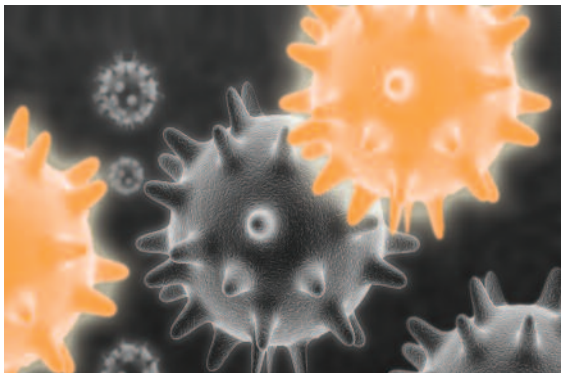

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Contemporary Management of Non-small Cell Lung Cancer

PROGRAM OVERVIEW

Recent scientific discoveries in lung cancer have yielded a wealth of information to clinicians and health care professionals, but they have also increased confusion and produced new challenges and questions. The central issues revolve around which individualized strategies and best practices should be considered when selecting the most appropriate course of management for a particular patient. This judgment requires knowledge, competence, and performance when assessing the appropriate role of alternative strategies, stratification and evaluation of patient-specific characteristics, care coordination between providers, and patient communication and education about all available and emerging options.

This activity reviews the latest concepts in the management of non-small cell lung cancer (NSCLC) and provides tools to assist clinicians responsible for the care of patients with NSCLC.

PREACTIVITY SELF-ASSESSMENT

Please record the answers to the questions below on the Evaluation Form located on page 26.

Based on a scale of 1 = Not confident, 10 = Very confident, consider the educational objectives and then rate how confidently you can…

1. …use histological factors for determining the appropriateness of NSCLC patients for a particular type of therapy
2. …describe results of recent clinical trials that combine targeted therapies with chemotherapy in the treatment of advanced NSCLC
3. …implement strategies that optimize therapeutic decisions for patients based on individual molecular, genomic, and clinical features
4. …choose among different strategies for the treatment of patients with recurrent and progressive disease for improved outcomes

A 53-year-old accountant who is a life-long never-smoker presents to her physician complaining of cough and chest congestion that have steadily worsened over the past 2 months. She also reports generalized fatigue, chest pain, and unexplained weight loss of about 8 pounds over the past few weeks.

5. Which of the following diagnostic tests would you consider to be the most appropriate next step in the management of this patient?
   a) Brain magnetic resonance imaging
   b) Computed tomography scan of the chest, abdomen, and adrenals
   c) Endobronchial ultrasound
   d) Mediastinoscopy
   e) Pulmonary function tests

Further histologic examination confirms that the tumor is adenocarcinoma and is epidermal growth factor receptor (EGFR) mutation positive. The patient demonstrates adequate pulmonary function and good performance status.

6. Considering the results of staging, what is the most appropriate first-line treatment for this patient?
   a) Bevacizumab
   b) Carboplatin
   c) Gefitinib
   d) Erlotinib
   e) Surgery

7. Which of the following treatment modalities has been shown to increase survival in patients with resected early-stage NSCLC?
   a) Adjuvant chemotherapy
   b) Chemoradiotherapy
   c) Intensity modulated radiotherapy
   d) Tomotherapy
   e) All of the above

8. What is the significance of the patient's EGFR–mutation-positive status?
   a) EGFR mutations lead to increased growth-factor signaling
   b) EGFR is a critical gene on the nucleotide excision repair pathway
   c) Specific mutations in the EGFR gene correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib
   d) Screening for EGFR mutations in lung cancers may identify patients who will have a treatment response to certain biologic agents
   e) A and B only
   f) A, C, and D

ELSEVIER CME CONTINUING MEDICAL EDUCATION

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EDUCATIONAL OBJECTIVES

To support the attainment of improved knowledge, competence, and performance, the learner should be able to achieve the following objectives:

1. Use histological factors for determining the appropriateness of a particular type of therapy for a patient with NSCLC
2. Describe results of recent clinical trials that combine targeted therapies with chemotherapy in the treatment of advanced NSCLC
3. Implement strategies that optimize therapeutic decisions for patients based on individual molecular, genomic, and clinical features
4. Choose among different strategies for the treatment of patients with recurrent and progressive disease for improved outcomes

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INTENDED AUDIENCE

This internet enduring activity is intended for oncologists, radiation oncologists, radiologists, thoracic surgeons, and healthcare practitioners who manage patients with non-small cell lung cancer.

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CHAPTER 1 | DIAGNOSIS OF NON-SMALL CELL LUNG CANCER

Lung cancer is the leading cause of cancer-related mortality in the United States.[1] An estimated 22,520 new cases were diagnosed and an estimated total of 157,300 people died from non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC) in 2010.[1] Long-term outcomes associated with lung cancer are poor. Only 15% of patients remain alive ≥5 years after diagnosis. Late diagnosis is one barrier to improved outcomes.[2]

What diagnostic tests should I consider?

Common symptoms of lung cancer include cough, dyspnea, fatigue, weight loss, hemoptysis, and chest pain.[2] In patients with suspected NSCLC, a careful initial diagnostic evaluation is necessary to identify its location and determine the extent of primary and metastatic tumor involvement. Staging, which plays a critical role in selecting treatment, will be described in Chapter 2.

In addition to a careful history, physical examination, and routine laboratory evaluations, several other diagnostic tests are necessary to accurately diagnose and stage NSCLC, including:

- Chest radiograph
- Chest computed tomography (CT) scan
- Positron emission tomography (PET) scan
- Bronchoscopy
- CT-guided needle biopsy
- Mediastinoscopy
- Endobronchial ultrasound (EBUS)
- Endoscopic ultrasound (EUS)

In general, symptoms, physical signs, laboratory findings, or perceived risk of distant metastasis lead to an evaluation for distant metastatic disease. The history, physical examination, screening chemistries, and chest radiograph are limited in the detection of metastases. Thus, other studies, such as CT and PET scans, are necessary for these purposes. Clinical practice guidelines recommend that the CT scan extend inferiorly to include the liver and adrenal glands.[3]

CT scanning of the chest provides anatomic detail; however, the accuracy of chest CT scanning in differentiating between benign and malignant lymph nodes in the mediastinum is poor. PET scanning has much greater sensitivity and specificity than chest CT scanning for staging lung cancer in the mediastinum and detecting distant metastatic disease. With either test, a tissue biopsy, which can be performed with CT guidance, is required to confirm abnormal findings and ensure accurate staging.[4]

Pretreatment specimens can be obtained via bronchoscopy, needle biopsy, endobronchial biopsy, and transbronchial biopsy. Bronchoscopy is the preferred tool for local staging of central lesions and is recommended for the pretreatment evaluation of stages I, II, and IIIA tumors, whereas CT-guided biopsy is recommended for peripheral lesions.[2] The tumor detection rate with flexible bronchoscopy in patients with endoscopically visible lung tumors is high. The addition of cytology-based sampling techniques, such as bronchial washings and brushings, significantly increases the overall diagnostic yield compared with forceps biopsy alone.[5]

Mediastinoscopy is considered the gold standard for evaluating the mediastinal nodes and is a key step in the staging process. Mediastinoscopy is recommended as part of the initial evaluation, especially if imaging results are inconclusive and the probability of mediastinal involvement is high, based on tumor size and location.[2] Additional tests such as bone scan and CT/magnetic resonance imaging (MRI) of the brain may be indicated if initial assessments suggest metastases or if patients with stage III disease are under consideration for aggressive local and combined modality treatments. Brain MRI is recommended for patients with stages II, III, and IV disease to rule out metastatic disease when considering aggressive combined-modality therapy.[2]

EBUS—ultrasound performed within the airways—enables an analysis of the delicate multilayer structure of the tracheobronchial wall. EBUS has emerged as a tool for the staging of more advanced lung cancer, especially with regard to endoluminal, intramural, and extraluminal tumor spread.[6]

EUS allows a precise analysis of the structures beyond the mucosal surface and enables cytologic confirmation of ultrasound findings.[6] It is useful for staging NSCLC in the presence of mediastinal lymphadenopathy and can also be used to detect occult metastases. In this application, EUS complements, but does not replace, mediastinoscopy.[7] However, when assessing the mediastinal nodes to determine which patients are candidates for surgery, EBUS and EUS play an important role. If a mediastinal lesion is accessible by one of these techniques for biopsy, the need to perform mediastinoscopy might decrease substantially with less morbidity for the patients.

