Medical Management of Non-Small Cell Lung Cancer

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BACKGROUND

Lung cancer is the leading cause of cancer-related mortality in both men and women. The prevalence of lung cancer is second only to that of prostate cancer in men and breast cancer in women. Lung cancer recently surpassed heart disease as the leading cause of smoking-related mortality. Most lung carcinomas are diagnosed at an advanced stage, conferring a poor prognosis. The need to diagnose lung cancer at an early and potentially curable stage is obvious. In addition, most patients who develop lung cancer smoke and have smoking-related damage to the heart and lungs, making aggressive surgical or multimodality therapies less viable options.

PATHOPHYSIOLOGY

Non–small cell lung cancer (NSCLC) accounts for approximately 75% of all lung cancers. NSCLC is divided further into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. All share similar treatment approaches and prognoses but have distinct histologic and clinical characteristics.

Recently, advanced molecular techniques have identified amplification of oncogenes and inactivation of tumor suppressor genes in NSCLC. The most important abnormalities detected are mutations involving the *ras* family of oncogenes. The *ras* oncogene family has 3 members: H-*ras,* K-*ras,* and N-*ras*. These genes encode a protein on the inner surface of the cell membrane with GTPase activity and may be involved in signal transduction.

Animal studies performed on mice suggest the involvement of *ras* mutations in the molecular pathogenesis of NSCLC. Studies in humans suggest that *ras* activation contributes to tumor progression in persons with lung cancer. The *ras* gene mutations occur almost exclusively in adenocarcinomas and are found in 30% of such cases. These mutations are not identified in adenocarcinomas that develop in persons who do not smoke. The K-*ras* mutation appears to be an independent prognostic factor. Studies are ongoing to develop management plans according to the presence or absence of *ras* gene mutations.

Other molecular abnormalities with less clear roles in tumor pathogenesis and progression include *c-myc* and *c-raf* among oncogenes and retinoblastoma (*Rb*) and *p53* among tumor suppressor genes.

FREQUENCY

Internationally

Lung cancer remains the most common malignancy, with an estimated 1.04 million new cases each year worldwide, which accounts for 12.8% of new cancer cases. Fifty-eight percent of new lung cancer cases occur in the developing world. Lung cancer is the most common cancer among men, with an incidence of approximately 37.5 new cases per 1 million population. The incidence is lower in women, at 10.8 cases per 1 million population.

Mortality/Morbidity

- Lung cancer is the cause of 921,000 deaths each year worldwide, accounting for 17.8% of cancer-related deaths.
- Lung cancer is highly lethal, with the highest recorded 5-year patient survival rates (14%) observed in the United States. In Europe, the 5-year overall survival rate is 8%, similar to that of the developing world.
- Estimates suggest that approximately 156,900 lung cancer–related deaths will occur this year in the United States (89,300 in men and 67,600 in women).

Sex

- Lung cancer is more common in men than in women. In the United States, northern Europe, and western Europe, the prevalence of lung cancer has been decreasing in men. In eastern and southern European countries, the incidence of lung cancer has been rapidly increasing. Most Western countries have encountered a disturbing trend of increasing prevalence in women and younger patients.

HISTORY

Lung cancers manifest with symptoms produced by the primary tumor, locoregional spread, metastatic disease, or ectopic hormone production. Approximately 7-10% of patients with lung cancer are asymptomatic and their cancers are diagnosed incidentally after a chest radiograph (CXR) performed for other reasons. The symptoms produced by the primary tumor depend on its location (i.e. central, peripheral).

- Symptoms due to primary tumor

- Central tumors are generally squamous cell carcinomas and produce symptoms of cough, dyspnea, atelectasis, postobstructive pneumonia, wheezing, and hemoptysis.
- Most peripheral tumors are adenocarcinomas or large cell carcinomas and, in addition to causing cough and dyspnea, can cause symptoms due to pleural effusion and severe pain as a result of infiltration of parietal pleura and the chest wall.

