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# Initial Evaluation of the Patient With Lung Cancer: Symptoms, Signs, Laboratory Tests, and Paraneoplastic Syndromes*

## ACCP Evidenced-Based Clinical Practice Guidelines (2nd Edition)

*Stephen G. Spiro, MD; Michael K. Gould, MD, FCCP; and Gene L. Colice, MD, FCCP*

***Background:*** **This chapter of the guidelines is intended to provide an evidence-based assessment of the initial evaluation of patients recognized as having lung cancer and the recognition of paraneoplastic syndromes.**
***Methods:*** **The current medical literature that is applicable to this issue was identified by a computerized search and was evaluated using standardized methods. Recommendations were framed using the approach described by the Health and Science Policy Committee of the American College of Chest Physicians.**
***Results:*** **Patients with lung cancer usually present with multiple symptoms, both respiratory related and constitutional. There is usually a time delay between symptom recognition by the patient and the ultimate diagnosis of lung cancer by the physician. Whether this time delay impacts prognosis is unclear, but delivering timely and efficient care is an important component in its own right. Lung cancer may be accompanied by a variety of paraneoplastic syndromes. These syndromes may not necessarily preclude treatment with a curative intent.**
***Conclusions:*** **The initial evaluation of the patient with known or suspected lung cancer should include an assessment of symptoms, signs, and laboratory test results in a standardized manner as a screen for identifying those patients with paraneoplastic syndromes and a higher likelihood of metastatic disease.** ***(CHEST 2007; 132:149S–160S)***

**Key words:** evaluation; laboratory tests; paraneoplastic syndrome; signs; symptoms

**Abbreviations:** ACTH = adrenocorticotropic hormone; ADH = antidiuretic hormone; HOA = hypertrophic osteoarthropathy; LEMS = Lambert-Eaton myasthenic syndrome; PTH = parathyroid hormone; PTH-rP = parathyroid hormone-related peptide; SIADH = syndrome of inappropriate antidiuretic hormone; SVCO = superior vena cava obstruction; VEGF = vascular endothelial growth factor

Lung cancer, unfortunately, is usually recognized late in its natural history. In large part, this reflects the peculiarities of pulmonary anatomy. A pulmonary nodule could grow for a considerable period of time, and potentially spread outside the lung, before it would cause symptoms. Consequently, at the initial presentation most patients with lung cancer have advanced disease. In general, of 100 newly presenting patients with lung cancer, 80 will be inoperable at presentation and only approximately 20 will proceed to attempted resection.[1] These observations explain why the 5-year mortality rates for lung cancer remain at approximately 85 to 90%. An understanding of how patients with lung cancer initially present will possibly allow the earlier identification of this increasingly common disease.

### Materials and Methods

To update previous recommendations on the initial evaluation of the patient with lung cancer, guidelines on lung cancer diagnosis and management published between 2002 and May



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2005 were identified by a systematic review of the literature (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" section). Those guidelines including recommendations that are specific to the initial evaluation of the lung cancer patient were identified for possible inclusion in this section. Supplemental material appropriate to this topic was obtained by a literature search of a computerized database (MEDLINE). Recommendations were developed by the writing committee, graded by a standardized method (see "Methodology for Lung Cancer Evidence Review and Guidelines Development" section), and reviewed by all members of the lung cancer panel and the Thoracic Oncology Network prior to approval by the Health and Science Policy Committee, and the Board of Regents of the American College of Chest Physicians.