Which patients should I screen for NSCLC?

At present, no screening modality for the early detection of NSCLC has been shown to improve outcomes in patients considered at high risk for developing lung cancer.[8] Preliminary findings of newer screening technologies such as low-dose CT scanning and spiral CT scanning suggest that these modalities can detect lung cancer in earlier stages, but do not provide sufficient data to determine whether the newer technologies will result in improved patient outcomes.[9,10] Therefore, screening patients for NSCLC is not yet considered a standard of care.[2]

The National Cancer Institute is currently conducting the National Lung Cancer Screening Trial to compare patient outcomes associated with spiral CT and standard chest radiograph. More than 53,000 current or former smokers have been enrolled in the longitudinal study at more than 30 sites around the United States.[11] Preliminary unpublished data suggest that there may be a benefit in screening high-risk patients; however, the final report of the study will provide the level of evidence required to address this question.

CHAPTER 2 | STAGING NSCLC

How is NSCLC staged?

Disease stage determines treatment and serves as an indicator of prognosis. Early-stage disease at diagnosis has better overall survival at 5 years; a multimodal treatment approach including surgery, chemotherapy, and radiation may be appropriate, depending on the patient's clinical stage.[2]

The anatomic staging system for NSCLC is based on the TNM staging system. In this system, the tumor (T), node (N), and metastasis (M) factors are combined to identify the disease stage. In 2010, the American Joint Committee on Cancer (AJCC) and the Union Internationale Contre le Cancer adopted the Revised International System for Staging Lung Cancer, based on information from a clinical database of more than 5000 patients.[12] The revised system provides greater prognostic specificity for patient groups. It should be noted, however, that the correlation between clinical stage and prognosis predates the widespread availability of PET imaging.

The revised staging system redefines the primary tumor and metastasis classifications. In addition, a new international lymph node map defining the anatomic boundaries for lymph node stations has been developed.[12] In the new staging system, locally advanced disease is classified as stage III and advanced disease is now stage IV.

Because this new staging system is based on a much larger sample than was the previous edition, it is more accurate and incorporates changes that were awaited. Some of these changes include the role of pleural effusion with poor prognosis, which was moved from stage IIIB to IV, and multiple lesions in the same lobe, which are now classified as T3 rather than T4 because of the potential for a better prognosis.

Table 1 defines the primary tumor categories. **Table 2** identifies the regional lymph node classifications. **Table 3** delineates the distant metastasis categories. **Table 4** shows the stages based on the combination of T, N, and M factors.

Table 1. Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings, but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor ≤3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (ie, not in the main bronchus)*
T1a	Tumor ≤2 cm in greatest dimension
T1b	Tumor >2 cm but ≤3 in greatest dimension
T2	Tumor >3 cm but ≤7 cm or tumor with any of the following features (T2 tumors with these features are classified T2a if ≤5 cm):
	Involves main bronchus
	≥2 cm distal to the carina
	Invades visceral pleura (PL1 or PL2)
	Associated with atelectasis or obstructive pneumonitis that extends to the hilar region, but does not involve the entire lung
T2a	Tumor >3 cm but ≤5 cm in greatest dimension
T2b	Tumor >5 cm but ≤7 cm in greatest dimension
T3	Tumor >7 cm or one that directly invades any of the following:
	Parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, or parietal pericardium
	Tumor in the main bronchus (<2 cm distal to the carina* but without involvement of the carina)
	Associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following:
	Mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or separate tumor nodule(s) in a different ipsilateral lobe

* 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 T1a.

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Table 2. Regional Lymph Nodes (N)

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

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Table 3. Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe or tumor with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis

* Most pleural (and pericardial) effusions with lung cancer are caused by tumors. In a few patients; however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, the fluid is not bloody and it is not an exudate. If 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 having M0 disease.

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Table 4. Lung Cancer Staging and Prognostic Groups

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

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CHAPTER 3 | PATHOLOGY

What is the histologic classification of NSCLC?

The World Health Organization (WHO) classifies lung cancer into 2 histologic categories: NSCLC and SCLC. NSCLC is the most predominant type, accounting for about 85% of all lung cancer cases.[13] NSCLC is further delineated into 2 major cell types[2]:

- Squamous cell (epidermoid) carcinoma
- Nonsquamous carcinoma, which includes adenocarcinoma, large-cell carcinoma, and other cell types

The WHO classification system for NSCLC was updated in 1999.[14] The New WHO/International Association for the Study of Lung Cancer Histologic Classification of NSCLC appears in **Table 5**. In the

Table 5. WHO/International Association for the Study of Lung Cancer Histologic Classification of NSCLC

Classification	Subclassification	Sub-subclassification
Squamous cell carcinoma	Papillary	
	Clear cell	
	Small cell	
	Basaloid	
Adenocarcinoma	Acinar	
	Papillary	
	Bronchioalveolar carcinoma	• Nonmucinous • Mucinous • Mixed mucinous and nonmucinous or indeterminate cell type
	Solid adenocarcinoma with mucin	
	Adenocarcinoma with mixed subtypes	
	Variants	• Well-differentiated fetal adenocarcinoma • Mucinous (colloid) adenocarcinoma • Mucinous cystadenocarcinoma • Signet ring adenocarcinoma • Clear cell adenocarcinoma
Large cell carcinoma	Variants	• Large-cell neuroendocrine carcinoma • Combined large-cell neuroendocrine carcinoma • Basaloid carcinoma • Lymphoepithelioma-like carcinoma • Clear cell carcinoma • Large cell carcinoma with rhabdoid phenotype
Adenosquamous carcinoma		
Carcinomas with pleomorphic, sarcomatoid, or sarcomatous elements	Carcinomas with spindle and/or giant cells	
	Spindle cell carcinoma	
	Giant cell carcinoma	
	Carcinosarcoma	
	Pulmonary blastoma	
Carcinoid tumor	Typical carcinoid	
	Atypical carcinoid	
Carcinomas of salivary-gland type	Mucoepidermoid carcinoma	
	Adenoid cystic carcinoma	
	Others	
Unclassified carcinoma		

United States, the most common type of NSCLC is adenocarcinoma; this is also the most frequent cell type among nonsmokers.[2]

Why is the histologic classification of NSCLC important?

Pathologic examination of the tumor is necessary to delineate cell type, determine extent of invasion, and detect any molecular abnormalities of the lung cancer that may influence treatment decision and prognosis. Therefore, before patients begin treatment, it is critical that an experienced pathologist review the pathologic material and determine the histologic classification.

