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ADVANCES IN LUNG CANCER EVALUATION AND MANAGEMENT

SUPPLEMENT EDITORS:
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CLEVELAND CLINIC

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Lung cancer screening: Examining the issues

ABSTRACT

The goal of screening is to detect disease at a stage when cure or control is possible, thereby decreasing disease-specific deaths in the population. Many studies have attempted to demonstrate that lung cancer screening using chest radiography or computed tomography (CT) identifies patients with lung cancer and reduces cancer-related mortality. Until recently, there was no evidence confirming a reduction in disease-specific mortality with screening. Early cancer screening should result in a gradual population-wide stage shift toward earlier cancer stages over time, but stage shifting was not reported in early lung cancer screening studies. Lead-time, length-time, and overdiagnosis biases may each have an impact on screening studies reporting survival as an outcome. In this past year, the National Lung Screening Trial reported a significant reduction in cancer-related mortality as a result of screening with chest CT imaging. This will shape the direction of future screening programs.

Screening is the testing of an individual who is at risk for a disease, but who does not exhibit signs or symptoms of the disease. The goal of screening is to detect disease at a stage when cure or control is possible, and an effective screening program should reduce the number of disease-specific deaths in the screened population. Screening should focus on diseases that are associated with potentially serious consequences and that are detectable in the preclinical phase, yet it should avoid identifying "pseudodisease" (ie, positive test findings that would not be expected to affect the patient's health) or causing morbidity due to the test procedure itself.[1] Finally, screening is only worthwhile when treatment of the disease is more effective when administered early.

Dr. Mazzone reported that he has been a member of advisory committees for Boehringer Ingelheim and Oncimmune. He has research supported by Metabolomx.

This article was developed from an audio transcript of Dr. Mazzone's presentation at the "Advances in Lung Cancer Evaluation and Management" symposium held in Cleveland, Ohio, on April 30, 2011. The transcript was formatted and edited by *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness and was then reviewed, revised, and approved by Dr. Mazzone.

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Since lung cancer screening began in the 1950s,[2,3] many studies have attempted to define the medical benefits and economic impact of widespread screening. Many important unresolved issues remain, including the effectiveness of lung cancer screening for reducing disease-specific mortality, the potential harms of screening, its cost-effectiveness, and the potential impact of new research methods on the early identification of lung cancer.

DOES LUNG CANCER SCREENING REDUCE DISEASE-SPECIFIC MORTALITY?

Early studies examined the usefulness of large-scale chest radiograph programs, either with or without sputum cytology, for lung cancer screening. Although several studies reported that radiographic screening identified patients with early lung cancer and reported higher survival rates, reviews and meta-analyses of these reports concluded that screening did not significantly reduce disease-specific mortality.[4,5]

The utility of chest radiography for the detection of early lung cancer is limited by several factors, including poor sensitivity for the detection of small or subtle nodules and a relatively high false-positive rate.[6–8] More recently, several cohort studies and randomized, controlled trials have shown that computed tomography (CT) screening is effective for the identification of early lung cancer in high-risk patients (eg, individuals with chronic, heavy tobacco use or asbestos exposure).[9–11] A recent meta-analysis concluded that CT-based screening significantly increases the number of early lung cancers identified, but also increases the number of false-positive findings (nodules) and unnecessary thoracotomies for benign lesions.[12]

Lung cancer screening should increase the number of patients identified at early disease stages. Treatment of early-stage lung cancer should decrease the number of patients identified with late-stage cancer, resulting in a stage shift toward earlier disease for the population as a whole. Although lung cancer screening cohort studies and randomized, controlled trials have demonstrated that screening increases the number of early-stage lung cancer cases identified, these

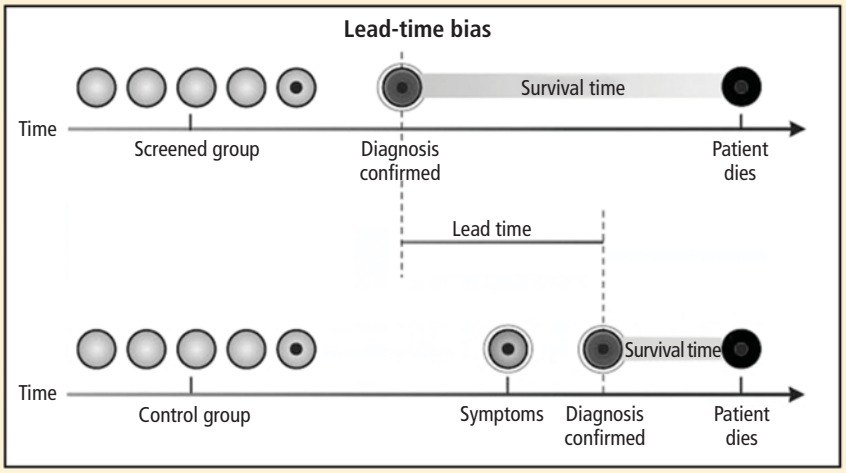

FIGURE 1. Lead-time bias. Patients identified by screening may live longer with disease than patients diagnosed clinically, although overall survival time is not improved.

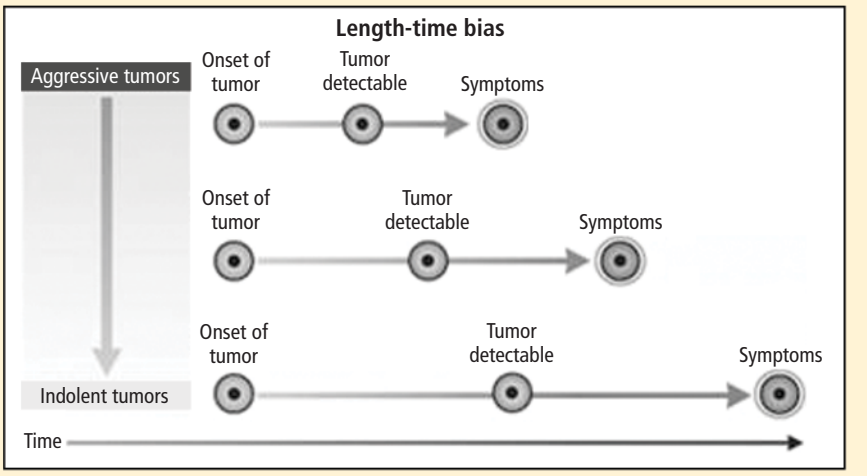

FIGURE 2. Length-time bias. Indolent tumors move more gradually from the detectable stage to the onset of symptoms. These tumors are therefore more likely to be identified by intermittent screening.

studies have generally not demonstrated decreased rates of late-stage lung cancers or stage shifting in the populations studied. In the 1970s, the National Cancer Institute began three large-scale screening trials at Mayo Clinic, Memorial Sloan-Kettering Cancer Institute, and The Johns Hopkins University, each enrolling approximately 10,000 patients. In the Mayo trial, the incidence of advanced-stage tumors was nearly identical for the screened versus unscreened patients, with 303 cancer cases detected in the screened group versus 304 cases in the control group.[13] CT-based cohort studies have also reported increased rates of early recognition of lung cancer and accompanying large increases in the number of diagnostic procedures performed. However, early controlled trials of CT screening showed no differences between screened and unscreened groups in the numbers of patients with late-stage tumors or deaths due to lung cancer.[14]

Results such as these have led some researchers to argue that survival benefits of screening largely reflect observational biases. For example:

- **Lead-time bias** occurs when screening results in earlier recognition of disease, but does not change the patient's eventual lifespan, creating the appearance that the patient's survival time with the disease is longer **(Figure 1)**.[15] Longer lead times should be observed in a successful screening program even if eventual mortality remains exactly the same, and lead time bias is therefore an expected outcome of screening.
- **Length-time bias** arises from the observation that any screening test that is applied intermittently is more likely to detect indolent tumors than aggressive, fast-growing tumors that would result in clinical symptoms **(Figure 2)**.[15] Indolent tumors move more gradually from the detectable state to the onset of clinical symptoms, and are therefore especially likely to be identified by screening.
- **Overdiagnosis bias** occurs when a screening test identifies disease that never would have affected the patient's life in the absence of screening. This type of bias might occur if screening identifies a lesion that is

so indolent that it would never cause clinical disease, or if the population is otherwise in such poor health that successfully screened patients would die from other causes.

There is no question that these biases affect reports of survival in lung cancer screening, although it is unclear whether they explain the reported benefit of screening observed in cohort studies. Screening advocates have argued that the failure to screen high-risk patients for lung cancer has the potential for significant harm. In contrast, opponents of screening have argued that there was a lack of data showing a reduction in the number of patients diagnosed with late-stage cancers or in cancer-related mortality.

IS LUNG CANCER OVERDIAGNOSED IN SCREENED POPULATIONS?

Although the apparent benefit of lung cancer screening is susceptible to different sources of bias, overdiagnosis has received the greatest attention on the basis of both theoretical concerns and observations from screening studies. Estimates of lung cancer growth suggest that a typical 10-cm tumor, which is usually large enough to be fatal, has progressed through approximately 40 volume doublings during the course of its existence. In contrast, a more survivable—and clinically detectable—1-cm tumor has progressed through approximately 30 volume doublings.[16,17] A lung tumor therefore spends most of its existence relatively undetectable. It has been estimated that the median doubling time is approximately 181 days, and that 22% of lung cancers have doubling times more than 465 days.[18] The appearance of tumors on CT may suggest the growth rate, with 1 study showing that solid malignant nodules had a mean doubling time of 149 days, compared with 457 days for partial ground-glass–opacity nodules, and 813 days for pure ground-glass nodules.[19]

These estimates suggest that if a 1-cm tumor with a history of 30 volume doublings continues to grow at a typical rate (ie, a 181-day doubling time), the patient will die of cancer within 5 years. If the tumor is among the 22% of those with a 465-day doubling time, the survival time would be 12.7 years. For malignant pure ground-glass nodules, the projected time to death is 22 years. Individuals with lung cancer are often elderly, long-term cigarette smokers with emphysema or other chronic health problems—many of whom would die of other causes before their lung cancers progressed enough to cause significant health problems.

As an argument against the significance of overdiagnosis in lung cancer screening, it has been noted

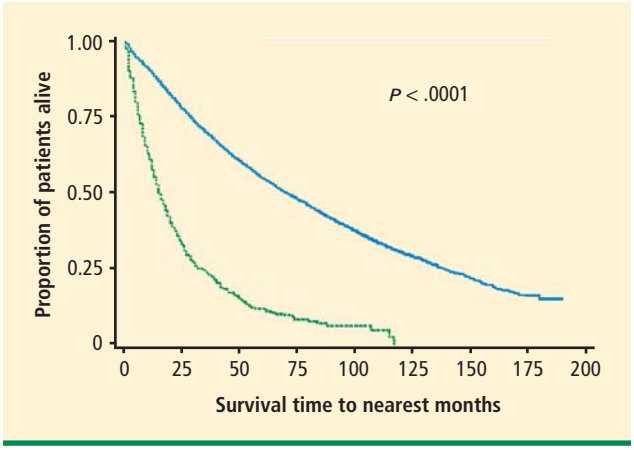

FIGURE 3. Survival is worse in untreated than in treated non–small cell lung cancer patients, arguing against overdiagnosis bias. Blue line: patients receiving surgery; green line: untreated patients who refused surgery.

Reprinted with permission from the American College of Chest Physicians (Raz DJ, et al. Natural history of stage I non-small cell lung cancer: implications for early detection. Chest 2007; 132:193–199).

that outcomes are worse for patients identified with early-stage lung cancer in screening studies who do not receive treatment. For example, the results of a study of 1,432 patients with stage I non–small cell lung cancer (NSCLC) are illustrated in **Figure 3**. Survival was much better in screened patients who were treated than in those who were untreated, with almost all the untreated patients dying within 10 years of diagnosis.[20] However, the subjects in this study were atypical of those in most screening studies. Thirty-three percent of the patients had squamous cell carcinoma and 61% had relatively large T2 lesions, compared with a typical screening study comprised of patients with more than 50% T1 lesions and a smaller percentage of squamous cell carcinoma.

Another argument against overdiagnosis comes from gene profiling studies that have compared genetic tumor markers for tumors identified by screening with tumors identified clinically. One study found that the expression profile of 3,231 genes was similar for patients with lung cancer identified by screening or by symptoms.[21] However, these investigators also found that nine genes known to be important in tumor growth differed between screened and non-screened populations.

The significance of overdiagnosis is supported by a long-term follow-up study from the Mayo Clinic chest radiography screening trial, which found that the number of lung cancer cases remained higher in the screening group than the control group (585 vs 500 cases) for up to 28 years after screening, suggesting an overdiagnosis of lung cancer by approximately

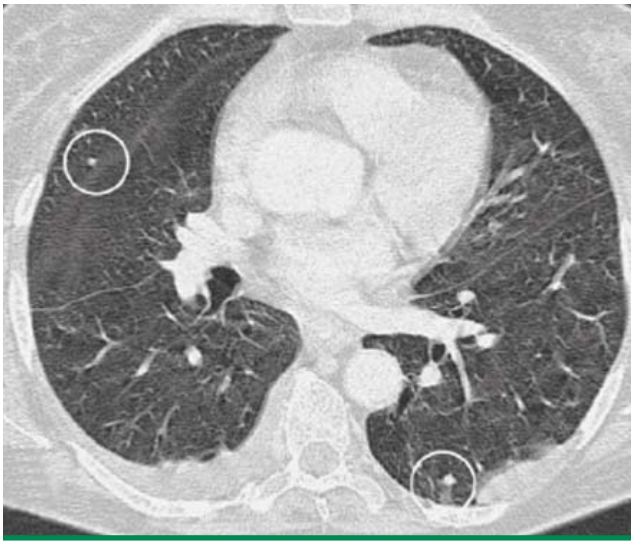

FIGURE 4. Benign lung nodules visualized on computed tomography.
Reprinted with kind permission from Springer Science+Business Media (Fischbach F, et al. Detection of pulmonary nodules by multislice computed tomography: improved detection rate with reduced slice thickness. Eur Radiol 2003; 13:2378–2383).

85 cases per 500 patients screened (approximately 17%).[22] Several studies have also demonstrated that screening populations may have tumors with more favorable histology or clinical characteristics, including higher levels of bronchioloalveolar carcinoma or well-differentiated adenocarcinoma.[23–25] Finally, autopsy series have found undiagnosed lung tumors in as many as 1% of patients who died from natural causes, with fewer advanced tumors found in the 1970s than in the 1950s.[26,27]

These arguments led most to believe randomized controlled trials of CT-based screening were needed. The largest of these, the National Lung Screening Trial (NLST), has recently reported results that will clarify the impact of lung cancer screening on cancer-related mortality.[28] This study enrolled 53,456 subjects between the ages of 55 and 74 years with a history of at least 30 pack-years of smoking. Patients were randomized to baseline screening followed by annual screening for 2 years using either low-dose helical CT or chest radiography and outcome follow-up 5 years after randomization. Data analysis after 6 to 8 years of follow-up found 442 lung cancer deaths in the chest radiograph arm versus 354 in the CT arm, representing a 20.3% reduction with CT.[29] Screening of 320 patients using low-dose helical CT would be required to avoid each lung cancer death. Thus, after years of debate, it has been demonstrated that it is possible to reduce lung cancer-specific mortality with CT-based screening.

ARE THERE SIGNIFICANT RISKS WITH CT-BASED SCREENING?

Lung cancer screening using chest CT may be associated with certain risks. The detailed high-resolution images produced by contemporary CT reveal small benign lung nodules in as many as 74% of patients **(Figure 4)**.[24,30] Although these nodules rarely represent a significant health problem, they require follow-up procedures and contribute to patient anxiety.[31] In one study, every 1,000 individuals screened with CT imaging resulted in the identification of nine cases of stage I NSCLC, 235 false-positive nodules measuring at least 5 mm, and four thoracotomies for benign lesions.[12]

Radiation from CT tests is a potential concern, although it is difficult to quantify the importance of this risk. One estimate of CT-related radiation exposure found that annual CT screening of 50% of the eligible population between 50 and 75 years of age in the United States would result in approximately 36,000 new cancers, or a 1.8% increase in the rate of cancer over the expected rate.[32] Many patients and health care professionals are already concerned about the degree of radiation exposure from medical diagnostics. A recent study that examined cumulative radiation exposure due to medical imaging in 952,420 adults aged 18 to 64 years found that approximately 57.9% of men and 78.7% of women receive at least some annual health care-related radiation exposure.[33] Radiation exposure was considered moderate (> 3–20 mSv/yr) for 18.1% of men and 20.3% of women, and was considered high (> 20–50 mSv/yr) or very high (>50 mSv/hr) for 2.3% of men and 2.1% of women.

IS SCREENING COST-EFFECTIVE?

It is difficult to calculate the cost-effectiveness of CT screening because the impact of screening on mortality and the economic implications of false-positive findings are not well understood. A cost-effectiveness analysis of helical CT screening assumed that screening would result in a 50% stage shift and a 13% reduction in mortality.[34] Under these assumptions, the cost-effectiveness was greater among current smokers ($116,300 per quality-adjusted life year saved by screening) than among currently quitting smokers ($558,600) or former smokers ($2,322,700). These investigators concluded that lung cancer screening is unlikely to be cost-effective, especially among those with the lowest levels of current tobacco exposure (quitting or former smokers).

Larger stage shifts or reductions in mortality would be expected to translate into greater cost-effective-

ness, although the real-world effects of screening on these parameters are uncertain. Data from a US nationwide survey suggested that only about one-half of all current smokers would opt for surgery following a positive screening result, which might significantly decrease the cost-effectiveness of treatment.[35]

It is unclear how well the methods used in screening studies such as the NLST would translate to actual clinical practice at a national level, or how the health care system would manage the many small lung nodules that would be identified using this approach.

HOW WILL FUTURE DEVELOPMENTS AFFECT LUNG CANCER SCREENING?

Ongoing studies will continue to refine our understanding of the impact of lung cancer screening. For example, the randomized Prostate, Lung, Colorectal, and Ovarian Screening Trial is examining chest radiograph screening versus control in both smokers and never-smokers between 55 and 74 years of age.[36] It is anticipated that this study will provide important information about how well chest radiographs perform for the identification of lung cancer in high- and lower-risk populations. Large randomized trials in Europe are comparing CT with no imaging for lung cancer screening.[37] Efforts to better characterize specific patient populations who are at the greatest risk of lung cancer may help to improve the efficiency and cost-effectiveness of screening. Advances in molecular testing may help to identify molecular and genetic tumor biomarkers that herald increased lung cancer risk and greater need for screening. More research is needed to better understand the optimal management of patients with small lung nodules on screening tests. Professional societies are poised to publish revised screening recommendations as data from the NLST become available. Finally, insurers will need to evaluate the evidence and develop reimbursement policies.

SUMMARY AND CONCLUSIONS

Lung cancer screening efforts conducted over the last several decades have shown that it is possible to identify early lung cancer in high-risk patient populations. However, demonstrating a clear improvement in cancer-related mortality has been more difficult. Biases inherent to noncontrolled trials of screening may explain some of the beneficial effects on survival observed in some studies. Recent results from the NLST have for the first time demonstrated a significant reduction in lung cancer mortality in high-risk patients screened for lung cancer with chest CT, although there are continuing concerns about the cost of screening, the risks from radiation exposure, and the additional testing resulting from the identification of small benign lung nodules. Ongoing research will help to maximize the benefit of lung cancer screening and minimize the related risks.

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Treatment implications of the new lung cancer staging system

ABSTRACT

The American Joint Commission on Cancer along with the International Association for the Study of Lung Cancer (IASLC) has published new guidelines for lung cancer staging based on observations from 100,869 lung cancer patients. Revised tumor, node, metastasis (TNM) criteria were derived from IASLC patient survival curves, and were validated using data from the Surveillance, Epidemiology, and End Report program. The seventh edition TNM classification revised the T1, T2, T3, and M1 descriptors.

It is estimated that 10% to 15% of newly diagnosed lung cancer patients will be assigned a different disease stage as a result of these changes.

The tumor, node, metastasis (TNM) staging system for lung cancer was first developed in 1973 using a sample of 2,155 patients who were treated at the MD Anderson Cancer Center in Houston, Texas.[1] Important limitations of this first staging system included the relatively small number of patients studied, the geographic restriction of all patients to a single medical center, the limited generalizability to patients from other parts of the world, and the lack of external validation of TNM staging as a predictor of clinical outcome. This system was revised in 1997 using data from 5,319 patients at the MD Anderson Cancer Center, and it remained unchanged until the American Joint Committee on Cancer (AJCC) seventh edition was published in 2009.

The AJCC seventh edition TNM staging guidelines are the result of a multinational undertaking led by the International Association for the Study of Lung Cancer (IASLC), in which data from 100,869 patients were collected from study centers in North America, Asia, Australia, and Europe from 1990 to 2000.[2] Staging recommendations for non–small cell lung cancer were developed using data from 67,725 patients. Of these, 53,640 were clinically staged, and 33,933 underwent pathologic staging. In 20,006 patients, both clinical and pathologic staging information were available.[2] Approximately 95% of patients underwent follow-up for at least 2 years or until death.

The revised AJCC lung cancer staging system provided a much larger and more diverse patient database than the earlier TNM staging system, with robust long-term follow-up and rigorous validation of the prognostic significance of TNM groupings. The revised TNM descriptors were validated internally by confirming the consistency of Kaplan-Meier survival curves across different study centers. External validation of the staging system was performed by using patient survival data from the Surveillance, Epidemiology, and End Report (SEER) program of the National Cancer Institute.[2] Data analysis was conducted by Cancer Research and Biostatistics, an independent statistical center in Seattle, Washington.

Potential limitations of the revised staging system included the lack of standardization of diagnostic technology across different regions and time periods, as well as the exclusion of patients from Africa, South America, and India.[3] In addition, the AJCC seventh edition continues to classify patients entirely on the basis of anatomic characteristics. Certain tumor molecular markers are now recognized as both prognostic and predictive of the responses to certain treatments, but these have yet to be taken into consideration in lung cancer staging.

UNDERSTANDING REVISED SEVENTH EDITION TNM DESCRIPTORS

A summary of TNM descriptors in the sixth and seventh editions of the AJCC staging criteria, the use of the most recent criteria in lung cancer staging, and

Dr. Rodriguez reported that she has no relationships that pose a potential conflict of interest with this article.

This article was developed from an audio transcript of Dr. Rodriguez's presentation at the "Advances in Lung Cancer Evaluation and Management" symposium held in Cleveland, Ohio, on April 30, 2011. The transcript was formatted and edited by *Cleveland Clinic Journal of Medicine* staff for clarity and conciseness and was then reviewed, revised, and approved by Dr. Rodriguez.

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TABLE 1
Revisions to the AJCC lung cancer staging system TNM classification[3,7]

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

( ) = change in classification; M = metastasis; T = tumor

changes in staging from one edition to the next are summarized in **Table 1**.

T1 comprises two subcategories

In the previous AJCC staging system published in 2002 (sixth edition), the T1 tumor size classification was defined as a tumor measuring greater than 3 cm in size without invasion more proximal than the lobar bronchus.[4] In the seventh edition TNM classification, the T1 category is separated into T1a, which is defined as tumor measuring greater than 2 cm, and T1b, ie, tumor measuring 2 to 3 cm.[5] This new classification is based on data from both pathologic and clinical staging datasets, which demonstrate significant differences in median survival for tumors measuring smaller than 2 cm versus tumors that were 2 to 3 cm in size within the T1 category. These survival differences were subsequently validated using the SEER patient database.[5]

T2 also subdivided

A similar subdivision was performed for the T2 category. In the sixth edition TNM classification, a T2 tumor was defined either as a tumor greater than 3 cm in size, or with at least one of the following criteria: involvement of a mainstem bronchus 2 cm or more distal to the carina; invasion of the visceral pleura; or atelectasis extending to the hilar region, but not involving the entire lung.[4] In the seventh edition, the T2 category is divided into T2a (tumor size, 3 to 5 cm) and T2b (tumor size, 5 to 7 cm).[5] The median survival difference between these two subsets varied from approximately 10% to 27% across different study sites.[2] Validation of the T2a and T2b classification using the SEER database demonstrated that the proportion of patients who survived 5 years was 14% higher for patients in the T2a than the T2b group (hazard ratio, 1.45; $P < .0001$), confirming the prognostic importance of these two subcategories.