- Symptoms due to locoregional spread
  - These symptoms can include superior vena cava obstruction, paralysis of the recurrent laryngeal nerve, and phrenic nerve palsy, causing hoarseness and paralysis of the diaphragm; pressure on the sympathetic plexus, causing Horner syndrome; dysphagia resulting from esophageal compression; and pericardial effusion (i.e. Pancoast tumor).
  - Superior sulcus tumors can cause compression of the brachial plexus roots as they exit the neural foramina, resulting in intense, radiating neuropathic pain in the ipsilateral upper extremity.
- Paraneoplastic syndromes
  - Most paraneoplastic syndromes are caused by small cell lung cancer.
  - Squamous cell carcinomas are more likely to be associated with hypercalcemia due to parathyroidlike hormone production.
  - Clubbing and hypertrophic pulmonary osteoarthropathy and the Trousseau syndrome of hypercoagulability are caused more frequently by adenocarcinomas.
- Summary of clinical characteristics by histologic subtype
  - Adenocarcinoma is the most frequent NSCLC in the United States, representing 35-40% of all lung cancers, usually occurring in a peripheral location within the lung and arising from bronchial mucosal glands. Adenocarcinoma is the most common histologic subtype, manifesting as a scar carcinoma. This is the subtype observed most commonly in persons who do not smoke. This type may manifest as multifocal tumors in a bronchoalveolar form.
  - Bronchoalveolar carcinoma is a distinct subtype of adenocarcinoma with the classic manifestation as an interstitial lung disease on a CXR. Bronchoalveolar carcinoma arises from type II pneumocytes and grows along alveolar septa. This subtype may manifest as a solitary peripheral nodule, multifocal disease, or a rapidly progressing pneumonic form. A characteristic finding in persons with advanced disease is voluminous watery sputum.
  - Squamous cell carcinoma accounts for 25-30% of all lung cancers. The classic manifestation is a cavitary lesion in a proximal bronchus. This type is characterized histologically by the presence of keratin pearls and can be detected based on results from cytologic studies because it has a tendency to exfoliate. It is the type most often associated with hypercalcemia.
  - Large cell carcinoma accounts for 10-15% of lung cancers, typically manifesting as a large peripheral mass on a CXR. Histologically, this type has sheets of highly atypical cells with focal necrosis, with no evidence of keratinization (typical of squamous cell carcinoma) or gland formation (typical of adenocarcinomas). Patients with large cell carcinoma are more likely to develop gynecomastia and galactorrhea.

PHYSICAL FINDINGS

Summary of all signs and symptoms.

- In approximately two thirds to three fourths of patients, the cancer is diagnosed at an advanced stage; patients may have lost weight and may have obvious respiratory distress.
- Head and neck
  - Commonly, no signs are found upon examination of the head and neck regions, but when the cancer has spread to the supraclavicular lymph nodes, careful examination may reveal enlargement of involved nodes, which helps in the clinical staging process.
  - Superior sulcus tumors, because of their presence at the apex of the lung, can compress the cervical sympathetic plexus, causing classic Horner syndrome. Findings include ipsilateral ptosis, miosis, and anhidrosis (ie, lack of sweating).
  - Superior vena cava syndrome is commonly caused by small cell carcinomas, but any centrally located tumor or mediastinal spread can give rise to superior vena cava syndrome. This results from obstruction of blood flow to the heart from the head and neck regions and upper extremities due to tumor compression of the superior vena cava. Patients have facial edema, dusky skin coloration, and, possibly, conjunctival edema. Edema of the upper extremities and prominent veins on the upper thoracic wall with retrograde flow may be present.
- Respiratory system
  - Findings are variable and depend on location and spread.
  - Centrally located obstructing tumors can cause collapse of the entire lung with an absence of breath sounds on the side of the lesion.
  - Peripheral lesions can cause individual segments or lobes to collapse, leading to findings of dullness to percussion and/or decreased breath sounds.
  - Pleural effusions give rise to characteristic findings of dullness and decreased breath sounds, depending on the size.
- Cardiovascular system: Cardiac findings are usually noted when the tumor causes an effusion. Findings can range from simple effusion to tamponade.
- Gastrointestinal system: The most common site of metastatic spread is the liver, which may manifest as tender hepatomegaly.
- Musculoskeletal system
  - Bone is another common site of spread for lung carcinomas.

- Patients may report bone pain, and tender spots may be found during the examination.
- The examination should include fist percussion of the spine to look for tender spots, which may suggest vertebral column metastases.

- Central nervous system: A neurologic examination should be performed to look for focal neurological deficits caused by brain metastases and/or signs of spinal cord compression.

CAUSES

- Smoking
  - Unlike many other malignancies, whose causes are largely unknown, the cause of lung cancer is tobacco smoking in as many as 90% of patients (78% in men, 90% in women).
  - For a person who currently smokes, the risk of developing lung cancer is 13.3 times that of a person who has never smoked. The risk also varies with the number of cigarettes smoked. The risk ranges from 10 times higher than controls for those smoking 20 or fewer cigarettes per day to 20 times higher than controls for those smoking more than 20 cigarettes per day.
  - Because not all persons who smoke develop lung cancer and because not all patients with lung cancer have a history of smoking, other factors, including genetic susceptibility, also play roles.
  - Once a person quits smoking, the risk of lung cancer increases for the first 2 years and then gradually decreases, but it never returns to the same level as that of a person who has never smoked.
- Passive smoking
  - As many as 15% of the lung cancers in persons who do not smoke are believed to be caused by secondhand smoke. The US Environmental Protection Agency recently recognized passive smoking as a potential carcinogen.
  - Cigarette smoke contains *N*-nitrosamines and aromatic polycyclic hydrocarbons, which act as carcinogens. The *N*-nitrosamines are hydroxylated by the P-450 enzyme system, leading to the formation of carcinogens that cause formation of DNA adducts.
- Asbestos
  - Asbestos exposure has been shown to be strongly associated with the causation of lung cancer, malignant pleural mesothelioma, and pulmonary fibrosis.
  - The silicate type of asbestos fiber is an important carcinogen.
  - Asbestos exposure increases the risk of developing lung cancer by as much as 5 times.
  - Tobacco smoke and asbestos exposure act synergistically, and the risk of developing lung cancer for persons who currently smoke tobacco and have a history of asbestos exposure approaches 80-90 times that of control populations.
- Radon
  - Radon is an inert gas produced as a result of uranium decay. Radon exposure is a well-established risk factor for lung cancer in uranium miners. Approximately 2-3% of lung cancers annually are estimated to be caused by radon exposure.
  - The US National Research Council's report of the Sixth Committee on Biological Effects of Ionizing Radiation has estimated that radon exposure causes 2100 new lung cancers each year, while it contributes to lung cancer causation in approximately 9100 persons who smoke.
  - Household exposure to radon has never been clearly shown to cause lung cancer.
- HIV infection: A recent report from the State of Texas Health Department suggested a 6.5-fold increase in lung cancer in patients infected with HIV. Other large series do not support an increased prevalence of lung cancers in subjects with HIV infection.
- Other environmental agents
  - Aromatic polycyclic hydrocarbons, beryllium, nickel, copper, chromium, cadmium, and diesel exhaust all have been implicated in causing lung cancer.
  - Dietary fiber and vegetables have been suggested as protective from lung cancer.
  - In a recent study, alpha-tocopherol and carotenoids have been found to be harmful rather than beneficial in decreasing the mortality from lung cancer.

LAB STUDIES

- Diagnostic strategy: Apart from a handful of asymptomatic patients, in whom lung cancer is diagnosed incidentally, virtually all patients with lung cancer are symptomatic at presentation. In the presence of a long history of smoking or other risk factors for lung cancer, the presence of persistent respiratory symptoms should prompt a CXR. Because benign conditions and metastatic malignancies can mimic lung cancer on radiographs, histologic confirmation is necessary. This can be achieved by sputum cytologic studies, bronchoscopy, or CT-guided transthoracic needle biopsy of the mass, depending on the location of the tumor.
- Sputum cytologic studies
  - Centrally located endobronchial tumors exfoliate malignant cells into sputum. (This location and tendency to exfoliate are most common in squamous cell carcinomas.) Therefore, sputum cytology can be a quick and inexpensive diagnostic test, if results are positive.
  - The false-positive rate for sputum cytology is 1%, but the false-negative rate is as high as 40%.
  - A positive finding for malignancy from a cytologic specimen is accurate in as many as 90% of cases, but any distinction between different histologic subtypes is not accurate. Discordant results are often observed between cytologic and histologic findings of specimens obtained from bronchoscopy or transthoracic biopsy.
- Complete blood cell count: This should be obtained in every patient, especially before instituting chemotherapy.
- Electrolytes and renal function studies: Because of the propensity of lung cancers to cause paraneoplastic

syndromes, serum electrolyte levels are evaluated. Also, for more information, see Paraneoplastic Syndromes.

- Staging workup for NSCLC
  - Because of the importance of stage on the therapeutic decision-making process, all patients with NSCLC must be staged adequately.
  - In the United States, the standard staging workup for NSCLC includes at least the following:
    - Complete history and physical examination
    - CT scan of the chest and upper abdomen (including liver and adrenals)
    - Complete blood cell counts
    - Liver and kidney functions tests
    - Serum electrolytes
  - Information obtained from these tests can then be used to guide further testing (e.g. imaging studies).
  - Invasive staging procedures such as mediastinoscopy and mediastinotomy may be required to assess mediastinal lymph nodes in patients who are candidates for potentially curative surgical resection.

IMAGING STUDIES

- A complete staging workup for NSCLC should evaluate the extent of disease.
- CXR: A chest radiograph is usually the first test ordered in patients in whom a lung malignancy is suggested.
  - If the tumor is clearly visible and measurable, a CXR can sometimes be used to monitor response to therapy.
  - Popcorn calcification is usually a radiologic characteristic of benign lesions.
- CT scan
  - Because common sites of spread of a NSCLC include the liver and adrenals, a CT scan of the chest and upper abdomen, to include the liver and adrenals, is the minimum standard for a staging workup for a person newly diagnosed with NSCLC.
  - A CT scan or MRI of the brain may be required if neurological symptoms or signs are present. Most thoracic surgeons perform imaging of the brain before attempting definitive resection of a lung malignancy.
- Bone scintigraphy: The skeletal system is another common site of metastases for lung cancers. If patients report bone pain or if their serum calcium and/or alkaline phosphatase levels are elevated, a bone scan should be obtained to search for bone metastases.
- Positron emission tomography
  - Positron emission tomography (PET) scanning is approved by the US Food and Drug Administration for the workup of solitary lung nodules.
  - Recent studies suggest that PET scanning is useful for searching for systemic spread if other diagnostic modalities cannot clarify an abnormality that may change the treatment of the patient's condition. However, false-positive and false-negative results can occur.
  - Recently, additional data have emerged that underscore the importance of PET scanning in patients with NSCLC. PET scans appear to be more sensitive, specific, and accurate than CT scans for staging mediastinal disease. While radiographs and CT scans show images of structures, PET scans reveal the nature of the area under study. PET scans often detect abnormalities not demonstrated on CT scans.
  - Published reports suggest that staging of NSCLC may be influenced by PET scan results in up to 60% of the cases and as many as 25% may be up-staged after PET scanning.
  - Caution is required when interpreting the results of PET scans in patients who may be denied potentially curative surgical resection based on PET results.
- MRI: MRI is most useful when evaluating a patient in whom spinal cord compression is suggested. In addition, brain MRI has a greater sensitivity than CT scan for detection of central nervous system metastasis.

PROCEDURES

- Bronchoscopy
  - When a lung cancer is suggested, especially if centrally located, bronchoscopy provides a means for direct visualization of the tumor, allows determination of the extent of airway obstruction, and allows collection of pathologic material under direct visualization.
  - Fiberoptic bronchoscopy has the advantage of providing direct visualization of the bronchial tree. Diagnostic material can be obtained with direct biopsy of the visualized tumor, bronchial brushings and washing, and transbronchial biopsies.
- Mediastinoscopy: This is usually performed to evaluate the status of enlarged mediastinal lymph nodes (seen on CT scan) before attempting definitive surgical resection of lung cancer.
- Thoracoscopy: This is usually reserved for tumors that remain undiagnosed after bronchoscopy or CT-guided biopsy. Thoracoscopy is also an important tool in the management of malignant pleural effusions.
- CT-guided biopsy: This procedure is preferred for tumors located in the periphery of the lungs because peripheral tumors may not be accessible through a bronchoscope.
- Biopsy of other sites: Diagnostic material can also be obtained from other abnormal sites (e.g. enlarged palpable lymph nodes, liver, pleural and pericardial effusions).

Histologic Findings

The World Health Organization classification of lung cancer is widely accepted. NSCLC includes squamous cell carcinoma, adenocarcinoma, and large cell carcinoma. Sometimes, lung cancers can exhibit 2 or more histologic patterns.

Adenocarcinoma appears to be increasing in incidence, especially in women, compared with squamous cell carcinoma, which was previously the most common type of NSCLC.

Squamous cell carcinoma has a distinct dose-response relationship to tobacco smoking and usually develops in proximal

airways, progressing through stages of squamous metaplasia to carcinoma in situ. Well-differentiated squamous cell carcinomas contain keratin pearls, while poorly differentiated squamous cell carcinomas may stain positive for keratin. Microscopic examination reveals cells with large, irregular nuclei and coarse nuclear chromatin with large nucleoli. Cells are arranged in sheets, and the presence of intercellular bridging is diagnostic.

Adenocarcinoma is the most common type of NSCLC. Histologically, adenocarcinomas form glands and produce mucin. Mucin production can be identified with mucicarmine or periodic acid-Schiff staining. The World Health Organization classification of lung cancer divides adenocarcinomas into (1) acinar, (2) papillary, (3) bronchoalveolar, and (4) mucus-secreting. Bronchoalveolar carcinoma is a distinct clinicopathologic entity that appears to arise from type II pneumocytes and may manifest as a solitary peripheral nodule, multifocal disease, or a pneumonic form, which can spread rapidly from one lobe to another. Stage for stage, adenocarcinomas are associated with worse prognoses than squamous cell carcinomas, with the exception of T1 N0 M0 tumors.

Large cell carcinoma is the least common of all NSCLCs. It is composed of large cells with prominent nucleoli, and no mucin production or intercellular bridging is identified. Many tumors previously diagnosed as large cell carcinomas are identified as poorly differentiated adenocarcinomas or squamous cell carcinomas after advanced immunohistochemical staining, electron microscopy, and monoclonal antibody studies. A variant of large cell carcinoma has been identified; it contains neuroendocrine features and is called large cell neuroendocrine carcinoma. Large cell neuroendocrine carcinomas are associated with a worse prognosis than large cell carcinomas.

STAGING

The staging of all NSCLC follows the TNM system. The current TNM staging system came into effect in 1997 after revisions for stage groupings for stages I, II, and III.

The most important prognostic indicator in lung cancer is the extent of disease. The American Joint Committee for Cancer Staging and End Results Reporting has developed the TNM staging system, which takes into account the degree of spread of primary tumor, the extent of regional lymph node involvement, and the presence or absence of distant metastases. The TNM system is used for all lung carcinomas except small cell lung carcinomas.

For TNM staging, NSCLC is divided into 4 stages, with further subdivision of stages I-III into A and B subtypes. These stages have important therapeutic and prognostic implications, which are discussed later.

- Tumor (T)
  - TX - Positive malignant cytology results, no lesion seen
  - T1 - Diameter smaller than or equal to 3 cm
  - T2 - Diameter larger than 3 cm
  - T3 - Extension to pleura, chest wall, diaphragm, pericardium, within 2 cm of carina, or total atelectasis
  - T4 - Invasion of mediastinal organs (eg, esophagus, trachea, great vessels, heart), malignant pleural effusion, or satellite nodules within the primary lobe
- Regional lymph node involvement (N)
  - N0 - No lymph nodes involved
  - N1 - Ipsilateral bronchopulmonary or hilar nodes involved
  - N2 - Ipsilateral mediastinal or subcarinal nodes
  - N3 - Contralateral mediastinal, hilar, any supraclavicular nodes involved
- Metastatic involvement (M)
  - M0 - No metastases
  - M1 - Metastases present
- Stage groupings
  - IA - T1 N0 M0
  - IB - T2 N0 M0
  - IIA - T1 N1 M0
  - IIB - T2 N1 M0 or T3 N0 M0
  - IIIA - T1-3 N2 M0 or T3 N1 M0
  - IIIB - Any T4 or any N3 M0
  - IV - Any M1

TREATMENT

Medical Care

The roles of surgery, chemotherapy, and radiation therapy for NSCLC are discussed in this section. Because most lung cancers cannot be cured with currently available therapeutic modalities, the appropriate application of skilled palliative care is an important part of the treatment of patients with NSCLC.

Chemotherapy therapy

- Only 30-35% of patients with NSCLC present with sufficiently localized disease at diagnosis to attempt curative surgical resection (stages IA and IB, IIA and IIB, and IIIA). Approximately 50% of patients who undergo surgical resection experience local or systemic relapse; thus, approximately 80% of all patients with lung cancer are considered for chemotherapy at some point during the course of their illness.
- At present, chemotherapy alone has no role in potentially curative therapy for NSCLC. Although the relapse rate after surgical resection of localized NSCLC is high, multiple randomized trials have failed to detect a benefit of adjuvant chemotherapy (ie, chemotherapy given after surgery). Two small, randomized trials have suggested that neoadjuvant chemotherapy (i.e. chemotherapy given prior to surgery) prolongs survival in subjects with stage IIIA disease. Other similarly designed trials fail to confirm this. Chemotherapy may be considered as part of multimodality therapy for locally advanced NSCLC and is used alone in the palliative treatment of stage IIIB NSCLC (owing to malignant pleural effusion) and stage IV NSCLC.
- NSCLC is only moderately sensitive to chemotherapy, with single-agent response rates in the range of 15% or better. Some newer agents (eg, gemcitabine, paclitaxel, docetaxel, vinorelbine) have shown promising single-agent activity, with

response rates from 20-25%. Combination chemotherapy regimens have been reported to achieve response rates as high as 50%, especially when newer agents are included.

- Patients with good performance status (ie, 0-2 on the Zubrod or Eastern Cooperative Oncology Group scale, >70% on Karnofsky scale; and less than 10% body weight loss are good candidates for chemotherapy. In such patients, platinum-based chemotherapy provides better palliative benefits than the best supportive care and may provide a modest survival advantage. Commonly used regimens include carboplatin-paclitaxel, cisplatin-gemcitabine, and cisplatin-vinorelbine, all of which achieve similar results.
- Several randomized controlled trials have failed to show a clear superiority of one combination over another. However, a recently reported meta-analysis compared a combination of gemcitabine-cisplatin with other platinum-containing regimens. This meta-analysis was initially presented at the 10th World Conference on Lung Cancer in Vancouver, Canada, and included data from 13 randomized trials. This meta-analysis showed an absolute survival benefit of 3.9% at 1 year in favor of gemcitabine-containing regimens. Gemcitabine-containing regimens were also superior in median progression-free and overall survival. The estimated pooled hazard ratio for overall survival was 0.9 in favor of gemcitabine-containing regimens (P <.001).
- Selected patients with good responses to first-line chemotherapy, good performance status, and a long disease-free period between initial chemotherapy and relapse may be candidates for second-line chemotherapy. Docetaxel (Taxotere) has been approved by the US Food and Drug Administration in this clinical setting, but other drugs (eg, gemcitabine, vinorelbine), if not used in the first-line regimen, may result in similar palliation and clinical benefit.

Biologic therapy

- With the increased understanding of molecular abnormalities in lung cancer, recent research efforts have focused heavily on identifying molecular targets and using this knowledge to develop molecular-targeted therapies.
- One such abnormality, which is common in NSCLC, is overexpression of the epidermal growth factor receptor (EGFR). Stimulation of the EGFR pathway leads to increased autophosphorylation of a tyrosine kinase pathway associated with EGFR. This leads to a series of intracellular events culminating in increased mitotic and growth potential, increased ability to metastasize, and increased angiogenesis (new blood vessel formation) in the cancer cells. Cancers overexpressing EGFR have been shown to have increased resistance to therapy, increased metastatic potential, and poorer prognoses.
- Several molecular-targeted therapies have been developed and are at various stages of testing in NSCLC.
- Gefitinib (ZD1839, Iressa) is one such approach and represents a class of EGFR pathway inhibitors that act intracellularly to block activation of EGFR pathway. Two large phase 2 trials (Iressa Dose Evaluation in Advanced Lung Cancer 1, Iressa Dose Evaluation in Advanced Lung Cancer 2) have led to the approval of gefitinib in the United States as a third-line therapy. The dose of gefitinib in this setting is 250 mg/d orally until disease progression or undue toxicity. The expected response rate in previously treated patients ranges from 10-18%, but, more importantly, therapy with gefitinib has been shown to improve quality of life and disease-related symptoms.
- Two large, phase 3 randomized trials testing the addition of gefitinib to standard chemotherapy in the first-line setting failed to show any improvement with the addition of gefitinib over chemotherapy alone. Several different explanations can be put forth to explain this lack of improvement, and ongoing studies are testing the optimum role of molecular-targeted therapies in the management of NSCLC.

Radiation therapy

- In the treatment of stage I and stage II NSCLC, radiation therapy alone is considered only when surgical resection is not possible because of limited pulmonary reserve or the presence of comorbid conditions.
- The role of radiation therapy as surgical adjuvant therapy after resection of the primary tumor is controversial. Radiation therapy reduces local failures in completely resected (stages II and IIIA) NSCLC but has not been shown to improve overall survival rates.
- Radiation therapy alone used as local therapy has been associated with 5-year survival rates of 12-16% in early-stage NSCLC (ie, T1 and T2 disease). No randomized trials have directly compared radiation therapy alone with surgery in the management of early-stage NSCLC.

Combined chemoradiotherapy

- The current standard of care in the management of good-risk (ie, Karnofsky performance score of 70-100, minimal weight loss) patients with locally advanced NSCLC is combined-modality therapy consisting of platinum-based chemotherapy and radiation. This results in statistically significant improvement in both disease-free and overall survival rates compared with either modality used alone.
- Current research efforts focus on the use of chemotherapy (with or without radiation therapy) in the neoadjuvant setting to try to improve resectability.
- Two recently reported randomized studies show longer survival in patients with unresectable stage III disease when treated with concurrent (rather than sequential) platinum-based chemotherapy and radiation therapy than when treated with other regimens.

Surgical Care

Surgical resection provides the best chance of long-term disease-free survival and possibility of a cure. In stages I and II NSCLC, surgical resection is almost always possible unless comorbid medical conditions are present or the patient's respiratory reserve is so low that the intended resection will leave the patient with crippling respiratory dysfunction. The role of surgery for stage III disease is controversial. Patients with completely resectable primary tumors (i.e. T4 N0) have a much better prognosis than those with spread to ipsilateral mediastinal or subcarinal lymph nodes (i.e. N2), signifying that spread beyond the primary tumor

is associated with a poor prognosis. Patients with stage IIIB or IV tumors are generally not surgical candidates.

- Preoperative evaluation: This should include a careful assessment of resectability, cardiopulmonary reserve, and perioperative risk.
- Pulmonary function tests: As a general guideline, most patients with a preoperative forced expiratory volume in one second of greater than 2.5 L are able to tolerate pneumonectomy. With a forced expiratory volume in one second of 1.1-2.4 L, a lobectomy is possible. With a forced expiratory volume in one second of less than 1 L, patients are not considered candidates for surgery. These factors are further modified by the presence of cardiac disease or other comorbid conditions.
- Surgical procedures: The standard surgical procedures for lung cancer include lobectomy or pneumonectomy. Wedge resections are associated with an increased risk of local recurrence and a poorer outcome.
- Postoperative evaluation: Residual pulmonary function after surgical resection is estimated using pulmonary function tests and radionuclide lung scans.
- Complications: The perioperative mortality rate is 6% for pneumonectomy, 3% for lobectomy, and 1% for segmentectomy. These rates reflect improvements in anesthesia and surgical techniques.
- Neoadjuvant chemotherapy: Two small reports have shown improvement in disease-free and overall survival rates with neoadjuvant cisplatin-based chemotherapy for stage IIIA NSCLC; this approach may be considered in patients with good performance status.