Histologic determination is important because, in the contemporary management of NSCLC, histology drives treatment. Treatment for nonsquamous carcinomas of the lung is very different from that for squamous cell carcinomas. For example, certain agents such as pemetrexed (an antifolate agent) and bevacizumab (a chimeric monoclonal antibody against vascular endothelial growth factor ligand) are approved only for the treatment of nonsquamous cell carcinomas.[13,15] Histology is also important because treatment for SCLC differs from that for NSCLC. SCLC is treated with a different chemotherapy regimen and is generally not treated surgically. In comparison, surgery is the first-line treatment for patients with early-stage NSCLC.[2]

CHAPTER 4 | TREATMENT FOR STAGES I–II NSCLC—SURGERY

For which patients is surgery most appropriate?

Surgery is the first-line option for patients in the early stages of NSCLC, stages I–II, provided that the patient has adequate pulmonary function reserve and that risk for surgical resection is acceptable. This group of patients generally has the best prognosis compared with those who cannot undergo surgery.[16] For patients with stage I and II disease who cannot undergo surgery, conformal radiotherapy is an option.[2] Chapter 5 provides a review of radiotherapy options.

The objective of any surgical approach is to obtain complete surgical resection of the tumor. Surgery can be a potentially curative therapeutic option in the early stages of NSCLC.

What are the different surgical therapeutic options available?

Surgeons may remove all or only a portion of a lobe or lung depending on the extent of disease and the patient's overall medical condition and cardiopulmonary status.[2] In patients who have the pulmonary capacity to tolerate such surgeries, lobectomy and pneumonectomy are preferred over limited-excision approaches, such as segmentectomy and wedge resection.[16] Data from clinical studies of patients with stage I NSCLC show a reduction in the rate of local recurrence for patients treated with lobectomy compared with limited-excision approaches.[17,18]

Patients with early-stage NSCLC who have comorbidities and/or impaired pulmonary function and cannot tolerate lobectomy or pneumonectomy are candidates for segmental or wedge resection of the primary tumor.[16]

Are the mediastinal lymph nodes also removed during pulmonary resection?

Current clinical practice guidelines recommend mediastinal lymph node dissection or systemic lymph node sampling in all patients.[2] The question of whether the mediastinal lymph nodes should be sampled or completely removed during pulmonary resection in patients with stage I and stage II NSCLC has been the subject of several studies. Data from a pooled analysis of 3 trials showed that 4-year survival was superior when patients underwent resection and complete mediastinal lymph node dissection compared with resection and lymph node sampling.[19] A randomized trial sponsored by the American College of Surgeons Oncology Group (ACOSOG 0030) is underway to determine whether complete mediastinal lymph node dissection or lymph node sampling improves overall survival in patients undergoing pulmonary resection for N0 or nonhilar N1 NSCLC. The preliminary results of this trial indicated no difference in operative mortality based on lymph node procedure.[20] Although both lymph node dissection and sampling are safe procedures

that provide critical staging information, at this point in time, evidence is lacking to recommend one technique rather than the other for patients with early-stage NSCLC.[16]

What is the role of video-assisted thoracic surgery?

Traditional open thoracotomy and lobectomy require a large, 8- to 10-inch incision and are commonly associated with substantial blood loss and a lengthy recovery. Video-assisted thoracic surgery (VATS) is a minimally invasive procedure emerging as a surgical alternative to open thoracotomy and lobectomy for patients with resectable lung cancer. VATS incorporates a thoracoscope inserted into the chest via small incisions to transmit images. The thoracoscope enables the surgeon to visualize structures within the chest clearly and precisely.

Compared with open lobectomy, patients undergoing video-assisted lobectomy had fewer respiratory complications and shorter length of stay.[21,22] In patients with stage I NSCLC, survival rates (5-year and overall) and recurrence rates for VATS with lymph node dissection were comparable with those of routine open pulmonary resection.[23,24] Based on these favorable outcomes, VATS is considered a reasonable approach for patients with resectable NSCLC who have no contraindications.[2]

Is robotic surgery an option for patients with resectable NSCLC?

Three-dimensional (3D) robotic surgery represents another surgical advance in the treatment of patients with resectable NSCLC. The use of robotic surgical systems enables a minimally invasive, less traumatic approach to thoracic surgery and offers an enlarged and enhanced 3D view inside the chest cavity, as well as improved maneuverability.

Although data from randomized comparative trials are lacking, potential benefits versus open lobectomy include shorter hospital stay, less pain, faster recovery, and faster return to everyday activities.[25] Conversely, robot-assisted surgery increases operating room time and adds cost for use of the robotic instrumentation. The technique is still evolving and requires further study in clinical trials before it can be routinely adopted in clinical practice.[26]

Does adjuvant chemotherapy improve survival in patients with resected early-stage NSCLC?

Although surgery provides the best chance for a cure for patients with early-stage NSCLC, adjuvant chemotherapy has been shown to increase survival in patients with resected early-stage NSCLC. Several landmark clinical trials provide evidence that adjuvant cisplatin-based chemotherapy extends long-term survival in patients with resected NSCLC.

The randomized controlled Adjuvant Navelbine International Trialist Association (ANITA) and JBR 10 trials compared the effectiveness of adjuvant vinorelbine plus cisplatin versus observation in patients with early stage NSCLC.[27,28] ANITA enrolled patients with stage IB to stage IIIA NSCLC; JBR 10 enrolled patients with stage IB to stage II NSCLC. In ANITA, adjuvant chemotherapy significantly improved survival for patients with completely resected stage II and stage III NSCLC, but not for patients with stage IB NSCLC. Updated results for JBR 10 indicated that after 9 years of follow-up, adjuvant cisplatin-based chemotherapy was associated with improved survival among patients with stage II but not stage IB NSCLC. In addition, no increase in death from other causes was reported in patients who received chemotherapy.[29]

The International Adjuvant Lung Cancer Trial reported similar findings in patients with resected stage I, stage II, and stage III NSCLC.[30] At 5 years, patients with resected NSCLC who received adjuvant chemotherapy had a significantly higher survival rate and longer disease-free survival than those who were merely observed. Nonetheless, after 7.5 years of follow-up, more deaths were reported among patients treated with adjuvant chemotherapy and the benefits of adjuvant therapy decreased over time.[31] To date, it is not clear why this phenomenon occurs.

The Cancer and Leukemia Group B 9633 trial compared paclitaxel plus carboplatin with observation in patients with stage IB NSCLC.[32] Although initial results suggested that adjuvant chemotherapy were associated with improved overall survival in patients with stage I NSCLC, updated results did not confirm a survival benefit. A subset analysis, however, indicated a benefit for tumors >4 cm.[33]

In the Lung Adjuvant Cisplatin Evaluation, a pooled analysis of more than 4000 patients, cisplatin-based chemotherapy administered postoperatively was associated with increased 5-year survival (absolute benefit of 5.4%). Patients with stage II and stage III disease and good performance status had the greatest benefit.[34] Based on these results, the National Comprehensive Cancer Network recommends paclitaxel plus carboplatin regimens only for patients who cannot tolerate cisplatin-based therapy.[2]

CHAPTER 5 | TREATMENT FOR STAGE III NSCLC—RADIATION AND CHEMOTHERAPY

For which patients is radiation therapy appropriate?

Radiation therapy combined with chemotherapy (concurrent chemoradiotherapy) is a standard of care for patients with stage IIIA NSCLC who have inoperable or unresectable carcinomas. Patients classified as having stage IIIA disease after surgery (pathological stage) may still benefit from adjuvant chemotherapy, as described in Chapter 4.

Radiation therapy after surgery is controversial but is generally reserved for patients with bulky disease in the mediastinal (N2) nodes or multiple lymph node involvement, as long as the patient is medically fit.

For patients with stage IIIB NSCLC who are usually not surgical candidates, chemotherapy alone or the combination of radiation and chemotherapy is recommended. Induction chemotherapy and/or radiation followed by surgery and adjuvant chemotherapy can also be considered in accordance with clinical practice guidelines.[2]

How is radiotherapy delivered?

Radiation therapy uses high-energy radiation to decrease the size of the tumors and kill cancer cells. The radiation may be delivered by a machine outside the body (external-beam radiation therapy), or it may come from radioactive material inserted into the body near the cancer cells (internal radiation therapy, also called brachytherapy).

In the management of NSCLC today, most radiotherapy is delivered using modern 3-dimensional conformational radiotherapy (3D-CRT) techniques that incorporate CT or PET-based treatment planning.[2] Such imaging enables an exact measurement of the size and location of the tumor and surrounding healthy tissue. These measurements determine the amount of radiation that needs to be aimed at the tumor, allowing higher doses of radiation to be delivered more accurately to the tumor while reducing the amount of radiation received by nearby healthy tissues.[35]

What is stereotactic body radiation therapy?

Stereotactic body radiation therapy (SBRT) is a noninvasive approach to the delivery of radiation that incorporates linear accelerator technology plus robotic and image guidance. Radiation is delivered externally via a linear accelerator mounted on a robotic arm. SBRT uses a large intense radiation beam that is redirected in many arcs to lessen the adverse effects on healthy tissue. Image-guidance technology tracks the patient and the tumor during treatment, adjusting the radiation beams after a short lapse if there is movement from the patient. Although SBRT can be administered as a one-session treatment, it is more commonly delivered as a fractionated treatment over time. Physicians often refer to SBRT by the brand names of the equipment, such as the CyberKnife®.[36]

SBRT is suitable for patients with inoperable stage I NSCLC with node-negative peripheral lesions <5 cm and for lung and brain metastases in patients with stage IV NSCLC.[2]

What is intensity modulated radiotherapy?

Intensity modulated radiotherapy (IMRT) is another high-precision method of delivering radiation to patients with cancer. IMRT uses hundreds of small radiation beam-shaping collimators to deliver a single dose of radiation. The collimators can be stationary or can move during treatment, allowing the intensity of the radiation beams to change during treatment sessions. This dose modulation allows different areas of a tumor or nearby tissues to receive different doses of radiation.

IMRT is carefully planned by using 3D CT images of the patient in conjunction with computerized dose calculations to determine the dose-intensity pattern

that best conforms to the tumor shape. Combinations of several intensity-modulated fields coming from different beam directions can be used to produce a custom tailored radiation dose.

IMRT is recommended when a large volume of normal lung tissue must be irradiated, or when tumors are located close to vital structures, such as the spinal cord.[2] Compared with 3D-CRT, IMRT is associated with a significantly lower risk of radiation pneumonitis and improved overall survival.[37]

What is tomotherapy?

Tomotherapy is a type of image-guided IMRT that is currently considered experimental. A tomotherapy machine is a hybrid between a CT imaging scanner and an external-beam radiation therapy machine. The part of the tomotherapy machine that delivers radiation for both imaging and treatment can rotate completely around the patient in the same manner as a normal CT scanner. Tomotherapy machines can capture CT images of the patient's tumor immediately before treatment sessions to allow for precise tumor targeting and sparing of normal tissue.

What concomitant chemotherapy treatments are offered to patients with stage III NSCLC?

For patients with stage III NSCLC, research suggests that concurrent chemoradiotherapy may produce better results than does radiotherapy alone.[38,39] Furthermore, this combined modality appears to result in better outcomes than sequential therapy.[40]

Based on the results of several key clinical studies, the best chemotherapeutic regimen for patients with stage III NSCLC is the combination of cisplatin and etoposide. Two important trials provide evidence supporting this regimen.

Southwest Oncology Group 9504 was a phase II trial that examined consolidation docetaxel after concurrent chemoradiation with cisplatin and etoposide in patients with stage IIIB NSCLC. Median survival was 26 months and 1-, 2-, and 3-year survival rates were 76%, 54%, and 37%, respectively.[41] The 5-year survival rate was 29%.[42]

The Hoosier Oncology Group trial was a phase III study that examined the role of cisplatin, etoposide, and concurrent radiation with or without consolidation docetaxel in patients with stage III NSCLC.[43] Median survival for all patients was 22 months. Patients treated with consolidation docetaxel did not show a survival advantage, but they did experience increased toxicities.

Because many patients with this stage of disease are elderly, have poor performance status, or are not good candidates for cisplatinum-based therapy, it is common practice in the United States to give a combination of carboplatin and a taxane (eg, paclitaxel or docetaxel) as a chemotherapy regimen used for radiosensitization. These regimens have not been compared in a phase III trial with cisplatin/etoposide.

CHAPTER 6 | TREATING ADVANCED NSCLC

What options are available for patients with newly diagnosed advanced (stage IV, metastatic) NSCLC and patients who had early stages (I-III) and failed chemotherapy, radiation, and/or surgery?

Chemotherapy, especially platinum-based regimens, can extend survival in patients with stage IV NSCLC and those who had early-stage disease and failed chemotherapy, radiation, and/or surgery but who have good performance status. The prognosis for patients with advanced NSCLC is poor; however, despite the inclusion of newer agents into the treatment paradigm. Before initiating treatment, it is important to determine tumor histology.

Specific agents, which can be used alone or as combination regimens, include the following:

- Paclitaxel
- Docetaxel
- Vinorelbine
- Etoposide
- Pemetrexed
- Irinotecan
- Gemcitabine
- Erlotinib
- Gefitinib
- Bevacizumab

In patients with advanced NSCLC, combination regimens are generally associated with better results than are single agents and can result in 1-year survival rates of 30% to 40%.[2] Combinations found in clinical trials to be beneficial in patients with advanced NSCLC include carboplatin-paclitaxel, cisplatin-paclitaxel,

cisplatin-gemcitabine, cisplatin-vinorelbine, cisplatin-pemetrexed, and cisplatin-docetaxel.[15,44,45] Many of these combination regimens offer similar results, allowing physicians to individualize treatment based on the patient's performance status and comorbidities, systemic first-line therapy, and tumor histology.

Two biologic therapies, erlotinib and bevacizumab, are now approved for the treatment of NSCLC in the United States. Erlotinib, a once-daily oral agent, is a small-molecule inhibitor of tyrosine kinase activity of the epidermal growth factor receptor (EGFR) signaling pathway. Bevacizumab blocks the vascular endothelial growth factor and has been shown to extend survival in patients with nonsquamous NSCLC. When added to a regimen of paclitaxel and carboplatin, bevacizumab improved overall survival, progression-free survival, and response rate in patients with recurrent or advanced NSCLC (stage IIIB or IV) compared with paclitaxel and carboplatin alone.[13] That discovery was a milestone in the treatment of lung cancer because it was the first time median survival for advanced NSCLC that surpassed 12 months. One-year survival rates were 51.9% for the bevacizumab group and 43.7% for the chemotherapy-alone group. However, another clinical trial that compared cisplatin plus gemcitabine with or without bevacizumab showed no increase in survival with the addition of bevacizumab.[46]

An investigational agent with the potential for increasing survival in patients with advanced disease is cetuximab, a chimeric monoclonal antibody targeting EGFR. In the First-Line ErbituX (FLEX) in Lung Cancer trial, cetuximab combined with cisplatin/navelbine chemotherapy followed by maintenance therapy with single-agent cetuximab was associated with improved overall survival in chemotherapy-naive patients (≥18 years) with advanced *EGFR*-expressing histologically or cytologically proven stage wet IIIB or stage IV NSCLC.[47] At the present time, this agent has not been approved by the US Food and Drug Administration (FDA) or the European Medicines Agency.

Chapter 7 provides details on other emerging targeted therapies for NSCLC.

