Lung Cancer

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Objectives:

1. To outline the various causes of lung cancer, and the types of clinical and radiographic presentations peculiar to each cell type.
2. To review the paraneoplastic syndromes associated with lung cancer.
3. To place in perspective the appropriate use of laboratory studies, imaging techniques, and diagnostic approaches to patients with lung cancer.
4. To review the results of various treatment modalities for both small-cell and non-small cell lung cancers.

Key words: non-small cell lung cancer; paraneoplastic syndromes; screening; small-cell lung cancer; solitary pulmonary nodule; staging; treatment

Classification of Lung Cancer (WHO Histologic Class)

The most important distinction is to separate small-cell bronchogenic carcinomas (18.2% of all lung cancers) from non-small cell bronchogenic carcinomas, because the management approach for the former cell type is vastly different from that for all subtypes of non-small cell bronchogenic carcinomas. Small-cell carcinoma is generally regarded as a disorder for which surgery is not indicated; all other cell types of bronchogenic carcinoma, depending on their stage, can be managed surgically with the potential for cure. Non-small cell carcinomas are split into squamous cell (30% of the total); adenocarcinoma, including bronchioloalveolar cell carcinoma (30.7% of the total); and large-cell undifferentiated carcinoma (9.4% of the total). Other cell types constitute a small minority of all lung cancers and will be discussed in another section.

International Staging System for Lung Cancer

Like cancers that originate in other sites, lung cancers are staged by the TNM system (T=primary tumor, N=regional lymph nodes, M=presence or absence of distant metastases). The TNM system is used by oncologists as a guide to estimate prognosis; it is used to select treatment in a given patient, and it helps in reporting and results (Fig 1).

There were several significant changes made in the international staging system in 1986. Additional changes to the staging system were added in 1997. These changes were made because the old system grouped patients in a way that did not as clearly separate patients into stages where the prognosis is significantly different, and it did not take into account a difference in management approach for subsets within the old system for separating the stages. The new system corrects both of these problems and creates a new stage IV.

Stage I Patients Redefined

- Only T1N0M0 and T2N0M0 patients are included. (Note the significant absence of T1N1M0, which is now placed in stage II with the new system, because the prognosis for survival with N1 metastasis is significantly worse, especially in the case of adenocarcinoma, than when there is no lymph node involvement.)

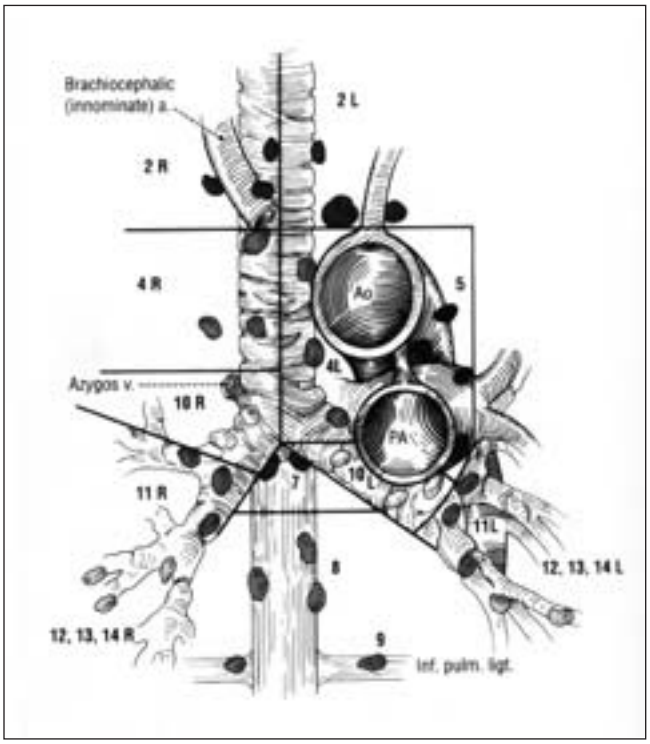

Figure 1. Regional lymph node involvement for tumor staging.

- The prognosis for 5-year survival, with surgical resection, is 70% to 80% for T1N0M0 patients and 50%to 60% for T2N0M0 patients.

Stage II Patients

- The survival pattern for T1N1M0 (Stage IIA) patients more closely resembles the survival patterns for patients with stage II lung cancer than the other stage I subsets.
- Stage IIB includes T2N1M0 and T3N0M0; T3N0M0 was moved from Stage IIIA to IIB.

Stage III Patients

Surgical oncologists have identified specific subgroups of patients with stage IIIA disease, who have a better prognosis for survival. Patients with stage III disease who have any of the following characteristics are candidates for surgery:

- Peripheral tumors that invade the chest wall.
- Tumors with direct extension into the mediastinum or pericardium.
- Superior sulcus tumors with no true Pancoast's syndrome.
- Tumors involving the proximal main bronchus and carina that are amenable to sleeve resection.

Stage IIIA and IIIB Patients

Patients with N2 involvement of only the ipsilateral mediastinal lymph nodes may undergo complete resection. They are categorized as IIIA patients, because a better outcome is anticipated for these patients than when mediastinal node metastasis is more extensive. Four large randomized trials have shown that chemotherapy and radiation therapy improve survival over radiation therapy alone, but the role of surgical resection as an adjunct to this combined method of treatment is still not clear. Stage IIIB patients include those with T4 tumors and with any N3 metastases (contralateral mediastinal, supraclavicular or scalene lymph nodes), but with MO disease. Selected stage IIIB patients (good performance status) are typically treated with chemoradiation.

New Categories

- T4 is for tumors of any size that invade the mediastinum or involve the heart, great vessels, trachea, esophagus, vertebral body, or carina; or for the presence of a malignant pleural effusion. (Note: There are a few T1 tracheal tumors and benign pleural effusions.)
- N3 is metastasis to contralateral mediastinal lymph nodes, contralateral hilar lymph nodes, ipsilateral or contralateral scalene, or supraclavicular nodes. This is useful for treatment planning and allows for separate stage groupings for patients with "limited" and "extensive" disease.
- Stage IV disease includes all patients with distant metastases.

Exceptions for Small-Cell Undifferentiated Lung Cancer

- The same TNM and staging systems (I-IV) are appropriate. However, medical oncologists and radiation oncologists typically divide their patients into "limited" or "extensive" disease, rather than use the TNM and / or staging system (I-IV), because of the difference in treatment for limited small-cell lung cancer (SCLC) vs extensive disease, as well as the marked difference in prognosis between limited vs extensive disease. There is a poor relationship between nodal status and survival for SCLC.
- Limited disease for SCLC is typically defined as no detectable disease outside of the hemithorax, with or without ipsilateral, mediastinal, hilar, or supraclavicular lymph nodes. Patients with unilateral pleural effusion have also been classified as having limited disease.
- Extensive disease for patients with SCLC is any disease occurring beyond the sites listed for limited disease.

Etiology of Lung Cancer

Tobacco causes 80% to 90% of all lung cancers. There is a clear dose-response relationship between the number of cigarettes smoked per day and the incidence of lung cancer. Cigarette smoking causes damage to the DNA in the cells of the bronchial epithelium. There is some experimental evidence suggesting that carcinogenic metabolites of nicotine exist and that nicotine itself may participate in lung carcinogenesis. The risk of dying in white men is reduced, due to lower rates of smokers and perhaps due to the use of low-tar, filtered cigarettes. The

rising rate in women parallels their increasing use of cigarettes of any kind. The risk of lung cancer increases in cigar and pipe smokers, depending on inhalation practices. Smokeless tobacco (chewing tobacco and snuff) are carcinogenic for the upper aerodigestive tract but not for the lungs.

Passive Smoking

It is estimated that 25% of lung cancer in nonsmokers comes from passive exposure to cigarette smoke. This translates into an estimate that passive smoking accounts for approximately 3,000 lung cancer deaths per year in the United States. Passive smoke differs significantly from mainstream smoke inhaled by the active smoker and may be even more carcinogenic. Several studies show that spouses of smokers have a twofold to threefold increased risk of developing lung cancer.

Other Carcinogens for Lung Cancer

These include asbestos, radon daughters, a variety of polycyclic hydrocarbons, cadmium, chloromethyl ethers (especially for SCLC), chromium, nickel, and inorganic arsenic. It has been conjectured that air pollution may promote action of other carcinogens but is not carcinogenic alone. As risk factors for lung cancer, most, if not all, of these environmental factors either require or are markedly augmented by concomitant exposure to cigarette smoke.

Dietary Factors

These are thought possibly to decrease the risk of developing lung cancer. Vitamin A intake is inversely associated with lung cancer risk, especially among cigarette smokers. The constituents of green and yellow vegetables, such as beta-carotene and selenium, appear to have potential as protective agents against lung cancer. More than 30 case-control and cohort studies suggested that people who eat more vegetables and fruit have a lower risk of lung cancer than those who eat fewer such foods or who have lower beta-carotene concentrations in their blood. These observations stimulated several large, controlled trials of beta-carotene supplementation that do not support the observed beneficial associations or a role for supplemental beta-carotene in the prevention of lung cancer. Instead, the same studies provide striking evidence for an excessive lung cancer incidence in smokers (an adverse effect). This stresses the importance of establishing the efficacy of chemoprevention agents in carefully conducted clinical trials.

Genetic Lesions and the Molecular Pathogenesis of Lung Cancer

Genetic lesions involve both activation of the dominantly acting cellular proto-oncogenes and the inactivation of the recessive (chromosomal deletion) or "tumor suppressor" genes.

Lesions in Dominant Oncogenes: Point mutations have been found in members of the *ras* family. *Ras* mutations occur in approximately 35% of non-small-cell lung cancers (NSCLCs; all histologic types) but are not present in SCLCs (<2% *ras* mutations). The most common change appears to be transcriptional activation and loss of transcriptional regulation. Certain L-*myc* restriction fragment polymorphisms have been associated with the metastatic behavior of lung cancer of several histologic types.

Lesions in Recessive Oncogenes: NSCLCs have many different cytogenetic abnormalities, including chromosomal deletions and nonreciprocal translocations. A prominent deletion occurs in chromosome region 3p(14-23) in SCLC. Other chromosomes where structural abnormalities have been identified include 1, 5, 7, 13, 14, 15, 16, 17, and 21. Recessive oncogenes show loss of DNA from one of the two chromosomes, presumably uncovering a recessive mutation on the remaining chromosome. SCLC probably has some type of abnormality of the *rb* gene, whereas only 20% of NSCLCs have an *rb* gene abnormality.

Other Genetic Abnormalities in Lung Cancer: Abnormalities of the p53 gene are common in NSCLC and appear to play an important role in the pathogenesis of early-stage NSCLC. The p53 gene appears to be frequently affected in all types of lung cancer, however. Several studies have demonstrated the presence of autocrine growth factor loops in lung cancer cells, including opioid and nicotine receptors. Lung cancer cell lines express multiple, high-affinity membrane receptors for opioid agonists and for nicotine. Nicotine may function to antagonize opioid action in lung cancer cells, thus promoting their growth. Two genetic changes are required for inactivation of each antioncogene, so lung cancer cells must suffer many separate genetic

lesions. Advances in cell and molecular biology have increased our understanding of the multiple events that lead to the development of lung cancer. The field cancerization theory suggests that multiple genetic abnormalities occur throughout the respiratory epithelium as a result of long-term carcinogen exposure. Mutations may all occur during adult life as a result of cigarette smoking, but it is also possible that some of them may be acquired during embryonic development of the bronchial epithelium. Future research should attempt to look for these mutations in the normal bronchial epithelium of cigarette smokers.

Inherited Predisposition to Lung Cancer: A predisposition to early age of onset of lung cancer may be inherited in a mendelian codominant fashion. Chronic obstructive pulmonary disease is associated with the development of lung cancer, and there appears to be a familial correlation with the development of such respiratory disease. Inheritance of an abnormality in carcinogen metabolism is another possibility. Inheriting genes predisposing to malignancy usually results in a high rate of secondary tumors (lung, head and neck, esophagus, and other organs). Likewise, patients cured of laryngeal tumors have an increased risk of developing lung cancer.

Clinical Features of Lung Cancer

Nearly 90% of patients with lung cancer are symptomatic at the time of presentation.

Local Effects of Endobronchial (Central) Tumors

These include cough, wheezing, hemoptysis, stridor, dyspnea (from obstruction), atelectasis, segmental emphysema, pneumonia (with or without abscess), and deep chest pain.

Parenchymal (Peripheral) Tumor Growth

This can cause pain from pleural or chest wall extension, cough, dyspnea from restrictive changes, symptoms of pleural effusion, and hemoptysis from peripheral cavitation.

Regional Spread of Tumor

Typical symptoms, when the lung cancer has spread to the mediastinum, include dysphagia (from esophageal compression or involvement) and the development of effusion (from lymphatic obstruction). Cardiovascular involvement can be associated with arrhythmias and heart failure (from pericardial involvement). The pericardium or the myocardium is involved in 15% to 35% of patients (autopsy data), but the frequency of clinical symptoms is unknown. Malignant pericardial effusion with tamponade may coexist.

The superior vena cava syndrome is more common if the primary tumor is on the right side. In NSCLC (usually squamous) the obstruction develops slowly, allowing development of a collateral venous system evident at the time of physical examination. Edema and suffusion may also be present.

Regional nervous system involvement includes Horner's syndrome seen with superior sulcus (Pancoast's) tumors. Symptoms include shoulder pain, with radiation to the ulnar nerve distribution of the arm and often with radiographic destruction of the first and second ribs. Hoarseness is due to involvement of the recurrent laryngeal nerve. This is more common on the left side because of the longer course of the nerve. Phrenic nerve paralysis produces elevation of the hemidiaphragm and the potential for dyspnea.