## Presenting Symptoms of Lung Cancer

Initial presenting symptoms in patients with lung cancer may be respiratory related, but are often constitutional and attributable to metastatic disease (Table 1).[2–7] Cough is reported to be the most common presenting symptom of lung cancer; other respiratory symptoms include dyspnea, chest pain, and hemoptysis.[8–10] Patients with lung cancer usually present with multiple symptoms, including both respiratory and constitutional.[8,9] In a series of 678 consecutive lung cancer patients, at presentation 183 patients (27%) had symptoms related to the primary tumor; 232 patients (34%) had nonspecific systemic symptoms suggestive of metastases, including anorexia, weight loss and fatigue; and 219 patients (32%) had symptoms specific to a metastatic site.[11] The percentage of patients found to have lung cancer incidentally through chest radiographs has been consistently low. In the series reported in 1970 by Carbone et al[11] of 678 consecutive newly diagnosed lung cancer patients in the United States, only 44 patients (6%) were asymptomatic. In a community-based survey of lung cancer patients in Sweden who had received new diagnoses between 1997 and 1999, only 24 of 364 patients (7%) were asymptomatic.[12] Buccheri and Ferrigno[8] described the initial presentation of 1,277 consecutive lung cancer patients who received diagnoses at a single center in Italy from 1989 to 2002. Only 154 of these patients (13%) were asymptomatic at diagnosis. Prognosis in lung cancer has been clearly related to the type of presenting symptoms.[11] There was a better 5-year survival rate reported for asymptomatic patients (18%) than for those patients with symptoms related to the primary tumor (12%). Those patients with nonspecific symptoms had a 6% 5-year survival rate, and those patients with symptoms indicating metastatic disease fared the worst, with none alive at 5 years.

**Table 1—*Range of Frequencies of Initial Symptoms and Signs of Lung Cancer**

| Symptoms and Signs | Range of Frequency, % |
|---|---|
| Cough | 8–75 |
| Weight loss | 0–68 |
| Dyspnea | 3–60 |
| Chest pain | 20–49 |
| Hemoptysis | 6–35 |
| Bone pain | 6–25 |
| Clubbing | 0–20 |
| Fever | 0–20 |
| Weakness | 0–10 |
| Superior vena cava obstruction | 0–4 |
| Dysphagia | 0–2 |
| Wheezing and stridor | 0–2 |

*Modified from references 2 to 7.

In addition to the time delay between the development of the lung cancer and initial symptoms, there are usually a series of other delays before treatment is eventually initiated. Patients with lung cancer may notice a new symptom or a change in their usual respiratory symptoms but delay in reporting this to their general practitioner. Corner and colleagues[9] interviewed 22 patients with newly diagnosed lung cancer in the United Kingdom. Patients in this study had noted many different symptoms prior to presentation to their general practitioner, with cough and breathing changes being the most common. Of note was that patients described the onset of these symptoms between 4 months and 2 years (median time, 12 months) before they presented to their general practitioner. Koyi et al[13] reviewed the clinical course of 134 patients with lung cancer in whom cancer was newly diagnosed in 1997 and 1998 in Graevleborg, Sweden. The mean delay between symptom onset and first visit to their general practitioner was 43 days (range, 0 to 256 days). The one specific symptom that has been described as prompting more rapid presentation was hemoptysis.[9]

Even when patients present to the general practitioner with a symptom compatible with lung cancer, the general practitioner may not consider lung cancer a possibility. In the review by Koyi et al,[13] the

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mean time from initial patient presentation to the general practitioner and the general practitioner obtaining a chest radiograph was 56 days (range, 0 to 477 days). This delay may be understandable. Although lung cancer is a huge public health problem, on average the general practitioner does not see lung cancer patients often and usually has little personal experience with the disease. It has been estimated that a general practitioner in the United Kingdom might encounter a new lung cancer patient only once in every 8 months of regular practice.[14] In addition, the presenting symptoms of lung cancer are nonspecific, common, and more usually attributable to benign causes. Okkes et al[15] reviewed detailed records of patient encounters for 54 general practitioners in the Netherlands from 1985 to 1995. For patients who presented with cough (11,092 separate patient encounters), lung cancer was not listed as a separate entity among the 20 most common eventual diagnoses. The 19th most common listing was "other diseases of the respiratory tract." This listing presumably included lung cancer but only accounted for 3% of all eventual explanations for cough as a presenting symptom. Hamilton and colleagues[10] performed a retrospective review of detailed general practitioner records for 247 patients who presented with lung cancer and compared the presenting symptoms in these patients with matched control subjects taken from the same general practitioners' practices. They found that the most common presenting symptoms for lung cancer patients were poor predictors of the eventual diagnosis. Even hemoptysis was more frequently explained by benign conditions than by lung cancer.