Is maintenance therapy an option for patients with advanced stage NSCLC?

Maintenance therapy can be offered to patients with tumor response or stable disease that has not progressed. Both erlotinib and pemetrexed are options for maintenance therapy shown to extend survival compared with placebo in patients with advanced NSCLC.

In the Sequential Tarceva in Unresectable NSCLC (SATURN) trial, erlotinib single-agent maintenance therapy was associated with extended survival, compared with placebo, among patients with stage IIIB and stage IV NSCLC whose disease did not progress after first-line treatment with platinum-based chemotherapy.[48] Mean overall survival was 12 months for erlotinib and 11 months for placebo. Furthermore, there was a 90% decrease in mortality (hazard ratio = 0.10) among patients whose tumors harbored EGFR mutation and received erlotinib. Patients receiving erlotinib also experienced more adverse events, such as rash and diarrhea; however, their quality of life did not appear to be negatively affected by the drug.

The JMEN study compared pemetrexed with placebo in patients with stage IIIB and stage IV NSCLC who had experienced disease progression after 4 cycles of platinum-based chemotherapy. None of the patients in this trial had received pemetrexed as part of their original treatment. Mean overall survival for patients with nonsquamous NSCLC was 15.5 months with pemetrexed and 10.3 months with placebo. In contrast, mean overall survival for patients with squamous NSCLC was 9.9 months with pemetrexed and 10.8 months with placebo. Moreover, a subanalysis based on histologic subclassification revealed that overall survival for patients with adenocarcinoma was 16.8 months.[49]

What agents are used for second-line chemotherapy and beyond?

In patients with advanced NSCLC, a number of agents are available as second-line therapy and beyond. Although these drugs are generally considered to provide better results than best supportive care, response rates are around 10%.[2] The greatest questions facing oncologists in clinical practice are when to

initiate second-line therapy and to which patients it should be offered. No consensus has been reached about whether it is better to initiate second-line chemotherapy immediately or to adopt a watchful-waiting approach until disease progression.[50]

Based on the results of several randomized clinical trials, the NCCN advocates 3 agents for second-line chemotherapy: docetaxel, pemetrexed (nonsquamous histology only), and erlotinib.[2] **Table 6** summarizes these trials.

CHAPTER 7 | EMERGING TREATMENTS FOR NSCLC

What new treatments for NSCLC other than pharmacotherapy are on the horizon?

The poor outcomes associated with conventional cytotoxic therapy for NSCLC have led clinicians to investigate other approaches that may extend survival and improve patient's quality of life. Although still considered experimental, less-invasive approaches emerging as treatment options for selected patients with NSCLC include the following:

- Radiofrequency ablation (RFA)
- Laser
- Cryoablation
- NanoKnife

For which kind of patients is radiofrequency ablation a reasonable option?

In RFA, the clinician uses imaging techniques such as ultrasound, CT, or MRI to guide a needle electrode into a cancerous tumor. High-frequency electrical currents then pass through the electrode, creating high temperatures that destroy the abnormal cells. RFA is generally performed in one visit.

RFA is emerging as a potential option for patients with early-stage NSCLC and negative lymph nodes who either decline surgery or are not surgical candidates because of poor performance status,

Table 6. Randomized trials supporting docetaxel, pemetrexed, and erlotinib as second-line chemotherapy

Trial	Patients (n)	Treatments	Response Rates (Complete and Partial)	1-Year Survival Rates	Comments
TAX 320[51]	373	Docetaxel 100 mg/m^2 Docetaxel 75 mg/m^2 Vinorelbine/ Ifosfamide	10.8% 6.7% 0.8%	32% 32% 19%	Patients treated with docetaxel 100 mg/m^2 had more AEs and 2 treatment-related deaths
TAX 317[52]	203	Docetaxel 100 mg/m^2 Docetaxel 75 mg/m^2 Best supportive care	6.3% 5.5% –	19% 37% 19%	5 reports of toxic deaths in docetaxel arm
Hanna et al 2004[53]	571	Pemetrexed 500 mg/m^2 Docetaxel 75 mg/m^2	9.1% 5.8%	29.7% 29.7%	Pemetrexed associated with significantly fewer side effects
Shepherd et al 2005[54]	731	Erlotinib 150 mg/d Placebo	8.9% <1%	29.7% 20.5%	Similar rates of pneumonitis and pulmonary fibrosis in both groups; increased risk of infection in erlotinib group, which may reflect longer follow-up

AEs = adverse events

comorbid medical conditions, significant cardiovascular risk, and/or poor pulmonary function. Patients with smaller isolated tumors (<3 cm) are considered good candidates for this approach.[2] RFA can also be considered as a palliative option to reduce tumor size in preparation for chemotherapy or radiation therapy, or to provide relief when a tumor causes pain and discomfort.

One clinical study assessed outcomes of 153 patients with stage I NSCLC who underwent CT-guided RFA, including 116 primary lung cancers and 73 metastases to the lung from other cancers. The majority of patients, who ranged in age from 17 to 94 years, also suffered from severe cardiopulmonary disease. For patients with stage I NSCLC, the 1-, 2-, 3-, 4- and 5-year survival rates were 78%, 57%, 36%, 27% and 27%, respectively.[55]

What is the role of lasers in the treatment of NSCLC?

Several laser types are used in the endobronchial management of NSCLC, including the neodymium: yttrium-aluminum-garnet (Nd:YAG), potassium-titanyl-phosphate (KTP), and carbon dioxide (CO2). The laser most commonly used endoscopically is the Nd:YAG laser.

Nd:YAG lasers result in the predominant effects of thermal necrosis and photocoagulation. Thermal necrosis uses higher energy levels to destroy tumor tissue. Most lung tumors; however, are quite vascular. In destroying tissue via laser, blood vessels can also be destroyed or perforated, leading to hemorrhage and an associated increase in morbidity and mortality.

Alternatively, lower levels of laser energy result in photocoagulation. By using lower energy levels, the surface of the tumor becomes heated; this causes tumor shrinkage and diminishes blood flow to that region. Such devascularization of the tumor enables more rapid mechanical debulking with improved control of bleeding.[56]

An experimental application of lasers in the treatment of patients with NSCLC is photodynamic therapy (PDT). PDT involves the use of an FDA-approved drug, photofrin, which is absorbed by tumors in high concentrations. When that drug is exposed to light from a cold laser, it destroys tumors without harming surrounding tissue. PDT may be curative for patients with NSCLC whose tumors are still small and confined to the airway. In addition, PDT can provide palliative relief to patients with advanced cancer who have difficulty breathing because of tumors blocking the airway.[57]

What is the application of cryoablation in NSCLC?

Cryoablation is another image-guided, noninvasive approach that has been applied to patients with NSCLC. Originally used as a palliative treatment for patients with advanced-stage NSCLC with inoperable tumors, cryoablation is now being applied to patients with early-stage disease.[58]

Cryotherapy employs liquid nitrogen or, more commonly, a nitrous oxide–driven probe to cool the tumor and the immediately surrounding tissue. Multiple freezing and thawing cycles result in tissue necrosis. Because the effects of cryotherapy are delayed, this approach is not indicated to achieve immediate debulking of an obstructive tumor. It can be used to treat in situ or microinvasive carcinomas.[58]

How does the NanoKnife destroy lung cancer cells?

The NanoKnife generates an electric field that can be precisely targeted to create holes in tumor cells without damaging adjacent organs. The minimally invasive procedure, known as irreversible electro-poration, uses an electric current rather than high temperatures or freezing to permanently open cell membrane pores in the tumor. Once the cell membrane pores are opened, the tumor cells begin to die.