Malignant Pleural Effusions

These can compromise lung function by compressing the lung. Malignant pleural effusions may be highly symptomatic, with shortness of breath and pain. Among NSCLCs, the frequency is highest with large-cell carcinoma (67%), followed by adenocarcinoma (60%) and squamous cell carcinoma (34%). However, because of the greater frequency of adenocarcinoma, this is the cell type most likely to be associated with a malignant pleural effusion.

Metastatic Disease Outside the Thorax

At autopsy, the frequency of extrathoracic metastases is 54% for squamous cell carcinoma, 82% for adenocarcinoma, and 86% for large-cell carcinoma. At the time of presentation, most small-cell carcinoma has already spread outside the thorax, though it may not be clinically evident even after all applicable staging maneuvers have been completed. Bone marrow involvement is seen in 15% to 25% of patients with SCLC at the time of diagnosis. At

presentation, cortical bone involvement occurs in approximately 22% of patients with SCLC and is the isolated site of metastatic disease in 10%.

- Extrathoracic lymph node involvement should be sought at the time of physical examination; scalene, supraclavicular, and axillary lymph nodes are the most frequently involved.
- Hepatic involvement may be detected during physical examination (generalized enlargement or a discrete mass or masses within the liver).
- The CNS is commonly involved by metastatic lung cancer. The brain is involved in approximately 10% of cases of SCLC at presentation, but 30% of patients will have parenchymal brain metastases sometime during the course of disease. For NSCLC the most common cell types to involve the brain are adenocarcinoma and large-cell carcinoma. Spinal cord involvement is usually preceded by back pain, followed by symptoms and signs of compression (bladder/bowel dysfunction, or paraplegia). Carcinomatous meningitis is less common and usually causes death within 4 to 6 weeks.
- Constitutional symptoms and signs include anorexia and weight loss (31% at time of presentation), weakness, fever (21% of cases, due to tumor), and clubbing (29%).
- Cutaneous manifestations of lung cancer include skin metastases, acanthosis nigricans, bullous lesions (erythema multiforme), dermatomyositis, scleroderma, and tylosis (hyperkeratosis of the palms and soles). Vascular and hematologic manifestations of lung cancer include anemia, thrombophlebitis (especially migratory), disseminated intravascular coagulopathy, nonbacterial thrombotic endocarditis with arterial emboli, granulocytosis, and leukoerythroblastosis.

Chest Radiographic Abnormalities Suggesting One Cell Type vs Another

- Squamous cell: Centrally located (64% of cases), atelectasis (23%), pneumonitis (13%), hilar adenopathy (38%), tendency to cavitate (5%).
- Adenocarcinoma: Defined nodule (72% of cases), peripheral location (65%), pleural and chest wall involvement (14%). In the past decade, many adenocarcinomas have presented with hilar (40%) or mediastinal (27%) masses from involved lymph nodes.
- Large-cell carcinoma: Large mass (41% of cases), peripheral location (61%), pneumonitis (24%), hilar adenopathy (32%).
- Small-cell carcinoma: Rapidly enlarging hilar or perihilar mass, hilar and mediastinal adenopathy. Rarely presents as a solitary peripheral nodule.
- Bronchioloalveolar cell carcinoma: Peripheral nodule/mass (60% of cases), pneumonic pattern. May be multicentric (40%).
- Carcinoid, adenoid cystic, and mucoepidermoid carcinoma: Often present on a normal chest radiograph, or a subtle central airway mass that may not be easily seen on a plain chest radiograph. Carcinoid tumors of the lung may present as a peripheral nodule or postobstructive pneumonitis.

Paraneoplastic Syndromes

These can be seen in both SCLC and NSCLC but are more common in the former. Parathyroid hormone secretion with hypercalcemia is a phenomenon associated with squamous cell lung cancer, whereas most of the other paraneoplastic syndromes are far more commonly seen with SCLC. It is estimated that approximately 20% of patients with SCLC will develop some type of paraneoplastic syndrome sometime during the course of their disease. The reason SCLC is more frequently accompanied by paraneoplastic syndromes is unclear; it may be related to its putative cell of origin, the APUD cell, which is of neuroendocrine origin, thus enabling it to elaborate a number of hormones and other biologically active proteins.

Specific Syndromes

- Parathyroidlike hormone secretion: Hypercalcemia is more common from this cause than from skeletal metastases. Parathyroidlike syndrome is unusual in SCLC; if hypercalcemia is seen in this setting, consider a coexistent non-small-cell histology, coexisting hyperparathyroidism, or transformation from SCLC to NSCLC.
- Hypertrophic pulmonary osteoarthropathy is seen more often in adenocarcinoma (1%-10% of cases).
- Antidiuretic hormone (ADH) is the most common paraneoplastic syndrome in SCLC. Approximately 5% to 10% of patients present with syndrome of inappropriate ADH. An additional 40% to 50% of patients can be shown to

have subclinical abnormalities compatible with syndrome of inappropriate ADH on appropriate clinical testing: radioimmunoassay for ADH. The source of the ADH can be the primary tumor and the metastases. Laboratory abnormalities include hyponatremia, increased excretion of sodium in the urine, normal volume status and adrenal/renal function, and failure to excrete maximally diluted urine with water challenge.

- Adrenocorticotropic hormone: SCLC is the most common tumor associated with ectopic corticotropin production. Approximately 3% to 7% of patients with SCLC will have Cushing's syndrome, but a much higher percentage have a subclinical form (11% to 72% by radioimmunoassay). The clinical features of Cushing's syndrome tend to be masked by anorexia and significant weight loss. Severe weakness and the profound mineralocorticoid effects of edema, hypertension, and hypokalemia are more common. The potassium level is less than 3.0 mEq/L in 70% to 90% of patients. Hyperpigmentation occurs in approximately 25% to 30% of patients.
- The calcitonin level is elevated in 38% to 67% of all patients with lung cancer, but SCLC is associated with the highest frequency. Calcitonin causes an immediate calciuresis, but it does not produce symptoms.
- Nephrotic syndrome and glomerulonephritis.
- Gynecomastia (secretion of gonadotropins).
- Hypoglycemia (insulinlike activity).
- Hyperpigmentation (melanocyte-stimulating hormone).

Paraneoplastic Neurologic Syndromes

- Neuromyopathies: This group of syndromes is the one most commonly associated with SCLC. The incidence of neuromyopathies for all lung cancers is 10%. The frequent use of *Vinca* alkaloids and *cis*-platinum may be confused with this diagnosis. Multiple small brain metastases, carcinomatous meningitis, and spinal cord or peripheral nerve compression by tumor can all mimic neuromyopathies, as can diabetes and use of steroids. Other considerations before diagnosing a neuromyopathy as due to the lung cancer itself are syndrome of inappropriate ADH and infectious agents (progressive multifocal leukoencephalopathy). The carcinomatous neuromyopathy can occasionally present up to 1 year before the clinical diagnosis of SCLC, but it is usually apparent at the initial presentation.
- Peripheral neuropathy is the most common paraneoplastic syndrome in SCLC, occurring in nearly 100% of patients sometime during its course. It is probably related to the high frequency of using *Vinca* alkaloids. Perhaps an underlying subclinical neuropathy exists in most patients with SCLC and the *Vinca* alkaloids precipitate this to the point where it can be clinically detected. The most common symptoms are decreased sensation and paresthesias in the extremities.
- Dementia: As the most common encephalopathy in SCLC, it is characterized by forgetfulness, loss of memory, or confusion. A response to treatment of SCLC is not necessarily associated with improvement in dementia. There is also a higher incidence if prophylactic whole-brain irradiation is used.
- Subacute cerebellar degeneration: Bilateral symmetrical truncal and extremity ataxia are characteristic features. Dysarthria and tremors are also frequently seen. The clinical course is usually rapid, with wheelchair existence within weeks or months.
- Eaton-Lambert syndrome: The clinical picture is very similar to myasthenia gravis, with proximal muscle weakness and easy fatigability. Symptoms are more pronounced in the lower extremities, with difficulty in walking, climbing stairs, and getting up from a chair. An electromyogram clearly distinguishes this syndrome from myasthenia gravis in that there is facilitation of muscular action potentials with repeated stimulation. Unlike the other neuromyopathies, the Eaton-Lambert syndrome frequently responds to treatment of the tumor.

Early Detection and Screening for Lung Cancer

National Cancer Institute sponsored trials at three major institutions (Johns Hopkins, the Mayo Foundation, and Memorial Sloan-Kettering Cancer Center) screened men who were at high risk (smokers over 45 years old, one or more packs per day for at least 20 years). In the John Hopkins and Memorial Sloan Kettering projects, annual chest radiographs in a control group were compared with chest radiographs and cytology in an experimental group. Cytology was not associated with a different

outcome over chest radiographs alone, but long-term survival in both studies was about three times greater than predicted from other data. Two randomized trials (the Mayo study mentioned above and a Czechoslovakian study) compared regular and frequent rescreening chest radiographs in an experimental group with sporadic and/or infrequent rescreening in a control group. Both studies demonstrated a striking advantage for screening with regard to stage distribution, resectability, survival, and fatality; but mortality was somewhat higher in the screened groups. Thus, it can be stated that intensive screening (every 4 months, compared with annual) with chest radiographs and sputum cytology does detect lung cancer early.

The mortality rate from lung cancer, despite its earlier detection and diagnosis, was not significantly different in the screened group compared with the control group. The better survival rate may be a function of earlier lead time. The Mayo group also found that 1.6% of the persons monitored developed lung cancer (4.7 per 1,000 persons screened per year). The screened group had fewer persons with symptoms (11%) than the control group at the time of detection. There are insufficient data at this time to recommend intensive screening of all high-risk people. Since these studies were complete, however, our understanding of lung cancer has improved. Patients at especially high risk include those with airflow obstruction, a family history of lung caner, exposure to multiple lung carcinogens including asbestos and radon (in addition to cigarette smoke), and previous history of lung or other aerodigestive cancers.

The three NCI-sponsored studies and the two other large screening studies in Czechoslovakia have been analyzed in many different ways. The possibility that screening may be associated with lung cancer "overdiagnosis" has been widely postulated to account for higher survival and incidence rates and equivalent mortality rates. Analysis of autopsy information and of disease outcome in individuals with screen-detected early-stage lung cancer who do not undergo surgical resection strongly supports the conclusion that screening does not lead to overdiagnosis of lung cancer. Similarly, lead time and length bias do not adequately account for the differences in cumulative incidence observed in the Mayo and Czech studies.

The failure to improve survival by screening patients for lung cancer with plain chest x-rays and sputum cytology led to an indifference to screening for over two decades. There is now a renewed interest in screening, particularly for high-risk populations (smokers, especially those with airflow obstruction demonstrated by spirometry) because of two new methods to screen for lung cancer. Low dose CT scanning allows imaging of the entire chest with a single breath hold with low radiation exposure. Tremendous enthusiasm for screening with low dose CT imagery of the chest has followed early reports in nonrandomized settings, with the conclusion that such screening will lower lung cancer mortality. Henschke et al compared low-dose spiral CT to plain chest x-rays in 1,000 smokers. They found noncalcified nodules in 23% of the participants by low-dose CT, compared to 7% by chest x-rays. Using strict criteria and follow-up three-dimensional reconstruction with high-resolution thin-section CT, 27 malignancies were identified from this population. Importantly, stage I malignancies were present in 23 of the 27, and no patient underwent a thoracotomy for benign disease. Twenty (74%) of the 27 CT-detected cases of malignant disease were not detected by plain chest x-rays. Swensen et al performed low dose CT screening coupled with sputum cytology screening on 1,520 smokers over the age of 50 and found noncalcified lung nodules in 66% over 1 year. There were 25 prevalence cases and 3 incidence cases of lung cancer; CT alone detected 23 of the cases. Twenty-two patients underwent surgical resection that is thought to be curative; seven patients had resection of benign nodules.

While these and other studies, notably from Japan, suggest that lung cancer can be identified and at an earlier stage by low dose CT screening, many caution that this screening method is not yet ready for widespread application. The high rate of abnormal screens, most of which are false positive, creates a necessity for follow-up CT scanning, subspecialty consultations, and other testing that create a high total cost for such screening. The National Cancer Institute has just commissioned a randomized prospective controlled trial, aiming to enlist 50,000 current or former smokers who will be followed for 8 years after three annual screening low dose CTs. Half the subjects will be randomized to be screened with CT imaging, and the other half by standard chest radiographs. Until the results of this and other longer-term studies are available, there should be caution and reservations about mar-

keting spiral CT directly to consumers. Screening with low dose spiral CT should only be done in the context of well-designed clinical trials.

A second screening method that holds promise for the detection of early-stage lung cancers is autofluorescence bronchoscopy, which is also undergoing extensive early multicenter trials for smokers with obstructive lung disease and identified carcinoma cells or severe dysplasia in sputum samples. Dual screening with both autofluorescence bronchoscopy and low-dose spiral CT may someday become the norm for patients at high risk for lung cancer. However, now is not the time to begin such dual screening outside the context of well-designed clinical trials, pending the outcome of additional studies to prove efficacy, cost-efficiency, and improved survival for patients who undergo such screening.

Solitary Pulmonary Nodule

Solitary pulmonary nodules (SPNs) are seen on a plain chest radiograph, are less than 4 cm in diameter, and are rounded or slightly ovoid. They are located in the lung parenchyma, and there are no other associated abnormalities on the plain chest radiograph. Granulomas and hamartomas constitute 40% to 60% of all SPNs and are the leading cause of SPNs in persons less than 35 years of age. In older patients, especially those with a history of cigarette smoking, the key concern is whether the SPN represents a malignancy. Availability of an old chest radiograph that shows the same lesion, stable or nearly stable in size for at least 2 years, will be the key arbiter of the proper treatment in such a situation.

While SPNs, especially those 2 cm in diameter or larger, can be definitively diagnosed as malignant with bronchoscopy (>65% yield) or transthoracic fine-needle biopsy (>85% yield), it is the rare patient who will truly benefit from such an approach. Generally speaking, when the SPN is strongly suspected to be malignant, it should be resected both for definitive diagnosis and for cure (assuming it turns out to be malignant). Exceptions, in which a lesser invasive procedure is justifiable, include patients who are poor surgical candidates or situations where the surgeon or patient refuses surgery. In these cases, an invasive diagnostic procedure less than a thoracotomy is appropriate to define the nature of the lesion and to facilitate alternative treatment planning (external beam radiation therapy).

The Role of Diagnostic Tests

A complete history and physical examination remain the key elements in the choice of all laboratory studies for staging the patient's cancer, particularly performance status, a history of weight loss, symptoms and signs suggestive of metastatic disease, and the function of the vocal cords and diaphragm.

Past and Current Chest Radiographs

Consider whether the abnormality has been stable over a 2-year span; if it is stable, then it is almost always associated with a benign lesion. Certain types of calcifications within a lesion indicate that it is benign, *eg*, concentric lamellated rings. Remember, however, that not all calcified lesions are benign.

Screening Blood Work and Other "Routine" Studies

Simple blood work is indicated as part of the pretreatment assessment of all patients known or strongly suspected of having lung cancer on the basis of their clinical and radiographic presentation. Appropriate studies and the rationale for doing them include a complete blood cell count (anemia is a poor prognostic indicator); a urinalysis (may identify renal paraneoplastic syndrome); serum liver function tests (alkaline phosphatase, alanine aminotransferse, total bilirubin, aspartate aminotransferase to screen for the presence of liver metastases—if liver function tests are abnormal, additional investigation is warranted, but liver enzymes are rarely abnormal unless there are extensive metastases); and a serum calcium test (to screen for parathyroidlike hormone syndrome and bone metastases); serum creatinine (many chemotherapeutic agents are nephrotoxic) and; serum albumin (a low value is a poor prognostic factor). No other laboratory tests are routinely recommended, although a creatinine clearance is needed if chemotherapy is contemplated, because many chemotherapeutic agents used in the treatment of lung cancer are nephrotoxic.

Fiberoptic Bronchoscopy

For central (endoscopically visible) cancer, fiberoptic bronchoscopy is 90% to 95% sensitive (or higher). The main goal is to establish a diagnosis and distinguish SCLC from NSCLC. For peripheral tumors, fiberoptic bronchoscopy has a reasonable sensitivity (60% to 75%) if the tumor is 2 cm or larger in diameter and fluoroscopy is used. Fiberoptic bronchoscopy is especially important before thoracotomy for NSCLC with curative intent to judge the proximal extent of the tumor for transection of the bronchus and to look for an occult central or contralateral second primary (1% to 3% frequency). Fiberoptic bronchoscopy can often be done by the surgeon at the same anesthetic sitting, just prior to thoracotomy (especially when the tumor is peripheral in its location).

Transbronchial Needle Aspiration

A transbronchial needle aspiration (TBNA) biopsy of the mediastinal/hilar lymph nodes can stage the extent of the disease at the same time the diagnosis is made. This is more important when stage IIIA disease is suspected than in any other situation. Some centers have a consistently higher yield than others (depending on technique). A higher yield can be expected if the TBNA is guided by findings from CT than if done "blindly" or as a routine part of every procedure.

The TBNA specimen should be obtained first, so as to avoid contamination with possible false-positive results. The need to perform TBNA is predicated, at least in part, on the institutional philosophy of whether stage IIIA NSCLC is a surgically resectable disease.

Fine-Needle Aspiration (FNA)

Percutaneous FNA biopsy has a greater sensitivity (90% to 95%) than bronchoscopy for malignant peripheral solitary nodules, especially if the diameter is less than 2 cm. A pneumothorax can be expected in 20% to 25% of patients; a chest tube will be required in 5% of all patients handled this way. Nondiagnostic results may not obviate the need for thoracotomy if the lesion is likely malignant. Bronchoscopy is still needed before thoracotomy (at the same anesthetic sitting, however) to exclude a second primary.

Specific indications for FNA include pulmonary masses in a patient unable to undergo a curative thoracotomy (because of compromised pulmonary function, medical contraindications to thoracotomy, or refusal of thoracotomy) who needs a definitive tissue diagnosis; an undiagnosed localized or worsening pneumonic infiltrate in an immunocompromised patient despite standard antibiotic therapy; a history of another malignancy and an abnormality on chest radiograph; and the evaluation of other masses on a chest radiograph or CT scan (*eg*, mediastinal masses) that need to be histologically evaluated to develop a therapeutic plan.

Thoracentesis/Pleural Biopsy

In the setting of lung cancer, a pleural effusion usually indicates that the cancer has seeded the pleura and the patient is not a candidate for curative treatment. There are occasional exceptions, however. Some pleural effusions will be parapneumonic in nature (benign), when a tumor obstructs a more centrally located bronchus with a postobstructive pneumonitis. Likewise, there are rare situations where a patient's lymphatics will be obstructed by a tumor that involves the more central lymph nodes, impeding fluid transfer through the pleural space with a benign effusion as a result. Therefore, it is important to sample the pleural fluid and to study it cytologically to determine if the tumor has seeded the pleural space, rendering the patient incurable. Cytologic analysis of a pleural effusion ultimately proven to be malignant is associated with a 55 to 60% true-positive yield. A second cytologic analysis of the fluid should be done for those whose first pleural fluid specimen is negative for malignant cells. Closed needle biopsy of the pleura adds only about 7% to the overall yield for malignancy, so it is generally not recommended as part of the approach to a patient with a suspected malignant pleural effusion. Instead, for patients with two negative cytologic studies of their pleural fluid, a thoracoscopy should be done, as the true-positive yield when malignancy is present is approximately 98 to 99%.

Bone Scan

There is general agreement that radionuclide scans of the bones are not warranted during a preoperative evaluation unless symptoms, signs,

or abnormal blood test results raise a suspicion of metastatic involvement of the bones. There are many other bone disorders that can give rise to one or more focal areas of increased uptake; thus, the false-positive rate is unacceptably high when bone scans are done routinely. Bone scans should be done when the clinical evaluation reveals bone pain, pathologic fractures, and / or an elevated alkaline phosphatase or serum calcium level. Additionally, a bone scan can be obtained when nonspecific findings indicate the presence of metastatic disease.

Bone Marrow Aspiration and Biopsy

This is not done as part of NSCLC staging. For SCLC, the incidence of bone marrow involvement is 15% to 25% at the time of diagnosis. Therefore, bilateral bone marrow aspiration and biopsy will show a higher incidence of involvement. Bone marrow involvement usually occurs in the setting of other metastatic disease. The bone marrow is the sole site of metastatic disease in 4% to 10% of patients at the time of initial presentation.