T3 redefined

The investigators also made changes to the T3 classification in the AJCC seventh edition staging system. Tumors measuring greater than 7 cm (classified as T2 using the sixth edition) were reclassified as T3. Additionally, the subset of sixth edition T4 tumors that were defined by the presence of additional nodules in the same lobe were reclassified as T3. The revised AJCC seventh edition TNM classification, therefore, defines T3 tumors as those greater than 7 cm in size, or tumors of any size with the following characteristics: invasion of the chest wall, diaphragm, mediastinal pleura, or parietal pericardium; more than 2 cm from carina; atelectasis of entire lung; or satellite nodules in the same lobe.

T4 redefined based on survival outcomes

Finally, tumors that were previously classified as M1 because of additional nodules in different lobes of the ipsilateral lung are classified as T4 in the seventh

edition. This change reflected the observation that 5-year survival outcomes for these patients differed markedly from other M1 tumors, but were similar to outcomes for patients with T4 tumors.[2] The revised AJCC seventh edition criteria for T4 lesions includes tumors of any size with invasion of the mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina, or a satellite tumor nodule in the same lung.

N criteria unchanged

The N criteria subcommittee recommended that the existing N staging criteria should be retained without revision from the sixth edition.

M1 reclassified and subdivided

In the sixth edition, M1 disease was defined as any distant metastasis, including separate tumor nodules in a different lung lobe. In the seventh edition, pleural dissemination is reclassified from category T4 to M1 owing to significantly poorer survival among these subgroup of T4 patients.[2] In addition, M1 disease is divided into two subcategories. M1a disease is defined as one or more tumor nodule(s) in a contralateral lobe, tumor with pleural nodules, or malignant pleural or pericardial effusion, whereas M1b disease is defined as any distant metastasis.

TABLE 2
The non–small cell lung cancer "stage shifters" in the IASLC population

	AJCC 6th edition characteristics	6th edition stage	7th edition stage	IASLC patients (%)
Upstaged	T2 $_{(>5 \text{ but} \le 7 \text{ cm})}$ N0 M0	1B	2A	3.8
	T2 $_{(>7 \text{ cm})}$ N0 M0	1B	2B	1.7
	T2 $_{(>7 \text{ cm})}$ N1 M0	2B	3A	0.8
	Malignant pleural involvement	3B	4	2.5
Downstaged	T2 $_{(\le 5 \text{ cm})}$ N1	2B	2A	4.4
	Separate tumor nodules in same lobe, N0	3B	2B	0.6
	Separate tumor nodules in same lobe, N1, N2	3B	3A	0.7
	Separate tumor nodules in different ipsilateral lobe, N0, N1	4	3A	0.4
	Separate tumor nodules in different ipsilateral lobe, N2, N3	4	3B	0.3
	T4 $_{(\text{extension})}$ N0, N1	3B	3A	1.6

AJCC = American Joint Commission on Cancer; IASLC = International Association for the Study of Lung Cancer

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WHAT ARE THE IMPLICATIONS OF A NEW STAGING SYSTEM?

It is estimated that approximately 10% to 15% of newly diagnosed patients with lung cancer will be assigned to a different disease stage on the basis of this new classification system.[6] **Table 2** compares cancer staging using the sixth and seventh edition TNM classification criteria and includes the proportion of patients in the IASLC database who would be upstaged or downstaged.[6] For example, 3.8% of patients in the IASLC database would be upstaged from the former stage 1B to the new stage 2A, and approximately 4.4% of patients would be downstaged from 2B to 2A.

These changes to lung cancer staging may have significant implications for clinical decision-making. In a recent survey, clinicians who treat lung cancer were presented with three patient scenarios in which the lung cancer stage differed between the sixth and seventh AJCC editions.[6] The clinicians were first presented with the clinical vignettes accompanied by their sixth edition designations, and then with their seventh edition designations. At each presentation, clinicians were asked to choose from several possible management options. Approximately 77% of clinicians surveyed changed their management strategy based on the change in staging classification.

SUMMARY AND CONCLUSIONS

The AJCC seventh edition TNM classification is based on internally and externally validated survival curves derived from tens of thousands of patients with different disease characteristics enrolled at study sites around the world. Because the treatments received by the patients are not included in this analysis, it is essential to exercise caution when using staging information to make treatment decisions. Prospective patient data will be required to determine whether this

classification system significantly improves long-term treatment outcomes. In addition, it will be important to consider the potential effects of different staging systems when comparing the results of clinical trials.

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Bronchoscopy and endobronchial ultrasound for diagnosis and staging of lung cancer

ABSTRACT

Various techniques, including standard bronchoscopy, transthoracic needle aspiration and mediastinoscopy, are used for diagnosis and staging of lung cancer. Minimizing the number of invasive procedures for lung cancer diagnosis and staging is preferred, however, and a growing number of bronchoscopic techniques are being used. Currently available techniques for the initial diagnosis of lung cancer include electromagnetic navigation bronchoscopy with computed tomography mapping and sample collection, endobronchial ultrasound (EBUS) using radial or convex probe tips, and the combination of the two approaches. EBUS with transbronchial needle aspiration (EBUS-TBNA) is highly specific and sensitive for the examination of mediastinal lymph nodes. Several studies have demonstrated the utility of this approach for less invasive lung cancer mediastinal staging. EBUS-TBNA has also been used in the collection of tissue samples for the analysis of tumor biomarkers that significantly influence the selection of cancer treatment strategies. Evidence suggests that EBUS-TBNA may be less useful for restaging patients with lung cancer after cytotoxic therapy.

Several techniques are available for the diagnosis of suspected lung cancer, including standard flexible bronchoscopy, transthoracic needle aspiration, and sputum cytology. Mediastinal staging of lung cancer is essential for treatment planning and assessment of prognosis, and has traditionally been performed surgically. Although cervical mediastinoscopy is regarded as the "gold standard" for sampling mediastinal lymph nodes, this procedure typically requires hospitalization and general anesthesia.[1] Current endobronchial ultrasound (EBUS) techniques provide less invasive lung cancer diagnosis and staging. Recent research has examined the application of endobronchial ultrasound-based assessment for initial diagnosis of lung cancer, mediastinal staging and restaging after neoadjuvant therapy, and evaluation of tumor genetic markers.

BRONCHOSCOPIC LUNG CANCER DIAGNOSIS

Evidence-based clinical guidelines for the diagnosis of lung cancer developed by the American College of Chest Physicians reviewed the sensitivity of standard bronchoscopy (ie, without EBUS or electromagnetic navigation) and ancillary procedures that are often performed in combination with flexible bronchoscopy, such as endobronchial biopsy, brushing, washing, and standard transbronchial needle aspiration (TBNA).[2] A comprehensive review of published studies from 1971 to 2004 was included in the analysis. Overall, the sensitivity of standard flexible bronchoscopy was 88% (67% to 97%) for the diagnosis of central bronchogenic carcinoma and 78% (36% to 88%) for the diagnosis of peripheral bronchogenic carcinoma. Newer techniques have been developed that appear to provide more consistent diagnosis of primary lesions.

Electromagnetic navigation bronchoscopy (ENB) is a functional tool in biopsy planning that uses computed tomography (CT) mapping to precisely locate peripheral lesions. After real-time navigation to the peripheral lesion with a steerable probe, tissue collection may be optimized by guiding sampling instruments directly to the lesion through an extendable working channel.[3] A prospective pilot study examined the feasibility and safety of ENB to reach peripheral lesions and lymph nodes in patients with suspected lung cancer lesions or enlarged mediastinal lymph nodes.[3] Diagnostic tissue was obtained in 80.3% of attempts, including 74% of procedures involving peripheral lung lesions and 100% of procedures involving lymph nodes.

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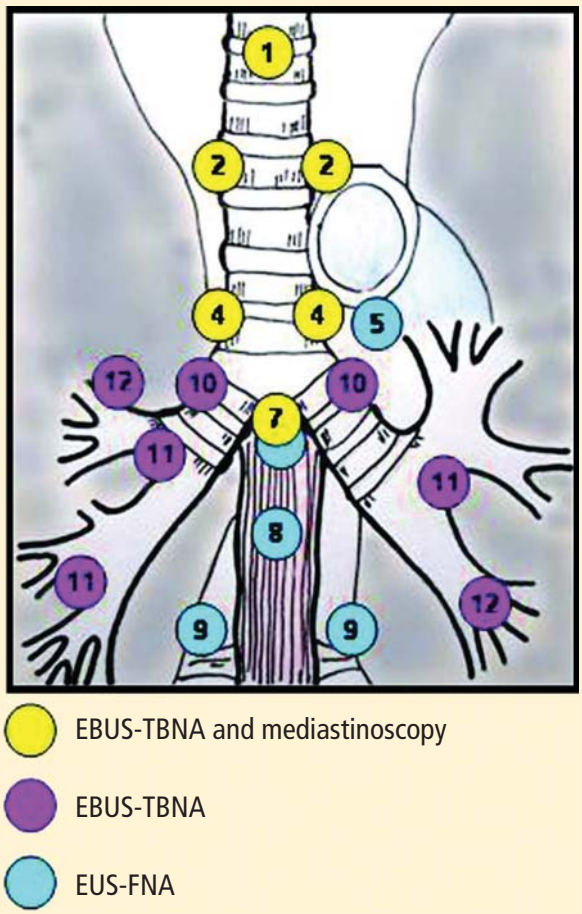

FIGURE 1. The diagnostic reach of various ultrasound sampling techniques is shown with 1, highest mediastinal; 2, upper paratracheal; 4, lower paratracheal; 5, subaortic; 7, subcarinal; 8, paraesophageal; 9, pulmonary ligament; 10, hilar; 11, interlobar; and 12, lobar. Endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA) is performed via the airway as opposed to endoscopic ultrasound with fine-needle aspiration (EUS-FNA), which is carried out in the esophagus.[7]

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IMPROVING DIAGNOSIS WITH ULTRASOUND

Another diagnostic method is EBUS, which uses reflected sound waves to better visualize lesions at the time of biopsy.[4] Radial probe endobronchial ultrasound (RP-EBUS) employs a rotating ultrasound transducer at the end of a probe, and is used either with or without a water-filled balloon to improve ultrasound transduction and image quality. Convex-probe ultrasound uses a curvilinear ultrasound probe at the end of a bronchoscope, which allows for real-time TBNA visualization.[4] A recent meta-analysis examined the yield of RP-EBUS for the evaluation of peripheral pulmonary lesions in 16 studies with a combined population of 1,420 patients.[5] The overall sensitivity of RP-EBUS for the detection of lung cancer was 73%, and the specificity was 100%. In a prospective, randomized clinical trial of patients with peripheral lung lesions, the combination of ENB and RP-EBUS produced a diagnostic yield of 88%, compared with 69% with RP-EBUS alone and 59% with ENB alone ($P = .02$).[6] Although this finding suggests that a multimodal approach combining ENB and RP-EBUS may improve lung cancer diagnosis, the sample size was relatively small (118 patients).

ENDOBRONCHIAL ULTRASOUND FOR LUNG CANCER STAGING

A promising application for EBUS is its use as a less invasive method for confirming metastatic mediastinal lymph nodes in the staging of lung cancer. **Figure 1** shows the distribution of the mediastinal lymph nodes and the various diagnostic techniques that may be used to sample different lymph node stations.[7]

In a prospective study of potentially operable patients from Japan with proven (n = 96) or suspected (n = 6) lung cancer, investigators compared CT, positron emission tomography (PET), and EBUS-TBNA for mediastinal lymph node staging using surgical histology as the reference standard.[7] The accuracy of staging was significantly greater with EBUS-TBNA (98%) than either PET (72.5%) or CT (60.8%) ($P < .00001$).

A recent retrospective study examined the use of EBUS-TBNA for clarification of 127 PET-positive hilar or mediastinal lymph nodes from 109 patients with suspected lung cancer.[1] In 77 patients (71%), EBUS-TBNA successfully identified cancerous lymph nodes and obviated the need for further surgical biopsy. In 96 patients with definitive reference pathology, the sensitivity of EBUS-TBNA was 91%, specificity was 100%, and diagnostic accuracy was 92%. The positive predictive value of EBUS was 100%, but the negative predictive value (ie, the proportion of patients with negative EBUS-TBNA who were also negative on surgical pathology) was only 60%. This suggests a relatively high rate of false-negative EBUS-TBNA findings in this PET-positive group of patients.

Another recent study prospectively evaluated the usefulness of EBUS-TBNA after PET-CT for mediastinal staging in 117 patients with potentially operable non–small cell lung cancer (NSCLC).[8] Patients were classified as either N2- or N3-positive or -negative using EBUS-TBNA, and patients who were N2- or N3-negative underwent surgical staging with lymph node dissection. Mediastinal node metastasis was

confirmed by EBUS-TBNA in 37 nodal stations of 27 patients. Ninety patients who were negative by EBUS-TBNA underwent surgery with lymph node dissection. Three were reclassified as positive and 87 as negative. The overall sensitivity of EBUS-TBNA for the detection of mediastinal metastases was 90% versus 70% with PET-CT ($P = .052$). For the subgroup of 61 patients who had a normal mediastinum by PET-CT, nine were found to have mediastinal metastases at surgical evaluation. Six of these nine false-negatives were correctly identified by EBUS-TBNA.

Similar results were found in a study examining the use of EBUS-TBNA in 97 patients with confirmed NSCLC, no enlarged lymph nodes on CT (ie, no lymph nodes larger than 1 cm in short axis), and no abnormal mediastinal PET findings.[9] Lymph nodes as small as 5 mm by ultrasound imaging at stations 2R, 2L, 4R, 4L, 7, 10R, 10L, 11R, and 11L were aspirated, and all patients underwent surgical staging. Malignant lymph nodes were detected by surgical staging in nine patients, and eight of these were identified by EBUS-TBNA. The sensitivity of EBUS-TBNA for the detection of mediastinal metastases was 89%; the specificity was 100%; and the negative predictive value was 99%.

Guided fine-needle aspiration with ultrasound bronchoscopy

An additional approach to mediastinal lung cancer staging is endoscopic ultrasound with bronchoscope-guided fine-needle aspiration (EUS-B-FNA) and EBUS-TBNA in a single procedure. The use of EBUS-TBNA and EUS-B-FNA for NSCLC staging was examined in a prospective study of 150 patients with confirmed or strongly suspected NSCLC.[10] Patients underwent EBUS-TBNA, and EUS-B-FNA then was used for nodes that were inaccessible through the airways. EBUS-TBNA diagnosed mediastinal metastases in 38 of 143 patients, and three more patients were identified by additional EUS-B-FNA. Surgery identified four additional patients with mediastinal metastases that were negative by both EBUS-TBNA and EUS-B-FNA. Overall sensitivity for the detection of mediastinal metastases was 84.4% with EBUS-TBNA alone versus 91.1% with EBUS-TBNA followed by EUS-B-FNA, but this was not statistically significant ($P = .332$).

A second study of 139 patients with confirmed NSCLC reported similar results when EBUS-TBNA and EUS-B-FNA were performed using a single ultrasound bronchoscope.[11] The sensitivity for detection of mediastinal metastases was 89% with EUS-FNA, 92% with EBUS-TBNA, and 96% with the combined approach. The specificity was 100% for all three approaches. The negative predictive values were 82% for the esophageal approach, 92% for the endobronchial approach, and 86% for the combined approach.

Meta-analyses support EBUS-TBNA for staging

The usefulness of EBUS-TBNA for NSCLC staging has been examined in two recent meta-analyses. The first included data from 11 studies of EBUS-TBNA with 1,299 patients.[12] Overall, the included studies yielded a pooled sensitivity of 93% and a specificity of 100% for the detection of metastatic mediastinal lymph nodes (95% CI). The sensitivity was higher for patients who were selected for evaluation on the basis of positive PET or CT findings than for patients without selection by PET or CT (0.94 vs 0.76) ($P < .05$). The authors concluded that EBUS-TBNA for lung cancer staging is accurate, safe, and cost-effective, and that selection of patients based on CT or PET findings resulted in higher sensitivity.

The second meta-analysis examined data from 10 studies evaluating the utility of EBUS-TBNA for lung cancer staging.[13] This meta-analysis also yielded high sensitivity (88%) and specificity (100%) of EBUS-TBNA for the identification of metastatic mediastinal lymph nodes.

EVALUATION OF EBUS VERSUS MEDIASTINOSCOPY AND OTHER INVASIVE TESTS

Although several studies suggest that EBUS-TBNA provides an accurate and less invasive method for assessment of mediastinal lymph nodes in the mediastinal staging of patients with NSCLC, few studies have directly compared EBUS-TBNA with mediastinoscopy. In a prospective crossover trial, 66 patients with suspected NSCLC underwent mediastinal staging using EBUS-TBNA followed by mediastinoscopy, with surgical lymph node dissection as the reference standard.[14] The overall diagnostic yield for all lymph nodes was significantly higher with EBUS-TBNA than with mediastinoscopy (91% vs 78%) ($P = .007$). However, this difference was primarily due to a higher success rate in the diagnosis of subcarinal lymph nodes (98% vs 78%) ($P = .007$), which can be difficult to evaluate with mediastinoscopy. Differences between the two methods at other node stations were not statistically significant **(Table)**. In the 57 patients who were diagnosed with NSCLC, the prediction of the correct pathologic stage did not differ significantly between the two approaches (93% with EBUS-TBNA vs 82% with mediastinoscopy) ($P = .083$).

A more recent randomized, multicenter clinical trial compared endosonographical staging (EUS-

TABLE

Diagnostic yield of EBUS-TBNA and mediastinoscopy is significant in the elevation for all lymph nodes, but varies across the lymph node stations

	Lymph node size in mm mean ± SD (range)	EBUS yield (%)	Mediastinoscopy yield (%)	*P*[a]
All lymph nodes	15 ± 2.6 (10–21)	109/120 (91)	94/120 (78)	.007
Lymph node station				
2 all	16 ± 3.1 (10–21)	24/25 (96)	22/25 (88)	.30
2 right	18 ± 1.6 (14–20)	12/13 (92)	11/13 (85)	.99
2 left	14 ± 3.6 (10–21)	12/12 (100)	11/12 (92)	.99
4 all	15 ± 2.6 (10–19)	45/54 (83)	40/54 (74)	.24
4 right	15 ± 2.6 (10–19)	29/34 (85)	24/34 (71)	.14
4 left	15 ± 2.6 (10–19)	16/20 (80)	16/20 (80)	.99
7	15 ± 2.4 (10–19)	40/41 (98)	32/41 (78)	.007

[a]*P* value by chi square test.

EBUS-TNA = endobronchial ultrasound–guided transbronchial needle aspiration

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FNA and EBUS-TBNA) with mediastinoscopy in 241 patients with resectable suspected NSCLC.[15] Patients were randomized to either surgical staging or to endosonography followed by surgical staging for those without nodal metastases using ultrasound-guided FNA. The sensitivity for detection of nodal metastases was 79% with surgical staging and 94% with endosonography and surgical staging ($P = .02$). Comparing the sensitivity of the two procedures alone, without follow-up surgical staging when ultrasound was negative, the sensitivities of the two approaches were similar: 79% with mediastinoscopy and 85% with endosonographic staging alone.

Another retrospective study examined the results of EBUS-TBNA for the initial diagnosis and staging of 88 patients with known or suspected lung cancer who underwent at least one invasive diagnostic or staging procedure before EBUS-TBNA.[16] The selection of EBUS-TBNA and bronchoscopy as the initial test for diagnosis and staging could have prevented at least one invasive test in 50% of patients, and could have been the only invasive test procedure in 47.7% of individuals. In 27 patients who underwent two or more invasive tests, EBUS-TBNA could have avoided at least one invasive test in 16 patients (59%).

PATHWAYS TO DIAGNOSIS

A proposed diagnostic algorithm for suspected NSCLC is shown in **Figure 2**.[17] When lung cancer is highly suspected on the basis of focused patient history and physical examination, the patient should undergo CT-PET or chest CT with contrast that also should assess the liver and adrenal glands. If the patient has radiographic evidence of metastatic disease, the next step is biopsy of the most accessible, most advanced lesion for tissue diagnosis and staging. In patients without evidence of metastatic disease, the next step is to evaluate the mediastinal lymph nodes. Patients with evidence of nodal involvement on PET-CT or without evidence of nodal involvement but with larger tumors (eg, stage T1b or larger) may be evaluated using EBUS-TBNA as the first invasive test if available or mediastinoscopy. Standard bronchoscopy in conjunction with EBUS-TBNA has the capability of sampling the primary lesion when the mediastinal staging fails to demonstrate malignant disease. Therefore, it can provide a definitive diagnosis in addition to mediastinal staging during one single procedure, whereas mediastinoscopy typically cannot assess the primary lesion if necessary.