During the procedure, the clinician inserts the NanoKnife probes into the tumor using image guidance. Once in place, the NanoKnife probes deliver high-voltage electrical pulses through the tumor. The tumor cells open their microscopic pores permanently in response to the electrical pulses. This ultimately causes the cells to die, dissolve, and be removed by the body's natural processes. The precision of the NanoKnife allows physicians to treat tumors that previously would have been difficult or impossible to resect because of their location.

Which emerging targeted therapies should I be aware of?

The term *targeted therapy* refers to agents that exert their effect via specific targets that are involved in cell-cycle regulation, proliferation, and tumor growth. By focusing on molecular and cellular changes that are specific to cancer, targeted cancer therapies may be more effective than other types of treatment with a better toxicity profile, thus causing less harm to normal cells. With the use of targeted therapies, physicians may have the choice to individualize or personalize treatment based on the patient's unique set of molecular targets—in other words, to target a specific patient's phenotype. By minimizing the side effects from conventional chemotherapies, patients' quality of life is expected to improve considerably.

Although certain targeted therapies such as gefitinib and erlotinib are already approved for NSCLC, many others are under investigation in clinical trials as second- or third-line therapies in patients with NSCLC, including sorafenib, sunitinib, BIBW2992, BIBF1120, SAHA, and many others.

Sorafenib is a small-molecule tyrosine kinase inhibitor (TKI) currently approved for the treatment of advanced renal cell carcinoma and some cases of hepatocellular carcinoma. Sorafenib has been shown to inhibit one of the kinases involved in the signaling pathway that is initiated when vascular endothelial growth factor (VEGF) binds to its receptors. This halts angiogenesis. In addition, sorafenib blocks an enzyme involved in cell growth and division. In the phase III Evaluation of Sorafenib, CArboplatin and Paclitaxel Efficacy (ESCAPE) in NSCLC trial, sorafenib failed to demonstrate benefit as first-line therapy. Other ongoing trials are evaluating whether single-agent sorafenib is beneficial in patients with recurrent NSCLC. Several phase I and phase II studies are examining the use of sorafenib in combination with conventional chemotherapy and other biologic agents.[59]

Sunitinib is another small-molecule TKI approved for the treatment of patients with metastatic renal cell carcinoma or gastrointestinal stromal tumor that is not responding to imatinib. Sunitinib inhibits multiple protein kinases involved in VEGF signaling; thereby, inhibiting angiogenesis and cell proliferation. Results from a phase II trial evaluating sunitinib as monotherapy in 64 patients who had refractory NSCLC showed a 9.5% partial response rate, 43% stable disease, progression-free survival of 11.3 weeks, and overall survival of 23.9 weeks.[60] Additional studies are currently evaluating sunitinib in combination with chemotherapy in patients with NSCLC.[59]

BIBW 2992 is a small molecule that targets the growth factor receptors human epidermal receptor (HER) 1 and HER 2. The compound's mechanism of action is distinctive in that it irreversibly binds to the receptor. LUX-Lung 2 is a phase II trial evaluating BIBW 2992 in patients with stage IIIB or stage IV NSCLC and EGFR mutations in exons 18 through 21 (by direct sequencing) who are treatment naive or who experienced disease progression after first-line chemotherapy. In the initial results reported in 2010, tumor size reduction was observed in 90% of patients. Median progression-free survival was estimated to be 12 months for the overall group.[61]

Suberoylanilide hydroxamic acid (SAHA) is a histone deacetylase inhibitor (HDAC) that demonstrates antitumor activity in NSCLC *in vivo*. Evidence from preclinical trials suggests that HDAC inhibitors, including SAHA, inhibit tumor repair of DNA double-strand breaks, which potentiates the cytotoxicity of radiation in solid tumors. At this time, SAHA is approved for the treatment of cutaneous T-cell lymphoma in patients with progressive, persistent, or recurrent disease on or following 2 systemic therapies. SAHA is currently under investigation in combination with radiotherapy in patients with stage III and stage IV NSCLC.[62]

CHAPTER 8 | THE ROLE OF MOLECULAR MEDICINE IN NSCLC TREATMENT

Can genetic biomarkers be used to individualize treatment?

Recent advances in tumor biology have identified genetic markers and mutations that play a role in disease progression and correlate with clinical responsiveness to certain treatment regimens. These discoveries have, in turn, led to the development of

novel biologic agents that target specific tumorigenesis pathways and have the potential to improve survival in patients with NSCLC.

The identification of genetic markers has the potential to enable oncologists to better individualize treatment using agents that induce better responses and a more suitable toxicity profile. Agents such as erlotinib have evolved into first-line treatment for NSCLC.

The following molecular markers are influencing the treatment of patients with NSCLC:

- *EGFR* mutation
- *Excisional repair cross-complementing group 1 (ERCC1)* gene mutation
- *Ribunucleotide reductase M-1 (RRM1)* gene mutation
- Thymidilate synthetase (TS) mRNA levels

At the present time, most of the evidence for these markers comes from retrospective data, and current treatment guidelines do not yet recommend using these markers to dictate treatment. However, as data accumulate, these markers may play an important role in treatment selection.

What effect does the EGFR mutation have on treatment?

The *EGFR* gene, a member of the HER family, is one of the most studied carcinogenesis pathways in NSCLC. A subgroup of patients with NSCLC has specific mutations in the *EGFR* gene that correlate with clinical responsiveness to the TKI gefitinib. These mutations lead to increased growth factor signaling and confer susceptibility to the TKI.

EGFR has been targeted either by monoclonal antibodies that block the receptor (eg, cetuximab) or by small molecules that inhibit the intracellular domain of the receptor (eg, erlotinib, gefitinib). Screening for *EGFR* mutations in lung cancers may identify patients who will have a treatment response to these biologic agents.[63–65] Today, TKIs that target *EGFR* have become the standard of care as first-line therapy for patients whose tumors harbor *EGFR* mutations. Recently, Zhou et al[66] presented the final results of the OPTIMAL trial, in which all patients who were randomized to either cisplatin/gemcitabine or erlotinib had an EGFR mutation. Progression-free survival was 3-fold higher for those who received erlotinib (13.1 months vs 4.6 months; hazard ratio = 0.16; P <0.0001); objective response rates were 83% and 36% for those treated with erlotinib and cisplatin/gemcitabine, respectively (P <0.0001). Overall survival data are not yet available.[66]

What is the clinical importance of the ERCC1 mutation?

ERCC1 gene mutations influence survival and toxicity associated with cisplatin-based chemotherapy and are potentially important predictors of outcome with these regimens in NSCLC. Patients with completely resected early-stage NSCLC and *ERCC1*-negative tumors seem to benefit from adjuvant cisplatin-based chemotherapy, whereas patients with *ERCC1*-positive tumors do not.

Although platinum has long been the mainstay of chemotherapy for lung cancer, it is associated with cytotoxicity that results from the disruption of the double-stranded DNA molecule in cells. Nucleotide excision repair (NER) is the primary DNA repair mechanism and *ERCC1* is a critical gene on the NER pathway. Research suggests a link between high *ERCC1* mRNA levels in tumors and resistance to cisplatin, carboplatin, and oxaliplatin. Customizing treatment so that patients receive therapy based on their baseline tumor *ERCC1* levels (depending on the clinical setting, adjuvant or metastatic) could translate into higher response rates and extended survival while avoiding unnecessary toxicity.[67–70]

How does RRM1 expression influence treatment?

The *RRM1* gene is a tumor-suppressor gene located in the 11p LOH region of the chromosome. *RRM1* is a biologically and clinically important determinant of malignant behavior in NSCLC and represents a strong predictor of outcome in patients with resectable disease. Increased expression of *RRM1* is a major determinant of gemcitabine resistance. Conversely, reduced expression of *RRM1* is associated with sensitivity to gemcitabine.[71]

Initial evidence also suggests a correlation between *RRM1* expression and platinum chemosensitivity, with increased *RRM1* levels making cells somewhat more resistant to carboplatin.[72] This could have important treatment implications for platinum-based chemotherapy.

What is the clinical benefit of determining thymidylate synthetase expression?

Research shows that, in NSCLC, thymidylate synthetase (TS) is expressed differently according to histologic cell type. Bhattacharjee et al[73] found higher baseline TS levels in squamous cell carcinoma compared with adenocarcinoma. The results of randomized clinical trials have shown a selective benefit for patients with nonsquamous histology treated with pemetrexed, a TS-inhibiting agent.

Scagliotti et al[74] detected significantly higher median TS levels in large cell carcinoma and small cell carcinoma compared with adenocarcinoma and found a strong correlation between TS mRNA and protein levels in small cell carcinoma and adenocarcinoma, but not in large cell carcinoma.

In one study, Gandara et al[75] examined the association between histology, gender, and *ERCC1, RRM1,* and TS expression in 2540 patients with NSCLC. A high concordance between *ERCC1* and *RRM1* was found; in addition, gender-related association suggested enhanced chemotherapy sensitivity in women that may be partly related to histology. *EGFR* mutation positivity was found to be associated with low *ERCC1* expression, which could explain 2 prior observations: enhanced platinum-based chemotherapy efficacy in patients with *EGFR*-mutation–negative cancers (as was seen in the IPASS study), 64 and a very low hazard ratio (0.10) and a 90% decrease in mortality in the SATURN trial for patients who had *EGFR* mutations treated with erlotinib once they attained either stable disease or objective response after platinum-based chemotherapy.[48]

CHAPTER 9 | A NOVEL MUTATION IN LUNG CANCER AS A TARGET FOR INNOVATIVE THERAPIES

Can the identification of EML4-ALK fusion genes lead to a cure for lung cancer?

The fusion of echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) has been identified in a small subset of patients with NSCLC. The translocated *EML4-ALK* gene and its variants are oncogenic and predict lack of benefit from therapies that inhibit EGFR activity. Patients with *EML4-ALK*–positive NSCLC appear to share similar features with those patients with *EGFR*-positive NSCLC; however, *EML4-ALK* and *EGRF* mutations seem to be mutually exclusive.[76]

EML4-ALK is most often detected in people who have never smoked or in those who are former light cigarette smokers (≤10 pack-years).[77] Studies suggest that 3% to 7% of lung tumors harbor *EML4-ALK* fusions. Adenocarcinomas seem to be the NSCLC cell type that most commonly harbor *EML4-ALK* fusions.[78]

The discovery of the *EML4-ALK* gene has led to the development of ALK inhibitors, given that ALK tyrosine kinase activity is necessary for oncogenesis. Several ALK inhibitors are being examined to determine whether lung cancers that harbor *EML4-ALK* genes are clinically responsive to pharmacologic ALK inhibition. In preclinical trials, ALK inhibitors led to apoptosis *in vitro* and growth inhibition *in vivo*. In a phase I dose-escalation trial, patients with *EML4-ALK*–positive NSCLC showed a 53% response rate (10/19 patients) and a disease control rate (complete response, partial response, and stable disease) of 79% (15/19) after treatment with crizotinib.[79] In an expanded cohort study instituted after the dose-escalation trial, at a mean treatment duration of 6.4 months, the overall response rate was 57% (47 of 82 patients, with 46 confirmed partial responses and 1 confirmed complete response.[80]

Currently, a major issue is determining the best way to assess for the presence of *ALK* fusions in lung tumors. No standard method for detecting *EML4-ALK* NSCLC exists at the present time. Several methods

under evaluation include polymerase chain reaction (PCR), immunohistochemistry (IHC), and fluorescence in situ hybridization (FISH).[76] However, none of these have been easily adopted by diagnostic molecular pathology laboratories.

The promise of ALK inhibitors against *EMK4-ALK* mutations brings us another step closer to personalized therapy and a potential cure for lung cancer. Ongoing investigation and development of new biologic agents will allow physicians to treat patients according to the genetic makeup of their tumors rather than empirically with cytotoxic chemotherapy agents.

CHAPTER 10 | REFERRING PATIENTS

What factors should I consider before referring patients to specialists?

Because lung cancer can be curable in the early stages (stages I to III) of the disease, patients need a complete work-up as soon as possible. Although metastatic lung cancer is incurable, today, with newer chemotherapies and targeted biologic agents, patients can live longer with good quality of life. When the diagnosis of lung cancer is made, palliative care as initial therapy should be an option only when the patients are in poor performance status. Otherwise, patients should be referred to the medical oncologist, surgeon, or radiation oncologist.

It is important to determine the patient's performance status to determine whether poor status is the result of active cancer or of other comorbid conditions, such as chronic obstructive pulmonary disease, insulin-dependent diabetes mellitus, congestive heart failure, or liver disease. Patients who have mild symptoms and good performance status often respond better to treatment and survive longer than those who are less active or have severe symptoms.

Two performance status scales are widely used to evaluate patients' performance status. Clinicians use these tools to assess how a patient's disease is progressing, to assess how the disease affects daily life, and to determine appropriate treatment and prognosis. These scales in the attached **Toolkit**.

How do I use the Karnofsky scale?

The Karnofsky scale describes the patient's independence and ability to perform certain levels of activity using scores that range from 0 to 100. Zero indicates death and 100, normal physical performance and attitude to perform normal activities. The Karnofsky scale is a widely used tool for assessing prognosis following treatment because it can be used to measure a patient's functional abilities before and after therapy to determine the treatment's effect.[81]

What is the ECOG scale?

The ECOG scale was designed to be a simpler tool to administer than the Karnofsky scale. It was developed by the Eastern Cooperative Oncology Group and first published in 1982.[82] The ECOG performance status scale is a modification of the one-dimensional Zubrod scale, which was a 5-point scale designed to measure activities the patient was capable of performing.[83]

The ECOG performance status scale is a 6-point scale ranging from 0 (fully active and capable of performing all pre-disease activities) to 5 (dead). The ECOG performance status scale and the Karnofsky scale have been compared to determine the predictive validity of both scales. The performance status assignments of both scales correlate strongly in pre- and post-treatment assessments, advanced and limited diseases, and response or nonresponse to treatment.

TOOLKIT Karnofsky Performance Status Scale[81]

Score	Status
100	Normal, no complaints
90	Able to carry on normal activities. Minor signs or symptoms of disease
80	Normal activity with effort
70	Cares for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but able to care for most of his needs
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special care and assistance
30	Severely disabled. Hospitalization indicated though death not imminent
20	Very sick. Hospitalization necessary. Active supportive treatment necessary
10	Moribund
0	Dead

ECOG Performance Status Scale[82]

ECOG Grade (PS)	Definition
0	Fully active, able to carry on all predisease activities without restriction (KS 90–100)
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (KS 70–80)
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about >50% of the time (KS 50–60)
3	Capable of only limited self-care, confined to bed or chair >50% of waking hours (KS 30–40)
4	Completely disabled, cannot carry on any self-care, totally confined to bed or chair (KS 10–20)
5	Dead

ECOG = Eastern Cooperative Oncology Group; KS = Karnofsky Scale; PS = performance status

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Contemporary Management of Non-small Cell Lung Cancer

A 52-year-old car salesman who is a life-long never-smoker presents to his primary care physician complaining of cough and chest congestion that have steadily worsened over the past 2 months. He also reports generalized fatigue, chest pain, and unexplained weight loss of about 8 pounds over the past few weeks.

