The core references for this chapter include the textbook Cancer Treatment (Haskell, 1995), CancerNet PDQ Information for Health Care Professionals on non-small cell and small cell lung cancers (CancerNet, 1996) and recent review articles (Karsell, 1993; Miller et al., 1992; Quint et al., 1995; Pugatch et al., 1995; Bragg, 1989; Non-Small Cell Lung Cancer Collaborative Group; Ihde, 1995). Recent review articles were selected from a MEDLINE search identifying all English language review articles published on lung cancer since 1992. Where the core references cited studies to support individual indicators, these have been included in the references. Whenever possible, these have been supplemented with the results of randomized controlled trials.

**IMPORTANCE**

Lung cancer is the most frequent cause of cancer mortality in the United States. It is estimated that 177,000 people will be diagnosed with lung cancer in 1996 and 158,700 will die from the disease (Parker, 1996). Tobacco inhalation is a major etiologic factor in the development of lung cancer and believed to be the cause of approximately 90 percent of the deaths from lung cancer. Currently, approximately 25 percent of the adult U.S. population smokes. Smoking cessation will be reviewed in another chapter.

**SCREENING**

Controlled trials of screening with chest x-ray and sputum cytology have failed to show a reduction in lung cancer mortality even for high-risk individuals (Eddy, 1989). There is consensus among the following organizations that screening for lung cancer is not supported by the current evidence: the American Cancer Society, the American College of Radiology, the National Cancer Institute, the U.S. Preventive Services Task Force, and the Canadian Task Force on the Periodic Health Examination. As such, we do not recommend any indicator for the screening or early detection of lung cancer.
DIAGNOSIS

The most common presenting symptoms of lung cancer are related to the local effects of tumor on the airways producing cough, dyspnea, hemoptysis, or chest pain (Patel and Peters, 1993). Many patients present with symptoms of metastatic disease including bone pain, hepatomegaly, or neurologic sequelae of brain lesions. Up to ten percent of lung cancer patients will have clinical manifestations of ectopic hormone production from the tumor, the most common of these being hypercalcemia from PTH-like factor. Occasionally, an unsuspected lung cancer will be discovered on a chest x-ray obtained for some other reason. While many of these symptoms may lead to a diagnostic work-up which reveals the diagnosis of lung cancer, they are not specific for lung cancer. Therefore, we have not proposed a quality indicator on the work-up of a chronic cough, hemoptysis, or other symptoms that may be worrisome for lung cancer.

Frequently lung cancer will be diagnosed during the evaluation of a mass or a solitary pulmonary nodule picked up incidentally on chest x-ray (Toomes et al., 1983; Khouri, 1987; Goldberg-Kahn et al., 1997; Lillington, 1982; Lillington et al., 1993; Libby et al., 1995). A pulmonary mass is defined as a lesion on chest x-ray with a diameter greater than 3 cm. Because lesions greater than 3 cm are almost always malignant, a pathological diagnosis should always be pursued on any patient with such a radiologic finding. Our recommended quality indicator states that any patient with a mass on chest x-ray greater than 3 cm should have documentation of a pathologic diagnosis in the chart (Indicator 1).

A solitary pulmonary nodule is defined as a coin-like lesion on chest x-ray or other imaging study that measures less than 3 cm in diameter. Forty to 50 percent of solitary pulmonary nodules in the United States are caused by lung cancer. When treated at this stage, lung cancer is highly curable, with reported five year survival rates up to 80 percent. Therefore, a pathologic diagnosis should be obtained in every solitary lung nodule that does not have the following benign characteristics:

1. Size is stable when compared with a chest x-ray or other radiographic image from at least two years previously,
2. Nodule has a benign calcification pattern which includes central, diffuse, speckled, laminar or popcorn calcifications, and
3. The density of the nodule on CT scan is greater than 168-200 Hounsfield units.

We recommend a quality indicator requiring that patients without a prior diagnosis of cancer (except non-melanoma skin cancer) who have a solitary pulmonary nodule on chest x-ray, that does not meet at least one of the numbered characteristics above, have documentation of a pathologic diagnosis in the chart (Indicator 2).

While early studies of sputum cytology reported sensitivities up to 98 percent, this appears to have declined, and more recent evaluations suggest it is only 20 to 50 percent sensitive in the current population of lung cancer patients (Karsell et al., 1993; Lukeman, 1973; Kanhouwa et al., 1976; Gagneten et al., 1976; Goldberg-Kahn et al., 1997; Khouri et al., 1987; Karsellet et al., 1993). However, in patients with cancers that involve the central airways, its sensitivity may be as high as 74 percent (Watanabe et al., 1991). If sputum cytology is not diagnostic, fiberoptic bronchoscopy can allow for visualization and biopsy of endobronchial lesions as well as cytology from bronchial washings (Shure, 1985; Edell, 1989; Cortese et al., 1979; Lukeman, 1973). Tumors too peripheral for bronchoscopy can be biopsied with transthoracic needle aspiration or core biopsy, either under CT or fluoroscopic guidance. The diagnostic yield of this technique is approximately 80 to 90 percent with a sensitivity for malignancy ranging from 64 percent to 97 percent, and specificity greater than 95 percent (Khouri et al., 1987; Berquist et al., 1995; Weisbrod, 1990; Gobien et al., 1983; Pavy et al., 1974; Lalli et al., 1978; Westcott, 1981; Gibney et al., 1981). The diagnosis of lung cancer can also sometimes be made from pleural or pericardial fluid cytology, from fine needle aspiration of an enlarged axillary or supraclavicular lymph node, or a lymph node biopsy at mediastinoscopy. In some patients, none of these techniques will be diagnostic and a thoracotomy may be necessary. However, in patients who have what appears to be unresectable lung cancer on imaging, the risk of mediastinoscopy or thoracotomy may not be warranted to make a diagnosis.

Lung cancer is usually divided into non-small cell and small cell lung cancer, and this distinction is relevant because the treatment and prognosis are different. Therefore, we will address the staging, evaluation and treatment of each separately.
TREATMENT

Non-Small Cell Lung Cancer

Non-small lung cancer includes three distinct histological types: adenocarcinoma, squamous cell, and large cell carcinoma (Table 7.1). As surgical resection offers the only hope of cure, the treatment approach depends upon determining whether patients are surgically resectable, generally Stages I and II (Table 7.2). In addition, while some patients may have disease which appears resectable, they may not be able to tolerate a lung resection because of poor pulmonary reserve or other medical illnesses. Only about 20 to 35 percent of patients present with resectable disease (Lince et al., 1971; Overholt et al., 1975).