Staging the Mediastinum

CT assessment is much more sensitive than chest radiographs to detect direct extension of the primary tumor and regional lymph node enlargement. In the absence of distant metastases or inadequate cardiopulmonary reserve, chest CT is generally felt to be an integral part of the pretreatment planning. Situations where a chest radiograph alone is adequate include obvious metastatic bone lesions, or the presence of large bulky contralateral mediastinal lymph nodes. The sensitivity and specificity of determining mediastinal lymph node involvement is a function of the cut point chosen. With a short axis diameter greater than 1.0 cm defined as abnormal, the sensitivity and specificity are both approximately 80%. Because of their imperfect specificity, however, abnormal mediastinal CT findings in an otherwise operable patient should never preclude thoracotomy unless pathologically confirmed.

MRI

Magnetic resonance imaging is not better than CT for evaluation of mediastinal metastases. It is more expensive than CT, but it can be of particular value in selected cases, such as determining whether the chest wall is invaded when the tumor is shown to be contiguous by plain chest radiograph or by CT assessment. Magnetic resonance imaging may also display invasion of vascular structures in the mediastinum with greater specificity than is possible with CT.

PET Scanning

There are several published studies which indicate that positron emission tomography (PET) scanning is more sensitive and more specific than CT for staging the mediastinum in lung cancer. PET is a metabolic imaging technique based on the function of a tissue rather than its anatomy. It is useful to differentiate neoplastic from normal tissue, but it is not infallible as some nonneoplastic diseases and infections may be positive on PET imaging. Size limitations are also an issue, with the lower limit of resolution of PET scanning at approximately 1 – 1.2 cm. The sensitivity of PET scanning is approximately 86%, and specificity is approximately 88% from combined studies. Thus, PET has both higher sensitivity and specificity for evaluation of mediastinal lymph node staging that CT scanning. While a negative mediastinal PET may obviate the need for mediastinoscopy prior to thoracotomy, a positive mediastinal PET should not be taken as a sign of unresectability, as there is a possibility of false-positive results on PET. Cost of PET and government-imposed controls (certificate of need) still make PET scanning a technique that is not available to all lung cancer patients.

Cervical Mediastinoscopy

The diagnostic yield ranges from 10% to 75%, depending on (1) the histologic type of tumor, (2) the size and location of the primary tumor, and (3) the extent of the disease. The value of mediastinoscopy in the preoperative evaluation is related directly to the therapeutic philosophy of the surgeon. If involvement of the mediastinum indicates that the tumor is not resectable, the surgeon will perform mediastinoscopy (or insist on some other sampling procedure of the mediastinum) routinely. Those who resect mediastinal tumors with curative intent will use mediastinoscopy less frequently. At the time of mediastinoscopy, the pretracheal / paratracheal lymph nodes can be sampled, as well as some of the subcarinal nodes (right at the bifurcation) and the azygous nodes. Mediastinoscopy helps to

exclude thoracotomy for patients with marginal chances for survival after thoracotomy: those with poor performance status, advanced age, or poor pulmonary function.

Anterior Mediastinotomy

Anterior mediastinotomy is done by resecting the second costal cartilage on either side. There is usually better exposure and less likelihood of surgical misadventure (uncontrollable bleeding) than with mediastinoscopy. At the time of mediastinotomy, the surgeon can sample the paratracheal, azygous, superior hilar nodes on the right side, and the nodes in the aortopulmonary window and the anterior mediastinum on the left side. The pretracheal, left paratracheal, and subcarinal lymph nodes cannot be sampled with this approach, however. The morbidity and mortality are essentially nil with transbronchial / transcarinal needle aspiration. The morbidity is 2% with mediastinoscopy or mediastinotomy. The false-negative rate is much higher with needle aspiration, generally approximately 8% with mediastinoscopy or mediastinotomy, but may be up to 20% in some series.

Supraclavicular/Scalene Node Biopsy

This is not routine in the absence of palpable adenopathy. It is not of value in patients with peripheral tumors. Its value in patients with central tumors, especially adenocarcinoma or those of unknown histologic type, is still debated. An alternative is needle aspiration / cytology in palpably enlarged lymph nodes.

Other Radionuclide Scans

Brain and liver scans have been replaced by CT assessment of these organs in patients with suspicious clinical findings, abnormal laboratory test results, or intermediate or advanced stages of tumor. Radionuclide scans are of controversial value in staging the mediastinum (bleomycin labeled with cobalt 57 and gallium 67).

CT for Detecting Occult Extrathoracic Metastases

Patients undergoing surgical therapy for NSCLC have occult metastatic disease 20% of the time in the adrenal glands, liver, kidney, and / or brain.

Brain CT Imaging and MRI: Some studies suggest an increased utility of CT scanning of the brain, even in the absence of symptoms or signs of CNS metastases, for patients with adenocarcinoma and / or undifferentiated carcinoma / large-cell carcinoma. If a comprehensive clinical evaluation is negative, however, NSCLC patients will be found to have brain metastases by CT assessment only 3% of the time. False-positive brain CT scans are a recognized phenomenon. Brain CT in patients with NSCLC should be done for patients with headaches, seizures, abnormal localized neurologic signs on examination, or for those with nonspecific findings that suggest widespread disease if metastatic disease has not been found elsewhere. A brain CT scan is usually warranted for patients with SCLC, since the incidence of asymptomatic brain metastases detectable by radionuclide scans is approximately 4% to 10%, and obviously higher if CT scanning is done. Magnetic resonance imaging, particularly when enhanced with gadolinium, would provide an even higher yield to detect occult metastases if this technology is readily available.

Hepatic and Adrenal (Abdominal) CT Imaging: The liver is one of the most frequent sites of metastatic involvement in SCLC, seen in 15% to 28% of patients at the time of presentation and 6% to 10% of patients as the sole site of metastatic disease. Screening liver function tests help determine which patients have metastatic liver disease, both for SCLC and NSCLC. In NSCLC the absence of hepatomegaly or discrete intrahepatic masses on physical examination plus normal liver function test results indicate that hepatic CT imaging should not be done routinely. Conversely, routine hepatic imaging is more reasonable for patients with SCLC, as involvement is so common and hepatic CT imaging provides useful information for staging and monitoring response to therapy. CT imaging is much superior to radionuclide imaging, particularly when contrast material is injected intravenously. Chest CT, done properly, will extend into the upper abdomen, and provide imaging of the adrenal glands and the upper part of the liver.

There are major pitfalls of CT in both organs, however. Cysts and hemangiomas within the liver are quite common. They usually are indistinguishable from metastases on CT imaging. When this happens, an echo will help to differentiate. Needle biopsy of the liver, or occasional open liver biopsy, may be needed before denying

an otherwise resectable patient with NSCLC the chance for a curative thoracotomy.

Adenomas occur in up to 2% to 10% of the population and look just like metastases in the adrenal by CT imaging. Thus, CT-guided needle aspiration biopsy to prove they are metastases is essential in NSCLC, provided this is the only site of extrathoracic disease, before denying an otherwise resectable patient with NSCLC the opportunity for curative resection.

Tumor Markers: None is useful to screen for lung cancer in the general smoking population. Markers that have been studied include carcinoembryonic antigen (CEA), total sialic acid, lipid bound sialic acid, β and α subunits of human chorionic gonadotropin, β_2-microglobulin, lipotropin, calcitonin, and parathyroid hormone. The routine monitoring of any of these substances is not recommended in the screening, staging, or evaluation of disease progression.

The CEA level may have prognostic value in the follow-up of patients with NSCLC after surgery, since a level above 15 ng/mL before surgery is associated with a reduced possibility of a successful resection. During follow-up, patients with an elevated CEA level relapse more often than patients with CEA levels that remain normal.

Prognosis

SCLC

With changes in the treatment over the past 15 to 20 years, the median survival time has increased from less than 3 months to approximately 1 year. For patients with limited disease, the median survival ranges from 1 to 2 years, and approximately 10% to 20% remain alive at 2 years. There is a potential for long-term cure. Thirty percent of patients with small-cell carcinoma die of local tumor complications, and 70% die of carcinomatosis. Fifty percent of patients with small-cell carcinoma have brain metastases at autopsy.

NSCLC

The most important determinant of survival duration is stage of the disease. Seventy-five percent of patients with squamous cell carcinoma die of complications of the thoracic tumor, as only 25% have extrathoracic dissemination at autopsy. Forty percent of patients with adenocarcinoma and large-cell carcinoma die of intrathoracic complications, whereas 55% have distant metastases. Fifty percent of patients with large-cell carcinoma and adenocarcinoma have brain metastases at autopsy. CNS deaths are seen in 8% to 9% of patients with large-cell carcinoma and adenocarcinoma. Two percent of CNS deaths are seen in patients with squamous cell carcinoma. Thus, there is a clear distinction between squamous cell carcinoma and other forms of lung cancer, in terms of the mode of death. Local/regional disease dominates squamous cell carcinoma. Carcinomatosis dominates the latter groups of patients. The median survival with metastatic NSCLC varies from 6 weeks to more than 1 year, depending on the initial Karnofsky performance status (the most important variable), the extent of disease, and the presence or absence of weight loss in the 6 months prior to diagnosis.

Lung Cancer as a Second Primary

This may occur after a prior diagnosis of nonpulmonary primary cancer (which is the case in up to 9.7% of all lung cancer patients). Lung cancer may occur as a second or even a third primary tumor after successful treatment of a prior primary lung cancer. Subsequent lung cancers may be any cell type, but the second tumor is usually NSCLC. This is a particular problem in long-term survivors of combined modality treatment for small-cell carcinoma (up to 4.4 per person per year). This underscores the need for patients with a lung cancer to stop smoking cigarettes.

Treatment

SCLC

The first basic tenet is a recognition that SCLC, more than other solid tumors, acts as a systemic disease. Current chemotherapy includes an induction phase; combinations of active drugs are more effective than any single agent. Drugs active as single agents are typically chosen for combination therapy (response rates shown are response rates for individual drugs when used alone):

- Cyclophosphamide (an alkylating agent): 40% response rate. Major toxicities: myelosup-pression, alopecia, and hemorrhagic cystitis.
- *Vinca* alkaloids: important antitumor activity.

Minor hematologic toxicity; potential for severe neurotoxicity.

- Doxyrubicin (Adriamycin): 30% to 40% response rate. Mucosal toxicity; potential for cardiac injury.
- VP-16 (etoposide): the most active new agent identified for SCLC.
- Cisplatin: toxicities include renal failure, peripheral and auditory neurotoxicity. There is a noticeable absence of neutropenia.

Combination Programs: The most active regimen currently in use is cisplatin plus VP-16, or this same regimen alternating with CAV (cyclophosphamide, Adriamycin, and vincristine). Treatment is given for 4 to 6 cycles, which takes about 4 to 5 months to complete. Newer agents are under investigation and will replace current programs because of greater efficacy and lesser toxicity.

Dose Intensification: Doses have been escalated to those requiring bone marrow transplants, without any benefits. This strategy has failed.

Maintenance: Maintenance chemotherapy adds toxicity and expense without benefit. Since there is no consistent evidence of benefit, maintenance chemotherapy is generally not part of most treatment programs.

Alternating Drug Regimens: The hypothesis is that emergence of drug-resistant tumor cells can be minimized by rapid alteration of equally effective non-cross-resistant combinations of drugs. However, as yet there has been no consistent evidence of benefit.

Salvage Regimens: A combination of VP-16 plus cisplatin is the first salvage regimen with effects on survival.

Combined Modality Treatment: Limited Stage Disease. Disease confined to one hemithorax (without distant metastasis) and the mediastinum, which can be encompassed within a radiation therapy treatment field, is treated with concurrent chest radiation and chemotherapy. This produces superior survival, compared to sequential therapy or chemotherapy alone. Of six recent randomized trials, plus one nonrandomized trial, five demonstrated benefit from added chest radiation. Concurrent radiation with the induction phase of chemotherapy is judged "best" at the present time, as there seem to be higher response rates for local control of intrathoracic disease. Most current programs employ prophylactic brain radiation because of the high incidence of brain involvement.

Extensive Stage Disease: Chemotherapy alone is used. Radiotherapy is not usually administered, since patients with metastatic disease usually relapse in the site of pervious metastases, even if they achieve a complete remission. The cause of death in these patients is usually widespread metastatic involvement, and not disease in the chest. Treatment is primarily aimed at the systemic disease, and the patient usually receives chemotherapy alone. Radiation may palliate symptoms, but it does not prolong survival.

Surgery: For patients with TNM stages I and II SCLC, uncontrolled data suggest that initial surgical resection followed by chemotherapy with or without brain radiation is superior to a "historical control" of surgery or radiation alone. It has been proposed that SCLC patients with disease limited to the chest undergo a surgical resection to improve local control, but this approach should only be undertaken with adequate research study design.

NSCLC

Surgery: Surgery is the most effective method for curing NSCLC. Lobectomy is the most widely used operation. Pneumonectomy must be done in 10% to 55% of patients. There is increasing interest in the use of conservative resections. The minimal operation encompassing all the known areas of disease is utilized, conserving pulmonary tissue and pulmonary function. Wedge resections, segmental resections, and sleeve lobectomies are increasingly more common. Resection via thoracoscopy has been used, but dissection of lymph nodes is not possible (and is clearly an important part of optimal lung cancer surgery). No matter what the extent of lung tissue resection, careful intraoperative staging is needed, including frozen sections of biopsies of surgical margins and lymph nodes. More aggressive resections may include the chest wall, diaphragm, and lower roots of the brachial plexus, and occasionally portions of the atria. Resection of ipsilateral mediastinal lymph nodes (N2 disease) is possible.

Intraoperative Radiation Therapy: Intraoperative radiation therapy (interstitial brachytherapy) may improve survival in selected patients with stage IIIA disease involving the N2 ipsilateral lymph nodes. Iodine 125 may be implanted directly into the tumor and, after loading catheters for use with iridium 192, may be helpful to improve survival

rates. The rationale for use of interstitial radiation therapy for lung cancer includes the delivery of a higher dose to the tumor and less radiation to normal tissue.

Determining Operability: This usually relates to the functional capacity of the cardiorespiratory system. Cardiorespiratory problems account for at least three quarters of postoperative morbidity and mortality. Cardiac complications cause about 20% of postoperative deaths. A history of cardiac disease doubles the risk of major morbidity (18% vs 9%). Pulmonary complications are more common than cardiac problems.

Spirometry: Spirometry is essential before pulmonary resection. If the preoperative FEV_1 is less than 2.0 L, split lung function should be determined with radionuclide imaging techniques. A postoperative predicted FEV_1 greater than 0.8 L is needed for a pneumonectomy to be possible without an increased risk of death or respiratory crippling following surgery. Many studies advocate exercise testing as a useful adjunct to predict a person's ability to tolerate a potential pneumonectomy (maximum $\dot{V}O_2$ >15 mL/kg/min indicates the patient can undergo surgery; maximum $\dot{V}O_2$ <10 mL/kg/min indicates the patient should not undergo surgery; maximum $\dot{V}O_2$ of 10-15 mL/kg/min indicates a "gray zone").

Morbidity and Mortality After Surgery: The overall 30-day operative mortality rate is 3.7%. Age is an important variable: for patients younger than 60 years, mortality is 1.3%; between 60 and 69 years, 4.1%; and older than 70 years, 7.1%.Some studies indicate a lower mortality, even among octogenarians, when resection does not require more than a lobectomy. The extent of resection also influences mortality: pneumonectomy, 6.2%; lobectomy, 2.0%; and lesser resections, 1.4%. Microscopic tumor at the bronchial margin does not appear to preclude prolonged survival. Microscopic extramucosal spread to peribronchial tissues is associated with much poorer outcome.

NSCLC with solitary cerebral metastases is a special situation because of the potential for cure in a few patients with resection of both the metastasis (should be done first) and the primary tumor. A recent randomized trial suggests that surgical resection of the brain metastasis followed by cranial irradiation is associated with better survival and much better control of neurologic symptoms than cranial irradiation alone.

It is important to recognize that not all pulmonary cancers in previously treated patients with NSCLC represent recurrence of the original tumor. Surgical resection with curative intent is sometimes possible for these patients.

Radiation Therapy: Radiation therapy is clearly inferior to surgery in the curative treatment of NSCLC. The limitations of radiation therapy relate to the tolerance of pulmonary tissues, as nearly any tumor can be eradicated by irradiation given sufficiently high doses. Selected reports indicate a high cure rate for early stages of carcinomas, but the studies are uncontrolled. Radiation therapy leads to a loss of lung function, and is a poor choice for patients who are inoperable because of insufficient pulmonary reserve. There is no established role for preoperative radiation therapy in patients with operable lung cancer, although uncontrolled studies suggest a benefit from preoperative radiation therapy for patients with Pancoast's tumors. There is no role for postoperative radiation therapy for patients without nodal involvement. Postoperative radiation therapy for stage II or III squamous cell lung cancer produces a striking and significant reduction in recurrences to the ipsilateral lung and mediastinum. Prior to death, however, clinically detectable distant metastases will eventually occur in 70% to 80% of patients, regardless of cell type. The effect of prophylactic cranial radiation is pronounced in preventing clinical brain metastases in patients with adenocarcinoma (0% vs 29%) but still not considered standard therapy. There is no survival benefit, however, and some patients will develop significant neuropsychological deficits. Palliative radiation is clearly beneficial in the management of specific symptoms, such as pain control, hemoptysis, superior vena cava syndrome, and atelectasis.

Chemotherapy: Single-agent chemotherapy has sufficiently poor response rates as to be of no significant value for patients with NSCLC. Many combinations of drugs have been reported to yield objective response rates of 20% to 50% over the past 15 years. Currently, there are two very active two-drug combinations for the treatment of patients with NSCLC: cisplatin with gemcitabine, and carboplatin with paclitaxol. If the tumor is stable after two or three cycles, there is no benefit from continuing therapy. Chemotherapy should be discontinued after 4 to 6 months in responsive patients in whom no further tumor regression is

occurring. Patients with NSCLC who experience objective responses to chemotherapy live longer than those who do not. Performance status and tumor extent are the most important prognostic factors affecting the results of chemotherapy. For unclear reasons, women receiving chemotherapy live longer than men.

- Stage IV Disease. Single agent chemotherapy is of little value. The most active traditional drugs include cisplatin and vinblastine. In recent years, several new drugs have demonstrated activity - vinorelbine, paclitaxel, docetaxel, carboplatin, topotecan, and gemcitabine. Combination chemotherapy offers a small survival advantage compared to best supportive care. Two of the best regimens are carboplatin plus paclitaxel and cisplatin plus gemcitabine. These therapies are cost effective compared to best supportive care. They should be offered to ambulatory patients. However, nonambulatory (poor performance status) patients have greater toxicity and lower response rates. Consequently, they are best not treated with chemotherapy.
- Stage IIIB Disease. Significant advances in the management of "unresectable" locally advanced NSCLC (Stage IIIB and many IIIA patients) have been made. The older traditional standard treatment of radiation alone has been replaced by chemo-radiotherapy. Although consensus exists that chemo-radiotherapy is superior, major issues that remain unresolved are: sequential vs concurrent modality treatment; induction chemotherapy vs concurrent treatment and; the specific choice of dose, and schedule of chemotherapeutic agents to be used with radiation. One common regimen is cisplatin plus etoposide plus radiation concurrently.
- Adjuvant Chemotherapy (Stage II and resectable IIIA patients). Genuine promise exists that systematic adjuvant chemotherapy will increase the cure rate in "operable" NSCLC. Since modern combination chemotherapy produces remission in 40% to 50% of good performance status patients with metastatic NSCLC, and since adjuvant chemotherapy increases survival in other common malignancies (colorectal and breast cancer), it is logical to suspect that adjuvant chemotherapy will prolong survival in NSCLC as well. A modern randomized trial is in progress in the United States and Canada, comparing surgery alone to surgery and 4 months of postoperative cisplatin plus vinorelbine chemotherapy. Preoperative ("neoadjuvant") chemotherapy may also be effective, but is less studied, as an adjuvant to surgery, particularly for Stage IIIA.Until recently, there have been no controlled trials for preoperative ("neoadjuvant") chemotherapy. Newer data suggest, but do not prove conclusively, that patients with stage IIIA NSCLC who are given several cycles of chemotherapy, followed by surgical resection and then postoperative radiation therapy, have a distinct survival advantage over those treated without the addition of preoperative chemotherapy. Preoperative chemotherapy ("neoadjuvant chemotherapy") is best considered an investigational approach requiring further validation in controlled trials before it is incorporated into a new standard of practice for such patients. All prospective randomized trials conducted before the introduction of cisplatin-based chemotherapy failed to show a survival advantage for postoperative chemotherapy (so-called "adjuvant" chemotherapy). Four large randomized trials with chemotherapy and radiation therapy produced superior survival when compared with radiation therapy alone. The role of surgery as an adjunct to chemo-radiotherapy has not been fully delineated.

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Notes

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