1. Which of the following diagnostic tests would you consider to be the most appropriate next step in the management of this patient?

a) Brain magnetic resonance imaging

b) Computed tomography scan of the chest, abdomen, and adrenals

c) Endobronchial ultrasound

d) Mediastinoscopy

e) Pulmonary function tests

2. A computed tomography scan of the chest reveals a 2.5-cm mass in the right lung. Further staging studies show metastasis in ipsilateral hilar lymph nodes, but no distant metastasis. According to the Revised International System for Staging Lung Cancer, in what stage is this patient?

a) Stage IA

b) Stage IB

c) Stage IIA

d) Stage IIB

e) Stage IIIA

3. Histologic examination determines that he has NSCLC. Considering that his history is negative for tobacco use, which of the following histologic types of NSCLC is this patient most likely to have?

a) Adenocarcinoma

b) Epidermoid carcinoma

c) Large-cell carcinoma

d) Squamous cell carcinoma

4. Further histologic examination confirms that the tumor is adenocarcinoma and *epidermal growth factor receptor (EGFR)* mutation positive but *excisional repair cross-complementing group 1 (ERCC1)* mutation negative. The patient demonstrates adequate pulmonary function and good performance status. Considering the results of staging, what is the most appropriate first-line treatment for this patient?

a) Bevacizumab

b) Carboplatin

c) Gefitinib

d) Erlotinib

e) Surgery

5. The surgeon completely resects the tumor via lobectomy with sampling of the mediastinal lymph nodes. The patient questions why the entire lobe was removed, rather than just the mass. Which of the following statements is TRUE with regard to the surgical options available to this patient?

a) In patients who have the pulmonary capacity to tolerate such surgeries, lobectomy and pneumonectomy are preferred over limited-excision approaches, such as segmentectomy and wedge resection

b) Data from clinical studies show an increase in the rate of local recurrence for patients treated with lobectomy compared with limited-excision approaches

c) Patients with early-stage NSCLC who have comorbidities and/or impaired pulmonary function and cannot tolerate lobectomy or pneumonectomy are candidates for limited-excision approaches

d) A and C only

e) A, B, and C

6. Which of the following treatment modalities has been shown to increase survival in patients like ours, with resected early-stage NSCLC?

a) Adjuvant chemotherapy

b) Chemoradiotherapy

c) Intensity modulated radiotherapy

d) Tomotherapy

e) All of the above

7. Before surgery, the patient researched his condition online and came across a patient testimonial advocating radiotherapy as the best way to increase survival following surgery. He asks why you are recommending postoperative chemotherapy rather than radiotherapy. Which of the following statements is TRUE with regard to improving survival following surgery in patients with resected early-stage NSCLC?

a) Postoperative radiotherapy is controversial in resected early-stage NSCLC

b) Radiation therapy after surgery is generally is reserved for medically fit patients who had bulky disease in the mediastinal (N2) nodes or had multiple lymph node involvement

c) In the Adjuvant Navelbine International Trialist Association trial, adjuvant chemotherapy significantly improved survival for patients with completely resected stage II and stage III NSCLC but not for patients with stage IB NSCLC

d) In the International Adjuvant Lung Cancer Trial, the benefits of adjuvant therapy decreased over time

e) All of these statements are true

8. What is the significance of the patient's *EGFR*–mutation-positive status?

a) *EGFR* mutations lead to increased growth-factor signaling

b) *EGFR* is a critical gene on the nucleotide excision repair pathway

c) Specific mutations in the *EGFR* gene correlate with clinical responsiveness to the tyrosine kinase inhibitor gefitinib

d) Screening for *EGFR* mutations in lung cancers may identify patients who will have a treatment response to certain biologic agents

e) A and B only

f) A, C, and D

9. What other genetic marker is most often detected in patients like ours who have never smoked or in those who are former light cigarette smokers (≤10 pack-years)?

a) BIBW2992

b) *EML4-ALK*

c) *ERCC1*

d) *RRM1*

e) TS

10. What is the significance of the patient's *ERCC1*-mutation-negative status?

a) *ERCC1* gene mutations influence survival and toxicity associated with paclitaxel-based chemotherapy

b) Patients with completely resected early-stage NSCLC and *ERCC1*-positive tumors seem to benefit from adjuvant cisplatin-based chemotherapy

c) Patients with completely resected early-stage NSCLC and *ERCC1*-negative tumors seem to benefit from adjuvant cisplatin-based chemotherapy

d) Increased expression of *ERCC1* is a major determinant of gemcitabine resistance

e) Increased *ERCC1* levels make cells somewhat more resistant to pemetrexed

CME TEST ANSWER SHEET AND EVALUATION FORM

Contemporary Management of Non-small Cell Lung Cancer

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PREACTIVITY SELF-ASSESSMENT ANSWERS

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1.	1	2	3	4	5	6	7	8	9	10	**5.**	a	b	c	d	e	
2.	1	2	3	4	5	6	7	8	9	10	**6.**	a	b	c	d	e	
3.	1	2	3	4	5	6	7	8	9	10	**7.**	a	b	c	d	e	
4.	1	2	3	4	5	6	7	8	9	10	**8.**	a	b	c	d	e	f

COURSE EVALUATION

Having completed the activity, please consider the educational objectives and then rate how confidently you can…

	Not confident									Very confident
…use histological factors for determining the appropriateness of NSCLC patients for a particular type of therapy	1	2	3	4	5	6	7	8	9	10
…describe results of recent clinical trials that combine targeted therapies with chemotherapy in the treatment of advanced NSCLC	1	2	3	4	5	6	7	8	9	10
…implement strategies that optimize therapeutic decisions for patients based on individual molecular, genomic, and clinical features	1	2	3	4	5	6	7	8	9	10
…choose among different strategies for the treatment of patients with recurrent and progressive disease for improved outcomes	1	2	3	4	5	6	7	8	9	10

CME TEST (Please circle correct answers)

1. a b c d e 2. a b c d e 3. a b c d 4. a b c d e 5. a b c d e 6. a b c d e 7. a b c d e 8. a b c d e f 9. a b c d e 10. a b c d e

How do you rate the overall quality of the activity?

Lowest				Highest
1	2	3	4	5

How do you rate the relevance of the educational content to your daily practice?

Not relevant				Very relevant
1	2	3	4	5

Was the information presented fair, objective, balanced, and free of bias in the discussion of any commercial product or service? ❑ Yes ❑ No

If not, please describe: _____

Suggested topics for future activities: _____

Suggested authors/faculty for future activities: _____

INTENT TO CHANGE PRACTICE

*Prior to participation in this program, please indicate how often you **had been using** histological criteria to aid in treatment selection*

❑ <25% of the time ❑ 26%–50% of the time ❑ 51%–75% of the time ❑ >76% of the time

*After participation in this program, please indicate how often you **plan to use** histological criteria to aid in treatment selection*

❑ <25% of the time ❑ 26%–50% of the time ❑ 51%–75% of the time ❑ >76% of the time

Please indicate what barriers you might have encountered:

❑ Already treating this way ❑ Time
❑ Patient non-adherence ❑ Not on formulary
❑ Not reimbursable by insurance ❑ Other: Please specify _____

PLEASE INDICATE

How you heard about this activity?

❑ Mail/Print ❑ Internet/Email ❑ Live Activity

Would you be willing to participate in post-activity follow-up surveys? ❑ Yes ❑ No

Would you be willing to participate in a focus group or teleconference aimed at identifying/creating future educational activities that would improve performance in practice or patient outcomes? ❑ Yes ❑ No

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