Consultations

The management of lung cancer is best achieved with a multidisciplinary approach; therefore, after diagnosis, consultations should be sought from the following specialists:

- Thoracic surgeon
- Radiation oncologist
- Medical oncologist
- Social worker
- Pulmonologist

Activity

The activity level as measured by a performance status scale (eg, Zubrod, Karnofsky; is an important prognostic factor. Patients should be encouraged to remain active during and after treatment for lung cancer. A declining activity level usually signifies progressive or recurrent disease but also may be due to adverse effects of treatment.

Medical

Unresectable NSCLC is treated with chemotherapy or a combination of chemotherapy and radiation therapy. Aggressive antiemetic support and growth-factor support, when appropriate, are other integral parts of medical treatment of affected patients. Antibiotics are commonly required for treatment of infectious complications but are not discussed in this article. Aggressive antiemetic support to prevent, not treat, nausea and vomiting is essential because of the highly emetogenic potential of chemotherapy drugs and the doses used in the treatment of NSCLC. This holds especially true for platinum-based chemotherapeutic regimens. The most common and effective agents are corticosteroids and the serotonin receptor antagonists, which include ondansetron (Zofran), granisetron (Kytril), and dolasetron (Anzemet).

Drug Category: *Antiemetics* -- Useful in the treatment of symptomatic nausea caused by chemotherapy.

Drug Category: *Antineoplastic agents* -- Used either to prolong survival or to palliate symptoms in advanced or unresectable lung cancer.

FOLLOW-UP

Deterrence/Prevention

- Cigarette smoking is the most common etiologic factor for lung cancer. The primary way to decrease the prevalence of lung cancer is to decrease the prevalence of smoking. Some measures for doing so include the following:
  - Public education about the hazards of smoking
  - More stringent legislation for tobacco control
  - Banishment of tobacco smoking in all public areas

Complications

- Spinal cord compression
  - The skeletal system is a common site of spread of lung cancer. When cancer metastasizes to the axial skeleton, it may grow and compress the spinal cord.
  - Patients usually report back pain and neurological symptoms in the form of decreased sensation in the lower half of the body, decreased strength, loss of bowel control, and loss of bladder control. A careful neurologic examination usually localizes the level of compression.
  - Suspected spinal cord compression is an emergency. Patients should immediately receive an adequate dose of a corticosteroid (usually intravenous dexamethasone at 10 mg followed by 6 mg q6h) and should undergo an immediate MRI scan of the vertebral column. If documented, spinal cord compression should be treated emergently with radiation therapy, and steroids should be tapered slowly.
- Metabolic complications
  - The most common metabolic complication associated with NSCLC is hypercalcemia, which is usually associated with squamous cell carcinoma.
  - Other findings can include hyponatremia, and syndrome of inappropriate secretion of antidiuretic hormone should be considered.
- Complications of therapy: Chemotherapy can give rise to various adverse effects.
  - Febrile neutropenia or bleeding may result from bone marrow suppression.
  - Hyponatremia or hypomagnesemia may result from cisplatin nephrotoxicity.
  - Renal failure or ototoxicity may result from cisplatin.

- Peripheral neuropathy may result from cisplatin, paclitaxel, and vinorelbine.

PROGNOSIS

- Prognostic factors for NSCLC are summarized.
- Estimated 5-year survival rates are as follows:
  - Stage IA - 75%
  - Stage IB - 55%
  - Stage IIA - 50%
  - Stage IIB - 40%
  - Stage IIIA - 10-35%
  - Stage IIIB - Less than 5%
  - Stage IV - Less than 5%