APPLICATIONS IN MOLECULAR TUMOR PROFILING

Genetic profiling of lung cancer tissue samples is essential to identify biomarkers that significantly influence treatment responses, and EBUS-TBNA has been used to obtain biopsy tissue samples for genetic analysis. One study examined the detection of *EGFR* gene mutations in biopsy tissue samples obtained from 46 patients with metastatic adenocarcinoma to the hilar or mediastinal lymph nodes diagnosed by EBUS-TBNA.[18] Recut sections of the paraffin-embedded samples yielded tumor cells in 43 patients, and tissue samples were examined for mutations of *EGFR* exons 19 and 21. Five patients underwent surgical resection, and three of these yielded samples with *EGFR* mutations at exon 21. Examination of the 43 EBUS-TBNA specimens revealed *EGFR* mutations in 11. These included three of the mutations that were identified from surgical specimens. A more recent study examined the concordance between mutations of *KRAS*, *EGFR*, *BRAF*, and *PIK3CA* obtained by EBUS-TBNA, EUS-B-FNA, and histologic samples obtained during surgical staging from

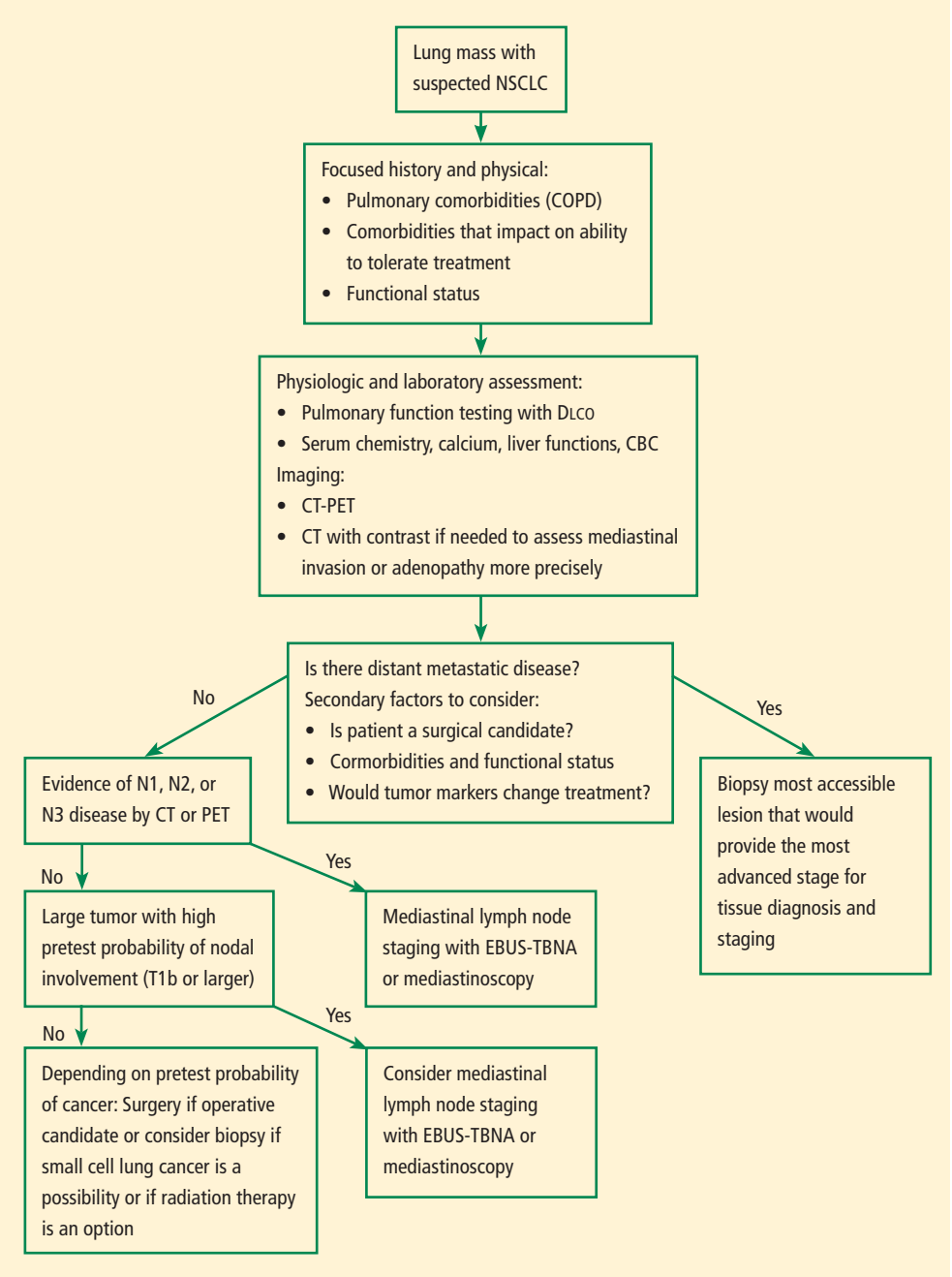

FIGURE 2. This diagnostic algorithm should be followed for patients with suspected non–small cell lung cancer (NSCLC).[17] CBC = complete blood count; COPD = chronic obstructive pulmonary disease; CT = computed tomography; DLCO = diffusion capacity of the lung for carbon monoxide; EBUS-TBNA = endobronchial ultrasound-guided transbronchial needle aspiration; PET = positron emission tomography

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43 patients.[19] *KRAS* mutations were identified in six patients, *EGFR* mutation in one patient, and *PIK3CA* mutation in one patient. The investigators observed 100% concordance between cytologic fine-needle aspirates and histologic specimens, suggesting no additional benefit of more invasive procedures for the evaluation of tumor biomarkers.

EBUS RESTAGING OF LUNG CANCER

The utility of EBUS-TBNA has also been investigated for restaging of lung cancer following neoadjuvant chemotherapy. Mediastinal restaging using EBUS-TBNA was performed in 124 consecutive patients with stage IIIA-N2 NSCLC who had received chemotherapy induction.[20] CT evaluation revealed partial responses for 66 patients and stable disease in 58. All patients subsequently underwent thoracotomy and attempted curative resection with lymph node dissection. Of 58 patients with stable disease on CT, 41 were EBUS-TBNA–positive for mediastinal metastasis, and all were thoracotomy-positive. However, in 17 patients who were EBUS-TBNA–negative, 14 were thoracotomy-positive and only three were thoracotomy-negative. Similarly, in 66 patients with partial response to treatment on CT, 48 were EBUS-TNA–positive and thoracotomy-positive. In 18 patients who were EBUS-TBNA–negative, 14 were thoracotomy-positive and only four were also thoracotomy-negative. Overall, the sensitivity of EBUS-TBNA was 77% in patients with partial responses and 75% in those with stable disease. The negative predictive value of EBUS-TBNA in this

series was very low: 22% in the partial response group and 18% in the stable disease group.

Similar results were obtained in a European study that examined EBUS-TBNA mediastinal restaging after neoadjuvant therapy in patients with pathologically confirmed N2 disease.[21] Patients with negative or uncertain EBUS-TBNA were reexamined using transcervical extended bilateral mediastinal lymphadenectomy, a surgical staging procedure that is not widely used in the United States. Of 85 mediastinal lymph nodes from 61 patients that were examined using EBUS-TBNA, nine patients (15%) had a false-negative result with EBUS-TBNA, and three patients (5%) had a false-positive result. On a per-patient basis, the sensitivity of EBUS-TBNA was 67% and the negative predictive value was 78%.

SUMMARY AND CONCLUSIONS

Newer technologies such as EBUS-TBNA make it possible to simplify the diagnosis and staging of lung cancer. Bronchoscopy with EBUS may be the preferred method for the initial diagnosis and staging of patients who have disease limited to the chest. EBUS is clearly superior to current modalities for mediastinum staging such as CT and PET, and appears to be similar to mediastinoscopy. Standard bronchoscopy with EBUS followed by mediastinoscopy, if necessary, appears to be the best strategy for initial diagnosis and staging of patients with suspected lung cancer radiographically limited to the chest. However, at this time, diagnosis and staging should rely on local expertise rather than a particular methodology. Patients with T1B lesions or higher should be considered for invasive mediastinal staging regardless of their PET or CT results. The available evidence suggests that EBUS is a reasonable initial test for mediastinal restaging following neoadjuvant chemotherapy. However, a negative EBUS in this setting should prompt additional invasive tests to confirm its findings.

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Preoperative evaluation of the lung resection candidate

ABSTRACT

Lung resection provides the greatest likelihood of cure for patients with localized lung cancer, but is associated with a risk of mortality, decreased postoperative lung function, and other complications. Lung function testing using spirometry, diffusing capacity of the lung for carbon monoxide, and peak oxygen consumption helps predict the risk of postoperative complications including mortality. Predicting postoperative lung function using the proportion of lung segments to be resected, radionuclide scanning, or other methods is important for assessing surgical risk. The American College of Chest Physicians, the European Respiratory Society/European Society of Thoracic Surgeons and the British Thoracic Society guidelines provide detailed algorithms for preoperative risk assessment, but their recommended approaches differ somewhat. Smoking cessation and pulmonary rehabilitation are perioperative measures that can improve patients' the short- and long-term outcomes.

For patients with localized lung cancer, lung resection provides the highest likelihood of a cure. However, only about 20% to 30% of patients are potential candidates for surgical resection because of the stage at which the disease is diagnosed or because of comorbid conditions.[1,2] In one study, poor lung function alone ruled out more than 37% of patients who presented with anatomically resectable disease.[3] The poor prognosis for patients who do not undergo surgery, the likelihood of early mortality from lung resection, and the potential for loss of lung function following resection are all important considerations in the preoperative pulmonary evaluation of candidates for anatomical lung resection.

PROGNOSIS OF LUNG CANCER POOR WITHOUT SURGICAL RESECTION

Several studies support the poor prognosis of lung cancer patients who do not undergo resection. In one study of 1,297 screen- and symptom-detected patients, the median duration of survival without surgery was 25 months for patients with screen-detected stage I lung cancer (n = 42) and 13 months for those with symptom-detected stage I disease (n = 27).[4] Another study of 799 patients with stage I lung cancer who were not treated surgically reported 5- and 10-year survival rates of 16.6% (n = 49) and 7.4% (n = 49), respectively.[5] In a study of 251 patients with squamous cell carcinoma on sputum cytology, yet negative chest imaging, the 5-year and 10-year survival rates were 53.2% and 33.5%.[6] Another study of 57 patients with potentially resectable disease who did not undergo surgery reported a median survival of 15.6 months, compared with 30.9 months for a group of 346 patients who underwent resection.[7]

PREDICTORS OF SURGICAL MORTALITY

Several large patient series describe perioperative mortality and the rate of complications for patients undergoing surgical resection for lung cancer. Reported surgical mortality rates in these studies vary from approximately 1% to 5%.[2,8–10] The median age of patients in most of these studies was 65 to 70 years, and many patients had significant medical comorbidity. Predictors of increased surgical mortality include pneumonectomy, bilobectomy, American Society of Anesthesiologists (ASA) Physical Status Scale rating, Zubrod performance status score, renal dysfunction, induction chemoradiation therapy, steroid use, older age, urgent procedures, male gender, forced expiratory volume in 1 second (FEV_1), and body mass index.[11] In France, a thoracic surgery scoring system

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for in-hospital mortality (Thoracoscore) was developed using data obtained from more than 15,000 patients who were enrolled in a nationally representative thoracic surgery database. Mortality risk factors included in the model were patient age, sex, dyspnea score, ASA score, performance status, priority of surgery, diagnosis, procedure class, and comorbid disease.[12] The model was highly accurate for the prediction of mortality, with a C statistic of 0.86. (1.00 corresponds to perfect outcome prediction.) The model was subsequently validated on 1,675 patients from the United States, where a similar accuracy was noted.[13] The online version of the Thoracoscore risk assessment tool is available at: http://www.sfar.org/scores2/thoracoscore2.php.

REDUCED PULMONARY FUNCTION AFTER RESECTION

Several outcome measures have been used to assess the impact of resection on pulmonary function and quality of life after surgery. Across various studies, postoperative FEV_1 values, diffusing capacity of the lung for carbon monoxide (DLCO) values, and peak oxygen consumption (VO_2 peak) were assessed at various time intervals after lobectomy or pneumonectomy. FEV_1 varied from 84% to 91% of preoperative values for lobectomy,[14–16] and 64% to 66% for pneumonectomy.[14–16] The DLCO was 89% to 96% of preoperative values after lobectomy and 72% to 80% after pneumonectomy.[14,16] VO_2 peak varied from 87% to 100% of preoperative values after lobectomy,[14–16] and 71% to 89% after pneumonectomy.[14–16]

Patients with chronic obstructive pulmonary disease (COPD) typically experience smaller declines in FEV_1 after lobectomy (0% to 8%) than those without COPD (16% to 20%). Declines in DLCO and VO_2 peak are more variable, with reported decreases of 3% to 20% in those with COPD, and 0% to 21% for those without the disease.[17–19]

Lobectomy patients continue to recover pulmonary function for approximately 6 months after surgery. In patients who undergo pneumonectomy, improvement is generally limited after 3 months.[14–16] Loss of lung function may vary significantly with the location of the resection. For example, resection of an emphysematous portion of the lung will probably result in less loss of function.

Few studies specifically examine quality of life after lung resection in patients with lung cancer. In general, patients who undergo resection have a lower quality of life before surgery than the general population.[20] Postsurgical decline in physical measures of health-related quality of life has been reported during the month after surgery, with a return to baseline after 3 months. Mental quality of life scores did not decrease after surgery, and there was little correlation between quality of life outcomes and measures of pulmonary function.[20]

LUNG FUNCTION TESTING

Lung function testing helps predict the risk of postoperative complications, including mortality. The two most commonly used measures of pulmonary function are FEV_1 and DLCO.

Both absolute FEV_1 value and percent of predicted FEV_1 strongly predict the risk of postoperative complications. It has been difficult to identify one cutoff value below which resection should not be considered. Studies have suggested preoperative absolute FEV_1 values of 2 L for pneumonectomy and 1.5 L for lobectomy as cutoffs signifying increased short- and long-term surgical risk.[21,22] Percent predicted FEV_1, which incorporates patient age, sex, and height, is more commonly used to individualize treatment, since absolute values do not take into consideration other patient-related variables. An FEV_1 of 80% predicted or higher has been proposed as a cutoff to proceed with resection without additional testing,[23] but this decision must be individualized to each patient.

Similarly, it has been difficult to identify one cutoff value for the DLCO. As one might expect, the lower the value the higher the risk for a given patient. Patients with DLCO values less than 60% predicted normal[24] had an increased mortality risk, longer hospital stay, and greater hospital costs in one report.

FEV_1 and DLCO are only modestly correlated with one another.[25] In one study, 43% of patients with FEV_1 greater than 80% of predicted had DLCO less than 80% of predicted.[26]

According to guidelines developed by the American College of Chest Physicians (ACCP), spirometry is recommended for patients being considered for lung cancer resection.[27] Patients with FEV_1 that is greater than 80% predicted or greater than 2 L and without evidence of dyspnea or interstitial lung disease are considered suitable candidates for resection, including pneumonectomy, without further testing. Lobectomy without further evaluation may be performed if the FEV_1 is greater than 1.5 L and there is no evidence of dyspnea or interstitial lung disease.

Although assessing FEV_1 values alone may be adequate in patients being considered for lung cancer resection who have no evidence of either undue dyspnea on exertion or interstitial lung disease, the

ACCP recommends also measuring DLCO when these signs are present. Guidelines from the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS) recommend routinely measuring DLCO during preoperative evaluation regardless of whether the spirometric evaluation is abnormal.[28] Similarly, the British Thoracic Society (BTS) recommends measuring transfer factor of the lung for carbon monoxide (TLCO) in all patients regardless of spirometric values.[29]

PREDICTING POSTOPERATIVE LUNG FUNCTION

Several methods have been used to predict postoperative lung function.

Segment method

The segment method estimates postoperative lung function by multiplying baseline function by the percentage of lung sections that will remain after resection.[30] For example, if preoperative FEV_1 is 1 L and surgery will result in the loss of 25% of lung segments, the predicted postoperative FEV_1 is 750 mL. In a study using 19 lung segments in the calculation, the predicted postoperative lung function correlated well with actual postoperative lung function for patients undergoing lobectomy, but only modestly for patients undergoing pneumonectomy.[30] Another method using 42 subsegments for the calculation, and correcting for segments that were obstructed by tumor, produced very similar results.[31]

Radionuclide scanning

In other studies, quantitative radionuclide scanning to identify the proportion of lung with poor perfusion produced fair to good correlations between predicted and actual postoperative FEV_1.[32–35] Techniques that are used less often include quantitative computed tomography (CT) and measurement of airway vibration during respiration.

Studies comparing different methods for predicting postoperative pulmonary function have found that perfusion imaging outperformed other approaches, and that the segment method is not a good predictor of outcome for patients undergoing pneumonectomy.[17,36]

Additional testing needed

For potential lung resection patients, the ACCP guidelines recommend that if either the FEV_1 or DLCO is less than 80% of the predicted value, postoperative lung function should be predicted through additional testing.[27] The ERS recommends that predicted postoperative FEV_1 should not be used alone to select lung cancer patients for lung resection, especially those with moderate to severe COPD.[28] These guidelines also recommend that the first estimate of residual lung function should be calculated based on segment counting, that only segments not totally obstructed should be counted, and that the patency of bronchus and segment structure should be preserved. In addition, patients with borderline function should undergo imaging-based calculation of residual lung function, including ventilation or perfusion scintigraphy before pneumonectomy, or quantitative CT scan before either lobectomy or pneumonectomy.[28] The BTS recommends the use of segment counting to estimate postoperative lung function as part of risk assessment for postoperative dyspnea. Ventilation or perfusion scintigraphy should be considered to predict postoperative lung function if a ventilation or perfusion mismatch is suspected. Quantitative CT or MRI may be considered to predict postoperative lung function if the facility is available.[29]

Predicting mortality and complications: FEV_1 and DLCO

The predicted postoperative FEV_1 value is an independent predictor of postoperative mortality and other complications. Although there is no absolute cut-off value, studies identify an increased risk of complications below predicted postoperative FEV_1 values ranging from 30%[37] to 40%.[38,39] Predicted postoperative DLCO is another outcome measure that can independently identify increased mortality risk in lung cancer resection patients. DLCO less than 40% has been associated with increased risk of postoperative respiratory complications even in those with predicted postoperative FEV_1 values above 40%.[26,39] One study stated that a combination of the two values, predicted postoperative FEV_1 and predicted postoperative DLCO—called the predicted postoperative product (PPP)—is the best predictor of surgical mortality.[40] Another study examined the utility of a prediction rule for pulmonary complications after lung surgery using a point system in which points were assigned based on predicted postoperative DLCO (1 point for each 5% decrement below 100%) plus 2 points for preoperative chemotherapy.[41] The risk of complications was 9% for those with scores less than 11, 14% for those with scores of 11 to 13, and 26% for those with scores greater than 13.

When surgery is considered, ACCP guidelines state an increased risk of perioperative mortality in those lung cancer patients with either a PPP less than 1,650, or a predicted postoperative FEV_1 less than 30%.[27] These patients should be counseled about nonstan-

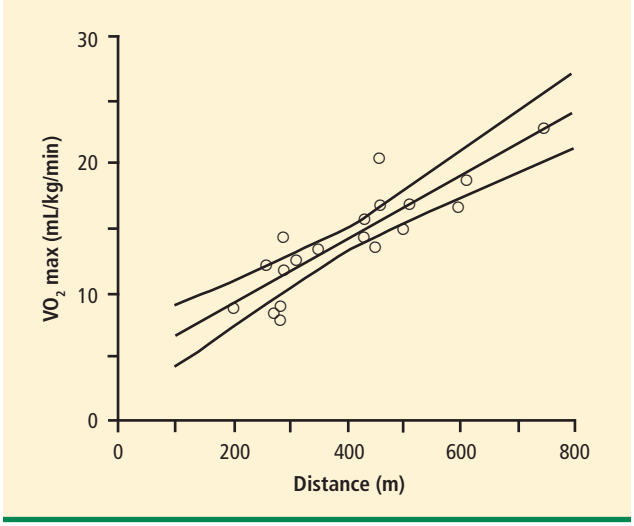

FIGURE. Distance walked during a shuttle walking test is strongly related to maximal oxygen consumption (VO_2 max).

dard surgery and nonsurgical treatment options. The ERS guidelines consider a predicted postoperative FEV_1 value less than 30% to be a high-risk threshold when assessing pulmonary reserve before surgery.[28]

EXERCISE TESTING

In general, standardized cardiopulmonary exercise testing using VO_2 peak has been shown to predict postoperative complications, including perioperative and long-term morbidity and mortality.[42,43] Lower values are associated with a greater risk of poor outcome. Peak VO_2 may not add significantly to the risk stratification of patients who have both FEV_1 and DLCO values greater than 80%.[44]

According to ACCP recommendations for exercise testing in patients who are being evaluated for surgery, either an FEV_1 or DLCO less than 40% of predicted postoperative (PPO) indicates increased risk for perioperative death and cardiopulmonary complications with standard lung resection. Preoperative exercise testing is recommended for these patients.[27] Maximal oxygen consumption (VO_2 max) less than 10 mL/kg/min, or the combination of VO_2 max less than 15 mL/kg/min with both FEV_1 and DLCO less than 40% PPO, also indicates increased risk for death and complications; these patients should be counseled about nonstandard surgery or nonsurgical treatment options. Guidelines from the ERS recommend exercise testing for all patients undergoing lung cancer surgery who have FEV_1 or DLCO less than 80% of normal values.[28] The VO_2 peak measured during incremental exercise on a treadmill or cycle should be regarded as the most important parameter.

Several studies have found that distance traveled during walking tests predicts postoperative complications and can be related to VO_2 max **(Figure)**.[45] According to ACCP guidelines, lung cancer patients who are potential candidates for standard lung resection are at increased risk for perioperative death and cardiopulmonary complications if they walk less than 25 shuttles on 2 shuttle walk tests or less than 1 flight of stairs. These patients should be counseled about nonstandard surgery and nonsurgical treatment options.[27]

Conversely, ERS/ESTS guidelines state that the shuttle walk test distance underestimates exercise capacity at the lower range, and does not discriminate between patients with and without complications.[28] These guidelines state that shuttle walk test distance should not be used alone to select patients for resection. It may be used as a screening test, since patients walking less than 400 m are likely to also have VO_2 peak less than 15 mL/kg/min. A standardized symptom-limited stair climbing test can be a cost-effective screening method to identify those who need more sophisticated exercise tests in order to optimize their perioperative management. The 6-minute walk test is not recommended.

British Thoracic Society guidelines recommend the use of the shuttle walk test as a functional assessment in patients with moderate to high risk of postoperative dyspnea.[29] A distance walk of more than 400 m is recommended as a cutoff for acceptable pulmonary function. These guidelines recommend against using pulmonary function and exercise tests as the sole surrogates for a quality of life evaluation.

ALGORITHMS FOR TESTING

The ACCP, ERS/ESTS, and BTS guidelines all include algorithms for the preoperative evaluation of candidates for lung cancer resection.[27–29] The guidelines differ from each other in many ways, including when to obtain a DLCO and cardiopulmonary exercise test, and in some of the cutoff values for various pulmonary function measures. ACCP guidelines begin with spirometry testing, supporting lobectomy in patients with spirometry results above the cutoff value of FEV_1 greater than 1.5 L and pneumonectomy in those with a cutoff value of FEV_1 greater than 2 L, and greater than 80% of predicted, unless the patient has dyspnea or evidence of interstitial lung disease. Measurement of the DLCO is recommended for those who do not meet the FEV_1 cutoffs, or in those with

unexplained dyspnea or diffuse parenchymal disease on chest radiograph or CT.[27]

A systematic review and set of treatment recommendations for high-risk patients with stage I lung cancer, developed by the Thoracic Oncology Network of the ACCP and the Workforce on Evidence-Based Surgery of the Society of Thoracic Surgeons, currently under review, will provide additional guidance regarding the use of lung function testing to evaluate risk of morbidity and mortality. These guidelines note that FEV_1, DLCO, and peak VO_2 all predict morbidity and mortality following major lung resection. Assessment of FEV_1 and DLCO, including calculation of the estimated postoperative value, is strongly recommended before resection. The predictive value of peak VO_2 is strongest in patients with impaired FEV_1 or DLCO, and assessment of peak VO_2 before major lung resection is recommended for these patients.

INTERVENTIONS TO DECREASE PERIOPERATIVE RISK

The impact of smoking cessation on perioperative outcome has been a matter of considerable debate. One large study found that the incidence of postoperative complications was actually greater when patients stopped smoking within 8 weeks before cardiac surgery.[46] However, a recent meta-analysis including lung resection patients found no relationship between smoking cessation in the weeks before surgery and worse clinical outcomes.[47] When a shorter duration of smoking cessation is examined, thoracotomy studies note that patients who continue to smoke within 1 month of pneumonectomy are at increased risk of major pulmonary events.[48,49] An examination of perioperative mortality or major complications using data from the Society of Thoracic Surgeons found that smoking cessation within 1 month preceding surgery did not significantly affect perioperative morbidity or mortality, whereas longer abstention from tobacco use was associated with better surgical outcomes.[50] The ACCP recommends that all patients with lung cancer be counseled regarding smoking cessation.[27] ERS/ESTS guidelines recommend smoking cessation for at least 2 to 4 weeks before surgery, since this may change perioperative smoking behavior and decrease the risk of postoperative complications.[28] Pulmonary rehabiliatation in the perioperative period has been shown to improve measures of activity tolerance, allowing resection of marginal candidates, and improving functional outcomes after resection.[51] The ERS/ESTS guidelines state that early pre- and postoperative rehabilitation may produce functional benefits in resectable lung cancer patients.[28]

SUMMARY AND CONCLUSIONS

Lung function testing helps predict the risk of postoperative mortality, perioperative complications, and long-term dyspnea for patients with lung cancer undergoing surgical resection. Predicted postoperative FEV_1 and DLCO should be evaluated in most resection candidates. Exercise testing adds to standard lung function testing in those with borderline values, discordance between standard measures, or discordance between subjective and objective lung function. Algorithms for preoperative assessment have been developed by the ACCP, the ERS/ESTS, and the BTS, which differ somewhat in the order of testing and specific testing cutoff values. Smoking cessation and pulmonary rehabilitation can help to reduce perioperative and long-term risks.

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Video-assisted thoracoscopic surgery for the treatment of lung cancer

ABSTRACT

A growing proportion of lung resections is being performed by video-assisted thoracoscopic surgery (VATS). VATS lobectomy is indicated for clinical stage I suspected lung cancer with pulmonary function sufficient to tolerate resection. Retrospective and matched analyses suggest less morbidity with fewer postoperative complications with VATS compared with open lobectomy. Five-year survival for VATS lobectomy in stage I non–small lung cancer patients approaches 80%. A potential oncologic benefit of VATS lobectomy (over thoracotomy) has been proposed through attenuation of postoperative cytokine release. Regardless of whether VATS or an open approach is utilized, thorough lymphadenectomy is important and may confer an additional survival benefit.

Video-assisted thoracoscopic surgery (VATS) is emerging as a therapeutic option for a variety of thoracic applications. When applied to the patient with lung cancer, the therapeutic benefit of VATS lobectomy appears to be confined to node-negative, relatively small tumors. Operable patients with larger tumors are currently best served by thoracotomy and mediastinal lymph node dissection. As an alternative to thoracotomy for stage I lung cancer, VATS lobectomy is associated with less postoperative pain, less surgical morbidity, fewer complications, and shorter hospitalization.[1–4]

LIMITED SPECIALIZED INSTRUMENTATION REQUIRED

Technologic innovation in minimally invasive surgery applied to the lung has lagged behind that of radiation oncology and interventional cardiology. VATS lobectomy requires relatively limited specialized instrumentation beyond standard minimally invasive surgical instruments commonly used for a variety of nonthoracic operations.

Video-assisted thoracoscopic surgery takes advantage of the reproducible anatomy of the lungs. However, knowledge of the vascular and bronchial anatomy is essential to avoid compromise of critical structures during VATS lobectomy.

The indication for VATS lobectomy at Cleveland Clinic is suspected clinical stage I lung cancer with pulmonary function sufficient to tolerate resection. A peripheral cancer or nodule of 3 cm or less is preferable for minimally invasive thoracic surgery.

Until 2007, the definition of a VATS lobectomy lacked uniformity. A standardized definition of VATS was provided by the Cancer and Leukemia Group B, which conducted a prospective multiinstitutional feasibility study of VATS lobectomy. It defined a true VATS lobectomy as one with individual identification and ligation of lobar vessels and bronchus, with accompanying hilar and mediastinal lymph node sampling or dissection, and performed without rib spreading.[5]

VATS OUTCOMES: FEWER COMPLICATIONS, SHORTER LENGTH OF STAY

The proportion of lung resections by VATS has increased steadily in the United States over the past decade, reaching 29% in 2007.[1] The obvious question is whether thoracoscopic lobectomy holds an advantage over thoracotomy in terms of morbidity. Park documented significantly less postoperative atrial fibrillation, blood transfusion, renal failure, and other complications when VATS lobectomy was compared with thoracotomy **(Table)**.[4]

In a propensity-matched analysis, Paul et al[1] found an overall lower rate of complications with VATS compared with open lobectomy (26.2% vs 34.7%; $P < .0001$), including a lower incidence of arrhythmia (7.3% vs 11.5%; $P = .0004$), a lower frequency

Dr. Murthy reported that he has received royalties from Hood Laboratories.

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TABLE
Postoperative complications: thoracotomy versus video-assisted thoracic surgery (VATS)

Complications	Conventional thoracotomy (n = 284) n (%)	VATS (n = 284) n (%)	*P* value
Atrial fibrillation	61 (21)	37 (13)	.01
Atelectasis	34 (12)	15 (5)	.006
Prolonged air leak	55 (19)	37 (13)	.05
Transfusion	36 (13)	11 (4)	.002
Pneumonia	27 (10)	14 (5)	.05
Sepsis	6 (2)	1 (0.4)	.12
Renal failure	15 (5)	4 (1.4)	.02
Chest tube duration, median (25th, 75th quartile), d	4 (3,6)	3 (2,4)	.0001[a]
Length of hospitalization, median (25th, 75th quartile), d	5 (4,7)	4 (3,6)	.0001[a]
Death	15 (5)	8 (3)	.20
No complications	144 (51)	196 (69)	.0001

[a]Wilcoxon signed-rank test.

Adapted from *The Journal of Thoracic and Cardiovascular Surgery* (Villamizar NR, et al. Thoracoscopic lobectomy is associated with lower morbidity compared with thoracotomy. J Thor Cardiovasc Surg 2009; 138:419–425), copyright © 2009, with permission from The American Association for Thoracic Surgery. www.sciencedirect.com/science/journal/00225223

of blood transfusion (2.4% vs 4.7%; $P = .0028$), a reduced need for reintubation (1.4% vs 3.1%; $P = .0046$), and a shorter length of stay (4.0 vs 6.0 days; $P < .0001$) and chest tube duration (3.0 vs 4.0 days; $P < .0001$). At Cleveland Clinic, length of hospital stay has been shortened by about 1 day in patients undergoing VATS compared with open lobectomy.

The advantage of thoracoscopic lobectomy compared with thoracotomy may be limited to reduction in associated morbidity alone. Five-year survival was 78% in a series of 411 patients with clinical stage I non–small cell lung cancer (NSCLC) who underwent VATS lobectomy and the more technically difficult VATS segmentectomy.[6] This rate of survival is equivalent to or better than any other reported series of patients with stage I NSCLC.

A potential oncologic benefit to the VATS approach through preservation of host immunity has also been suggested. Release of inflammatory mediators such as interleukin (IL)-6, IL-8, and IL-10 has been observed following thoracotomy and a subsequent immunosuppressive effect proposed. Liberation of these inflammatory cytokines appears attenuated by the VATS approach. Cellular proliferation and stimulation of tumor growth may be consequences of postoperative cytokine release, and limiting liberation of these products may have a direct beneficial tumor effect.[7]

MEDIASTINAL LYMPHADENECTOMY

Meticulous clinical staging of lung cancer directs clinical decision-making and has prognostic value. Imaging with computed tomography (CT) and fluorodeoxyglucose (FDG) positron emission tomography (PET) is neither sensitive nor specific for nodal metastases. The increasing popularity of less invasive staging and operative approaches for lung cancer imparts the risk of obtaining inadequate mediastinal information and the potential for undertreatment or overtreatment. At a minimum, systematic lymph node sampling is an essential component of any surgical approach (minimally invasive or open). Lymph node sampling should not be compromised by VATS, although more expertise is required for a complete VATS lymphadenectomy.

In patients with early-stage lung cancer, thorough lymphadenectomy may confer an important survival benefit even if sampled lymph nodes are found to be negative.[8] Resection of occult (undetected) disease is one potential explanation for this survival benefit.

CASE STUDY: LYMPHADENECTOMY VIA MINIMALLY INVASIVE TECHNIQUE

A 45-year-old man with a 15 pack-year history of tobacco use presented with chest pain. He quit smoking 3 years previously. Although his chest pain resolved, a lesion in the right chest was incidentally found on chest radiograph.

The patient underwent spirometry and had normal values. A follow-up CT revealed a 2.1-cm spiculated right upper lobe nodule. There was no significant nodule uptake of FDG (standardized uptake value: 1.5 to 1.8) on PET. Percutaneous fine-needle aspiration biopsy demonstrated atypical cells of unclear significance. Navigational bronchoscopy-directed biopsy also revealed atypical cells but was nondiagnostic. The concern was that because the size of the mass was 2.1 cm, surveillance was not a viable option.

Ultimately, because of the biopsy ambiguity, large nodule size, and excellent patient performance status, VATS resection was offered. As a prelude, the mediastinum was staged with mediastinoscopy. The entire central (N2) compartment was surveyed with

this technique and all samples were found to be free of cancer.

A VATS lobectomy was then performed. One utility incision (4 cm) was made and two to three ports (1 cm each) were placed within the thorax. No rib-spreading was utilized. An anatomic lobectomy with division of major vascular structures and the bronchus was performed similarly to an open procedure. When fully mobilized, the specimen (the right upper lobe in this case) was placed in a protective bag and delivered through the utility incision. Regional lymph nodes were also harvested for pathologic examination.

This patient was found to have a T1aN0M0 NSCLC and had an uneventful 3-day hospital course. Based on this final pathology and on institutional data, his projected survival was approximately 85%, 10% to 15% higher than national averages.[8]

SUMMARY

VATS lung resection is slowly becoming the standard of care for patients with stage I lung cancer. Advantages to the VATS approach compared with open lobectomy are less morbidity and shorter hospitalization. The perioperative stress response is attenuated with VATS, which suggests a potential superior oncologic outcome, although this remains to be proved. A complete mediastinal lymphadenectomy, regardless of the approach, may confer a survival advantage in early-stage lung cancer.

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Stereotactic body radiotherapy for stage I non–small cell lung cancer

ABSTRACT

Surgical resection for patients with stage I non–small cell lung cancer (NSCLC) produces high long-term survival rates, but many patients are ineligible for surgery because of medical comorbidity or other factors. Stereotactic body radiotherapy (SBRT) is the standard of care for patients with medically inoperable stage I NSCLC. Studies have reported local control rates with SBRT of about 95% when an adequate radiation dose is used. Lymph node failure averages less than 5%, while distant metastatic recurrence represents the most common site of failure. SBRT is generally safe and well tolerated even by patients with substantial pulmonary comorbidities. On average, lung function tests reveal little or no change from baseline, although individual patients may exhibit changes in pulmonary function after treatment. Most studies report pneumonitis rates of 0% to 5%. Ongoing clinical trials are investigating single-fraction SBRT and evaluating the maximal tolerated dose for centrally located tumors.

Surgical resection for patients with stage I non–small cell lung cancer (NSCLC) is typically associated with survival rates of 60% to 70% after 5 years, and as high as 80% in some series.[1] Although lobectomy or pneumonectomy improves outcomes compared with sublobar resection for many patients, a substantial number are ineligible for standard surgical resection because of cardiovascular disease or other conditions that are associated with unacceptably high perioperative risk. Observation alone is not a good strategy for patients who are ineligible for surgery. Studies comparing treatment outcomes associated with resection, radiation, and observation have demonstrated much shorter survival times and higher mortality for patients treated with observation only.[2]

Stereotactic body radiotherapy (SBRT) is the new standard of care for patients with medically inoperable stage I NSCLC. SBRT differs from standard radiation therapy in terms of dose, fractionation, field size, and targeting. Compared with standard radiation, SBRT offers a shorter and more convenient treatment regimen with improved local control and survival while lowering treatment cost.[3,4] Although cancer-specific outcomes of patients in SBRT series are similar to those in surgical groups, they are not truly comparable because of dissimilarities between the two populations. The inoperable group has higher rates of comorbidity and death compared with the medically operable group; as many as one-third die from comorbid conditions rather than cancer, leading to short follow-up in many SBRT series. Surgical resection remains the standard of care for operable stage I NSCLC.

STEREOTACTIC RADIATION FOR PATIENTS WITH INOPERABLE LUNG CANCER

Standard external beam radiation has had disappointing outcomes for stage I NSCLC, likely because of inadequate treatment doses. Delivery of 60 Gy (in two consecutive courses of 30 Gy in 10 fractions) was associated with a 5-year survival rate of 38% for patients with primary tumors less than 2 cm in size, 22% for tumors 2 to 3 cm in size, 5% for tumors 3 to 4 cm in size, and 0% for larger tumors.[5] Most studies, but not all, have reported improved treatment outcomes for patients receiving higher radiation doses.[6] Biologic and statistical modeling of tumor responses across different radiation dose levels suggests that doses as high as 80 to 90 Gy are needed to achieve a recurrence-free survival rate of 50% **(Figure 1)**, though this level is beyond the dose achieved by most standard external beam regimens.[7]

Modern standard external beam radiation doses without chemotherapy for stage I lung cancer are

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approximately 60 to 74 Gy. The dose fractionation schedule used with SBRT delivers much higher equivalent doses (83 Gy to 150 Gy), although the true biologically equivalent dose (BED) is not yet perfectly understood.[8] Most clinical studies that have examined the effectiveness of SBRT have demonstrated local control rates in excess of 90% to 95% when an adequate dose (BED ≥ 100 Gy) is utilized, since the dose-response curve appears to plateau at this level.[9] These response rates are higher than the 50% to 60% rate observed with conventional radiation.[3,4] Efforts to confirm these comparative results in randomized trials have been largely abandoned because of the perceived advantage with SBRT.

PERIPHERAL VERSUS CENTRAL TUMORS

Stereotactic body radiotherapy has been referred to as "radiosurgery," in part because the extremely high doses used to treat tumor are ablative to the immediate surrounding tissue. The consequences of ablation depend on whether the treatment involves parallel or serial tissue. Parallel tissue, such as lung, kidney, or liver, remains functional after the ablation or removal of small subunits if adequate volume of functional organ remains. With serial tissue such as the spinal cord or bowel, damage to one section results in loss of function at distal sites. Although the lung is parallel tissue, it includes serial structures such as the trachea and proximal bronchial tree. Tumors located within 2 cm of the proximal bronchial tree are classified as central, whereas tumors outside this zone are peripheral.

Peripheral tumors

Peripheral lung tumors are surrounded by only parallel tissue, and no maximum point-dose limit has been identified for their treatment. A recent cooperative group study (Radiation Therapy Oncology Group [RTOG] 0236) enrolled 55 patients, 80% with tumor stage IA (T1 N0) and 20% with stage IB (T2 N0).[10] Patients with bronchoalveolar histology were excluded from the study. Patients received three radiation treatments of 20 Gy each (BED of 180 Gy) to their known tumor with a small margin, and were followed with serial computed tomography (CT). After a median follow-up of 34 months, only one of the 55 evaluable patients had a local tumor failure, for a local control rate of 97.6%. Three patients had recurrences in the initially involved lobe for a 3-year local control rate of 90.6%; two patients had nodal failures for a 3-year local regional control rate of 87.2%; and 11 patients had disseminated recurrences, for a 3-year distant failure rate of 22.1%.

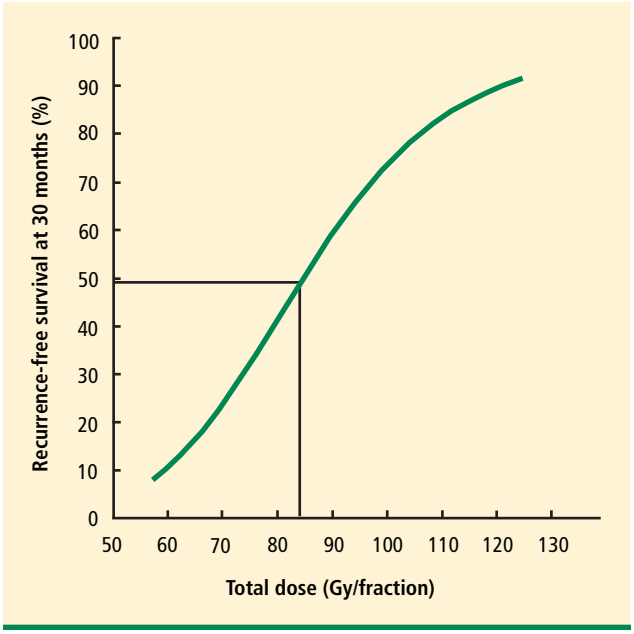

FIGURE 1. Recurrence-free survival at 30 months as a function of increasing radiation dose.[31]

Survival after 3 years was approximately 50%, which is much better than the survival rate typically attained with standard radiation therapy. Further, only 10 of the 26 deaths were attributed to lung cancer while 16 patients died of comorbid conditions such as stroke or myocardial infarction, illustrating the difficulty in tracking overall survival as a measure of efficacy in this medically fragile population.

Adverse events in this study were relatively rare. Seven patients had grade 3 or higher pulmonary complications, including hypoxia, pneumonitis, and pulmonary function test changes. Of note, the study scored changes in pulmonary function as toxicity; however, in this population, where nearly all patients have underlying lung disease, chronic obstructive pulmonary disease (COPD) exacerbations are also common.

Our own analysis of pulmonary function changes in patients treated with SBRT at Cleveland Clinic demonstrated that while there was no significant change in average baseline, pulmonary function in almost 10% of patients met criteria for a grade 3 pulmonary toxicity. A similar number of patients had a proportional improvement in pulmonary function, however. Given a nearly comparable distribution of pulmonary function changes in both directions with no significant deviation from baseline in aggregate, most of these fluctuations may be related to changes

in the patient's underlying comorbidities rather than effects of treatment.

RTOG 0236 demonstrated an excellent level of local control (97.6%) using 3 fractions of 20 Gy each (BED 180 Gy total). As noted, the dose response may plateau at 100 Gy BED,[9] which raises the question of whether the radiation dose levels used in this study were higher than necessary. A recently completed randomized phase 2 clinical trial conducted by the RTOG compared 34 Gy in a single fraction versus 48 Gy in 4 fractions, and a similar study by Roswell Park Cancer Institute, Buffalo, New York, and Cleveland Clinic is comparing 60 Gy in 3 fractions versus 30 Gy in a single fraction. These studies, once mature, should help define the optimal radiation dose and treatment schedule for patients with inoperable peripheral tumors.

Central tumors

Centrally located tumors are in proximity to both parallel tissues (normal lung) and serial tissues (trachea, bronchial tree, or esophagus), as well as imperfectly categorized tissues (heart and great vessels). An important question is whether it is possible to reach a radiation dose level of 100 Gy BED or higher in these tumors without causing excessive toxicity to normal tissues. Although there is a potential risk of cardiotoxicity with chest radiotherapy, clinical studies of SBRT for lung cancer have not demonstrated any evidence of toxicity to the heart or the great vessels with focal radiation. Some studies have suggested that radiotherapy of central lung tumors may be associated with other adverse events.

Awareness of central versus peripheral tumor locations was first raised in an early phase 2 study in which patients were treated with 60 to 66 Gy in 3 fractions over a period of 1 to 2 weeks. Grade 3 or higher toxicity during 2 years of follow-up was noted for 46% of patients with central tumors and 17% of patients with peripheral tumors.[11] Six deaths that occurred during the study were considered to be possibly treatment-related, including four cases of bacterial pneumonia, one patient with pericardial effusion, and one patient with hemoptysis that was later ascribed to carinal recurrence.

Other studies using lower fraction sizes, however, have demonstrated excellent efficacy and safety in treating central tumors with SBRT. In early Japanese studies[12,13] that used smaller fractions without tissue constraints, no differences in toxicity were noted with treatment of central versus peripheral tumors. A European study similarly demonstrated more than 90% local control at 3 years for a regimen of 60 Gy in 8 fractions (7.5 Gy/fraction).[14] Currently the RTOG is conducting a dose escalation study examining doses from 50 Gy to 60 Gy (10 Gy to 12 Gy per fraction in 5 fractions). The study has reached its highest level (60 Gy in 5 fractions) with no evidence of excessive toxicity reported.

SAFETY AND TOLERABILITY

Overall, the data suggest that for both central and peripheral tumors, SBRT is well tolerated in the medically inoperable population. On average, studies that have examined the effects of radiation therapy on pulmonary function have demonstrated little or no loss of function with SBRT. Some studies have described transient decreases in function with subsequent return to baseline.[15,16] Even if overall group median lung function scores do not change significantly as a result of SBRT, individual patients may exhibit large increases or decreases in forced expiratory volume in 1 second (FEV_1) or diffusing capacity of the lung for carbon monoxide (Dlco) after radiation therapy **(Figure 2)**. These changes may be a function of underlying comorbidities as well as SBRT, given the minimal change in the average pulmonary function test measures.[17]

Radiation pneumonitis (an inflammatory complication of radiation frequently characterized by cough, fever, and shortness of breath) is rare—less than 5% in most series. An outlier is a single series that utilized 48 Gy in 4 fractions, a common and well-tolerated dose; the investigators reported a 30% rate of grade 2 through 5 (symptomatic) pneumonitis.[18] Pneumonitis was significantly associated with the conformality index, a measure of how tightly the radiation beam is focused on the target tumor, emphasizing the importance of treatment technique on outcomes.

Other notes of caution for patients receiving SBRT include chest wall toxicity and neuropathy. Chest wall toxicity may include a variety of adverse events such as rib fractures, chest wall pain, and skin changes. These events have been described at chest wall radiation doses greater than 30 Gy.[19] One study reported brachial plexopathy in 7 of 37 patients who received doses above 100 Gy BED delivered to the brachial plexus.[20] Another recent study found that the probability of chest wall toxicity increased as the volume of chest wall receiving a 60 Gy dose increased above 15 to 20 cc.[21] Esophagitis and skin reactions are rare except in cases where the patient is being treated for a tumor in extremely close proximity to the esophagus or skin.[22]

Computed tomography after SBRT often reveals substantial focal fibrosis in the region of high-dose lung radiation.[23,24] Despite the often striking radiographic appearance, symptoms are rare and fibrosis

may sometimes be mistaken for tumor recurrence. CT images should be read by those experienced in following post-SBRT changes. Findings suspicious for recurrence are typically evaluated by positron emission tomography (PET) followed by biopsy only if PET demonstrates sufficient hypermetabolism.

OPERABLE PATIENTS

Surgical resection is the standard of care for operable patients with lung cancer. Some studies are beginning to examine whether SBRT may also be useful in potentially operable patients. A Japanese study examined outcomes for 87 operable patients who underwent SBRT for stage I NSCLC and who were followed over a 55-month period.[25] The local control rate was 92% for T1 tumors, a success rate approaching that of lobectomy. The success rate decreased to 73% for T2 tumors. Five-year overall survival rates were 72% for stage IA and 62% for stage IB, paralleling the surgical experience. Similar early results have been reported from the Netherlands.[26] An RTOG study of medically operable patients recently completed enrollment after accruing 33 patients, with final results pending maturation of the data.

A major barrier to the introduction of SBRT to the operable population is the limited nature of the available data; SBRT technology has been implemented only recently and follow-up has been modest, owing to the nature of the medically inoperable population. In addition, it is difficult to determine during the first few months after SBRT which patients will be well controlled. Waiting for response to become apparent is an appropriate strategy for an inoperable patient with no alternatives, but operable patients need a trigger to indicate initiation of salvage therapies.[27] In addition, lymph node dissection during surgery often provides information that is essential to tumor staging, and this information might be unavailable for patients treated with SBRT. It is also difficult to weigh the efficacy and tolerability of SBRT against surgical management because the two patient populations are not comparable.

High-risk operable patients

Comparisons of surgery and SBRT for stage I NSCLC are in their infancy and subject to extreme selection bias. Some attempts to create matched populations have demonstrated similar outcomes in matched patients.[28,29] Markov modeling suggests improved efficacy for surgery overall, but the model turns in favor of SBRT in patients whose predicted surgical mortality exceeds 4%.[30]

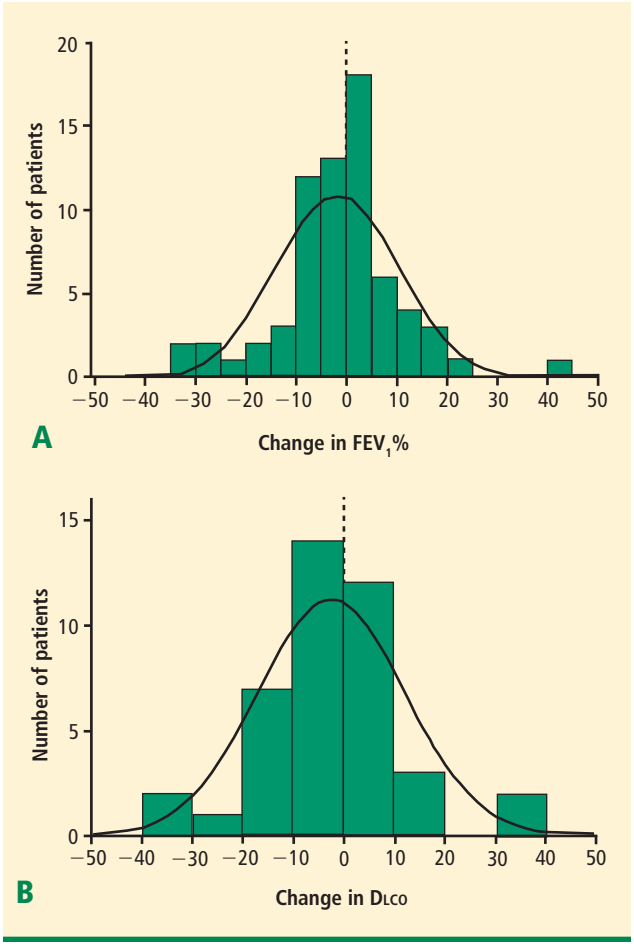

FIGURE 2. Although pulmonary function does not change significantly as a result of stereotactic body radiotherapy, some patients, as in this study, may exhibit increases in forced expiratory volume in 1 second (FEV_1) **(A)** or diffusing capacity of the lung for carbon monoxide (D_{LCO}) **(B)**.

Reprinted with permission from *Journal of Thoracic Oncology* (Stephans KL, et al. Comprehensive analysis of pulmonary function test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. J Thorac Oncol 2009; 4:838–844).

High-risk operable patients are currently eligible for the American College of Surgeons Oncology group (ACOSOG)/RTOG 0870/Cancer and Leukemia Group B (CALGB) 140503 study; a randomized phase 3 clinical trial that is comparing lobectomy versus sublobar resection for small (< 2 cm) peripheral NSCLC. This study should help to clarify how this higher-risk patient group should be managed.

CLEVELAND CLINIC EXPERIENCE

At Cleveland Clinic, more than 700 patients with stage I NSCLC have been treated with SBRT since 2003. Peripheral tumors are typically treated with a radiation dose of 60 Gy in 3 fractions spaced over 8

to 14 days, or alternatively 30 Gy to 34 Gy in a single fraction. Occasional large tumors near the chest wall or spinal cord are treated with doses up to 50 Gy in 5 fractions over 5 consecutive days. For central tumors, radiation dose regimens include 50 Gy (5 fractions over 5 consecutive days) or 60 Gy (8 fractions over 10 days), depending upon tumor size and proximity to critical structures.

SUMMARY AND CONCLUSIONS

Many patients with NSCLC are ineligible for surgery because of COPD, cardiovascular disease, or other conditions associated with unacceptably high perioperative risk. SBRT is the standard of care for patients with medically inoperable stage I NSCLC. Modern standard radiation doses are typically between 50 to 60 Gy in 3 to 5 fractions. Local control rates in excess of 90% to 95% have been reported with these doses. SBRT is generally well tolerated by patients with both peripheral and centrally located tumors. On average, lung function is not substantially altered by SBRT, although individual patients may exhibit increased or decreased FEV_1 and DLCO values after treatment. Pneumonitis has been relatively rare in most studies, with typical rates of 0% to 5%. SBRT has been shown to produce reasonable rates of local control in potentially operable patients, although data are extremely limited in this population and there are important questions about salvage therapy and postprocedural evaluation in these patients. Several ongoing clinical trials are continuing to define the efficacy and safety of different radiation dosing procedures for patients with inoperable NSCLC.

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Locally advanced non–small cell lung cancer: What is the optimal concurrent chemoradiation regimen?

ABSTRACT

The optimal chemoradiation regimen for patients with locally advanced non–small cell lung cancer (NSCLC) has yet to be defined. Disease and patient heterogeneity prevent a "one size fits all" approach to treatment. Concurrent chemoradiation up front is the definitive strategy for patients with unresectable stage III NSCLC; the addition of consolidation chemotherapy following definitive treatment has produced conflicting results with respect to overall survival. Biologic therapies have yet to show value as add-on treatment to chemoradiation.

The population of patients with stage III non–small cell lung cancer (NSCLC) presents a management challenge for clinicians. The standard of care for locally advanced NSCLC is chemotherapy plus radiation, but the optimal chemoradiation regimen is a work in progress, building upon decades of clinical trial research. Optimal therapy may require patient participation in a current phase 3 clinical trial.

Understanding the background behind the design of phase 3 clinical trials may permit better understanding of optimal chemoradiation. Most recent research has focused on optimization of chemotherapy with less attention paid to radiation dose and technique, the use of targeted agents, and imaging and planning.

A dilemma in the management of stage III NSCLC is how best to combine the correct treatments in the right sequence to achieve simultaneous local, regional, and distant control, as the disease occurs at multiple levels and cure is not possible without local disease control. Another dilemma concerns administration of radiation therapy when the lung, heart, esophagus, or spinal cord may impede delivery of treatment. Additionally, patients may not present with symptoms until an advanced stage of disease, and their performance status is frequently impaired and often influenced by comorbidities such as smoking.

FACTORS RELATED TO PROGNOSIS AND CHOICE OF TREATMENT

Most potentially curable patients with NSCLC present with locally advanced mediastinal disease. Despite improvements in staging procedures and therapy, however, the prognosis of locally advanced NSCLC remains poor with a survival rate of less than 20% at 5 years.

Prognostic indicators

Poor outcomes can be attributed to the heterogeneity of locally advanced stage III NSCLC and the factors that influence this heterogeneity. Within stage IIIA and stage IIIB, subdivisions vary considerably depending on tumor size, tumor location, and nodal involvement. With routine positron emission tomography (PET) and assessment of intracranial dissemination, a significant number of "stage III" patients are identified with advanced-stage disease and upstaged. Revisions in the staging system that define clinically distinct subsets within stage III attempt to bring more coherence to patient subsets **(Table)**.[1]

Factors that affect treatment choice

Clinical and patient factors can influence the choice of concurrent chemoradiation therapy. Weight loss, performance status, comorbidity, and pulmonary reserve influence survival and patient outcome. Comorbidities are frequently observed in elderly patients and smokers. More than one-half of patients

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TABLE
Clinically distinct subsets within stage III non–small cell lung cancer[1]

Old staging system			New staging system		
Stage IIIA	T_3N_1	Peripheral lesion with chest wall invasion or tumor < 2 cm distal to carina	**Stage IIIA**	$T_{1–2}N_2$	Peripheral lesion (≤ 7 cm) with or without visceral pleural invasion, involvement of main bronchus > 2 cm distal to carina, or obstructing pneumonitis extending to hilar region not involving entire lung Prognosis and therapy largely defined by N_2 disease (ipsilateral mediastinal nodes)
	$T_{1–3}N_2$	Prognosis and therapy defined by N_2 status (ipsilateral mediastinal nodes)[a]		$T_3N_{1–2}$	Tumor > 7 cm invading chest wall, phrenic nerve, mediastinal pleura, parietal pericardium, tumor < 2 cm from carina, or atelectasis or obstructing pneumonitis involving entire lung; or separate tumor nodules in the same lobe as primary Prognosis and therapy largely defined by N_2 disease (ipsilateral mediastinal nodes)
				$T_4N_{0–1}$	Tumor of any size involving major mediasti nal structures (eg, heart, great vessels) or separate tumor nodule(s) in a different lobe ipsilateral to primary
Stage IIIB	$T_{1–4}N_3$	Prognosis and therapy largely defined by N_3 disease (contralateral mediastinal, SC nodes)[a]	**Stage IIIB**	$T_{1–4}N_3$	Prognosis and therapy largely defined by N_3 disease (contralateral mediastinal, SC nodes)
	$T_4N_{0–2}$	Locally invasive primary tumor (T_4) and no malignant pleural effusion; no contralateral or SC nodes[a]		T_4N_2	Locally invasive primary tumor (T_4); no contralateral or SC nodes
	$T_4N_{0–3}$	Malignant pleural effusion (T_4)[b]			

[a]Candidates for combined modality therapy
[b]Treated as stage IV
M = presence of distant metastasis; N = spread to nearby lymph nodes; SC = supraclavicular; T = extent of tumor

with stage III NSCLC are currently thought to be ineligible for concurrent regimens if inclusion is restricted to patients younger than 75 years and those with fewer than two serious comorbidities. The exact contribution of comorbidity, age, and other clinical parameters to the reported toxicity is unclear.

Tumor biology

The biology of different types of NSCLC can vary considerably (eg, bronchoalveolar vs squamous cell vs adenocarcinoma). Sometimes cancer grows indolently, even with nodal presentations. Molecular profiling to understand this phenomenon is still in its infancy.

CURRENT APPROACHES TO CHEMORADIATION

Treatment of unresectable stage III NSCLC requires control of local disease and distant metastases. Much work has been undertaken to determine the safety and efficacy of sequential chemoradiation (chemotherapy followed by radiation therapy) and concurrent chemoradiation (chemotherapy during radiation therapy).

Sequential chemoradiation

Dillman et al[2,3] ushered in an era of combined modality therapy when in 1990 they demonstrated that a 5-week course of induction chemotherapy followed by radiotherapy in stage III NSCLC resulted in improved median survival compared with radiotherapy alone (13.8 months vs 9.7 months) in a randomized trial.

Sause et al[4,5] later showed that in "good risk" patients (Karnofsky Performance Status > 70) with surgically unresectable NSCLC, induction chemotherapy followed by radiation therapy produced supe-

rior short-term survival compared with hyperfractionated radiation therapy or standard radiation therapy alone.

Concurrent chemoradiation

The next step in the search for optimal sequencing was the study of concurrent chemotherapy and radiation. In phase 3 studies that compared sequential chemoradiation with concurrent chemoradiation, a consistent advantage in overall survival was conferred by concurrent chemoradiation therapy. Even with concurrent chemoradiation, however, survival was still modest (16% and 21% to 5 years in the two largest comparisons), and median survival improved only from 14.5 months with sequential therapy to 17.1 months with concurrent therapy in the largest comparison.[6]

Further support for concurrent chemoradiation on the end point of overall survival comes from two meta-analyses. A Cochrane meta-analysis demonstrated a significant 14% reduction in the risk of death with concurrent chemoradiation compared with sequential treatment.[7] The NSCLC Collaborative Group discovered a significant survival advantage with concurrent chemoradiation compared with sequential treatment (hazard ratio: 0.84) with an absolute benefit of 5.7% at 3 years (3-year survival of 18.1% with sequential chemoradiation vs 23.8% with concurrent chemoradiation).[8]

Applying the results of clinical trials to appropriate patients offers the best chance to improve outcomes. The heterogeneity of the NSCLC population makes application of therapeutic advances challenging. One must consider that the selection criteria used in clinical trials, including performance status, weight loss, disease stage, and volume of disease have a great bearing on the results achieved.

When toxicity between the two multimodality approaches was compared, the risk of grade 3 or 4 acute esophagitis was found to increase from 4% with sequential chemoradiation therapy to 18% with concurrent treatment, but no difference in acute pulmonary toxicity has been observed.[8]

Some investigators used lower doses of chemotherapy in the concurrent chemoradiation arms to minimize radiation toxicity. However, the dose intensity in sequential treatment should be maintained so that the advantage of controlling micrometastatic disease is not lost.

These clinical trials highlight that timing of chemoradiation precludes a significant proportion of patients from receiving uninterrupted radiation therapy, either because of toxicity from chemotherapy, leading to a reduction in performance status, or disease progression during sequential chemotherapy.

ATTEMPTS TO IMPROVE RADIOTHERAPY

Methods to improve radiotherapy have centered on evolving radiologic imaging and computer technology, with the objective of enhanced precision of radiation delivery. The routine use of PET in planning radiotherapy allows for dose escalation and control of toxicity.

Radiotherapy dose and outcomes

Three-dimensional (3D) conformal radiation techniques permit the use of higher doses of targeted radiation to spare normal tissue. A meta-analysis of six trials of concurrent chemoradiation therapy concluded that an increased dose of radiation improves both local control and survival.[9] A better understanding of normal lung tolerability to radiation therapy is needed to optimize radiation dose.

A clinical trial to test the efficacy of high-dose conformal radiation therapy is in progress. Patients with unresectable stage IIIA or IIIB NSCLC are being randomized to concurrent chemoradiation therapy with carboplatin and weekly paclitaxel with either 74 Gy of radiation in 37 fractions over 7.5 weeks, or 60 Gy of radiation in 30 fractions over 6 weeks. Results will be stratified by radiation therapy technique (3D conformal radiation or intensity-modulated radiation therapy). Following an impressive survival rate (median overall survival: 22.7 months) obtained with the addition of cetuximab to the chemoradiation regimen in the phase 2 Radiation Therapy Oncology Group 0324 trial, an amendment to the design further randomized patients in each radiotherapy group to cetuximab or no cetuximab.[10] Those randomized to cetuximab will continue on consolidation therapy with carboplatin, paclitaxel, and cetuximab, while the group randomized to no cetuximab will receive consolidation therapy with carboplatin and paclitaxel only.

Another approach in stage III NSCLC is the use of molecular biomarkers to predict response. Tumor typing for specific molecular sensitivities is generally thought to help predict response to systemic chemotherapy, but within the setting of radiotherapy, patients with a mutation of the epidermal growth factor receptor (EGFR) were found to have more radiosensitive tumors and decreased local recurrence rates than those without the *EGFR* mutation.[11,12] Interactions between systemic therapy and radiation may also prove to be important in response to therapy and prognosis.

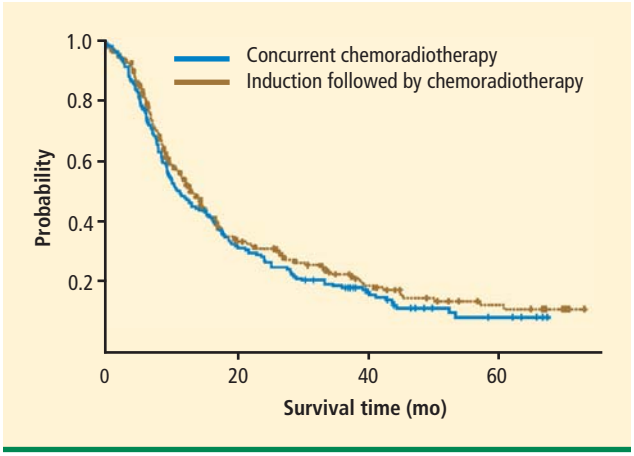

FIGURE 1. At median follow-up of 38 months among patients with non–small cell lung cancer, there was no statistically significant difference in median survival between those randomized to immediate concurrent radiotherapy and those who received induction chemotherapy followed by identical chemoradiation (12 months vs 14 months, respectively).

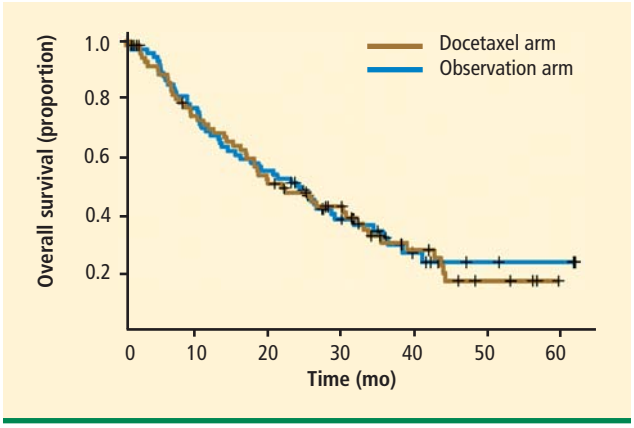

FIGURE 2. The Hoosier Oncology Group found that no survival advantage was conferred by consolidation docetaxel after cisplatin-etoposide (median survival: 21.1 months), over cisplatin-etoposide and concurrent radiation alone (observation arm, median survival: 23.2 months) in patients with stage III inoperable NSCLC.

ATTEMPTS TO IMPROVE SYSTEMIC THERAPY

Induction chemotherapy followed by chemoradiation was proposed as an alternative to concurrent chemotherapy as a way to potentially improve systemic control in patients with unresectable stage III NSCLC. Induction chemotherapy provided no survival benefit over concurrent chemoradiation alone in a randomized controlled comparison by Vokes et al **(Figure 1)**.[13] There was no significant difference in nonhematologic toxicity between the treatment groups, although the incidence of grade 3/4 esophagitis was very high (about 30%) in both arms. The patient selection may have influenced median survival in this trial; approximately 25% of patients enrolled had weight loss in excess of 5%, which has been shown to be a poor prognostic factor.

A three-arm study compared sequential chemotherapy/radiotherapy, induction chemotherapy followed by concurrent chemoradiation, and concurrent chemoradiation followed by consolidation chemotherapy.[14] In the sequential and induction arms, paclitaxel and carboplatin were administered for two cycles prior to radiation therapy; in the consolidation arm, the drugs were given following radiation therapy. The median survival was 16.3 months in the consolidation arm, 12.7 months in the induction arm, and 13.0 months in the sequential arm. The induction and consolidation arms were associated with greater toxicity. The incidences of grade 3/4 esophagitis and pulmonary toxicity were highest in the consolidation arm (28% and 16%, respectively). Although the study was not powered for direct comparison of the three treatment arms, the prolonged median survival for concurrent treatment followed by consolidation chemotherapy adds support to the argument that providing the definitive treatment up front followed by systemically active doses of chemotherapy is the preferred therapeutic approach in stage III NSCLC.

The Southwest Oncology Group (SWOG) study 9504 conducted in patients with stage IIIB NSCLC adds to the evidence of a benefit with consolidation chemotherapy after definitive chemoradiation.[15] In this trial, consolidation with docetaxel following concurrent cisplatin-etoposide and radiotherapy extended median overall survival to 26 months.

In the Hoosier Oncology Group (HOG) LUN 01-24 study, consolidation with docetaxel after cisplatin-etoposide did not have a survival advantage over cisplatin-etoposide and concurrent radiation alone, but it was associated with increased toxicity in patients with stage III inoperable NSCLC **(Figure 2)**.[16]

The dose intensity and delivery of consolidation docetaxel were similar in the SWOG 9504 and the HOG LUN 01-24 studies. Although no difference in median survival was observed between the consolidation and observation arms in HOG LUN 01-24, the median survival for the observation arm in this trial was much higher than the 15 months demonstrated with the same concurrent regimen (cisplatin-etoposide and chest radiotherapy) in the SWOG 9019 trial.[17] A difference in stage distribution across the

two trials might explain the differences in survival in the observation arms.

LITTLE PROGRESS WITH BIOLOGIC THERAPIES

The improvements observed when combining chemotherapy with radiation therapy in sequence with systemically active doses of third-generation agents have come at a price of increased toxicity, and most patients will still suffer relapse and ultimately die of metastatic disease. A significant proportion of patients will not be fit enough for more aggressive regimens.

The addition of thalidomide as an immunomodulator agent to chemoradiation did not improve overall or progression-free survival; it was also associated with a higher rate of grade 3+ toxicities in patients with stage IIIA/B NSCLC.[18]

In CALBG 30407, a regimen of pemetrexed disodium and carboplatin together with radiation therapy with or without cetuximab was studied in patients with stage III unresectable NSCLC.[19] Median survival was 22.3 months with pemetrexed-carboplatin; the addition of cetuximab conferred no significant benefit, with maintenance beyond 4 cycles being unfeasible in nearly 50% the patients enrolled.

Integrating the vascular endothelial growth factor inhibitor bevacizumab into combined modality therapy was tested in SWOG 0533. The study consisted of 3 treatment arms in which bevacizumab was introduced at different times in the concurrent chemoradiation setting in patients with stage III NSCLC. Accrual into the trial was terminated because of an unacceptable level of toxicity. Despite the risk stratification, restrictive eligibility criteria, and careful bevacizumab deployment, the approach still proved to be unfeasible.

The small-molecule epidermal tyrosine kinase inhibitors gefitinib and erlotinib had demonstrated efficacy as single agents, but the randomized SWOG 0023 trial of maintenance gefitinib after concurrent chemoradiation and consolidation therapy with docetaxel was terminated early when an interim analysis suggested lack of efficacy of maintenance gefitinib.

CONCLUSIONS

Stage III NSCLC is a heterogeneous disease with considerable variations in prognosis and treatment options. The goals of treatment are local control through the use of radiation therapy and chemotherapy and eradication of distant micrometastases through chemotherapy. For patients with good performance status, concurrent chemoradiation is the standard of care.

Phase 3 trials of full-dose chemotherapy, as either induction or consolidation, have not optimized outcomes. Integration of targeted agents is now under investigation. Any future progress will likely rely on molecular selection, which will require accruing a large number of patients into many clinical trials.

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The role of surgery for locally advanced non–small cell lung cancer

ABSTRACT

Accurate clinical staging of patients with locally advanced non–small cell lung cancer (NSCLC) is critical in identifying surgical candidates, who are typically patients with stage N2 disease. Preoperative staging by 18^{F}-fluorodeoxyglucose–positron emission tomography can alter staging and therefore influence the selection of therapy. The staging evaluation should include an assessment of the mediastinal lymph nodes; mediastinal lymph node involvement is a negative prognostic indicator. When the treatment plan potentially includes surgery, multidisciplinary evaluation including physiologic evaluation is essential, as surgery is aggressive with potential morbidity. Multimodality therapy offers the best chance for improved progression-free and overall survival. Patients with potentially resectable NSCLC who are downstaged following induction chemotherapy have a superior prognosis compared with those whose stage is unaltered.

Although not every patient with locally advanced non–small cell lung cancer (NSCLC) is a surgical candidate, surgery is worth considering for a subpopulation of patients who can benefit. For patients with stage III disease, choosing the optimal treatment is difficult and best done by a team skilled in managing this type of cancer.

Accurate clinical staging is extremely important to optimize treatment and outcome. The most common staging system used is the tumor, node, metastasis (TNM) system, which was revised in 2009. Surgery as a potential option for patients with lung cancer is becoming more accepted for patients with N2 disease but is still controversial for N3 disease. For the most part, surgical candidates are those with N2 or T4N1 disease. This article therefore focuses on staging and the utility of surgery in patients with N2 disease.

NONINVASIVE STAGING

Computed tomography (CT) of the chest and upper abdomen with intravenous contrast, including the liver and adrenal glands, is standard procedure for noninvasive staging of NSCLC. Contrast CT or magnetic resonance imaging of the brain is necessary to rule out brain metastasis in the patient with NSCLC for whom surgery is being considered.

Fused 18^{F}-fluorodeoxyglucose (FDG)-positron emission tomography (PET) is being used increasingly for staging patients with NSCLC. Preoperative staging by FDG-PET improves the detection of occult metastatic disease and alters staging **(Figure 1)**. Pieterman et al[1] demonstrated that the use of PET for clinical staging resulted in downstaging of 20 patients and upstaging of 42 patients compared with standard approaches (CT, ultrasonography, bone scanning, and needle biopsies) in a series of 102 patients with potentially resectable NSCLC. For mediastinal lymph node staging, the sensitivity and specificity of FDG-PET were 91% and 86%, respectively, compared with 75% and 66%, respectively, with CT.

At Cleveland Clinic, we have found that PET stage and pathologic stage correlate less than 70% of the time, which reflects the high incidence of histoplasmosis and other endemic inflammatory diseases of the mediastinum.

MEDIASTINAL SAMPLING

The staging evaluation includes an assessment of the mediastinal lymph nodes. Nodal sampling of the mediastinum is advised for every patient with potentially resectable NSCLC, even in the absence of an enlarged mediastinal lymph node on CT, because mediastinal lymph node involvement is a negative prognostic indicator; absence of tumor involvement of the mediasti-

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nal lymph nodes confers a more favorable prognosis.

Cervical mediastinoscopy was first introduced for lung cancer staging in 1959 and is considered the gold standard in mediastinal staging. The sensitivity and specificity approach 100% in experienced hands. A single-center experience of 2,137 cervical mediastinoscopies revealed a complication rate of 0.6% and death from mediastinoscopy in 0.05%.[2] Node stations obtainable with cervical mediastinoscopy are 2R, 4R, 3, 2L, and 4L, and sometimes 10R. These are central mediastinal nodal stations.

De Leyn et al[3] demonstrated that even small tumors can have lymph node involvement. Cervical mediastinoscopy was positive in their series in 9.5% of stage T1 tumors, 17.7% of T2, 31.2% of T3, and 33.3% of T4.

ENDOBRONCHIAL ULTRASOUND (EBUS) AND EBUS STAGING

Endobronchial ultrasound involves the use of a bronchoscope with an ultrasound probe mounted on it to evaluate nodal stations for suspicious lesions that require biopsy. Needle aspiration biopsy is performed by advancing a needle housed in a sheath of the endoscope, using ultrasound to identify target nodal tissue and obtain sample tissue for evaluation.

BRAIN IMAGING

Although brain metastases are uncommon, occurring in only 1% to 5% of asymptomatic patients with NSCLC, their identification is paramount when the treatment for stage III NSCLC is potentially high-morbidity surgery.

PHYSIOLOGIC EVALUATION

When the treatment plan potentially includes surgery, a multidisciplinary evaluation is essential and should involve specialists in medical oncology, radiation oncology, pulmonary medicine, thoracic surgery, and pathology.

Because surgery for stage III NSCLC is aggressive, prior physiologic evaluation is necessary to assess operative risk. Pulmonary function evaluation should include spirometry, measurement of arterial blood gas values, diffusion capacity (transfer factor of the lung for carbon monoxide), 6-minute walk test, and cardiopulmonary exercise testing.

Stress testing, whether by nuclear imaging or dobutamine echocardiogram, is also indicated, especially if considering pneumonectomy. A quantitative ventilation-perfusion scan is indicated for a more definitive evaluation of pulmonary function.

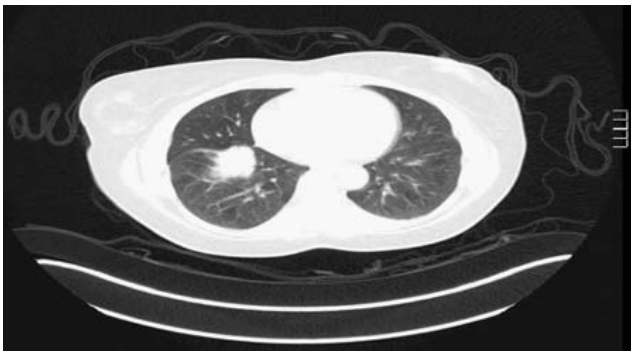

FIGURE 1. Fused ^{18}F-fluorodeoxyglucose-positron emission tomography is used for staging patients with non–small cell lung cancer. This image shows an N2-node.

RESULTS OBTAINED WITH MULTIMODALITY THERAPY

Southwest Oncology Group 8805

The Southwest Oncology Group (SWOG) study 8805 used a trimodality approach in patients with bulky stage III NSCLC: induction chemoradiation with concurrent cisplatin, etoposide, and radiotherapy (45 Gy) followed by surgical resection.[4] The 3-year survival rate with this treatment strategy was 26%. Patients in this trial who were downstaged following induction therapy so that they had node-negative disease at the time of surgery had a superior prognosis, with a 3-year survival rate of 41%. Therefore, a subset of patients with stage III NSCLC stands to benefit from surgery, but identifying this group prior to surgery may not be possible.

Trial of accelerated multimodality therapy

An accelerated multimodality induction regimen given over 12 days was tested in 105 patients with stage IIIa (n = 78) and stage IIIb (n = 27) NSCLC, 97% of whom had mediastinal involvement.[5] Seven patients had T4 disease. The induction regimen consisted of a 12-day course of concurrent cisplatin, paclitaxel, and radiotherapy. A 4-day continuous infusion of cisplatin (20 mg/m^2/day) and a 24-hour continuous infusion of paclitaxel (175 mg/m^2) were administered on day 1. Concurrent accelerated fractionated radiotherapy consisted of twice-daily fractions of 1.5 Gy.

All patients completed induction therapy. Of the 105 patients, 98 were candidates for surgical treatment and 83 underwent curative resections (lobectomy, n = 42; pneumonectomy, n = 36; and bilobectomy, n = 5).

Surgical mortality was 7% and morbidity was 31% (supraventricular arrhythmia, 18%; recurrent laryngeal nerve palsy, 6%; pneumonia or adult respiratory

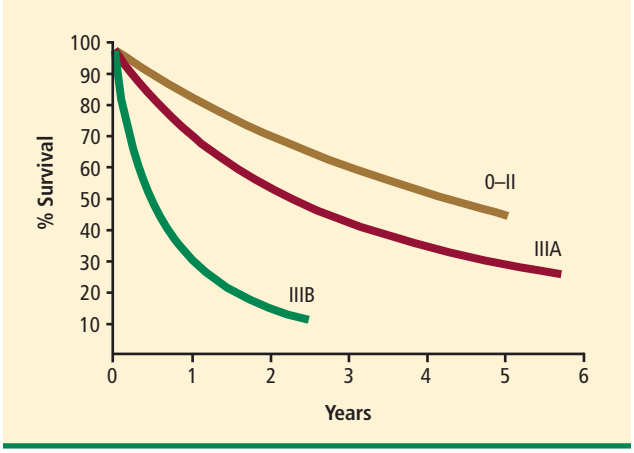

FIGURE 2. Pathologic stage is the most powerful predictive factor in patients with resectable non–small cell lung cancer. Survival among patients with pathologic stages 0 to II is superior to those with residual N2 (stage IIIA) disease. Nonresponders (stage IIIB) have the poorest survival.

Adapted from *The Journal of Thoracic and Cardiovascular Surgery* (DeCamp MM, et al. Value of accelerated multimodality therapy in stage IIIA and IIIB non–small cell lung cancer. J Thor Cardiovasc Surg 2003; 126:17–27), copyright © 2003, with permission from The American Association for Thoracic Surgery. www.sciencedirect.com/science/journal/00225223

distress syndrome, 3%; bronchopleural fistula, 3%; wound infection, 2%; reoperation for bleeding, 1%).

Survival after resection was 70% at 1 year, 42% at 3 years, and 26% at 5 years. As with SWOG 8805, nodal downstaging was associated with improved survival. Patients with disease that was downstaged to pathologic stage 0 to II had a 5-year survival that approached 50%, whereas patients with persistent stage IIIb disease had a 2-year survival of just 18% **(Figure 2)**. Patients with postresection N0 to N1 status had a 5-year survival of 55%, which declined to approximately 31% with N2 status. Few patients with N3 status survived to 3 years.

Profiles of patients with favorable and unfavorable prognoses were developed. A younger patient with adenocarcinoma whose disease was downstaged with induction therapy had a favorable prognosis, whereas an older patient with squamous carcinoma that did not respond to treatment and continued in pathologic stage IIIb had an unfavorable prognosis.

SURVIVAL DATA FAVOR SURGERY

An accurate head-to-head comparison of chemoradiation with or without surgery in patients with resectable NSCLC is difficult because patients selected for surgery must meet performance status criteria, whereas an evaluation of performance status is not mandated for patients treated with definitive chemoradiation alone. The quality of postoperative care and the management of postoperative complications also differ from institution to institution.

A controlled trial in which patients with stage IIIa NSCLC were randomized to chemoradiation with or without surgical resection was performed by Albain et al.[6] The induction regimen consisted of 2 cycles of cisplatin and etoposide plus radiotherapy (45 Gy). At 5 years, overall survival was 27% in patients who underwent resection and 20% in those who continued radiotherapy without resection, a difference that did not achieve statistical significance. Progression-free survival was superior in the group assigned to surgery compared with those not undergoing resection (median: 12.8 months vs 10.5 months).

A Surveillance Epidemiology and End Results registry of more than 48,000 patients with stage III NSCLC revealed significantly better overall survival in those who received neoadjuvant radiotherapy plus surgery compared with radiation therapy alone, postoperative radiation therapy, and surgery alone.[7]

CLEVELAND CLINIC EXPERIENCE WITH ACCELERATED PROTOCOL

At Cleveland Clinic, the current protocol for stage IIIa and IIIb NSCLC is an accelerated multimodality regimen consisting of paclitaxel, 50 mg/m^2 twice weekly for 3 weeks; carboplatin (target area under the concentration vs time curve dosing) twice weekly for 3 weeks; and daily erlotinib (phase 1 dose escalation protocol) with concurrent radiotherapy, 1.5 Gy twice daily, as induction therapy, followed by a preoperative evaluation and surgery if local control is achieved with induction treatment.

This protocol has been used in 30 patients with stage IIIa disease (median age: 61 years) with no operative mortality (62% lobectomy, 38% pneumonectomy) and a median length of stay of 6.2 days. Forty percent of patients had their disease downstaged following induction therapy. Three-year survival is approximately 60% and, at 5 years, survival is still 55%.

CONCLUSION

Multimodality therapy for NSCLC is effective and achieves favorable survival. Pathologic downstaging is an important predictor for survival but patients with residual N2 disease still have meaningful survival with resection.

A team approach to evaluation and treatment among medical oncology, radiation oncology, pulmonary medicine, and thoracic surgery is critical to successful outcome.

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The role of adjuvant chemotherapy in early-stage and locally advanced non–small cell lung cancer

ABSTRACT

Adjuvant chemotherapy benefits only a small proportion of patients in the setting of resected early-stage non–small cell lung cancer, and in unselected patients, any benefit is modest. Analysis of clinical trials of adjuvant chemotherapy revealed that differential expression of DNA repair proteins and a 15-gene expression profile affected outcomes with treatment. Biomarkers and gene expression profiles are now being studied in prospective clinical trials to gauge their value in selection of adjuvant therapy and individualization of therapy.

Despite surgery, 40% to 75% of patients with stage I to IIIA non–small cell lung cancer (NSCLC) will die within 5 years. After multiple trials showed no survival advantage to chemotherapy in the adjuvant setting for the treatment of locally advanced NSCLC, the first hint of benefit came in 1995 with the publication of a meta-analysis of 14 clinical trials, which showed a nonsignificant 5% improvement in 5-year survival with chemotherapy after surgery.[1]

A second meta-analysis, this one conducted by the Lung Adjuvant Cisplatin Evaluation (LACE) Collaborative Group, demonstrated a hazard ratio (HR) of 0.89 (P = .005) on the end point of overall survival with the use of postoperative cisplatin-based chemotherapy in patients with NSCLC; this translates to a 5-year absolute improvement of 5.4% from chemotherapy.[2] The survival benefit was confined to patients with stage II and stage III disease.

Post hoc exploratory subgroup analyses of the Cancer and Leukemia Group B (CALGB) 9633[3] and Adjuvant Navelbine International Trialist Association (ANITA)[4] trials revealed a significant survival benefit to four cycles of cisplatin-based adjuvant chemotherapy in patients with stage Ib disease who had tumors 4 cm or larger.

BIOMARKERS

Prognostic and predictive biomarkers beyond cancer stage are needed, as only 10% to 15% of patients with resected NSCLC who receive chemotherapy derive a benefit. Predictive markers can be used to guide therapeutic decision-making, and prognostic markers permit estimation of patient outcome independent of treatment modality.

Excision repair cross-complementation group 1 (ERCC1) is a rate-limiting protein in the excision repair complex of nucleotide excision repair of damaged DNA.[5] Nucleotide excision repair removes platinum-DNA adducts from tumor DNA, thus repairing DNA damage caused by systemic chemotherapy. In NSCLC, patients with tumors expressing low levels of ERCC1 show worse nucleotide excision repair capability and a worse overall prognosis in the absence of treatment compared with patients with higher expression of ERCC1. ERCC1 positivity is therefore a favorable prognostic biomarker. In a major retrospective biomarker analysis of the International Adjuvant Lung Cancer Trial (IALT), patients with low levels of ERCC1 activity had statistically superior survival after adjuvant chemotherapy compared with observation after surgery, whereas patients with ERCC1-positive tumors who have intact nucleotide excision repair had no benefit from adjuvant chemotherapy compared with patients who have surgery alone **(Figure 1)**.[6]

As with ERCC1, expression of the DNA mismatch repair protein mutS homolog 2 (MSH2)[7] is both prognostic and predictive after surgery. In

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a separate biomarker analysis from the IALT study, approximately two-thirds of patients with NSCLC had MSH2-negative tumors by immunohistochemistry, indicating lack of expression of MSH2 in tumors. Patients with expression of MSH2, who have intact mismatch repair, had a better prognosis and benefitted less from systemic chemotherapy than those with an absence of MSH2 expression.[8]

Individually, ERCC1 and MSH2 have similar power in predicting benefit from adjuvant chemotherapy in NSCLC; the HR for death was similar in patients with low expression of either gene.[8] The two biomarkers combined, however, were more powerful than either alone in their ability to predict a survival advantage with chemotherapy.[8] In an evaluation of 658 patients with NSCLC for whom both biomarkers were available, patients who expressed low tumor levels of both ERCC1 and MSH2 had an HR for death that was 35% lower with adjuvant chemotherapy compared with surgery alone after median follow-up of 7.5 years; the presence of two positive biomarkers was associated with an increase in the HR for death by 32%. Validation of these findings in a phase 3 setting will be necessary before these biomarkers can be used in the clinical setting.

The Southwest Oncology Group (SWOG) is conducting a trial (SWOG 0720) in patients with stage I NSCLC to determine whether a subset based on ERCC1 and ribonucleotide reductase M1 (RRM1) status will derive benefit from adjuvant therapy with gemcitabine together with cisplatin. Ribonucleotide reductase subunit 1 is the regulatory subunit of ribonuclease reductase, which is an enzyme that catalyzes the deoxynucleotide production required for DNA repair.

Two other clinical trials, under way but not completed, testing various forms of chemotherapy and targeted therapy based on *ERCC1* and epidermal growth factor receptor (*EGFR*) mutation status are the Tailored Post-Surgical Therapy in Early Stage NSCLC (TASTE) and the International Tailored Chemotherapy Adjuvant (ITACA) trials. The TASTE trial is comparing standard chemotherapy (cisplatin plus pemetrexed) with customized adjuvant treatment based on EGFR and ERCC1 status in patients with stage II or IIIa nonsquamous NSCLC. The ITACA trial is a phase 3 study of pemetrexed, cisplatin, and radiotherapy determined by thymidylate synthase (TS) and ERCC1 gene expression levels in patients with stage II to III completely resected NSCLC. TS is an enzyme responsible for maintaining intracellular levels of thymidine, important for DNA synthesis and repair, and may serve as a predictor of response to pemetrexed.

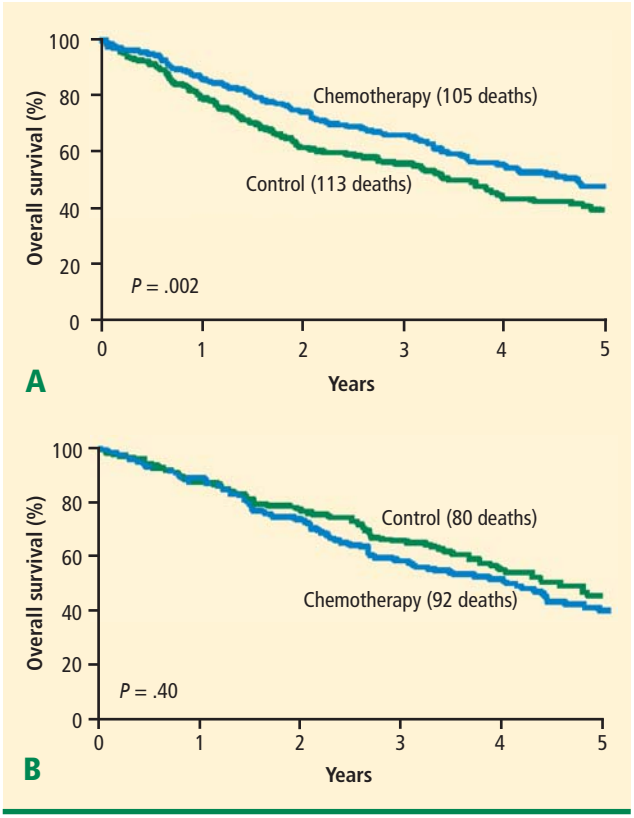

FIGURE 1. In the International Adjuvant Lung Cancer Trial, the hazard ratio (HR) for overall survival in patients with excision repair cross-complementation group 1 (ERCC1)–negative tumors who were assigned to chemotherapy was 0.65 **(A)** compared with controls, whereas the adjusted HR for survival with chemotherapy in patients with ERCC1-positive tumors was 1.14 **(B)**.

GENE EXPRESSION PROFILING

Gene expression profiles, already used to predict benefit from chemotherapy in early-stage breast cancer, may inform treatment decisions in lung cancer as well. A15-gene signature that could predict risk of recurrence and death after surgery alone for stage Ib or II NSCLC was identified using fresh frozen tissue of patients from the National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) JBR.10 trial of vinorelbine/cisplatin.[9] The risk profile was subsequently validated with reverse transcriptase-quantitative polymerase chain reaction (RT-qPCR) in the same cases and in four independent sets of patients.[9]

This 15-gene expression profile was unique in that it could also predict response to systemic chemotherapy, whereas most other gene profiles have served

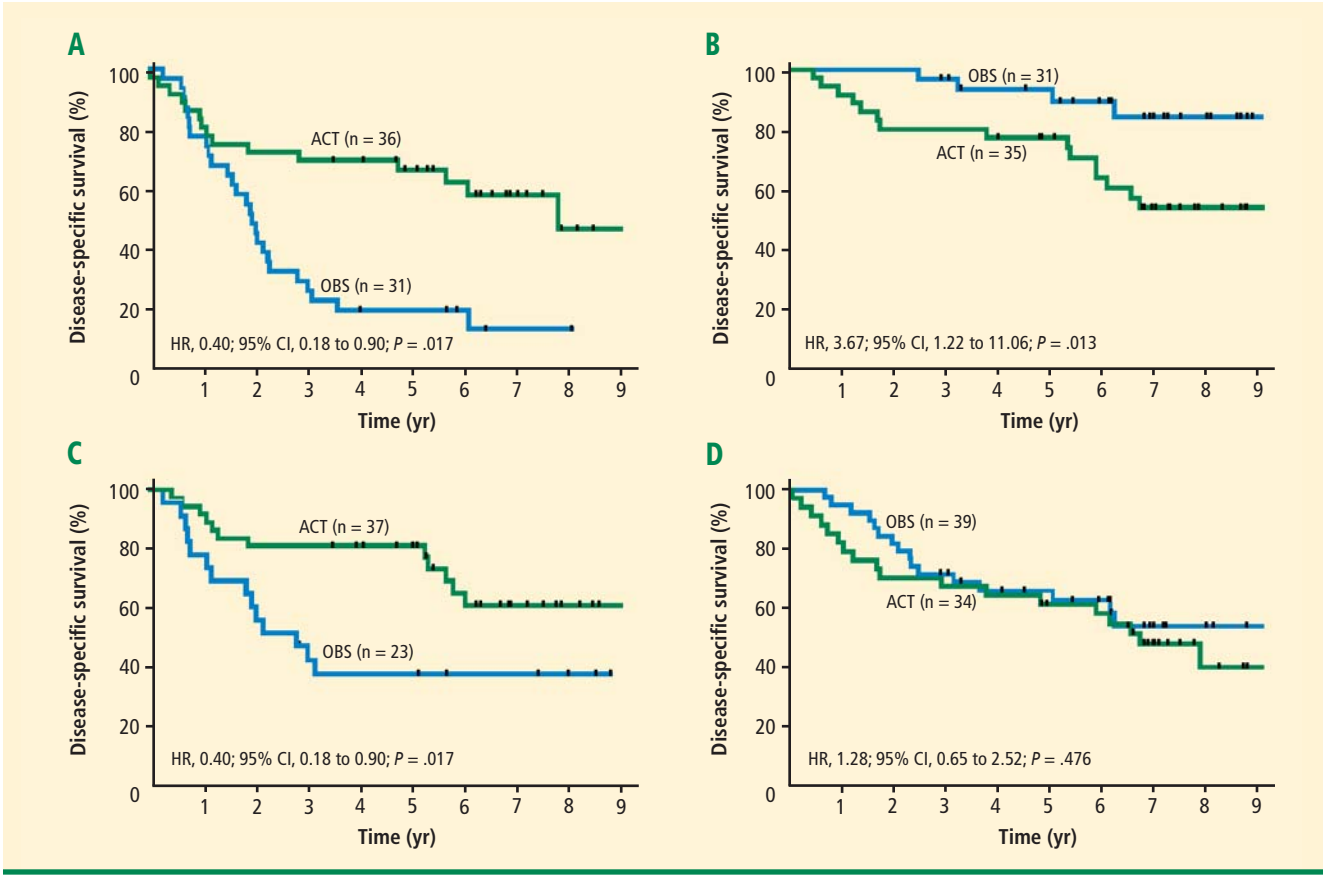

FIGURE 2. The predictive effect of a 15-gene profile with adjuvant chemotherapy in the JBR.10 trial. Only high-risk groups by microarray or reverse transcriptase-quantitative polymerase chain reaction benefited from adjuvant chemotherapy (panels **A** and **C**). ACT = adjuvant cisplatin-based chemotherapy; OBS = observation

only as prognostic markers following surgery. Adjuvant chemotherapy significantly reduced the risk of death among patients identified as high risk using the 15-gene signature, with an HR of 0.40 in those deemed high risk by RT-qPCR and 0.33 by microarray technique, compared with observation **(Figure 2)**. This benefit with chemotherapy was absent among the low-risk individuals.[9]

Among those patients with stage Ib disease, the gene expression profile was both prognostic (HR of 13.22 for disease-specific survival in the high- vs low-risk population) and predictive (HR of 0.44 for the use of adjuvant chemotherapy in the high-risk patients but no survival benefit observed with chemotherapy in low-risk patients).[9]

USE OF BIOMARKERS TO SELECT TREATMENT

As alluded to earlier, the use of biomarker expression to guide treatment selection is an area of intense investigation. In the metastatic setting, therapy targeted to the *EGFR* mutation has proven to be remarkably beneficial in patients with *EGFR*-activating mutations. In the adjuvant setting, the NCIC CTG BR.19 trial enrolled an unselected population of patients with completely resected stage Ib to IIIa NSCLC; the patients were randomized to 2 years of treatment with the tyrosine kinase inhibitor gefitinib, which targets EGFR, or placebo. Tissue samples from trial participants were collected and revealed *KRAS* mutation in 27%, a high *EGFR* gene copy number by fluorescence in situ hybridization (FISH) in 41%, and an activating *EGFR* mutation in 21%.

The NCIC CTG BR.19 trial was greatly underpowered because enrollment was stopped at 503 patients when, in 2008, the SWOG 0023 investigators reported a worse overall median survival with maintenance gefitinib after definitive chemoradiation in patients with stage III NSCLC.[10] As a result of the early termination of patient accrual, the median duration of adjuvant gefitinib in NCIC CTG BR.19 was

less than 5 months. Further, only 20% were exposed to chemotherapy and only 21% of the final study population had an *EGFR* mutation. In the overall study population, the HR for overall survival among gefitinib recipients was 1.23, indicating harm, and there was a trend in favor of placebo on the end point of disease-free survival. Neither *KRAS* nor *EGFR* copy number was predictive or prognostic, and *EGFR* mutation status was not prognostic.[11] Patients with wild-type *EGFR* had a trend toward detriment with maintenance gefitinib that was similar to that of the overall population, and those with *EGFR* mutation experienced no benefit with maintenance gefitinib.

In the Randomized Double-Blind Trial in Adjuvant NSCLC with Tarceva (RADIANT), patients with resected stage I to IIIa NSCLC, with the option for postoperative chemotherapy, were assessed for EGFR expression by immunohistochemistry or FISH and then randomized to erlotinib or placebo for 2 years. The trial completed accrual in 2010 and results are expected in 4 to 5 years.

Cleveland Clinic is currently accruing patients for a phase 2 trial of patients with resected stage I to IIIa NSCLC. All patients will have their tumors screened for activating *EGFR* mutations; those with activating mutations will receive adjuvant erlotinib for 2 years . starting within 6 months of surgery.

SUMMARY

Although adjuvant chemotherapy has been well established for patients with early-stage NSCLC, stage alone is not an ideal biomarker to predict the utility of chemotherapy, as the vast majority of patients derive no benefit from chemotherapy.

Biomarkers have been poorly validated and therefore are inappropriate for clinical use at this time. Validation of gene arrays has been disappointingly slow in lung cancer because of the absence of large tumor banks that are available in breast cancer and colon cancer.

It remains unclear whether targeted therapies improve outcomes over traditional chemotherapy in the adjuvant setting in NSCLC, as tumors in the metastatic and adjuvant settings are not the same.

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Selection of chemotherapy for patients with advanced non–small cell lung cancer

ABSTRACT

Chemotherapy remains the first-line treatment for most patients with stage IV non–small cell lung cancer (NSCLC), but optimal regimens are now defined by histology. Platinum-based regimens with pemetrexed, bevacizumab, or both are reasonable first-line options for patients with nonsquamous NSCLC. The standard treatment for squamous NSCLC remains a platinum doublet with a drug other than pemetrexed. Maintenance therapy is emerging as a treatment strategy for patients who do not progress after four cycles of first-line chemotherapy. In the maintenance setting, pemetrexed and erlotinib significantly prolong overall survival compared with placebo after the completion of first-line chemotherapy.

Despite enthusiasm for the use of molecular testing and molecularly targeted agents in patients with advanced non–small cell lung cancer (NSCLC), most patients are not candidates for upfront treatment with molecular agents. Chemotherapy therefore remains the backbone of treatment for this patient population.

This article presents the best available evidence for selection of chemotherapy for patients with advanced NSCLC and examines the controversy surrounding maintenance therapy.

EVOLUTION OF CHEMOTHERAPY IN NSCLC

The first evidence that chemotherapy produced a significant survival benefit in patients with advanced NSCLC came in 1995 when a meta-analysis showed that platinum-based chemotherapy conferred a 2-month improvement in median survival over best supportive care.[1]

This finding led to a decade of randomized phase 3 clinical trials that compared different platinum-based regimens. The quintessential trial in this regard was Eastern Cooperative Oncology Group (ECOG) 1594, in which three platinum doublets were compared with cisplatin and paclitaxel on the end point of overall survival (OS) in patients with advanced NSCLC. No significant differences were found among the regimens tested.[2]

Bevacizumab adds to platinum doublet in nonsquamous NSCLC

With the introduction of bevacizumab, an antibody against vascular endothelial growth factor, knowledge of NSCLC histology became important. In the ECOG 4599 trial, published in 2006, bevacizumab added to platinum doublet chemotherapy in patients with advanced nonsquamous NSCLC significantly improved the response rate, progression-free survival (PFS), and median OS compared with platinum doublet chemotherapy alone.[3] This trial was limited to patients with nonsquamous NSCLC because its predecessor trial had revealed an excess of life-threatening pulmonary hemorrhage in association with bevacizumab in patients with squamous cell carcinoma.

Pemetrexed superior to docetaxel in nonsquamous histology

In 2004, Hanna et al[4] demonstrated pemetrexed to be noninferior to docetaxel on efficacy outcomes as second-line therapy in advanced NSCLC. Pemetrexed had a significantly better toxicity profile, however, which led to its approval for this indication. Post hoc analyses of this trial suggested a differential effect of pemetrexed based on histology. In the pemetrexed arm, patients with nonsquamous histology appeared to have superior survival compared with patients who had squamous histology, whereas in the docetaxel arm, histology did not affect outcome.[5] Further, the

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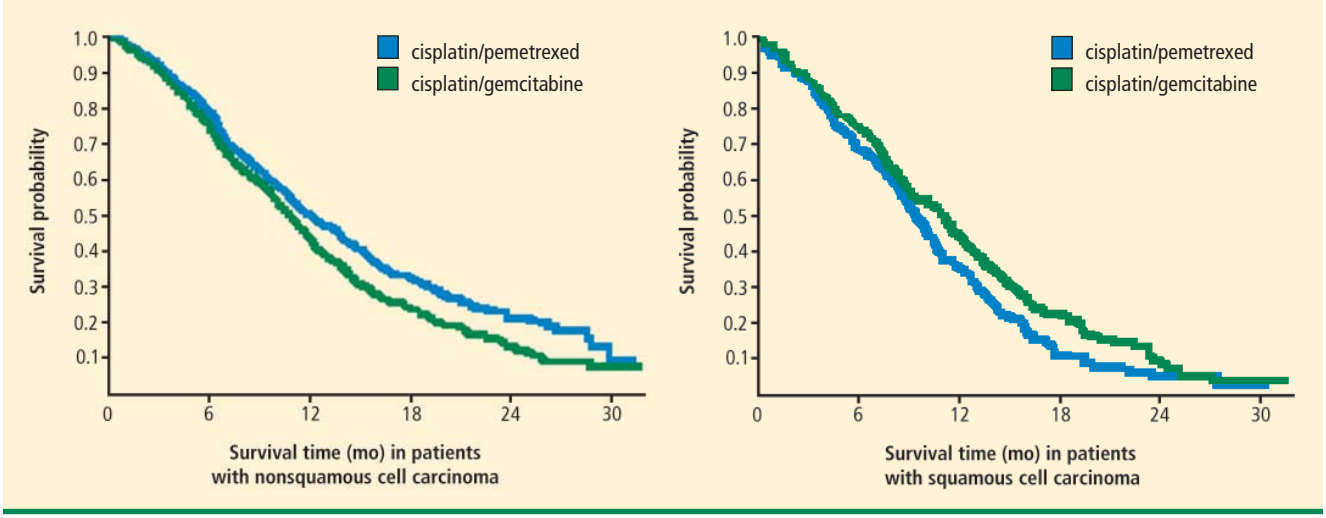

FIGURE. In a phase 3 trial that compared cisplatin/pemetrexed with cisplatin/gemcitabine based on histology, survival was superior in the pemetrexed treatment group among patients with nonsquamous non–small cell lung cancer.

nonsquamous histologic subgroup had superior OS with pemetrexed compared with docetaxel.[6]

Pemetrexed and gemcitabine perform differently based on histology

A phase 3 trial with a noninferiority design compared cisplatin/pemetrexed with cisplatin/gemcitabine as first-line therapy on OS. The noninferiority criteria were met, with no difference in median OS between the two groups (median OS: 10.3 months in both arms).[7]

A preplanned subgroup analysis based on histology demonstrated superior survival in the pemetrexed arm compared with the gemcitabine arm in patients with nonsquamous NSCLC (median survival: 11.8 months with pemetrexed vs 10.4 months with gemcitabine) **(Figure)**. Among patients with squamous cell carcinoma, gemcitabine was associated with a 1.4-month survival advantage compared with pemetrexed (10.8 months with gemcitabine vs 9.4 months with pemetrexed).[7] When assessed by subtype **(Table)**, median OS was improved by 1.7 months in the pemetrexed arm for patients with adenocarcinoma and by 3.7 months in patients with large-cell carcinoma. There was no significant difference in outcome between groups in patients with NSCLC without further subtype classification. This trial led to the approval of pemetrexed as first-line treatment for advanced, nonsquamous NSCLC.

In patients with advanced NSCLC with no tumor progression following first-line platinum-based chemotherapy, maintenance pemetrexed therapy improved OS and PFS compared with placebo, primarily in patients with nonsquamous histology.[8,9]

Based on this evidence, NSCLC is no longer an adequate pathologic diagnosis. Pathologists must differentiate squamous from nonsquamous histology to take full advantage of the safety of angiogenesis inhibitors and the efficacy of pemetrexed.

OPTIMAL FIRST-LINE REGIMEN FOR NONSQUAMOUS NSCLC

Both cisplatin/pemetrexed and carboplatin/paclitaxel plus bevacizumab have level 1 evidence to support their use as first-line treatment of NSCLC with nonsquamous histology. Carboplatin/pemetrexed/bevacizumab is also being used in the community despite the absence of randomized trial evidence to support its use for this indication.

A single-arm phase 2 trial of carboplatin/pemetrexed/bevacizumab followed by maintenance pemetrexed/bevacizumab in 49 patients produced a response rate of 55%, PFS of 7.8 months, and OS of 14 months.[10] Although the results are impressive, they should be considered hypothesis-generating rather than treatment-changing in light of the small number of patients enrolled and the single-arm design.

An open-label randomized phase 3 trial, PointBreak, is comparing two regimens in patients who have advanced nonsquamous NSCLC: (1) carboplatin/pemetrexed/ bevacizumab followed by maintenance pemetrexed/bevacizumab and (2) carboplatin/

TABLE
Cisplatin/pemetrexed vs cisplatin/gemcitabine in first-line non–small cell lung cancer: Survival comparison[7]

	Median survival time (mo)		
	Cisplatin/ pemetrexed	Cisplatin/ gemcitabine	Adjusted *P* value
Adenocarcinoma (n = 847)	12.6	10.9	.033
Large cell cancer (n = 153)	10.4	6.7	.027
Squamous cell carcinoma (n = 473)	9.4	10.8	.050
Non–small cell lung cancer (n = 252)	8.6	9.2	.586

paclitaxel/bevacizumab followed by bevacizumab.[11] Although potentially practice-changing, PointBreak will not answer whether bevacizumab adds benefit to cisplatin and pemetrexed, nor will it determine which first-line regimen is superior because of the different maintenance regimens.

SQUAMOUS NSCLC: PLATINUM DOUBLET OPTIMAL

No agents are currently approved specifically for the treatment of squamous cell carcinoma, which appears to have a high level of expression of insulin-like growth factor receptor (IGF-1R). A 64% response rate observed with an IGF-1R antagonist added to paclitaxel/carboplatin in patients with NSCLC of squamous cell histology in a phase 2 trial led to the design of a phase 3 trial in which patients were randomized to carboplatin/paclitaxel with or without the IGF-1R antagonist figitumumab. The trial ended prematurely in 2009 because of an imbalance of deaths in the experimental arm.[12] As expected, hyperglycemia was more common in the experimental arm. Unexpectedly, the incidences of grade 5 infections and cardiovascular events were also significantly higher in the experimental arm.

A randomized phase 3 trial of carboplatin/paclitaxel compared with carboplatin and nanoparticle albumin-bound (nab) paclitaxel was conducted in 1,052 patients with stage IIIb/IV NSCLC with the primary end point being overall response rate (ORR).[13] The rationale for substituting nab-paclitaxel for paclitaxel was that paclitaxel is dissolved in polyoxyethylated castor oil. This decreases the efficacy of paclitaxel and contributes to its toxicities, including hypersensitivity reactions and neuropathy. In metastatic breast cancer, nab-paclitaxel was shown to be more efficacious than solvent-based paclitaxel.[14]

The nab-paclitaxel trial met its primary end point of superior response rate: 33% in the nab-paclitaxel arm versus 25% in the standard paclitaxel arm. However, on final analysis there was no difference in PFS or OS between the two arms, making the difference in ORR of little clinical significance. No hypersensitivity reactions occurred in the nab-paclitaxel arm, while three occurred in the paclitaxel arm. Grade 3 sensory neuropathy occurred significantly less often in the group assigned to nab-paclitaxel compared with paclitaxel (3 vs 10, respectively; $P < .001$). Although there appears to be no efficacy advantage of nab-paclitaxel over standard paclitaxel for advanced NSCLC patients, use of nab-paclitaxel might be considered in patients with stage IV NSCLC who have poorly controlled diabetes or who already suffer significant neuropathy.

Although not a prespecified end point, the response rate in patients with squamous cell histology nearly doubled among those treated with nab-paclitaxel compared with standard paclitaxel. However, this did not translate into significant differences in PFS or OS in this subgroup, and the use of nab-paclitaxel in this patient population specifically is not advised.

In light of the data, the standard treatment for squamous NSCLC remains a platinum doublet other than pemetrexed. A phase 3 clinical trial, ECLIPSE, is currently enrolling patients at the Cleveland Clinic. The trial will randomize chemotherapy-naïve patients with stage IIIb/IV NSCLC and a Karnofsky performance status of 0 or 1 to receive carboplatin and gemcitabine with or without the polyadenosine diphosphate–ribose polymerase inhibitor iniparib.

MAINTENANCE THERAPY

The utility of maintenance therapy—the uninterrupted continuation of therapy for patients who do not progress after completing first-line chemotherapy—in patients with advanced NSCLC is controversial. Two kinds of maintenance therapy have emerged.

Switch maintenance, also known as early second-line therapy, is so termed because patients are immediately switched to a second-line agent different from the first-line doublet therapy.

Continuation maintenance is the continuation of one or more drugs from the induction regimen, the best example being continuation of single-agent

bevacizumab in the ECOG 4599 regimen.

Five major trials of successful maintenance therapy for nonprogressors after first-line chemotherapy have been presented over the past 4 years, and these have led to new indications for the maintenance drugs.[8,15–18] PFS in favor of active maintenance has been documented in trials of early versus delayed maintenance docetaxel,[15] pemetrexed versus placebo,[8] erlotinib versus placebo,[16] bevacizumab/erlotinib versus bevacizumab/placebo (ATLAS trial),[17] and gemcitabine or erlotinib versus placebo (IFCT-GFPC 0502).[18] The magnitude of improved PFS associated with each treatment has been similar. As a result, improved of PFS with maintenance therapy is now widely accepted.

To improve survival: maintenance therapy or better second-line therapy?

The utility of maintenance therapy can be confounded by the lack of a predefined second-line treatment. Some argue that the benefit to maintenance may also be realized by appropriate use of the same agent as salvage therapy in the case of disease progression.

Overall survival improved with maintenance therapy in only two trials; one compared pemetrexed with placebo and the other compared erlotinib with placebo.[8,16] The validity of these findings, however, remains in question. In the trial of pemetrexed, only 19% of the patients in the control arm ever received pemetrexed, and in the erlotinib trial, only 21% of the patients in the control arm ever received erlotinib after progression. Whether maintenance therapy was responsible for an improvement in OS or whether ineffective second-line therapy dampened survival in patients in the control arms is unknown.

In the IFCT-GFPC 0502 phase 3 study, patients received four cycles of cisplatin/gemcitabine.[19] If patients did not progress, they were randomized to observation, continuation maintenance with gemcitabine, or switch maintenance to erlotinib. Predefined second-line therapy in all arms was pemetrexed. The primary end point chosen was PFS, even though maintenance therapy had already been established to extend PFS. The median PFS in the gemcitabine maintenance arm was 3.8 months, compared with 1.9 months in the observation arm. The hazard ratio (HR) of 0.55 ($P < .0001$) was similar to that observed with pemetrexed in the maintenance trial noted above.[19] Subgroup analysis showed improvement in PFS with the gemcitabine maintenance group compared with observation in all subgroups, including those based on histology. The HR in the erlotinib maintenance arm was 0.82 ($P = .002$), similar to that observed with erlotinib in the Sequential Tarceva in Unresectable NSCLC (SATURN) trial.[16]

In the IFCT-GFPC 0502 study, 60.4% of patients in the gemcitabine arm, 63.2 % of those in the erlotinib arm, and 76.1% in the observation arm received postmaintenance treatment with pemetrexed.[19] Nearly one-half (49.6%) of patients in the observation arm received third-line treatment with erlotinib.

In the overall study population, a trend toward improved OS was observed with maintenance gemcitabine or erlotinib compared with observation, but did not achieve statistical significance, possibly because the trial lacked adequate power to detect a difference on this end point.

A subgroup analysis of patients who received second-line pemetrexed showed a significant improvement in OS in the maintenance arms compared with the observation arm. About 25% of the patients never advanced to second-line pemetrexed. Because patients who never received second-line pemetrexed may represent the sickest patients, the relevance of this finding to the overall population of patients with stage IV NSCLC is unknown.

Ongoing maintenance trials

Two ongoing clinical trials of maintenance are exploring bevacizumab with or without pemetrexed as maintenance following first-line cisplatin/pemetrexed/bevacizumab (AVAPERL) and bevacizumab alone, pemetrexed alone, or a combination of the two as maintenance following first-line therapy with carboplatin/paclitaxel/bevacizumab (Eastern Cooperative Oncology Group). Preliminary results from the AVAPERL study were reported recently and support the use of pemetrexed and bevacizumab as maintenance therapy compared with bevacizumab alone.[20]

CONCLUSIONS ABOUT MAINTENANCE THERAPY

Pemetrexed and erlotinib significantly prolong OS survival compared with placebo when used as maintenance therapy in advanced NSCLC patients who do not progress after four cycles of first-line chemotherapy. Whether this improvement in OS can be attributed to maintenance therapy or more effective second-line therapy is open to debate.

Maintenance chemotherapy should be discussed with all patients whose tumors do not progress after four cycles of first-line chemotherapy. The use of maintenance therapy may be most reasonable in very symptomatic patients who receive palliative benefit from chemotherapy, or as a means of encouraging noncompliant patients to return for care.

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The emerging role of palliative medicine in the treatment of lung cancer patients

ABSTRACT

The symptom burden of patients with lung cancer is extensive and includes loss of appetite, dyspnea, and other symptoms that lead to decreased quality of life. Randomized controlled trial data indicate that early palliative care improves quality of life and depressive symptoms and may extend survival in advanced non–small cell lung cancer compared with standard care. Combining an appetite stimulant (megestrol acetate) with an atypical antipsychotic (olanzapine) leads to greater weight gain and appetite improvement compared with an appetite stimulant alone. Cancer-related dyspnea appears to be a "central" effect that stems from altered afferent inputs in the setting of ventilatory muscle weakness; various treatment options that have shown success in treating cancer-related dyspnea are opioids, tunneled pleural catheters, bilevel positive airway pressure, and nebulized furosemide. Buprenorphine is a unique opioid with activity at mu and nociceptin receptors (also called opioid-receptor-like receptors); it improves pain states dominated by central sensitization.

Several important developments in the palliative care of patients with lung cancer have occurred over the past few years, including publication of a landmark study comparing early with as-needed palliative care, the release of new data on the treatment of cancer-related anorexia, elucidation of new mechanisms and treatment options for dyspnea, and the availability of buprenorphine. This article reviews these emerging concepts.

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LUNG CANCER SYMPTOMS: COMMON AND SEVERE

The symptom burden of lung cancer is usually great. At least 80% of patients experience fatigue, 65% suffer loss of appetite, 77% have cough, 73% report dyspnea (both from local symptoms and weight loss), 57% have chest pain, and 17% have hemoptysis.[1]

When symptoms are present, they are usually severe. Thirty-eight percent of the patients who report fatigue have severe fatigue, 47% have inadequate appetite to the point of requiring intervention, and more than one-half of patients who have chest pain require opioids for relief.[1]

Symptom frequency and severity are worse in individuals who survive 3 months or less.[1] Increasing symptom burden is therefore prognostically important, particularly in patients with advanced stages of lung cancer. As a result, self-assessment of quality of life has a significant ability to predict survival in patients with advanced non–small cell lung cancer (NSCLC).[2]

Patients with lung cancer tend to suffer from groups of symptoms or symptom clusters. Lutz et al[1] found that 79% of patients reported three or more symptoms; these results were similar to the findings of a study by Hollen et al,[3] in which 81% of patients suffered from three or more symptoms, all them severe except for cough.

EARLY PALLIATIVE CARE HAS CLINICAL BENEFITS

A landmark study by Temel et al[4] examined the benefits of early palliative care integrated with standard oncologic care versus standard oncologic care and palliative care only "as needed" on patient-reported outcomes, the use of health services, and the quality of end-of-life care among patients with metastatic NSCLC. The study was a prospective, nonblinded, randomized, controlled trial of outpatients conducted at a single center. The intervention was based on guidelines from the National Consensus Project for Quality Palliative Care, with specific attention to symptom management, goals of care, decision-mak-

TABLE 1
Bivariate analyses of quality-of-life outcomes at 12 weeks

Variable	Standard care (N = 47)	Early palliative care (N = 60)	Difference between standard and early care (95% CI)	*P* value	Effect size
FACT-L score	91.5 ± 15.8	98.0 ± 15.1	6.5 (0.5–12.4)	.03	0.42
LCS score	19.3 ± 4.2	21.0 ± 3.9	1.7 (0.1–3.2)	.04	0.41
TOI score	53.0 ± 11.5	59.0 ± 11.6	6.0 (1.5–10.4)	.009	0.52

CI = confidence interval; FACT-L = Functional Assessment of Cancer Therapy-Lung; LCS = lung cancer subscale; TOI = Trial Outcome Index

ing regarding treatment, and coordination of care. Patients assigned to the intervention met monthly with both a palliative care service and an oncologist, and 90% of the patients randomized to intervention complied with at least 50% of the visits.

Measures of health-related quality of life and mood were obtained using the Functional Assessment of Cancer Therapy-Lung (FACT-L), the Hospital Anxiety and Depression Scale, and the 9-item depression scale of the Patient Health Questionnaire.

Measures of health care service utilization included use of antitumor therapy within 14 days of death, late or no referral to hospice, hospital admissions, and emergency room visits. Patients were considered to have received aggressive care if they met any one of the following three criteria: chemotherapy within 14 days of death, no hospice care, or admission to hospice within 3 days of death.

Quality of life scores improved significantly in patients assigned to intervention compared with standard care **(Table 1)**. The mean improvement in the Trial Outcome Index, which is the sum of the scores on the lung cancer and physical and functional well-being subscales of the FACT-L scale, was 6 points higher in the early palliative care group compared with the standard care group at 12 weeks. The benefits were not only statistically but also clinically significant.

Compared with standard care, early palliative care was associated with an increase in the number of advance directives, earlier hospice referral (11 days vs 4 days), fewer hospitalizations and emergency room visits, and fewer instances of inappropriate oncologic care (defined as chemotherapy within 14 days of death). The percentage of patients with depressed mood was also lower among those assigned to early palliative care versus standard care (16% vs 38%).

A 2.7-month difference in median survival (P = .02) in favor of the group assigned to early palliative care was also observed, although survival was not a primary end point of the trial. This outcome needs to be validated in future studies.

CANCER-RELATED ANOREXIA AND CACHEXIA: TREATMENT IMPROVES APPETITE

The main hallmark of cancer-related anorexia and cachexia is weight loss; this symptom cluster is most often associated with hypophagia. The coexistence of anorexia and appetite-related anhedonia is common in lung cancer patients, such that 25% of lung cancer patients with anorexia report no distress with not eating, nor do they derive pleasure from eating. Others report that early satiety and changes in taste dramatically affect appetite. To some, anorexia is a distressful reminder of progression of their cancer.

Megestrol acetate and medroxyprogesterone acetate at least partially improve appetite in a subset of anorectic cancer patients. The use of medroxyprogesterone acetate has resulted in weight gain but not muscle mass in some patients with cancer-related anorexia, but has had less effect on fatigue and quality of life in these patients.

Olanzapine is an atypical antipsychotic with an affinity for multiple neurotransmitter receptors. Several of these, such as the serotonin receptors 5-HT_2 and 5-HT_3, histamine receptors, and dopamine receptors, are implicated in anorexia, nausea, and vomiting. Case reports suggest that olanzapine has antiemetic activity in patients with advanced cancer and usefulness as prophylaxis against chemotherapy-related nausea and vomiting.[5] Reduced risk of extrapyramidal symptoms compared with standard antiemetics enhances the value of olanzapine for prevention of cancer-related anorexia.

Navari et al[6] conducted a randomized trial to determine the effectiveness of megestrol acetate and olanzapine for the treatment of cancer-related anorexia. Eighty patients were randomized to receive oral megestrol acetate 800 mg/d, or oral megestrol acetate 800 mg/d plus olanzapine 5 mg once nightly, for 8 weeks. Patients were removed from the study if they did not take the study medication for a 48-hour period or if intolerable toxicity developed that was attributable to the study agents.

The MD Anderson Symptom Inventory (MDASI) was completed weekly to assess key symptom outcome variables. A change of 3 cm on the visual analog scale over two separate time periods for a symptom was considered sufficient to define a change in the symptom.

Quality of life was measured using a valid 28-item self-reported instrument (Functional Assessment of Cancer Therapy-General). Patients were examined by their physicians every 2 weeks.

In the group assigned to megestrol acetate, 15 patients had a weight gain of at least 5%—a change that was considered significant. Appetite improved in two patients, nausea decreased in three patients, and quality of life improved in five patients at both 4 weeks and 8 weeks. The improvements in appetite, nausea, and quality of life for the whole group on megestrol acetate alone were not significant, and there was no improvement in mean symptom scores measured by the MDASI.

There were incremental improvements of all measures in patients randomized to megestrol acetate plus olanzapine. Among patients receiving the combination, 33 had a weight gain of at least 5%; 25 reported an improvement in appetite, 21 experienced a reduction in nausea, and 23 had an improvement in quality of life at both 4 weeks and 8 weeks. All outcome variables were improved on the MDASI

CANCER AND DYSPNEA: NUMEROUS INTERVENTIONS HAVE BEEN ASSESSED

Reduced inspiratory capacity caused by weakened inspiratory muscles results in an increased Borg rating of perceived exertion (RPE) relative to oxygen levels. Both central nervous system activation of muscle and loss of muscle tissue contribute to dyspnea and fatigue in lung cancer patients.[7] Cancer fatigue, also measured by the Borg RPE scale, appears to be a "central" mechanism that stems from a mismatch between efferent output for afferent inputs in the setting of ventilatory muscle weakness, thereby increasing the perception of dyspnea. Several interventions have been used to relieve dyspnea, ranging from oxygen therapy to treatment with opioids.

Oxygen saturation

The association between hypoxemia and dyspnea is poor.[8] In a randomized prospective trial, Abernethy et al[9] found no benefit to oxygen therapy compared with medical air without added supplemental oxygen in individuals who had normal oxygen saturation but symptomatic dyspnea.

Bilevel positive airway pressure

Bilevel positive airway pressure has been shown to reduce the need for invasive ventilation; improve oxygen saturation; and reduce dynamic hyperinflation, thus relieving dyspnea.[10] It has been effective in dyspneic patients with motor neuron disease, cancer, heart failure, status asthmaticus, stroke, drug overdose, and interstitial lung disease.

Indwelling pleural catheters

Tunneled pleural catheters reduce the severity of dyspnea in 95% of patients.[11] These catheters are inserted on an outpatient basis, allowing for outpatient drainage. Autopleurodesis occurs in about 45% of patients, in which case the catheter can be removed. Adverse reactions are few (incidence < 10%), but consist of empyema, pneumothorax, cellulitis, or catheter obstruction. The disadvantage is the expense of catheter maintenance.

Nebulized furosemide

Case reports suggest that inhalation of nebulized furosemide, 20 mg four times daily, dramatically improves dyspnea in patients with advanced cancer and severe shortness of breath that is unresponsive to opioids.[12] Nebulized furosemide appears to have a direct effect on either pulmonary stretch receptors or irritant receptors in the airways; it also has a diuretic effect. Response occurs quickly with an onset of effect in 20 to 30 minutes.

B-type natriuretic peptide

The level of N-terminal precursor of B-type natriuretic peptide (NT-pro-BNP) can predict response to sunitinib in renal cancer,[13] and the BNP level predicts 30-day mortality in pulmonary embolism.[14] Measurement of BNP to detect dyspnea in patients with lung cancer is not useful, however, because the BNP level increases with cardiac and pericardial metastases. The BNP level is also persistently elevated after chest radiation therapy, and it increases with anthracycline cardiotoxicity. It is not a useful marker for distinguishing pulmonary from nonpulmonary or cardiac from noncardiac causes of dyspnea.

TABLE 2
Comparison of analgesic equivalence by dosage[26,27]

Drug	Dosage		
Buprenorphine SL	0.8 mg/d	1.2 mg/d	1.6 mg/d
Buprenorphine TD	35 µg/h	50 µg/h	70 µg/h
Morphine	60–90 mg/d	90–140 mg/d	140–225 mg/d
Tramadol	300–400 mg/d	450–660 mg/d	600–800 mg/d
Fentanyl	25 µg/h	35.7 µg/h	50 µg/h

SL = sublingual; TD = transdermal

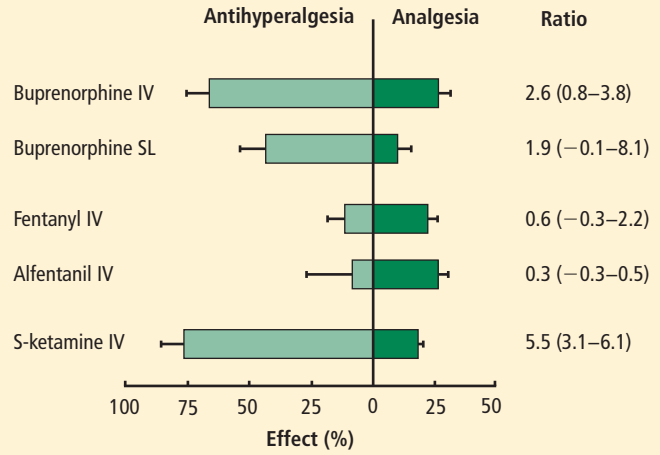

FIGURE. Ratios of antihyperalgesic and analgesic effects for buprenorphine, two pure µ-opioid-receptor agonists (fentanyl and alfentanil), and the *N*-methyl-D-aspartate antagonist ketamine.[25] The ratios were calculated using area-under-the-curve analysis. Buprenorphine and ketamine had higher antihyperalgesia-to-analgesia ratios than the pure µ-opioid-receptor agonists. IV = intravenous; SL = sublingual

Lung ultrasound

Portable diagnostic lung ultrasound can be used to detect pneumonia, pleural effusions, pulmonary emboli, pneumothorax, atelectasis, and lung abscesses as potential causes of dyspnea.[15–18] In addition to the advantage of portability, there is no radiation exposure and the technology permits echocardiography to be conducted.

Opioids

Evidence supports opioids for pharmacologic relief of dyspnea in the palliative care of patients with chronic obstructive pulmonary disease and cancer. Studies have been conducted with morphine sulfate, hydromorphone, dihydrocodeine, intranasal and transmucosal fentanyl, oxycodone, and diamorphine.[19–21]

The response to opioids is unrelated to the severity of dyspnea.[22] Responses and safe administration occur even in patients with reduced oxygen saturation or elevated carbon dioxide partial pressure.[20] Opioids can be used safely in the opioid-naïve population.[20] Recommended dosages in these patients are 2.5 to 5.0 mg of morphine sulfate every 4 hours, 5 mg of oxycodone every 4 hours as needed, and 1 mg of hydromorphone every 4 hours in the opioid-naïve. In opioid-tolerant patients, it is recommended that therapy start with these doses and then be increased in 25% increments every 24 hours, as needed.

BUPRENORPHINE: UNIQUE OPIOID

Buprenorphine is a mu- and nociceptin (ORL-1)-receptor partial agonist with intravenous, subcutaneous, sublingual, transdermal, and intranasal routes of delivery.[23] An agent that acts as an ORL-1 agonist can induce analgesia by blocking nociceptive responses at the level of the spinal cord. It is a kappa antagonist (depending upon the kappa ligand used in the assay), which may contribute to its antihyperalgesia. The parent drug has a high affinity and low intrinsic efficacy for the mu receptor. The main metabolite, norbuprenorphine, is a delta opioid-receptor agonist.

There is a differential dose-response curve for analgesia and respiratory depression with buprenorphine, with less respiratory suppression but no loss of analgesia at high doses. This ceiling effect on respiratory suppression leads to an improved therapeutic index at higher doses; increasing the dosage increases the safety margin.[24] In addition, unlike other potent opioids, buprenorphine does not reduce gonadotropins or sex hormones and is not immunosuppressive. Analgesic potency of sublingual and transdermal buprenorphine is compared with equivalent dosages of morphine, tramadol, and fentanyl in **Table 2**.

Secondary hyperalgesia is an increased sensitivity to painful stimuli around an area of injury and occurs frequently following injury. The increased pain sensation is a result of central sensitization derived from

brainstem neurons that facilitate pain; it is not derived from afferent signals from the primary site. Secondary hyperalgesia is less responsive to opioids than primary hyperalgesia at the site of injury.

Pain is improved with buprenorphine predominantly through modulation of central sensitization and less so at the primary site. Koppert et al[25] demonstrated in human volunteers that buprenorphine reduced the area and duration of secondary hyperalgesia more than pain at the site of injury (half-life of 171 minutes vs 288 minutes, respectively). Buprenorphine had a much greater antihyperalgesic effect than analgesic effect compared with potent opioids such as fentanyl. In contrast, the analgesic effects with fentanyl and alfentanil were much greater than their antihyperalgesic effects **(Figure)**, suggesting the possibility of a combination of opioid therapy for superior pain relief or choices based on pain phenotype (eg, secondary or primary hyperalgesia).

SUMMARY

Early palliative care improves quality of life and decision-making in patients with advanced lung cancer and may improve survival, although survival data need to be confirmed. Olanzapine and megestrol acetate are superior to megestrol acetate alone for the treatment of anorexia. Oxygen is no better than medical air in the management of dyspnea associated with normal oxygen saturation. Buprenorphine is a unique opioid that has value for pharmacologic relief in patients at risk for respiratory depression.

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Personalized targeted therapy in advanced non–small cell lung cancer

ABSTRACT

Personalized targeted therapy for advanced non–small cell lung cancer (NSCLC) primarily relies on the concept of "oncogene addiction," in which multiple genetic abnormalities are addicted to one or a few genes for tumor cell maintenance and survival. Several molecular aberrations have been identified in NSCLC, with subsequent development of drugs targeted to these aberrations; gefitinib, erlotinib, and cetuximab for the treatment of NSCLC harboring epidermal growth factor receptor mutation or overexpression, and crizotinib for the treatment of NSCLC with the EML4-ALK fusion translocation oncogene being some examples. A more recent actionable target is MET, a multifaceted receptor tyrosine kinase within the human kinome. Cellular heterogeneity within an oncogene-addicted tumor can cause resistance to targeted therapy after an initial response. As our understanding of tumor heterogeneity and tumor resistance mechanisms evolves, more rational therapies and combinations of therapies can be expected.

The efficacy of therapy targeted to a specific oncogene is convincing evidence of "oncogene addiction," or the concept that some cancers rely on or are "addicted to" a specific gene for their survival and proliferation. In the case of non–small cell lung cancer (NSCLC), drugs that target epidermal growth factor receptor (EGFR) have been proven more effective than conventional chemotherapy in patients with sensitizing *EGFR* mutations.[1]

Lung cancer oncogenes can drive oncogenic signaling pathways within tumor cells. Activation of EGFR signaling that drives cell proliferation through pathways such as RAS/RAF/MEK/ERK and the cell survival pathways P13K and AKT has been demonstrated in never-smokers. In heavy smokers, *KRAS* oncogene mutation is the dominant promoter of activation of oncogenic signaling pathways; it predicts a poor prognosis (especially for lung adenocarcinoma), and it is essentially mutually exclusive with *EGFR* mutations.

More than 50% of cases of NSCLC have known oncogene mutations for which targeted therapeutics are available.[2] For example, gefitinib and erlotinib are the effective inhibitors for the *EGFR* oncogene mutation, sunitinib for platelet-derived growth factor receptor (*PDGFR*) amplification, and lapatinib for the less common *ERBB2* insertion.

A number of molecular aberrations have been identified in NSCLC **(Table 1)**.[3] Known molecular alterations include:

- *EGFR* mutations and amplifications
- *EML4-ALK* translocation fusions
- *KRAS* mutations
- *PIK3CA* mutations
- *MET* mutations, alternative splicing, amplification, and overexpression

PLATINUM DOUBLET AS STANDARD

Multiple platinum-based combinations of chemotherapy are in use as first-line therapy for advanced NSCLC. An overall survival (OS) benefit has been established with the use of doublet regimens, but no platinum-based doublet regimen has been proven superior to another on the end point of OS in clinical trials.[4]

Adding a third agent increases the response rate in advanced NSCLC but does not improve OS; the exception is bevacizumab, a monoclonal antibody targeted to vascular endothelial growth factor (VEGF). Sandler et al[5] demonstrated a survival benefit when bevacizumab was added to paclitaxel-carboplatin in a recent study that led to US Food and Drug Adminis-

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tration (FDA) approval of bevacizumab for the treatment of NSCLC.

The next oncogene target explored in advanced NSCLC was EGFR. The tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, lapatinib, and the monoclonal antibody cetuximab are all clinical inhibitory agents targeting EGFR.

Previously treated NSCLC

Several trials have demonstrated that previously treated NSCLC patients with *EGFR* mutations have a longer time to progression when treated with the TKI gefitinib compared with conventional cytotoxic chemotherapy **(Table 2)**. The first of these trials was the phase 2 Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL) trial.[6] Gefitinib was eventually approved for the treatment of unselected patients with advanced NSCLC based on the phase 2 results. Gefitinib has since been replaced by erlotinib in the United States, but is still available in Asia and some European countries. The Iressa Survival Evaluation in Lung Cancer (ISEL) trial was a phase 3 study of gefitinib conducted in patients who had received one or two prior chemotherapy regimens.[7] There was no significant improvement in OS with gefitinib in the overall study population, but a subset analysis of patients of Asian origin showed a significant improvement in survival in this subgroup treated with gefitinib.

In the phase 3 National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) BR.21 trial, erlotinib demonstrated significant superiority over placebo as second- or third-line chemotherapy on PFS and OS in unselected patients with NSCLC. The results led to its approval as treatment for advanced NSCLC in patients who have received at least one prior chemotherapy regimen.[8]

Patient survival in NCIC CTG BR. 21 was evaluated in a series of patient subsets in exploratory univariate analyses. The effect of erlotinib on survival was similar across most subsets. A greater effect on survival by erlotinib was observed in patients who had never smoked (hazard ratio [HR] = 0.42). In the subgroup of patients who never smoked, EGFR status was predictive of erlotinib survival benefit. Patients who never smoked and were EGFR-positive had a survival benefit with erlotinib (HR = 0.27). There were too few EGFR-negative patients who never smoked to reach a conclusion.

Sensitizing mutations lead to better response

With the approval and clinical use of EGFR-TKIs came knowledge of EGFR kinase mutations that sensitize the mutated RTK to EGFR-TKI; this mechanism translates into dramatic tumor responses.[9,10] Certain *EGFR* mutations contribute to sensitivity to EGFR-TKI treatment. The most common sensitizing mutations are the Exon 21 L858R mutation and the Exon 19 short in-frame deletions. The Exon 20 tends to yield resistant alterations (eg, prototypical T790M mutation and some Exon 20 Dup/Ins) in patients who initially derived benefit from targeted therapeutics. Although advances have been made in targeted therapeutics in lung cancer and other cancers, clinical resistance, particularly acquired or secondary resistance, remains the rule rather than the exception, which inherently limits the long-term clinical success of targeted therapeutics. A higher level of

TABLE 1
Molecular aberrations in non–small cell lung cancer

Molecular aberration	Frequency in NSCLC (%)	Comment
EGFR mutation	10–16.6	Indicates sensitivity to EGFR inhibitors
EGFR amplification	30.8–59.2	May be associated with response to EGFR inhibitors
EML4-ALK fusion	5–7	Indicates sensitivity to ALK inhibitors (eg, PF-02341066, crizotinib)
KRAS mutation	19–21	Usually in smokers; associated with poor prognosis irrespective of therapy; conflicting data with respect to resistance to EGFR inhibitors
PIK3CA mutation	2	May be involved in EGFR resistance
PIK3CA amplification	12–17	May be involved in EGFR resistance
MET mutation	12–14	Contributes to EGFR resistance
MET amplification	11.1–21	Contributes to EGFR resistance

EML4 = echinoderm microtubule-associated protein-like 4; *ALK* = anaplastic lymphoma kinase; *EGFR* = epidermal growth factor receptor; *KRAS* = GTPase *KRAS*; *MET* = hepatocyte growth factor receptor; NSCLC = non–small cell lung cancer; *PIK3CA* = phosphatidylinositol 3-kinase p110 alpha catalytic subunit isoform

TABLE 2
Phase 2 and 3 studies of epidermal growth factor receptor tyrosine kinase inhibitors in previously treated non–small cell lung cancer

Study	No. patients	Drug	Dose (mg)	RR (%)	CB (%)	PFS (mo)	OS (mo)
Phase 2							
IDEAL I[6]	104	Gefitinib	250	18.4	54.4	2.7	7.6
	106		500	19	51.4	2.8	8
IDEAL II[25]	102	Gefitinib	250	12	NR	NR	7
	114		500	9	NR	NR	6
Phase 3							
NCIC CTG BR.21[8]	488	Erlotinib	150	8.2	45	2.2[a]	6.7[a]
	243	Placebo		0.7	NR	1.8	4.7
ISEL[7]	1,129	Gefitinib	250	8	40	3[b]	5.6
	563	Placebo		1.3	32	2.6[b]	5.1

[a]Significant difference in progression-free survival (PFS) or overall survival (OS).

[b]Time to treatment failure.

CB = clinical benefit (response + stable disease); NR = not reported; RR = response rate

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understanding of the mechanisms of resistance could have a substantial impact in maintaining the clinical efficacy of these targeted therapies.

The Iressa Pan-Asia Survival Study (IPASS) was a phase 3 study in which patient selection was based on clinical factors that predict a higher probability of harboring sensitizing *EGFR* mutations, thus enriching the mutant population, rather than screening for mutation status.[11] Patients selected for participation were East Asians with advanced lung adenocarcinoma who were never smokers or former light smokers. They were randomized to treatment with platinum-based doublet chemotherapy (carboplatin-paclitaxel) or the EGFR-TKI gefitinib.

The primary end point—PFS—favored gefitinib over the chemotherapy doublet in the overall patient population. Of the 1,217 patients enrolled, *EGFR* mutation data for 35.9% could be evaluated. Sixty percent of the patients' tumors harbored sensitizing *EGFR* mutations and, in this subset, the benefit of gefitinib was greater than it was in the overall population. In patients without an *EGFR* mutation, particularly those without Exon 19 deletions or Exon 21:L858R mutations (sensitizing mutations), platinum-based doublet chemotherapy performed better than gefitinib on the PFS end point. Of the mutation-positive patients, 4.2% had T790M mutations, which confers resistance to TKIs; this finding underscored the observation that all mutations cannot be treated the same.

The important message from the IPASS results is that even in a population preselected for *EGFR* mutation occurrence, the actual presence of the alteration of the target (*EGFR* mutations) leads to better survival with gefitinib. Molecular profiling of the tumor, therefore, is ultimately superior to profiling by patient phenotype or ethnicity. Thus, molecular selection trumps clinical selection.[12]

On the basis of IPASS and four similar phase 3 randomized controlled trials, the American Society of Clinical Oncology issued a clinical opinion that "patients with NSCLC who are being considered for first-line therapy with an EGFR-TKI (patients who have not previously received chemotherapy or an EGFR-TKI) should have their tumor tested for *EGFR* mutations to determine whether an EGFR-TKI or chemotherapy is the appropriate first-line therapy."[13]

Monoclonal antibody against EGFR

The First-Line Erbitux in Lung Cancer (FLEX) phase 3 worldwide study demonstrated that cetuximab, a monoclonal antibody directed against EGFR, as add-on therapy to a platinum-based doublet (cisplatin and vinorelbine) can extend median OS in patients with advanced EGFR-expressing NSCLC (stage wet IIIB or stage IV).[14] As a result, the use of cetuximab combined with cisplatin-vinorelbine has been endorsed by a National Comprehensive Cancer Network (NCCN) guideline as a first-line option for the treatment of advanced NSCLC.

EML4-ALK fusion gene as target for crizotinib

The *EML4-ALK* fusion translocation oncogene was first identified in 2007 in a small proportion of

patients with NSCLC,[15,16] and a targeted therapy (crizotinib, an inhibitor of the ALK tyrosine kinase) has been developed. A single-arm phase 1 trial of crizotinib in patients selected for the *EML4-ALK* fusion gene has been completed.[17] Of the approximately 1,500 NSCLC patients screened for the trial, 82 were identified as having advanced ALK-positive disease and were entered. These patients tended to be younger than those with ALK-negative disease, most had little or no exposure to tobacco, and all had adenocarcinoma.

The mean treatment duration was 6.4 months. Most treatment-related side effects were grade 1 or grade 2 gastrointestinal adverse events. The overall response rate was 57%. The disease control rates were 87% at 8 weeks and 66% at 16 weeks. Crizotinib has since moved to phase 2 and phase 3 trials and received FDA approval on August 26, 2011, for treatment of EML4-ALK–positive patients as assayed by a simultaneously approved companion molecular diagnostic test.

Crizotinib-resistant mutations of the ALK-kinase domain have recently been identified; L1196M and C1156Y mutations have been found to confer resistance to crizotinib in initially responsive patients.[18]

MET: An emerging molecular target

An emerging molecular target being tested in clinical trials is MET, a multifaceted receptor kinase that, when activated, induces tumor cell activities such as cell proliferation and angiogenesis, epithelial-mesenchymal transition, and cell scattering, leading to tumor cell invasion and metastasis.[19]

MET receptors and EGFR in lung cancer often are coexpressed and coactivated. Dual targeting of MET and EGFR pathways simultaneously is an attractive combined targeted strategy and is being studied in the hope of overcoming secondary resistance to EGFR-TKI as well as enhance the primary response to targeted therapy. A number of MET targeting agents, including both small molecular inhibitors and monoclonal antibodies, are currently undergoing various stages of clinical development.[20,21]

In a phase 2 study, erlotinib plus the MET inhibitor ARQ197 was compared with erlotinib plus placebo in 117 previously treated EGFR-inhibitor–naïve patients with advanced NSCLC.[22] In the population of patients with nonsquamous NSCLC, both PFS and OS were extended incrementally by the use of combined inhibition that targeted both the EGFR and MET pathways. Interestingly, the benefit on PFS appears to be more significant in *EGFR* wild type and *KRAS*-mutant molecular subgroups. A phase 3 global trial using a similar design, with a goal of enrolling 1,000 patients, has been activated in an attempt to validate the findings from the phase 2 study.

UNDERSTANDING RESISTANCE MECHANISMS WILL OPEN DOORS

Other than novel and more rational combined TKI in lung cancer, a deeper understanding of the resistance mechanisms in the context of oncogene addiction targeting would ultimately have a large impact on the long-term clinical success in lung cancer targeted therapy.

Resistance arises because of cellular heterogeneity within an oncogene-addicted tumor. Tumor shrinkage indicates a response to a molecularly targeted therapy, but residual tumor may be a source of slow-growing drug-tolerant "persistor" cells that promote tumor regrowth, regeneration, and heterogeneity.[23,24] Coaddiction, reversible resistance, and addiction-switching models have been proposed to explain resistance, but it is unlikely that a single mechanism can fully explain tumor cell maintenance.

FUTURE OF TARGETED THERAPY IN LUNG CANCER

Technologic advances provide hope for the future of targeted therapy in lung cancer. Some of these advances are cancer genome deep sequencing and tumor molecular profiling. A greater understanding of tumor heterogeneity at the molecular level and tumor-resistant mechanisms, both intrinsic and acquired, should provide further therapeutic opportunity. In the modern era of targeted cancer therapy, identification of novel "druggable" driver oncogene targets can lead to swift development of inhibitors of those targets and adoption of improved and rational combinations of drugs. It is hoped that a better tumor response and more durable responses can be achieved with targeted therapy.

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