Table 7.1
Histologic Types Of Lung Cancer

<table>
<thead>
<tr>
<th>Cellular Classification</th>
<th>Subtypes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-Small Cell</strong></td>
<td></td>
</tr>
<tr>
<td>Squamous Cell (also epidermoid)</td>
<td>Spindle cell variant</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Acinar</td>
</tr>
<tr>
<td></td>
<td>Papillary</td>
</tr>
<tr>
<td></td>
<td>Bronchoalveolar</td>
</tr>
<tr>
<td></td>
<td>Solid tumor with mucin</td>
</tr>
<tr>
<td><strong>Large Cell</strong></td>
<td>Giant cell</td>
</tr>
<tr>
<td><strong>Adenosquamous</strong></td>
<td>Clear cell</td>
</tr>
<tr>
<td><strong>Small Cell</strong></td>
<td>Oat cell</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
</tr>
<tr>
<td></td>
<td>Mixed (small cell with other cell types of lung cancer)</td>
</tr>
</tbody>
</table>

The purpose of staging and preoperative evaluation in non-small cell lung cancer is to determine who has disease which can be cured surgically. Methods available for staging include physical exam, laboratory tests, chest x-ray, CT or MRI of the chest, mediastinoscopy, CT of the abdomen, CT or MRI of the brain, and bone scan (Benfield, 1975; Miller et al., 1992; Quint, 1995; Pugatch, 1995). In addition, the morbidity and mortality of lung resections are not inconsequential and must be carefully weighed when deciding to proceed.
with surgery. Immediate postoperative mortality is age-related but overall is approximately five to eight percent with pneumonectomy and three to five percent with lobectomy. The assessment of pulmonary reserve with pulmonary function tests and arterial blood gas evaluation, as well as the stratification of cardiac risk with surgery, is performed preoperatively to determine if a patient is an operative candidate. The use of these tests and the evaluation of patients for non-operative disease is driven in large measure by expert opinion, the local availability of diagnostic tests, and individual circumstances.

An absolute contraindication to lung resection is the presence of distant metastases. Frequent sites of metastases include bone, liver, adrenal glands, brain, peripheral lymph nodes, and the thorax, including the contralateral lung, mediastinum, and pericardium. Initial staging and evaluation is usually guided by patient symptoms and directed at identifying any metastatic lesion that would necessarily preclude surgery.

Though no currently available studies are sensitive or specific for identifying lung cancer metastases, many tests, including chest x-ray, liver function tests, CT scans, and bone scan, are routinely utilized to evaluate patients who present with lung cancer (Haskell, 1995). While chest x-ray is not very accurate at identifying metastatic lung cancer in the thorax, it has almost always been obtained in the diagnostic evaluation of lung cancer. Lytic lesions of the bones or nodules in the contralateral chest visible on chest x-ray are generally considered evidence of metastatic disease. Liver function tests are almost always elevated with hepatic involvement of lung cancer; however, they are not very specific. A CT scan of the entire abdomen or the use of upper abdomen cuts obtained with chest CT is recommended by some experts to look for metastases in the liver and adrenal glands, although isolated lesions to the liver or the adrenals are rare (Salvatierra et al., 1990; Sider et al., 1988). In fact, approximately 50 percent of the adrenal masses detected in patients with non-small cell lung cancer are benign (Oliver et al., 1984). CT scan of the brain with intravenous contrast is useful to rule out CNS metastases, although it is probably not indicated in patients who do not have symptoms (Jacobs et al., 1977). Routine bone scan is not indicated in patients without symptoms suggestive of bone metastases (pain) as the sensitivity and specificity of bone scan for predicting metastases is 71
percent and 27 percent compared with 100 percent and 54 percent for clinically assessment alone (Michel et al., 1991; Ramsdell et al., 1978). The value of CT imaging of the abdomen and bone scan in patients without symptoms has not been proven. Compelling evidence exists that routine scans of abdomen, brain, and bone have no useful role in patients who do not have clinical or laboratory evidence of metastases to these sites (Bragg, 1989). While each of these tests may be useful in individual circumstances, we do not recommend any of these as quality indicators for the staging of lung cancer.

In addition to distant metastases, locally advanced disease may preclude resection. In general, tumor metastases to scalene or supraclavicular lymph nodes or contralateral hilar or mediastinal lymph nodes; tumor with invasion of the mediastinum, including the heart, great vessels, trachea, esophagus, or carina; or the presence of a malignant effusion with positive cytology (Stage IIIB) are not considered surgically resectable. The management of patients with Stage IIIA disease, which includes tumor involving the mainstem bronchus but not the carina, tumor associated with atelectasis or obstructive pneumonia but not involving the entire lung, or metastases in the ipsilateral mediastinal and subcarinal lymph nodes, remains controversial. In some cases, patients with Stage IIIA disease may be resectable. In any case, if metastatic disease is not present, further staging evaluations are performed to determine if the patient has Stage I, II, or IIIA lung cancer that is potentially resectable.

Once again, chest x-ray, routinely performed for diagnosis of lung cancer, may be useful in determining the extent of disease in the thorax, although it is not very accurate for the evaluation of the mediastinum. Chest x-ray is 61 to 71 percent accurate in detecting hilar adenopathy and 47 to 60 percent accurate in the mediastinal adenopathy, just slightly better than chance (Swensen et al., 1990).

Chest CT, though heavily relied upon, is only slightly better than chest x-ray in helping to evaluate the extent of disease in the chest (Quint et al., 1995). For identifying chest wall invasion, the reported sensitivity of CT ranges from 38 percent to 87 percent with a specificity of 40 to 90 percent. When trying to differentiate between tumors that are greater or less than two cm from the carina, CT has a sensitivity of 56 percent to 89 percent. It is not as useful at determining if the carina or mediastinal structures are
involved, which is a more crucial question (Quint et al., 1995; Wursten et al., 1987; Izbicki, 1992; Glazer et al., 1989; Webb et al., 1991). The positive predictive value of CT scan for assessing mediastinal metastases ranges between 49 and 68 percent with sensitivities of 29 to 95 percent and specificities of 46 to 94 percent (Webb et al., 1991; Izbicki et al., 1992; McLoud et al., 1992; Underwood et al., 1979; Inouye et al., 1986; Daly et al., 1987; Dales et al., 1990). While many experts recommend CT scan of the chest for staging, others do not because of its limited ability to predict resectability and mediastinal involvement. In the few studies of magnetic resonance imaging, it does not appear to be any better than CT in the staging of lung cancer (Webb et al., 1991; Webb et al., 1985; Pandovani et al., 1993). Therefore, we do not include routine chest imaging with plain films, CT, or MRI as a recommended quality indicator for the staging of non-small cell lung cancer.

 mediastinoscopy is believed to be the most accurate way of assessing patients for mediastinal lymph node involvement prior to thoracotomy. However, there is no consensus regarding the indications for mediastinoscopy prior to surgical resection (Pearson, 1986; Fishman et al., 1975; Hutchinson and Mills, 1976). Patients who have negative findings at mediastinoscopy have only an eight percent incidence of unresectability at thoracotomy (Pearson, 1986). Well-differentiated peripheral carcinomas with a normal mediastinum on CT scan tend to have an incidence of positive mediastinal node involvement at mediastinoscopy of less than five percent. Therefore, many experts do not believe that patients who have lesions with these characteristics benefit from mediastinoscopy (Hutchinson et al., 1976). Most experts recommend mediastinoscopy in patients whose radiographic studies show mediastinal abnormalities. Many centers perform mediastinoscopy on all patients with mediastinal lymph nodes greater than 1 cm on CT scan (Haskell, 1995). Transbronchial needle aspiration sampling of mediastinal lymph nodes is sometimes used as an alternative to mediastinoscopy prior to thoracotomy (Schure et al., 1984; Wang, 1983). The decision to proceed immediately to thoracotomy or to obtain more staging information with either mediastinoscopy or transbronchial needle aspiration of mediastinal lymph nodes is a complex one that involves weighing the individual patient’s risk from the surgical procedure and the likelihood of mediastinal spread of disease based upon the
evidence at hand. We therefore do not recommend including mediastinoscopy or mediastinal lymph node biopsy in a quality indicator.

The preoperative evaluation should also attempt to identify patients who would not tolerate lung resection because of poor pulmonary status as well as patients who are at high risk for cardiothoracic surgery. Pulmonary function testing is performed on all patients prior to surgery. If pulmonary function tests show a one second forced expiratory volume of less than 40 percent of predicted or a maximum ventilatory volume level less than 50 percent of predicted, or if the arterial partial pressure of carbon dioxide on a blood gas is greater than 45 mm Hg, resection is generally contraindicated (Shields, 1982; Pett, 1986; Mountain, 1983). Lung perfusion may be assessed using 99mTc-macroaggregated albumin. If the product of the percentage isotope uptake in the contralateral lung and the forced expiratory volume exceeds 0.8 liter, the patient should be able to tolerate a pneumonectomy (Olsen, 1975; Ryo, 1990). As cardiac complications are responsible for about 20 percent of post-operative deaths, and a history of cardiac disease doubles the risk of major surgical morbidity from nine percent to 18 percent, assessing cardiac risk is an important part of determining if a patient can undergo curative resection for lung cancer (Haskell, 1995). At a minimum, an EKG should be performed as part of the preoperative evaluation of every patient prior to lung resection. However, in patients with an abnormal EKG or symptoms suggestive of coronary artery disease, more extensive cardiac evaluation may be indicated. In addition, intractable congestive heart failure or ventricular arrhythmias, as well as a myocardial infarction within three months, are contraindications to surgery (Mountain, 1983).

As a quality indicator for staging and preoperative evaluation of non-small cell lung cancer, we propose that prior to lung resection, patients should have a pathologic diagnosis of lung cancer or a highly suspicious mass on CT scan, pulmonary function tests, and an EKG (Indicator 3).

Resectable Non-Small Cell Lung Cancer (Stage 0, I, and II)

Surgery is the only potentially curative therapy for non-small cell lung cancer. While surgery has not been evaluated in any kind of a controlled manner, the survival of patients with Stage I and II lung cancer who undergo resection with curative intent is generally much better than that of lung cancer patients generally. This is taken as indirect evidence for the
efficacy of surgery. The five year survival for Stage I patients is approximately 60 to 70 percent and Stage II is 40 to 50 percent compared with 15 percent overall (Naruke et al., 1988; Mountain, 1988). The surgical resection of non-small cell lung cancer can be accomplished by pneumonectomy, lobectomy, or a segmental or wedge resection depending on the extent of the tumor and lymph node involvement. Local recurrence appears to be greater for patients treated with a segment or wedge resection. Similarly, several non-randomized trials have shown an increase in the local recurrence rate with wedge or segment resections. A survival advantage was noted for lobectomy in patients with tumors greater than 3 cm, but not for those with tumors smaller than 3 cm (Warren et al., 1994; Martini et al., 1995). The Lung Cancer Study Group has compared lobectomy and limited excision for patients with Stage I non-small cell lung cancer in a randomized controlled trial. While there was a reduction in local recurrence for patients treated with lobectomy, there was no difference in overall survival (Ginsberg, 1995).

Patients who are inoperable but have "resectable" disease may be considered for radiation therapy with curative intent, typically 6,000 cGy delivered to the midplane of the tumor. No randomized controlled trials have compared radiation therapy to surgery or to supportive care. Retrospective studies of patients with early stage lung cancer (Stage I and II) treated with radiation therapy demonstrate two year survival rates of 40 to 56 percent and five year survival rates of 10 to 32 percent, though patients with T1 lesions do somewhat better (Hilton, 1960; Zhang et al., 1989; Haffty et al., 1988; Sandler et al., 1990; Talton et al., 1990; Dosoretz et al., 1992). In a retrospective study of patients 70 years and older who had resectable lesions smaller than 4 cm, but who were medically inoperable or refused surgery, survival at five years following radiotherapy was comparable to historical controls who had undergone surgical resection (Noordijk et al., 1988).

Although many patients treated surgically subsequently develop metastases, trials of adjuvant chemotherapy have not demonstrated a statistically significant benefit to survival (Holmes, 1994; Lad et al., 1988; LeChevalier, 1990). Likewise, while postoperative radiation appears to decrease local recurrences, it had no benefit on survival in a controlled trial (Weisenburger et al., 1986).
Because surgical resection offers the best chance of long-term survival for patients with Stage I and II non-small cell lung cancer, we recommend a quality indicator requiring that all patients with adequate pulmonary reserve, who do not have medical record documentation that they are an "unacceptable risk" for surgery and who do not have another metastatic cancer, be offered lung resection with pneumonectomy, lobectomy, or wedge resection (Indicator 4). Patients who are not offered lung resection surgery should be offered radiation therapy to the chest (≥ 5000 cGy) (Indicator 5).

**Stage III Non-Small Cell Lung Cancer**

The treatment of patients with Stage IIIA lung cancer remains controversial. Select patients (less than ten percent) may be able to undergo a surgical resection, however, patients with mediastinal lymph node involvement do not do as well as patients with early stage disease (Mountain, 1994; Martini et al., 1987). In several randomized trials of immediate surgery or preoperative radiation therapy followed by surgery, preoperative radiation therapy either had no effect or decreased the resectability rate of lung cancer and was associated with shortened survival (Warram et al., 1975; Shields, 1972). The exception to this is superior sulcus tumors which appear to have improved resectability and patient survival when treated with preoperative radiation therapy (Hilaris et al., 1974; Mallams et al., 1964). The results for postoperative radiation therapy in Stage IIIA lung cancer are comparable to those obtained in patients with Stage II lung cancer. Though a few uncontrolled series suggested an improvement in survival with postoperative radiation, the only randomized controlled trial found that while postoperative radiation therapy decreases the local recurrence rate, it does not appear to benefit survival (Weisenburger et al., 1986). Uncontrolled trials and one randomized controlled trial suggest that neoadjuvant chemotherapy with or without radiation therapy may increase the numbers of patients with Stage IIIA lung cancer who are resectable, and may prolong their survival. However, not all the randomized trials comparing this approach to standard therapy have been completed, and the favorable results seen so far may be the result of patient selection (Eagan et al., 1987; Penfield Faber et al., 1989; Weiden et al., 1991; Albain et al., 1991; Rusch et al., 1993; Bitran et al., 1986; Martini et al., 1988; Gralla, 1988; Burkes et al., 1989; Rosell et al., 1994).
For most patients with Stage III lung cancer, the only treatment options are radiation therapy, chemotherapy, or chemotherapy plus radiation therapy. For patients with locally advanced "unresectable" lung cancer, radiation therapy results in only an approximate five percent five year survival rate (Perez et al., 1987; Curran et al., 1990; Cox et al., 1991). Randomized trials comparing radiation therapy alone with radiation therapy and neoadjuvant (up-front), concurrent, or adjuvant (after radiation therapy) chemotherapy have shown that patients with excellent performance status have an improved survival with combined modality therapy when cisplatin was included in the chemotherapy regimen (Trovo et al., 1992; LeChevalier et al., 1991; Mattson et al., 1988; Soresi et al., 1988; Ansari et al., 1991; Morton et al., 1991; Dillman et al., 1990; Schaake-Koning et al., 1992; Sause et al., 1995). A recent meta-analysis of randomized clinical trials showed a ten percent reduction in the risk of death for cisplatin-based chemotherapy with radiation therapy compared with radiation therapy alone (Non-Small Cell Lung Cancer Collaborative Group, 1995).

As a quality indicator for the treatment of patients with Stage III non-small cell lung cancer, we recommend that patients with a good performance status be offered at least one modality of treatment: surgical resection, chemotherapy, or radiation therapy (Indicator 6).

Metastatic Non-Small Cell Lung Cancer (Stage IV)

While chemotherapy is often used in Stage IV non-small cell lung cancer to palliate symptoms and prolong survival, its role in the treatment of patients with metastatic disease remains extremely controversial. Numerous regimens have been tried and none seems superior to the others (Bunn, 1989; Ruckdeschel et al., 1985; Dhingra et al., 1985; Hoffman, 1985; Klatersky et al., 1990; Ruckdeschel et al., 1986; Robert et al., 1984; Einhorn et al., 1986). Randomized trials comparing chemotherapy with no chemotherapy or delayed chemotherapy have produced mixed results. Chemotherapy has been shown in some trials to significantly improve survival from approximately 10 to 17 weeks for control patients to 28 to 37 weeks for patients receiving chemotherapy (Ganz et al., 1989; Rapp et al., 1988; Cartei et al., 1993; Cellerino et al., 1988; Williams et al., 1988; Kaasa et al., 1991). Several meta-analyses of randomized trials of chemotherapy in patients with metastatic non-small cell lung cancer have demonstrated that treatment with chemotherapy
is associated with approximately a six week gain in survival compared with patients who receive supportive care (Non-Small Cell Lung Cancer Collaborative Group, 1995). Clinical trials suggest that chemotherapy is most active in patients with good performance status and a pretreatment weight loss of less than ten percent (Gralla, 1989). Although this gain in survival from chemotherapy is minimal, it represents an average of responders and nonresponders. Responders may have a more pronounced survival benefit from chemotherapy. We therefore recommend including a quality indicator which state that patients with metastatic non-small cell lung cancer with a good performance status should be offered chemotherapy (Indicator 7).

Brain Metastases

Brain metastases constitute nearly one third of all recurrences in patients with non-small cell lung cancer, and autopsy data suggest that the incidence may be as high as 50 percent (Van Raemdonck et al., 1992). With symptoms secondary to brain metastases, median survival without therapy is only one month. Whole brain irradiation will effectively palliate symptoms and modestly increase survival by three to six months (Martini, 1986). A solitary brain metastasis may be surgically resected with a marked benefit in long term survival for some individuals. In several series surgical resection of solitary brain lesions has been associated with an increase in median survival from four months to between ten and 16 months (Patchell et al., 1990; Mandell et al., 1986; Van Raemdonck et al., 1992). Patients whose lesions are not surgically resectable may benefit from stereotactic radiosurgery (Alexander et al., 1995; Loeffler et al., 1990). We propose a quality indicator requiring that patients with brain metastases be offered whole brain irradiation, surgical resection, or stereotactic radiosurgery (Indicator 8).

Small Cell Lung Cancer

Untreated, small cell lung cancer is the most aggressive of all types of lung cancer with a median survival of only two to four months. However, it is also the most responsive to chemotherapy and radiation therapy. Chemotherapy results in a four to five-fold improvement in the median survival (CancerNet PDQ, 1996; Haskell, 1995). Because it has such a high propensity for distant metastases, small cell lung cancer is not amenable to surgical treatment (Overholt et al., 1975).
Because small cell lung cancer is a systemic disease, and even when not clinically overt metastases are usually present at diagnosis, the TNM staging system is generally not used to stage patients. Instead, a simple system developed by the Veterans Administration Lung Cancer Study group is commonly used. It divides patients into two stages, limited and extensive (Table 7.3). The purpose of the staging in evaluation of small cell lung cancer is to identify patients who have limited disease and that may benefit from radiation therapy to the thorax in addition to systemic chemotherapy. Methods for staging include physical exam, laboratory tests, chest x-ray, CT or MRI of the chest, mediastinoscopy, CT of the abdomen, CT or MRI of the brain, bone scan, and bone marrow biopsy (Miller et al., 1992; Pugatch, 1995). Because there is little consensus on what staging evaluations are appropriate in the absence of specific symptoms, we do not recommend a quality indicator for the staging of small cell lung cancer.

**Limited Disease**

At the time of diagnosis, approximately one-third of patients will have tumor confined to one hemithorax or the mediastinum or supraclavicular lymph nodes. They are classified as having limited disease. Chemotherapy is the mainstay of treatment for small cell lung cancer; however, randomized controlled trials of combined modality therapy with radiation therapy and chemotherapy have shown a modest but significant improvement in survival compared with chemotherapy alone in patients with limited stage disease.

Chemotherapy produces objective responses in about 80 percent of patients with small cell lung cancer and appears to prolong survival approximately five-fold. Between five and ten percent of patients with limited disease may be cured with chemotherapy alone. In addition, while not well documented in the literature, patients experience a dramatic palliation of symptoms with chemotherapy (Ihde, 1994). A number of chemotherapy regimens have been proven effective in small cell lung cancer. Alternating chemotherapy regimens theoretically could decrease the number of resistant cancer clones, and thereby improve patients’ response to chemotherapy. A number of randomized trials have compared alternating drug regimens to standard therapy, but these have not proven to be more effective than the combination of Cisplatin and Etoposide (Goodman et al., 1990; Einhorn et al., 1988; Wolf, 1991). Although the optimal duration of treatment has not been clearly defined, randomized
trials comparing longer duration of therapy or maintenance therapy to four to eight cycles of chemotherapy every three to four weeks did not demonstrate any difference in overall survival (Giaccone et al., 1993; Spiro et al., 1989; Bleehen, 1989).

While randomized trials have shown a decrease in local recurrence with the addition of radiation therapy to the thorax, the results of combined modality therapy on overall survival have been mixed (Kies, 1987). However, two meta-analyses of the studies have shown a significant improvement in the absolute three year survival of approximately five percent for those receiving chemotherapy and radiation therapy compared with chemotherapy alone (Pignon, 1992; Warde et al., 1992). Concurrent chemotherapy and radiation therapy may produce better long-term survival than sequential combined modality therapy. Patients in a Phase II SWOG study of concurrent chest irradiation with etoposide and cisplatin chemotherapy had a four year survival of 30 percent compared with ten percent among patients in two earlier SWOG trials of sequential chemotherapy and chest radiation (McCracken et al., 1990). These studies suggest that the effective dose of radiation is in the range of 5,000 cGy or more.

We recommend a quality indicator requiring that all patients with limited disease small cell lung cancer be offered combined modality therapy with radiation therapy (\(\geq 5000\) cGy) to the chest and chemotherapy (Indicator 9).

**Extensive Disease**

Most patients with small cell lung cancer will present with extensive disease. The same combination chemotherapy regimens used in limited-stage disease appear to effectively palliate symptoms and prolong survival in extensive small cell lung cancer, however, long term survivors remain anecdotal (CancerNet, 1996; Haskell, 1995). Adding radiation therapy to chemotherapy in patients with extensive disease does not appear to prolong their survival. We propose a quality indicator requiring that all patients with extensive small cell lung cancer be offered chemotherapy (Indicator 10).

**Palliation of Symptoms**

Patients may develop a variety of symptoms secondary to small cell lung cancer including but not limited to cachexia, dyspnea, pain, superior vena cava syndrome, focal neurologic deficits, seizures, and paraneoplastic syndromes. While supportive care may ameliorate some of these symptoms,
either chemotherapy or radiation therapy can effectively palliate these symptoms in patients with small cell lung cancer (Kristjansen et al., 1988; Kristensen et al., 1992; Dombernowsky et al., 1978; Kane et al., 1976). We propose quality indicators that require patients with bone pain secondary to metastases and those with brain metastases be offered chemotherapy or local radiation therapy if they have not received it previously (Indicators 11 and 12).

**Prophylactic Cranial Irradiation**

Brain metastases occur with such frequency in patients with small cell lung cancer that some experts advocate prophylactic cranial irradiation. At diagnosis, ten percent of patients have subclinical brain metastases and brain metastases are present in 50 percent of patients at autopsy (Haskell 1995). Up to ten percent of complete responders present with brain metastases as the only site of recurrence (Haskell, 1995). While prophylactic cranial irradiation has been shown to be effective in reducing the frequency of clinically detected brain metastases, in randomized trials it has not improved survival (Pedersen et al., 1988). Its use has been associated with late neurologic complications, so it remains controversial. Therefore, we do not recommend including prophylactic cranial irradiation as a quality indicator.

**FOLLOW-UP**

**Non-Small Cell Lung Cancer**

While up to 50 percent of patients with Stage I and II lung cancer will eventually have a recurrence and die from their disease, there have been no studies on the appropriate follow-up of these patients (CancerNet PDQ, 1996). Patients with isolated recurrences may benefit from resection (as in the case of isolated brain metastasis described above) or other palliative treatment with radiation therapy or chemotherapy. However, the routine use of imaging studies to identify patients for such recurrences or for a second primary lung cancer has not been evaluated.

Patients with Stage III and IV lung cancer generally die from complications of the disease and require supportive care to alleviate their symptoms (CancerNet PDQ, 1996). Again, there are no studies evaluating the appropriate medical follow-up of these patients. As such, we do not recommend
a quality indicator for the follow-up of patients with non-small cell lung cancer.

**Small Cell Lung Cancer**

Patients with small cell lung cancer, except for the rare patient with limited disease, generally die within several years of diagnosis and require supportive care to alleviate their symptoms (CancerNet PDQ, 1996). As in the case of non-small cell lung cancer, there are no studies of the appropriate medical follow-up of patients with small cell lung cancer. As such, we do not recommend a quality indicator for the follow-up of patients with non-small cell lung cancer.
### Table 7.2
Definition Of Stages Of Non-Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>Definitions Of Stage For Quality Indicators</th>
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</thead>
<tbody>
<tr>
<td>Stage 0</td>
<td>T1s N0 M0 - carcinoma in situ</td>
<td>Carcinoma in situ</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1 N0 M0 - Tumor &lt; 3.0 cm surrounded by lung or visceral pleura without evidence more proximal than the lobar bronchus (i.e., not in the main bronchus). T2 N0 M0 - Tumor with any of the following features • &gt; 3.0 cm • involving the mainstem bronchus, 2.0 cm or more distal to the carina • associated with atelectasis or obstructive pneumonia that extends to the hilum but does not involve the entire lung</td>
<td>Tumor may involve the mainstem bronchus but must be 2 cm or more from the carina on chest x-ray, CT scan, or at thoracotomy. All lymph nodes biopsied at mediastinoscopy or thoracotomy are negative.</td>
</tr>
<tr>
<td>Stage II</td>
<td>T1 N1 M0 - Tumor &lt; 3.0 cm surrounded by lung or visceral pleura without evidence more proximal than the lobar bronchus (i.e., not in the main bronchus) and metastases in the ipsilateral peribronchial or hilar lymph nodes. T2 N1 M0 - Tumor with any of the following features &gt; 3.0 cm involving the mainstem bronchus, 2.0 cm or more distal to the carina associated with atelectasis or obstructive pneumonia that extends to the hilum but does not involve the entire lung and metastases in the ipsilateral peribronchial or hilar lymph nodes.</td>
<td>Tumor may involve the mainstem bronchus but must be 2 cm or more from the carina on chest x-ray, CT scan, or at thoracotomy. All mediastinal lymph nodes biopsied at mediastinoscopy or thoracotomy are negative but ipsilateral peribronchial or hilar lymph nodes are involved with tumor.</td>
</tr>
<tr>
<td>Stage</td>
<td>TNM</td>
<td>Definitions Of Stage For Quality Indicators</td>
</tr>
<tr>
<td>------------</td>
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<td>----------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Stage IIIa</td>
<td>T1-2 N2 M0 – Tumor of any size involving the mainstem bronchus, 2.0 cm or more distal to the carina associated with atelectasis or obstructive pneumonia that extends to the hilum but does not involve the entire lung and metastases in the ipsilateral mediastinal or subcarinal lymph nodes. T3 N0-2 M0 – Tumor of any size with direct extension into the chest wall, diaphragm, mediastinal pleura, parietal pericardium, or in the main stem bronchus &lt; 2.0 cm distal to the carina but not involving the carina and any of the following lymph node statuses: • no lymph nodes involved • metastases in the ipsilateral peribronchial or hilar lymph nodes • metastases in the ipsilateral mediastinal or subcarinal lymph nodes.</td>
<td>Mediastinal or subcarinal lymph nodes biopsied at mediastinoscopy or thoracotomy are involved with tumor but no contralateral nodes are involved with tumor. or Tumor extends into the chest wall, diaphragm, mediastinal pleura (but not mediastinal organs), or pericardial pleura, or involves the mainstem bronchus less than 2 cm from but not including the carina either on CT scan or at thoracotomy. Ipsilateral lymph nodes may be involved with tumor but no contralateral lymph nodes are involved with tumor.</td>
</tr>
<tr>
<td>Stage IIIb</td>
<td>Any T N3 M0 – Tumor of any size or invasion and metastases in contralateral mediastinal or hilar lymph nodes or any scalene or supraclavicular lymph nodes. T4 any N M0 – Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina; or a malignant effusion with or without lymph nodes involved.</td>
<td>Scalene or supraclavicular lymph nodes are positive for tumor or contralateral mediastinal lymph nodes are involved with tumor.</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T Any N M1 – distant metastases are present</td>
<td>Distant metastases are present.</td>
</tr>
</tbody>
</table>

Source: CancerNet, 1996
Table 7.3  
Definition of Stages of Small Cell Lung Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition of Stage</th>
<th>Definitions of Stage for Quality Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited stage</td>
<td>Tumor confined to one hemithorax, the mediastinum, and the supraclavicular nodes, which is encompassable within a “tolerable” radiotherapy port.</td>
<td>Tumor is confined to one half of the chest but may involve the mediastinum on the opposite side and both supraclavicular area lymph nodes.</td>
</tr>
<tr>
<td>Extensive stage</td>
<td>Extensive stage small cell lung cancer means tumor that is too widespread to be included within the definition of limited stage disease.</td>
<td>Tumor does not meet the definition of limited disease.</td>
</tr>
</tbody>
</table>

Source: CancerNet, 1996
REFERENCES


LeChevalier T, Arriagada R, Tarayre M, Lacombe-Terrier M-J, et al. Significant effect of adjuvant chemotherapy on survival in locally advanced non-small cell lung carcinoma. *Journal of the National Cancer Institute* 58:


### RECOMMENDED QUALITY INDICATORS FOR LUNG CANCER

The following apply to men and women age 18 and older.

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Quality of Evidence</th>
<th>Literature</th>
<th>Benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Patients without a prior diagnosis of cancer (except non-melanoma skin</td>
<td>II-2, III</td>
<td>Benfield, 1975; Berquist et al., 1980; Cortese et al., 1979; Edell, 1989;</td>
<td>Reduce morbidity and mortality from lung cancer.</td>
<td>Experts regard pulmonary lesions &gt;3 cm as probably malignant and recommend prompt resection if possible. Calcification patterns are not predictive of malignancies for masses &gt; 3 cm.</td>
</tr>
<tr>
<td>cancer) with a mass (&gt;= 3 cm) on chest x-ray or CT scan of the chest should</td>
<td></td>
<td>Gagneten, et al., 1976; Gibney et al., 1981; Gobien 1983; Goldberg-Kahn et</td>
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<tr>
<td>have one of the following diagnostic endpoints documented in the chart within</td>
<td></td>
<td>al., 1997; Haskell, 1995; Kanhouwa and Matthews, 1976; Karsell and</td>
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<tr>
<td>2 months of the radiological study:</td>
<td></td>
<td>McDougall,1993; Khouri et al., 1987; Lalli et al., 1978; Libby et al., 1995;</td>
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<tr>
<td>• Chest CT with multiple nodules;</td>
<td></td>
<td>Lillington 1982; Lillington and Caskey,1993; Lince and Lulu 1971; Lukeman</td>
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<td>• Sputum cytology diagnostic of cancer (expectorated or bronchoscopic</td>
<td></td>
<td>JM 1973; Miller et al., 1992; Overholt 1975; Pavy, 1974; Pugatch, 1995;</td>
<td></td>
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<tr>
<td>washing);</td>
<td></td>
<td>Quint, 1995; Shure, 1985; Toomes et al., 1985; Watanabe, et al., 1991;</td>
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<tr>
<td>• Cytology report from a fine needle aspiration of the mass;</td>
<td></td>
<td>Weisbrod 1990; Westcott 1981</td>
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<tr>
<td>• Pathology report from lymph node biopsy that is diagnostic of cancer;</td>
<td></td>
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<tr>
<td>• Pathology report from lung biopsy; or</td>
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<td>• Operative report indicating surgical resection of the mass.</td>
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<tr>
<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
<td>Comments</td>
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<tr>
<td>2. Patients without a prior diagnosis of cancer (except non-melanoma skin cancer) with a solitary nodule (&lt; 3 cm) on chest x-ray or CT scan of the chest should have one of the following diagnostic endpoints documented in the chart within 2 months of the radiological study:</td>
<td>II-2, III</td>
<td>Berquist, 1980; Cortese et al., 1979; Edell et al., 1989; Gagneten et al., 1976; Gibney, 1981; Gobien, 1983; Goldberg-Kahn, 1997; Haskell 1995; Kanhouwa and Matthews 1976; Karsell and McDougall, 1993; Khouri et al., 1987; Khouri, 1985; Khouri, 1987; Lalli et al., 1978; Libby, 1995; Lillington and Caskey, 1993; Lillington, 1982; Lincke and Lulu, 1971; Lukeman, 1973; Overholt et al., 1975; Pavy, 1974; Shure, 1985; Toomes et al., 1983; Watanabe et al., 1991; Weisbrod, 1990; Westcott, 1981</td>
<td>Decrease mortality.</td>
<td>40-50% of solitary lung nodules are caused by lung cancer. CT may find smaller nodules than chest x-ray.</td>
</tr>
<tr>
<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
<td>Comments</td>
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<tr>
<td>3. Patients with non-small cell lung cancer should have both of the following not more than 3 months prior to lung resection:</td>
<td>II-2, III</td>
<td>Haskell, 1995; Mountain, 1983; Naruke, 1988</td>
<td>Avoid the risk of thoracotomy in patients who would not tolerate a lung resection (reduce mortality from surgery).</td>
<td>Patients with an FEV1&lt;40% are at high risk for respiratory failure following lung resection. A history of cardiac disease doubles the risk of surgical morbidity.</td>
</tr>
<tr>
<td>a. Pulmonary function assessment with either pulmonary function tests (FEV1, maximum ventilatory volume) or a quantitative ventilation scan or a quantitative perfusion scan;</td>
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<tr>
<td>b. EKG.</td>
<td>II-2, III</td>
<td>Haskell, 1995; Warren, 1994</td>
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<tr>
<td>4. Patients with Stage I and II non-small cell lung cancer should be offered a lung resection (pneumonectomy, lobectomy, or wedge resection) within 6 weeks of diagnosis unless any of the following are documented:</td>
<td>II-2, III</td>
<td>Haskell, 1995; CancerNet, 1996; Warren et al., 1995; Ginsberg, 1995; Hilton, 1960; Zhang et al., 1989; Haffty et al., 1988</td>
<td>Provide curative treatment to patients who are of acceptable surgical risk.</td>
<td>With surgical resection, the five year survival is approximately 60-70% for Stage I and 40-50% for Stage II lung cancer compared with 15% overall.</td>
</tr>
<tr>
<td>a. another metastatic cancer;</td>
<td>II-1, II-2, III</td>
<td>Haskell, 1995; CancerNet Non-small Cell Lung Cancer 1996; Martini, 1995; Ginsberg, 1995</td>
<td></td>
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</tr>
<tr>
<td>b. FEV1&lt;40% on pulmonary function tests;</td>
<td>II-1, II-2, III</td>
<td>Haskell, 1995; Olsen et al., 1975; Ryo, 1990; Mountain, 1983; Naruke, 1988</td>
<td></td>
<td></td>
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<tr>
<td>c. maximum ventilatory volume &lt;50% on pulmonary function tests;</td>
<td>II-2, III</td>
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<tr>
<td>d. pCO₂&gt; 45 mm Hg on an arterial blood gas;</td>
<td>II-2, III</td>
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<tr>
<td>e. &lt;=0.8 liter perfusion to contralateral lung by quantitative perfusion scan;</td>
<td>II-2, III</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>f. documentation in chart that patient is medically “unacceptable risk” for surgery.</td>
<td>II-2, III</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Indicator</td>
<td>Quality of Evidence</td>
<td>Literature</td>
<td>Benefits</td>
<td>Comments</td>
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<tr>
<td>5. Patients with Stage I or II non-small cell lung cancer who do not undergo a lung resection should be offered radiation therapy to the chest (&gt;5000 cGy) within 6 weeks of diagnosis.</td>
<td>II-2, III</td>
<td>Haskell, 1995; CancerNet, 1996; Sandler et al., 1990; Talton, 1990; Dosoretz et al., 1992; Noordijk et al., 1988; Holmes et al., 1994; Lad., 1988; LeChevalier, 1994</td>
<td>Provide life-prolonging and potentially curative treatment to patients who are not able to undergo surgery.</td>
<td>In a retrospective study of patients 70 years and older who were medically inoperable or refused surgery, survival at 5 years following radiotherapy was comparable to historical controls that had undergone surgical resection.</td>
</tr>
</tbody>
</table>
6. Patients with Stage III non-small cell lung cancer with good performance status should be offered at least one of the following within 6 weeks of diagnosis:
- thoracotomy with surgical resection of the tumor;
- radiation therapy to the thorax;
- chemotherapy.

II-1, II-2, III Albain, 1991; Ansari et al., 1991; Bitran et al., 1986; Bunn 1989; Burkes et al., 1989; CancerNet, 1996; Cox et al., 1991; Curran and Stafford et al., 1990; Dillman et al., 1990; Eagan, 1987; Gralla, 1988; Haskell, 1995; Hilars, 1974; LeChevalier et al., 1991; Mallams, et al., 1964; Martini et al., 1988; Mattson et al., 1988; Morton et al., 1991; Non-small Cell Lung Cancer Collaborative Group 1995; Penfield Faber, et al., 1989; Perez et al., 1987; Rosell et al., 1994; Ruckdeschel et al., 1985; Rusch, et al., 1993; Sause et al., 1995; Schaake-Koning et al., 1992; Shields, 1972.; Soresi et al., 1988; Trovo, 1992; Weiden, 1991; Weisenburger, 1986

Provide the option of potentially life-prolonging therapy to patients who may benefit.

Randomized trials comparing radiation therapy alone with radiation therapy and chemotherapy have shown that patients with excellent performance status have an improved survival with combined modality therapy.
<p>| 7. | Patients with Stage IV non-small cell lung cancer and good performance status should be offered chemotherapy within 6 weeks of diagnosis. | I, II-2, III | Haskell, 1995; CancerNet, 1996; Dhingra et al., 1985; Hoffman, 1985; Klaterisky et al., 1990; Ruckdeschel et al., 1986; Robert et al., 1984; Einhorn et al., 1986; Ganz et al., 1989; Rapp et al., 1988; Cartei et al., 1993; Cellerino et al., 1988, Williams et al., 1988; Kaasa et al., 1991; Cancer Bulletin 1991; Non-small cell lung cancer collaborative group, 1995; Bralla 1989; Van Raemdonck et al., 1992; Alexander et al., 1995; Loeffler et al., 1990; CancerNet Non-small Cell Lung Cancer, 1996; Haskell, 1995 | Provide the option of potentially life-prolonging therapy to patients who may benefit. | In a recent meta-analysis, patients with metastatic non-small cell lung cancer who received chemotherapy had approximately a six week gain in survival compared with patients who receive supportive care alone. Although this gain in survival from chemotherapy is minimal, it represents an average of responders and nonresponders. Responders may have a more pronounced benefit from chemotherapy. |
| 8. | Patients with non-small cell lung cancer who have metastases on MRI or CT of the brain should be offered one of the following treatments within 2 weeks of the MRI or CT: • radiation therapy to the brain; • surgical resection of the metastasis; • stereotactic radiosurgery. | II-2, III | Patchell et al., 1990; Mandell, 1986; Van Raemdonck et al., 1992; Alexander et al., 1995; Loeffler et al., 1990; CancerNet Non-small Cell Lung Cancer, 1996; Haskell, 1995 | Palliate symptoms and prolong life. | Whole brain irradiation will effectively palliate symptoms and modestly increase survival by 3 to 6 months. |</p>
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Quality of Evidence</th>
<th>Literature</th>
<th>Benefits</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>9. Patients with limited small cell lung cancer¹ should be offered combined modality therapy with radiation therapy (≥ 5,000 cGy) and chemotherapy within 6 weeks of diagnosis.</td>
<td>I, II-2, III</td>
<td>CancerNet Non-small Cell Lung Cancer, 1996; Haskell, 1995</td>
<td>Provide life-prolonging and potentially curative treatment as well as palliation of symptoms.</td>
<td>Meta-analyses have shown a significant improvement in the absolute 3 year survival of approximately for those receiving chemotherapy and radiation therapy compared with chemotherapy alone (10% versus 5%).</td>
</tr>
<tr>
<td>11. Patients with small cell lung cancer who have metastases on MRI or CT of the brain should be offered either of the following within 2 weeks of diagnosis of brain metastases (unless they have received both previously): • chemotherapy; • radiation therapy to the brain.</td>
<td>II-2, III</td>
<td>Haskell, 1995; CancerNet,1996; Dombernowsky and Hansen 1978; Kane et al., 1976</td>
<td>Palliate symptoms.</td>
<td>Chemotherapy and radiation therapy are both effective for the palliation of symptoms caused by small cell lung cancer.</td>
</tr>
<tr>
<td>12. Patients with small cell lung cancer who have bone pain and a corresponding positive radiographic study³ should be offered either of the following within 3 weeks of presenting with the complaint of pain (unless they have received both previously): • chemotherapy; • radiation therapy to the region.</td>
<td>II-2, III</td>
<td>Haskell, 1995; CancerNet,1996; Dombernowsky and Hansen 1978; Kane et al., 1976</td>
<td>Palliate symptoms.</td>
<td>Chemotherapy and radiation therapy are both effective for the palliation of symptoms caused by small cell lung cancer.</td>
</tr>
</tbody>
</table>

**Definitions and Examples**

1 If pathological diagnosis has been obtained, date of diagnosis will be considered to be the date of the first pathology report. If pathological diagnosis was not available prior to definitive surgery, date of diagnosis will be the date of the radiological study that suggested the diagnosis of probable lung cancer.

2 Good performance status: A patient with good performance status may have symptoms from cancer but is still participating in his/her normal daily activities. This would exclude any patients in a nursing home or any patients spending more than just regular sleeping hours in bed.

3 Corresponding positive radiographic study: This would include a bone scan with increased uptake in the region of pain or an x-ray, CT scan or MRI scan of the painful area that demonstrates a metastasis.

4 Limited small cell lung cancer: Tumor is confined to one half of the chest but may involve the mediastinum on the opposite side and both supraclavicular area lymph nodes.
Extensive small cell lung cancer: Tumor is not confined to one-half of the chest and involves more than the mediastinum on the opposite side and both supraclavicular area lymph nodes.

Quality of Evidence Codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Randomized controlled trials</td>
</tr>
<tr>
<td>II-1</td>
<td>Nonrandomized controlled trials</td>
</tr>
<tr>
<td>II-2</td>
<td>Cohort or case analysis</td>
</tr>
<tr>
<td>II-3</td>
<td>Multiple time series</td>
</tr>
<tr>
<td>III</td>
<td>Opinions or descriptive studies</td>
</tr>
</tbody>
</table>