Delays in the eventual diagnosis of lung cancer may also occur after referral of the patient to a specialist consultant. In the study by Koyi et al,[13] on average it took the consultant 33 days to establish the diagnosis of lung cancer, but in 10% of all patients it took > 60 days to reach the diagnosis. This delay is sometimes related to evaluating changes in either the chest radiograph or chest CT scan over time, at least in lung cancer patients who present with a solitary nodule and in whom a wait-and-watch approach is sometimes adopted (see the chapter in these guidelines on "Management of Patients With Pulmonary Nodules").

Overall, the time from recognition of the first symptom related to lung cancer by the patient to diagnosis of the disease and an eventual treatment decision may be lengthy. For instance, in the careful assessment of 134 patients in whom lung cancer had been newly diagnosed in Sweden, on average it took 203 days from symptom onset to treatment decision.[13] How these delays might affect overall prognosis for lung cancer, though, is not clear. In a small study from California, a group of 84 patients who underwent surgical resection of a stage I or II non-small cell lung cancer was divided into those who had an interval of < 90 days between the initial presentation and undergoing the actual operation (n = 46) and those with an interval of > 90 days (n = 38).[16] The mean time from presentation to operation for the entire group was 126 days (range, 1 to 641 days). No difference in 5-year survival was found between those whose delay was < 90 days and those with a delay of > 90 days. A larger study[17] of 1,082 patients with stage I and II lung cancer reported from Spain found that delays between the date of pathologic diagnosis and operation (mean interval, 35 days; range, 1 to 154 days) did not affect long-term survival. However, a study from Sweden[18] of 466 patients who had received treatment for non-small cell lung cancer showed that patients with more advanced disease had shorter time intervals between the first symptoms and treatment (median time delay from symptom to treatment for stage IV disease: patients with advanced disease, 3.4 months; patients with stage I-II disease, 5.5 months). Paradoxically, patients with short treatment delays had a worse prognosis, although the authors were unable to fully control for the obvious selection biases that confound observational studies of the relationship between the timeliness of care and survival.[18]

The relationship between the time from symptom onset to lung cancer diagnosis and prognosis is not clear. Confounding factors include tumor biology, as well as issues relating to the health system and access to care. Important considerations with delays in treatment, besides potentially missing the opportunity for cure or effective palliation, are the emotional distress of patients and their family members. Although further work is clearly needed to better facilitate the process from identification of disease to treatment decision for the lung cancer patient, timely care for these patients should be expected. The British Thoracic Society[19] recommended that all patients with suspected lung cancer should be evaluated by a respiratory specialist within 7 days and that the results of diagnostic tests should be communicated to the patient within 2 weeks. The RAND Corporation, in a quality indicator published for lung cancer care,[20] specified that a diagnosis of lung cancer should be established within 2 months of presentation and that treatment should begin within 6 weeks of diagnosis.

### Recommendation

**1. It is recommended that patients with known or suspected lung cancer receive timely and efficient care.** Grade of recommendation, 1C



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## Presenting Radiographic Features of Lung Cancer

The chest radiograph plays a pivotal role in the recognition of lung cancer. Certainly, in the asymptomatic patient an abnormality on the chest radiograph would be the first clue to the presence of lung cancer. In patients with symptoms related to the primary tumor, the chest radiograph may often strongly support a suspicion of carcinoma of the lung. For patients presenting with either nonspecific systemic complaints or symptoms suggestive of metastatic disease, the chest radiograph will be helpful in focusing attention quickly on the lung as the most likely primary site. The radiographic appearance of lung cancer at initial presentation may be quite variable. In general, lung cancers present slightly more often on the right side than the left, and in the upper lobes rather than in the lower lobes.[21–23] Lung cancers may be seen centrally or peripherally, with a predominance of central locations at presentation. It has been estimated that up to 40% of the radiographic findings associated with lung cancer are related to central tumors causing airway obstruction with secondary atelectasis and lung parenchyma consolidation.[24,25] Peripheral tumors are classically thought to present as solitary pulmonary nodules (see chapter in these guidelines on "Management of Patients With Pulmonary Nodules"), but could also present radiographically as lung masses, ground-glass opacities or complex abnormalities.

Clues from the chest radiograph may suggest the diagnosis of lung cancer, but may not be helpful in identifying a histologic subtype. Adenocarcinoma is the most common type of lung cancer, accounting for 30 to 35% of all cases.[26] Although adenocarcinomas are traditionally thought to occur more frequently peripherally, they may develop centrally as well. Squamous cell carcinoma may account for about 30% of all lung cancers. They have typically been thought to arise in the central bronchi and extend into the hilum and mediastinum, but may also develop in the lung parenchyma where they may cavitate[27,28]; they may be slower growing and metastasize late.[27] Large cell carcinoma comprises 10 to 20% of all lung cancers and is also seen more commonly peripherally. Small cell lung carcinoma comprises 15 to 25% of all lung cancers, and, like squamous cell carcinoma, also usually develops in the proximal airways and involves the hilum and mediastinum. Unlike squamous cell carcinoma, evidence of regional and/or distant metastatic disease at the time patients present with small cell lung carcinoma is the norm.

## Symptoms Related to the Primary Tumor

Of the presenting symptoms in patients with lung cancer, cough, dyspnea, chest pain, and hemoptysis may be related to the primary tumor (Table 1). Cough is the most common presenting symptom in patients with lung cancer. Many lung cancers occur in the central airways and may lead to postobstructive pneumonia or may cause lymph node enlargement, which may lead to cough. The failure of acute exacerbations of COPD to clear should raise suspicion of the presence of a neoplasm. Dyspnea develops commonly and is usually associated with increasing cough and amounts of sputum. If the tumor is occluding a main airway, it can cause breathlessness, which may be associated with a unilateral wheeze. Chest discomfort is also commonly reported by lung cancer patients at diagnosis. This is often of an ill-defined nature, intermittent and aching in quality. Definite pleuritic pain may occur as a result direct spread of the tumor to the pleural surface.

Hemoptysis is a common presenting symptom in patients with lung cancer. It is rarely severe and usually consists only of blood streaking of the sputum. The most common description is that of coughing up blood for several days in succession. The chest radiograph finding is usually abnormal in patients with hemoptysis from lung cancer. However, it has been estimated that up to 5% of patients with hemoptysis and either a normal chest radiograph finding or a chest radiograph finding with no localizing abnormalities will have lung cancer.[29] Lung cancers in these cases may be within the endobronchial tree, an area in which even CT scanning may fail to detect the cancer.[30] Consequently, in patients presenting with hemoptysis who are $>40$ years of age and have COPD and a history of smoking, even though the chest radiograph findings may be unremarkable, there should still be a high index of suspicion for lung cancer. Besides careful observation, the clinician may consider further diagnostic tests, such as chest CT scan or bronchoscopy. Sputum cytology may be a useful screening tool in these patients.[29]

## Symptoms and Signs of Intrathoracic Spread

The intrathoracic spread of lung cancer, either by direct extension or lymphatic spread, produces a variety of symptoms and signs. These may be caused by the involvement of nerves (*eg*, recurrent laryngeal nerve, phrenic nerve, brachial plexus, and sympathetic nerve trunks), chest wall and pleura, vascular structures (*eg*, superior vena cava, pericardium, and heart), and visceral structures (*eg*, the esophagus).



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Recurrent laryngeal nerve palsy, which causes hoarseness, has been reported in 2 to 18% of lung cancer patients. It is more common in left-sided tumors because of the circuitous route of the left recurrent laryngeal nerve around the aortic arch. It is associated with poor expectoration with coughing and an increased risk of aspiration. Phrenic nerve dysfunction may be noted on the chest radiograph by the presence of an elevated hemidiaphragm, or it can present with breathlessness in patients already compromised by lung disease. The superior sulcus or Pancoast tumor arises posteriorly in the apex of an upper lobe near the brachial plexus, commonly infiltrating the eighth cervical nerve root and the first and second thoracic nerve roots. This causes pain, cutaneous temperature change, and muscle wasting along the relevant nerve root. Symptoms and signs may be misleading initially, often resulting in a delay of many months before the true diagnosis is revealed. Horner syndrome occurs because of the involvement of the sympathetic chain and stellate ganglion, and is recognized by the typical triad of small pupil with ipsilateral ptosis and lack of facial sweating.

Chest wall and pleural invasion by the primary tumor, causing localized chest pain, is a common presenting symptom. More than 50% of patients with lung cancer complain of chest pain during the course of their disease. The pain is usually dull, tends to be persistent, poorly localized, and unrelated to breathing or coughing. Retrosternal pain may be due to hilar and mediastinal nodal involvement. When chest pain is particularly severe, persistent, and localized, it is usually related to either direct invasion of the pleura or chest wall by the primary tumor, or to a rib metastasis. Tenderness may be elicited at the site of rib involvement, and, rarely, a soft tissue mass can be palpated. Pleural involvement occurs in 8 to 15% of patients with lung cancer. Pleuritic chest pain can occur with the early phase of neoplastic pleural invasion but may disappear with the onset of a pleural effusion. Pleural effusion, which may result in dyspnea, is generally caused by direct pleural extension but may also be secondary to mediastinal node involvement and lymphatic obstruction.

Lung cancer accounts for 46 to 75% of all cases of superior vena cava obstruction (SVCO). The most common histologic subtype associated with SVCO is small cell carcinoma.[4,31,32] Direct invasion by the primary tumor into the mediastinum or lymphatic spread with enlarged right paratracheal metastatic lymph nodes causes the SVCO. The patient will complain of swelling of the face, including the neck and eyelids, upper torso, neck, and arms. Dilated veins will be visible over the upper torso, shoulders and arms. Other symptoms related to SVCO include headache, dizziness (particularly on bending forwards), drowsiness, blurring of vision, cough, and dysphagia.[31,33] Metastases to other vascular structures in the mediastinum, such as the heart and pericardium, usually occur by direct lymphatic spread. At autopsy, cardiac involvement occurs in about 15% of patients, and a small number of patients will have tamponade.[34] In patients with primary lung cancer, the pericardium is the most common site of cardiac involvement, causing an effusion or supraventricular arrhythmias.[35]

Metastatic disease causing enlargement of the subcarinal lymph nodes can cause dysphagia by compressing the middle third of the esophagus. Very occasionally, tracheal primary tumors may grow into the esophagus, also causing dysphagia.

## Symptoms, Signs, and Laboratory Tests Indicating Extrathoracic Metastases

About one third of patients present with symptoms as a result of distant metastases. The most common sites of distant metastasis from lung cancer are the bones; liver; adrenal glands and intraabdominal lymph nodes; brain and spinal cord; and lymph nodes and skin. Lung cancer can metastasize to virtually any bone, although the axial skeleton and proximal long bones are most commonly involved. The primary symptom resulting from bone involvement is pain, which may have a pleuritic component when the ribs are involved. Bone pain is present in up to 25% of all patients at presentation.

Liver metastases occur commonly with lung cancer. However, liver function test results are seldom abnormal until the metastases are numerous and large, or they block the hepatic ducts, which is when jaundice will occur. Hepatic metastases most commonly produce symptoms of weakness and weight loss. When present, hepatic metastases carry a very poor prognosis. Adrenal lesions and paraaortic lymph node metastases may occur and are most commonly seen with small-cell lung cancers; in the latter cell type, they are often discovered during staging. Clinical evidence of adrenal insufficiency is rarely seen.

Intracranial metastases occur in 10% of lung cancer patients at presentation. Spinal cord metastases are less common and tend to occur in patients with cerebral metastases. