%) did not complete followup.

24 Classification and Prognostic Factors

The World Health Organization 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.

25 Certain prognostic factors are predictive of survival in patients with NSCLC. Good prognostic factors include early-stage disease at diagnosis, good performance status (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.

26 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.

27 Pathologic Evaluation of Lung Cancer

Pathologic evaluation is performed 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). 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 sampled to assess the staging and therapeutic options.

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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 World Health Organization for carcinomas of the lung. The principles of pathology review are listed in the algorithm.
Bronchioloalveolar Carcinoma

Bronchioloalveolar carcinoma (BAC) is an important subtype of pulmonary adenocarcinoma.\textsuperscript{34} Data suggest that gefitinib and erlotinib are useful for patients with BAC.\textsuperscript{35-37} BAC includes only noninvasive tumors where the neoplastic cells spread out along pre-existing alveolar structures (lepidic spread). Pure BAC requires absence of invasion of stroma, pleura, or lymphatic spaces.\textsuperscript{38} BAC is divided into 3 subtypes: 1) mucinous, 2) nonmucinous, and 3) a mixed mucinous and nonmucinous or indeterminate form. Nonmucinous BAC expresses the thyroid transcription factor-1 (TTF-1). Mucinous BACs express CK20 and CK7, but reportedly lack TTF-1 expression.\textsuperscript{39} BACs are usually CK7+ and CK20- and therefore distinguishable from CK7- and CK20+ metastatic adenocarcinoma of the colorectum. Mucinous BACs are often CK7+/CK20+.\textsuperscript{40} CDX-2 is a highly sensitive and specific marker of adenocarcinomas of intestinal origin that could be used to distinguish mucinous BAC from metastatic primary gastrointestinal cancers.

Immunohistochemical Staining

Immunohistochemistry is most valuable in 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) are used routinely. The stains that are negative in mesothelioma, but positive in adenocarcinoma, are CEA (carcinoembryonic antigen), B72.3, Ber-EP4, and MOC31. Stains that are sensitive and specific for mesothelioma include WT-1, calretinin, D2-40,\textsuperscript{41} and cytokeratin 5/6. 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. TTF-1 is a homeodomain-containing 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, whereas metastatic adenocarcinomas to the lung (e.g., from breast cancer) are usually TTF-1 negative. However, TTF-1 is positive in tumors from patients with thyroid cancer.\textsuperscript{42} 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- 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 be used to differentiate them from primary lung tumors. Neuroendocrine tumors of the lung are diagnosed with chromogranin (reacts with cytoplasmic neuroendocrine granules) and synaptophysin (reacts with a cell membrane glycoprotein). All typical and atypical carcinoid tumors stain with chromogranin and synaptophysin, whereas small cell lung carcinoma is negative in 25% of the cases.

Nearly all 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.\textsuperscript{43}
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. A new lung cancer staging system has been proposed by the International Association of the Study of Lung Cancer (IASLC). The revised staging is available from the AJCC (7th edition). These NCCN guidelines have been updated with the new AJCC (7th edition) staging revisions. 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 new TNM staging revisions take effect 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 IIB to stage IIA; 2) T2aN1M0 is downstaged from stage IIB 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, mediastinoscopy examination of resected lymph nodes).

For 1996-2004, the overall 5-year relative survival rate for lung cancer was 15.2% (from 17 SEER [Surveillance, Epidemiology, and End Results geographic areas in the United States). Of lung and bronchus cancer cases, 16% were diagnosed while the cancer was still confined to the primary site (localized stage); 25% were diagnosed after the cancer had spread to regional lymph nodes or directly beyond the primary site; 51% 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: 49.5% for localized, 20.6% for regional, 2.8% for distant, and 8.3% 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 is stage 1A or 1B 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, and the regulatory subunit of ribonucleotide reductase (RRM1). 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 or exon 21 L858R mutation does not appear to be prognostic of survival for patients with NSCLC, independent of therapy.\textsuperscript{54} However, the presence of the EGFR exon 19 deletion or exon 21 L858R mutation is predictive of treatment benefit from EGFR-TKI therapy.\textsuperscript{36, 55} High ERCC1 levels are prognostic of better survival for patients with NSCLC when compared to low levels of ERCC1 expression, independent of therapy.\textsuperscript{56, 57} High levels of ERCC1 expression are also predictive of poor response to platinum-based chemotherapy.\textsuperscript{57, 58} 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.\textsuperscript{28} Presence of K-ras mutations is also predictive of lack of benefit from platinum/vinorelbine chemotherapy or EGFR TKI therapy.\textsuperscript{36, 59} High RRM1 levels are prognostic of better survival for patients with NSCLC compared to low levels of RRM1 expression, independent of therapy.\textsuperscript{60, 61} High levels of RRM1 expression are also predictive of poor response to gemcitabine-based chemotherapy.\textsuperscript{58, 62, 63}

**EGFR Mutations, Gene Copy Number, and Level of Expression**

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.

Three different methods are currently used to determine the EGFR status in tumor cells. The methods include mutation analysis, gene copy number determination, and the level of EGFR expression. The most commonly found EGFR mutations are deletions in exon 19 (E19del) and a mutation in exon 21 (L858R). 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 mutations are found in approximately 10\%-15\% of Caucasian patients with NSCLC and in 30\%-40\% of Asian patients.

The prognostic effect of EGFR mutations E19del 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.\textsuperscript{54} Mutations were found in 40 patients, and 20 had E19del 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, \textit{P} < 0.001) than overall survival for patients without mutations (N=45, 10 months).\textsuperscript{31}

The predictive effects of EGFR mutations E19del 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.\textsuperscript{54, 65} 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.\textsuperscript{36} A recent prospective study has demonstrated that the objective response rate in North American patients with non-squamous cell histology and EGFR mutations (53% E19del, 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.

**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). 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.

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. Initially, studies used semiquantitative determination of ERCC1 mRNA levels. Using prospectively collected fresh-frozen tumor samples, an association between ERCC1 mRNA levels and response to 2 cycles of gemcitabine and carboplatin was described. Tumors with low ERCC1 expression had a better response than tumors with high ERCC1 expression in 35 patients with inoperable, locally advanced NSCLC. In a retrospective analysis of tumor specimens from 56 patients with advanced NSCLC who were treated with gemcitabine and cisplatin, no significant correlation between disease response and ERCC1 mRNA levels was observed. However, overall survival was significantly longer in patients with low ERCC1 expression (14.2 months) when compared to patients with high expression (4.7 months).

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). 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; \( P = 0.002 \)). Most recently, Bepler and colleagues reported that in situ ERCC1 protein levels in tumor specimens collected prospectively from a community-based randomized phase III clinical trial were significantly and inversely correlated with disease response to carboplatin/gemcitabine or gemcitabine alone (\( P = 0.003, r = 0.39 \)); that is, response was better in patients with low levels of ERCC1 expression.

**K-ras Mutations**

K-ras is a GTP-binding protein and involved in G-protein coupled receptor signaling. In its mutated form, it is constitutively active, able to transform immortalized cells, and promotes cell proliferation and survival. Initially, K-ras was described as mutated in codon 12 in 5/10 adenocarcinomas and 0/15 squamous and 0/10 large cell carcinomas. Current data suggest that approximately 25% of adenocarcinomas in a North American population have K-ras mutations. K-ras mutation prevalence is associated with cigarette smoking.
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.\textsuperscript{61}

In fresh frozen tumor specimens that had been prospectively collected on patients treated with gemcitabine and carboplatin, RRM1 expression levels were predictive of tumor response. Tumors with low RRM1 expression responded significantly better to treatment than tumors with high levels of expression.\textsuperscript{58} In addition, RRM1 mRNA levels were significantly associated with overall survival in patients with advanced stage NSCLC who were treated with gemcitabine and cisplatin.\textsuperscript{72} In this analysis, patients with low RRM1 levels had a median overall survival of 13.7 months while patients with high levels had a median overall survival of 3.6 months. The addition of a vinca alkaloid to a gemcitabine regimen abolished the effect of RRM1 expression on overall survival, which suggests that a substantial interaction exists between the biomarker and treatment regimen on patient outcome.

Most recently, Bepler and colleagues reported that in situ RRM1 protein levels in tumor specimens collected prospectively from a community-based randomized phase III clinical trial 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.\textsuperscript{62,63}

**Treatment Approaches**

**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. Determination of resectability, surgical staging, and pulmonary resection should be performed by board-certified thoracic surgeons who perform lung cancer surgery as a prominent part of their practice. Thoracic surgeons should actively participate in multidisciplinary discussions and meetings regarding lung cancer patients (e.g., multidisciplinary clinic and/or Tumor Board). Patients with pathologic stage II or greater should be referred to medical oncology for evaluation. Consider referral to medical oncologist for patients with stage IB and consider referral to radiation oncologist for stage IIIA. 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.\textsuperscript{73,74} Resection (including wedge resection) is preferred over ablation (i.e., radiofrequency ablation, cryotherapy, stereotactic radiation).\textsuperscript{74} However, it is controversial whether lung-sparing surgeries (i.e., sublobular resection), such as segmentectomy and wedge resection, are useful in patients with severely reduced pulmonary function who are otherwise not candidates for surgery.\textsuperscript{74-76}
The American College of Surgeons Oncology Group is conducting a randomized trial (ACOSOG Z0030) of 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.77, 78

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 recently proposed a new lymph node map.79 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 selected patients: 1) those who are not eligible for lobectomy because of poor pulmonary reserve or other major co-morbidity; and 2) those with a peripheral nodule 2 cm or less with at least one of the following (pure BAC histology [category 2B], nodule has 50% or more ground glass appearance on CT [category 2B], and/or radiologic surveillance confirms a doubling time of 400 days or more [category 2B]). Segmentectomy (preferred) or wedge resection should achieve parenchymal resection margins 1) 2 cm or more, or 2) the size of the nodule or more.80, 81

Video-assisted thoracic surgery (VATS) is a relatively new minimally invasive surgical treatment that is currently being investigated in all aspects of lung cancer.82, 83 Published studies suggest that VATS has several advantages over the standard thoracotomy (or pleurotomy).84-88 Acute and chronic pain associated with VATS is minimal; thus, this procedure requires shorter length of hospitalization.89 VATS is also associated with low postoperative morbidity and mortality, minimal risk of intraoperative bleeding, or minimal locoregional recurrence.90-94

In stage I NSCLC patients who have VATS 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.95-97 VATS has also been shown to improve discharge independence in older populations and in high-risk patients as well.98, 99 Recent data show that VATS improves the ability of patients to complete postoperative chemotherapy regimens.100, 101 Based on its favorable effects on postoperative recovery and morbidity, VATS is included in the guidelines as a reasonable and acceptable approach for patients who are surgically resectable with no anatomic or surgical contraindications as long as standard oncologic and dissection principles of thoracic surgery are not compromised.

Radiation Therapy

General Principles
Radiation therapy can be used as 1) an adjunct 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) an important palliative modality for patients with incurable NSCLC. The terminology and
abbreviations for RT are described in the algorithm (see Table 1). 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.

For resected tumors with pathologic mediastinal nodal involvement (pN2) and negative surgical margins, adjuvant chemotherapy (category 1) followed by postoperative radiotherapy is preferred, although the sequencing between radiation and chemotherapy in this setting has not been established. For patients with negative margins, most NCCN institutions give sequential chemotherapy/RT. For tumors with pN2 and positive resection margins, postoperative concurrent chemoradiation is recommended if the patient is medically fit. Radiation therapy should start earlier, because local recurrence is the most common failure in this group of patients.

Conformal RT with or without chemotherapy should be offered to patients with curable stage I-II NSCLC who are medically inoperable but have reasonable performance status and life expectancy. Modern 3-dimensional conformal RT techniques with CT or CT/positron emission tomography (PET)–based treatment planning should be used on all patients. Both treatment outcome and cost should be considered. In patients receiving RT or chemoradiation with curative intent, treatment interruptions or dose reductions for manageable acute toxicities (i.e., grade 3 esophagitis, hematologic toxicities) should be minimized by conformal treatment planning and aggressive supportive care. RT can be offered to primary or distant sites as palliative care for stage IV patients with extensive metastases.

To avoid postoperative pulmonary toxicity, preoperative chemoradiotherapy should be avoided if at all possible, if pneumonectomy is required. 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 definitive and palliative RT are summarized in the algorithm (see Table 2). Tissue heterogeneity correction should be used in RT treatment planning for all patients. Preoperatively, a dose of 45-50 Gy in 1.8 to 2 Gy fraction size is often recommended. Doses greater than 50 Gy in the preoperative setting have been reported to be safe and achieved favorable survival outcome; however, this should only be performed with an experienced team.

The postoperative RT dose should be based on margin status. After surgery, lung tolerance to RT is remarkably smaller than for patients with intact lungs. Every effort should be made to minimize the [postoperative] dose of RT. Although the dose volume constraints for normal lungs are a useful guide, more conservative constraints should be used for postoperative RT (see Table 3). For definitive RT, the commonly prescribed dose is 60-70 Gy. A dose of 74 Gy or more was associated with better survival in patients treated with radiation alone or with sequential chemotherapy followed by radiation in a retrospective study. The radiation dose is one significant factor for
overall survival in patients with stage I-II after radiation alone\textsuperscript{117} or stage III disease treated with concurrent chemoradiation.\textsuperscript{118} When radiation is given concurrently with chemotherapy, a dose up to 74 Gy may be delivered safely,\textsuperscript{119-121} if the dose to normal structures is strictly limited (see Table 3). 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 per 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.\textsuperscript{122} GTV should be confined to visible tumors (include both primary and nodal diseases) on CT or PET-CT.

In patients who receive postoperative radiotherapy, CTV should consist of the bronchial stump and high-risk draining lymph node stations.\textsuperscript{123} Regarding CTV of nodal regions, elective nodal irradiation (ENI) remains controversial\textsuperscript{124} and should be individualized based on tumor volume, dosimetric parameters of adjacent normal structures, and comorbid conditions. Involved field radiation to high dose without ENI has been shown to allow higher dose radiation with acceptable toxicity and low risk of isolated nodal relapse.\textsuperscript{115, 116, 125-128}

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 largely empirical.\textsuperscript{129-136} For patients receiving postoperative RT, more strict DVH parameters should be considered for lung. The exact limit is unknown for lobectomy cases; mean lung dose should be limited to less than 8.5 Gy in pneumonectomy patients.

**Radiation Simulation, Planning and Delivery**

Treatment planning should be based on CT scans obtained in the treatment position. IV contrast should be used for better target delineation whenever possible, especially in patients with central tumors or with nodal diseases. PET/CT is preferable in cases with significant atelectasis and when IV contrast is contraindicated. PET-CT can significantly improve the target accuracy.\textsuperscript{137}

In patients who receive induction chemotherapy, attempts should be made to obtain a baseline planning CT before induction chemotherapy. If feasible, the initial radiation fields should cover the pre-chemotherapy tumor volume and the cone-down fields should cover the post-chemotherapy tumor volume. However, in patients with compromised lung function or large initial tumor volume, the post-chemotherapy volume can be used to avoid excessive pulmonary toxicity. Photon beam energy should be individualized based on the anatomic location of the tumors and beam angles. 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, 15 MV or 18 MV energies can be considered for more optimal dose arrangement.

In certain situations when a large volume of normal lung is being irradiated or when tumors are located close to critical structures (i.e., spinal cord), intensity modulated radiotherapy (IMRT) may be considered for high-dose radiation to avoid overdose to normal tissues. A significantly lower risk of radiation pneumonitis and improved overall survival have been observed when using IMRT compared to 3-D conformal RT for lung cancer.\textsuperscript{138}
When IMRT is used, the National Cancer Institute (NCI) IMRT guideline should be followed (http://www.rtog.org/pdf_document/NCI_IMRT_Guidelines_2006.pdf). Under strictly defined protocols, proton therapy may be allowed. When IMRT and proton therapy are used, daily image guidance at delivery should be used for quality assurance. Use of the modality of image-guided RT (IGRT) should be based on institutional experience and on the treatment accuracy.

Whenever feasible, respiratory motion should be managed. Acceptable methods of accounting for tumor motion, per the 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-held breath-hold without respiratory monitoring; 4) forced shallow breathing with abdominal compression; and 5) real-time tumor-tracking methods.

Stereotactic Body Radiation Therapy (SBRT)
In patients with stage I NSCLC, SBRT provides a statistically significantly higher 5-year survival than 3-D conformal RT. SBRT can be considered for inoperable stage I patients with node negative peripheral lesions (see Figure 1) that are less than 5 cm in maximal dimension or for limited lung metastasis. SBRT can also be used for brain metastases (see section on “Whole Brain Irradiation and SBRT”). Decisions about whether to recommend SBRT should be based on multidisciplinary discussion.

SBRT fractionation regimens for lung tumors range from one single fraction to 3 fractions, 4 fractions, and 5 fractions (see Table 4). Although the optimal number of fractions may be estimated based on the tumor size and total dose, an accumulated biological equivalent dose (BED) of 100 Gy or more is associated with better survival. The RTOG 0915 trial is currently comparing the outcomes between one single fraction and 4 fractions. SBRT normal tissue dose volume constraints should be strictly followed (see Table 5).

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 recent 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. Patients with stage I NSCLC (n=13) had a 2-year overall survival of 75% (45%–92%).

Whole Brain RT and SBRT
Many patients with NSCLC have brain metastases (30%-50%), which substantially affect their quality of life. Surgery followed by whole brain RT with or without SBRT is a reasonable option for select patients with a single brain metastasis. Patients with a single brain metastasis who cannot tolerate or refuse surgery may be treated with whole brain RT and/or SBRT. Decisions about whether to recommend surgery, whole brain irradiation, SBRT, or combined modality therapy for brain metastases should be based on multidisciplinary discussion, weighing the potential benefit over the risk for each individual patient.
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 SBRT with or without whole brain RT, survival was similar in both groups. In a subset of 92 of these patients who received SBRT 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 SBRT plus whole brain radiation had fewer CNS recurrences but had worse neurocognition when compared with patients receiving SBRT alone.

The role of prophylactic cranial irradiation (PCI) is controversial. Although it closed early because of poor accrual, a recent 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%) although overall survival was not improved. The dose and fractionation of PCI is the same as used for small cell lung cancer (25 Gy in 10 fractions over 2 weeks) (see Small Cell Lung Cancer Guidelines).

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. Currently, concurrent chemoradiation appears superior to sequential therapy for patients with unresectable stage III disease. Surgery is rarely done for patients with stage IV disease. For patients with stage IV disease who have a good PS, platinum-based chemotherapy is beneficial.

Surgery Followed by Chemotherapy
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. 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; \( P < .03 \)) and disease-free survival rate (39.4% versus 34.3% at 5 years; hazard ratio, 0.83; 95% CI, 0.74 to 0.94; \( P < .003 \)) 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. Recent data from the IALT found that after 7.5 years of followup, there were more deaths in the chemotherapy group and that the benefit of chemotherapy decreased over time. However, 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). 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, \( P = .04 \) and relapse-free survival (not reached versus 46.7 months, hazard ratio for recurrence, 0.60; \( P < .001 \)) when compared with observation alone. The 5-year survival rates were 69% and 54%, respectively (\( P = .03 \)).

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. 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. The NCCN guidelines have been revised by deleting certain chemotherapy options for early-stage disease.

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. 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. Adjuvant chemotherapy significantly improved the 5-year overall survival in patients with completely resected stage II and III disease, although no benefit was observed in 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.

Chemoradiation

The major controversies in NSCLC relate to the management of patients with stage IIIA disease. 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. For patients with unresectable stage IIIA or stage IIIB disease, combined modality therapy (chemoradiation) is superior to radiation alone. However, concurrent chemoradiation appears to be superior to sequential therapy. Concurrent chemoradiation has a higher rate of grade 3 or 4 esophagitis than sequential therapy. For patients with negative margins, most NCCN institutions give sequential chemotherapy followed by RT; for patients with positive margins, most NCCN institutions give concurrent chemo/RT with (or without) chemotherapy.
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).119, 194, 195 Other concurrent regimens can also be used, such as cisplatin with gemcitabine, paclitaxel, or vinorelbine.196

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.197 Results from SWOG 9504 have shown a median survival of 26 months and a 5-year survival rate of 29%.198 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.199, 200 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.201

Chemotherapy

For disseminated disease (stage IV) in selected patients with a solitary metastasis, especially a brain metastasis, surgical resection of the metastasis may improve survival.202 Surgical resection of a solitary metastasis located in sites other than the brain remains controversial.

Patients with stage IV disease who have a good PS, benefit from chemotherapy, usually with a platinum-based regimen.177-179 Many drugs are active against stage IV NSCLC. These drugs include the taxanes (paclitaxel, docetaxel), vinorelbine, etoposide, pemetrexed, the camptothecin analogs (irinotecan), and gemcitabine. 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.188,203-206 Phase III randomized trials have shown that many of the platinum-doublet combinations are similar for objective response rates and survival.207, 208 The platinum-doublet regimens differ slightly for toxicity, convenience, and cost; thus, clinicians can individualize therapy for their patients. In spite of the development of new chemotherapy regimens, the prognosis for advanced inoperable lung cancer remains poor. Other carboplatin-based regimens include gemcitabine/carboplatin, docetaxel/carboplatin;203, 209, 210 gemcitabine/docetaxel is another option.211

Note that albumin-bound paclitaxel can be substituted for paclitaxel or docetaxel 1) for patients who have experienced hypersensitivity reactions after receiving paclitaxel or docetaxel despite premedication, or 2) for patients in whom the standard premedications (i.e., dexamethasone, H2 blockers, H1 blockers) are contraindicated.212, 213

Specific targeted therapies have been developed for the treatment of advanced lung cancer.214, 215 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). 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.

Erlotinib was approved by 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 can also be given as first-line therapy in patients with advanced or metastatic NSCLC who have known active EGFR mutation or gene amplification.

A large phase III randomized trial (FLEX) recently 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, \( P = .04 \)).

**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, biologic agents (which were initially 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.

Bevacizumab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., platinum-doublet chemotherapy given with bevacizumab). Likewise, cetuximab (category 1) may be continued beyond 4-6 cycles of initial therapy (i.e., cisplatin, vinorelbine, and cetuximab therapy). Pemetrexed (category 2B) may also be given as continuation maintenance therapy. There are no randomized trials supporting the continuation maintenance of conventional cytotoxic agents beyond 4-6 cycles of therapy.

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. Pemetrexed (category 2B) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy, in patients with histologies other than squamous cell carcinoma. Erlotinib (category 2B) or docetaxel (category 3) may be initiated after 4-6 cycles of first-line platinum-doublet chemotherapy.

**Initial Clinical Evaluation**

The NCCN guidelines begin with a patient who has already been given a pathologic diagnosis of NSCLC. 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, including a pathology review, chest CT (including the upper abdomen and adrenals), a complete blood cell (CBC) and platelet count, and chemistry profile. The panel also recommends that smoking cessation counseling be made available to patients. Based on the initial evaluation, the clinical stage is determined and 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.224-226

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,227 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.

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.228 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.229

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.224 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.230 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).231 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, in 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. 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.

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, stage III, and stage IV diseases to rule out metastatic disease if aggressive combined-modality therapy is being considered.

Initial Therapy
Stage I, Stage IIA, and Stage IIB (T1-2, N1) Disease

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. The principles of surgical therapy are listed in the algorithm.

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 algorithms include 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 determination is made regarding the surgical resectability.

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. The principles of RT and chemotherapy are listed in the algorithm. For patients with negative margins, most NCCN institutions give sequential chemotherapy and radiation (i.e., chemotherapy followed by RT); for patients with positive margins, most NCCN institutions give concurrent chemoradiation with (or without) chemotherapy. 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.

In superior sulcus tumors, among the patients treated by surgery and postoperative radiotherapy with or without concurrent chemotherapy, the overall 5-year survival rate has been approximately 40%. Neoadjuvant concurrent chemoradiation followed by surgical resection of a superior sulcus tumor has demonstrated 2-year survival in the 50% to 70% range. 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 (including mediastinoscopy, mediastinotomy, EBUS-FNA, EUS-FNA, and CT-guided FNA), bronchoscopy, brain MRI, and PET/CT scan; pulmonary function tests (PFTs) should be ordered if not previously done. 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, as defined in the 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. Although definitive concurrent chemoradiation is recommended (category 1), induction chemotherapy with (or without) RT is another option for patients with T1-3, N2 disease. 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. 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%. Intrapulmonary metastases...
have been downstaged in the recent TNM revised staging.\textsuperscript{51, 252, 253}

After surgery, concurrent chemoradiation (if tolerated) is recommended for those with positive margins and chemotherapy is recommended for those with negative margins.

The recommended initial treatment options for patients with separate pulmonary nodule(s) in the contralateral lung include surgery, induction chemotherapy before surgery, or induction chemoradiation before surgery. For unresectable T4, N0-1 tumors without pleural effusion, concurrent chemoradiation (category 1) is recommended followed by chemotherapy (category 3).\textsuperscript{198-200}

In patients with synchronous nodules (either in contralateral lung or ipsilateral 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.

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 by either mediastinoscopy, supraclavicular lymph node biopsy, thoracoscopy, needle biopsy, mediastinotomy, EUS biopsy, or EBUS).\textsuperscript{254, 255}

In addition, PFTs (if not previously done), 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. If these tests are positive, concurrent chemoradiation (category 1) followed by consolidation chemotherapy (category 2B) is recommended.\textsuperscript{198, 200}

For metastatic diseases that are confirmed by PET/CT scan and brain MRI, treatment is detailed in the algorithm.

For patients with T4 extension, N2-3 disease (stage IIIB), 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. If either the contralateral or ipsilateral mediastinal node is positive, the patient needs to be treated with concurrent chemoradiation therapy (category 1), although panel members did not all agree that consolidation chemotherapy (category 2B) should be given after chemoradiation.\textsuperscript{198-200}

**Stage IV Disease**

Pleural or pericardial effusion is a criterion for stage IV, M1a disease. Note that with the revised staging, T4 with effusion has been reclassified as stage IV, M1a.\textsuperscript{51} 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 sanguinous effusion is considered malignant no matter what the results of cytologic examination. If the pleural effusion is considered negative, the algorithm tracks back to the confirmed T and N stage. However, all pleural effusions, whether malignant or not, are associated with unresectable disease in 95% of cases.\textsuperscript{256}

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.

The 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. 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. The 5-year survival rates with such an approach range from 10% to 20%;\(^{214, 257}\) median survival is about 40 weeks.\(^{168}\) Follow-up whole brain RT (category 1) with or without SBRT (category 2B) may be used.\(^{156, 169}\) Stereotactic radiosurgery alone or followed by whole brain radiation is an additional treatment option.\(^{155}\) Such therapy can be effective in patients who have surgically inaccessible brain metastases and in individuals with multiple lesions.\(^{258}\) After their brain lesions are treated, further treatment options for these patients with T1-2, N0-1 or for those with T3, N0 then include 1) surgical resection of the lung lesion followed by chemotherapy (category 2B); 2) SRS (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 3).\(^{259, 260}\) However, resection generated major disagreement among the panel members (category 3).

Some panel members feel that resection of adrenal glands 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); 2) chemoradiation (category 2B); or 3) RT (category 2B). Patients with T1ab, N0 tumors and with negative surgical margins (R0) are observed. 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. If the surgical margins are positive in patients with T2ab, N0 tumors, these patients should have either re-resection with chemotherapy or chemoradiation and chemotherapy.

For patients with T1ab-2ab, N1 or T3, N0 disease and negative surgical margins, the panel recommends 1) chemotherapy (category 1); or 2) chemoradiation (category 3) and chemotherapy for patients with adverse factors (i.e., inadequate mediastinal lymph node dissection, extracapsular spread, multiple positive hilar nodes, and close margins). If surgical margins are positive (T1ab-2ab, N1 or T3, N0), 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
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.

In the case of marginally resectable superior sulcus tumors (T4 extension, N0-1), if the lesion converts to a resectable status following initial treatment, resection is performed and chemotherapy is given. 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 IIIA disease and positive mediastinal nodes (T1-3, N2), if there is no disease progression after initial treatment, patients should be treated with surgery with (or without) chemotherapy (category 2B). 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.

In patients with separate pulmonary nodules in the contralateral lung, the option for adjuvant therapy includes surgery, if initial therapy consisted of induction chemotherapy or induction chemoradiation therapy. If the margins are negative, observation is usually recommended; another option is adjuvant chemotherapy in select patients with or without RT (if not given previously). If the resection margin is positive, RT is given (if not given previously) followed by chemotherapy.

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. For patients with comorbidities or those who cannot tolerate cisplatin, carboplatin combined with paclitaxel can be used. A number of phase II studies have evaluated neoadjuvant chemotherapy for stage III NSCLC, with or without RT, followed by surgery. Three phase III trials have assessed neoadjuvant chemotherapy followed by surgery compared with surgery alone in the treatment of stage III NSCLC. 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. 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. 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). 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. The ANITA trial also found that postoperative RT increased survival in patients with N2 disease who received adjuvant chemotherapy.

Surveillance and Treatment of Recurrences and Metastases
Surveillance
The guidelines suggest routine history and physical examinations every 4 to 6 months in the first 2 years and then annually for patients with stages I to IV disease. 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 this recommendation. PET or brain MRI is not indicated for routine follow-up. Smoking cessation counseling 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 NCCN guidelines include an algorithm for long-term followup care of NSCLC survivors. 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. Palliation of symptoms can be achieved with external-beam RT by reducing tumor size. In addition, various regional therapy options are listed for locoregional recurrences. Resectable local recurrence may be managed by re-resection or external-beam RT. For patients with endobronchial obstruction, relieving airway obstruction may increase survival especially in severely compromised patients and may improve the quality of life. Obstructed airways can be treated with brachytherapy (endobronchial RT), laser treatment, or endobronchial stent placement; these modalities can be used individually or in combination. In addition, photodynamic therapy (PDT) offers a simple and effective alternative to conventional techniques for palliative debridement of endobronchial obstructions in lung cancer patients.

Mediastinal lymph node recurrence should be treated with concurrent chemoradiation (if RT has not been given previously). For superior venal cava (SVC) obstruction, external-beam RT or stent placement is indicated. For severe hemoptysis, several treatment options are recommended (i.e., external-beam RT, brachytherapy, laser therapy, PDT, surgery, or embolization). Ultimately, surgery may be done to remove the bleeding site. After the treatment for the locoregional recurrence, if no further disseminated disease is evidenced, observation or systemic chemotherapy (category 2B) is recommended. However, for observed disseminated disease, systemic chemotherapy and best supportive care should be applied right away, depending on the performance status.

For distant metastases with localized symptoms, diffuse brain metastases, or bony metastasis, palliation of symptoms can be achieved with external-beam RT. In addition, orthopedic stabilization should be performed if patients are at risk of fracture, and bisphosphonate therapy should be considered in patients with bone metastasis. For other solitary metastasis, the treatment guidelines follow the same pathway as that for stage IV, M1b (solitary site) tumors.

In a small subset of patients, recurrence will be suspected only on the basis of positive sputum cytology. In this situation, the guidelines recommend further evaluation with bronchoscopy, hematoporphyrin fluorescence, or autofluorescence. If tumor in situ (Tis) is detected, treatment options include endobronchial laser ablation, brachytherapy, photodynamic therapy, and surgical resection. Alternatively, the patient may be re-bronchoscooped every 3 months. If T1-3 tumors are discovered, the algorithms track back to the appropriate clinical stage. Surveillance may also detect a new lung primary, and these patients should be treated according to the staging findings.

For recurrent and metastatic disease, first-line therapy includes several options for patients with PS of 0-1: 1) chemotherapy (category 1); 2) bevacizumab in combination with chemotherapy for patients who meet the eligibility criteria; 3) cisplatin and pemetrexed (category 1) for patients who meet the eligibility criteria; 4) cetuximab in combination with vinorelbine and cisplatin (category 2B); or 5) erlotinib for EGFR mutation positive patients. Patients with PS of 2 can receive 1) cetuximab in combination with vinorelbine and cisplatin (category 2B) for patients who meet the eligibility criteria; 2) chemotherapy; or 3) erlotinib for EGFR mutation positive patients.
Eligibility criteria for bevacizumab include PS of 0-1, nonsquamous cell histology and no history of hemoptysis. Note that bevacizumab should not be given as a single agent, unless as maintenance if initially used with chemotherapy. Bevacizumab should be given until progression. Any regimen with a high risk for thrombocytopenia and, therefore, possible bleeding should be used with caution when combined with bevacizumab. Previously patients with brain metastases were excluded from receiving bevacizumab because of concerns about CNS hemorrhage; however, recent data suggest that bevacizumab can be used in patients with treated CNS metastases. \(^{273}\)

Eligibility criteria for cisplatin and pemetrexed include PS 0-1, adenocarcinoma or large cell histology (i.e., nonsquamous), and no prior chemotherapy. Panel members disagreed (category 2B) about using cetuximab with cisplatin and vinorelbine, because recent data only showed a slight improvement in survival with the addition of cetuximab (11.3 versus 10.1 months, \(P = .04\)). \(^{220}\) Note that full-dose cisplatin for PS 2 patients should be given selectively.

**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. \(^{216, 274}\) 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. \(^{216}\) 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). Of interest, a recent trial (AVAil) comparing cisplatin/gemcitabine with or without bevacizumab did not show an increase in survival with the addition of bevacizumab. \(^{275, 276}\)

A recent noninferiority trial in 1745 patients with advanced NSCLC (either stage IIIb or IV; most were stage IV) assessed cisplatin plus gemcitabine compared to cisplatin plus pemetrexed. \(^{206}\) 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. \(^{220}\) The response rate was increased with cetuximab (36% versus 29%, \(P = .012\)); there was no difference in progression-free survival. Overall survival was significantly 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.188, 203-206, 209, 210 New agent/non-platinum regimens are reasonable alternatives if available data show activity and tolerable toxicity (e.g., gemcitabine/docetaxel).211 As yet, there is no evidence that one platinum-based regimen is better than any other.207, 208

**Maintenance Therapy**

Patients should be reevaluated for tumor progression with a follow-up CT scan (i.e., after the first or second cycle). 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 (preferred) of chemotherapy or until the disease progresses. Another option for these patients is continuation maintenance therapy with bevacizumab (category 1), cetuximab (category 1), or pemetrexed (category 2B).216, 220 Switch maintenance therapy with pemetrexed (category 2B), erlotinib (category 2B), or docetaxel (category 3) is also an option.222, 223 Observation is another option. Note that pemetrexed is not recommended for patients with squamous histology.

A recent 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.222 Tumor response (P=.001) and progression-free survival (4.3 versus 2.6 months, P<.0001) were increased in patients who received pemetrexed, especially in patients with adenocarcinoma or large cell histology (i.e., nonsquamous). In patients with nonsquamous histology, preliminary results showed increased overall survival with pemetrexed (15.5 versus 10.3 months, P=.002).

**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).278 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.279 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.280, 281 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 cancers 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. 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. Based on recent data, pemetrexed is recommended in patients with adenocarcinoma or large cell histology (i.e., nonsquamous). 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 0-2; erlotinib may be considered for PS 3. Patients receiving erlotinib who have hepatic impairment should be closely monitored during therapy. Erlotinib should be interrupted or discontinued if changes in liver function are severe, such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside the normal range.
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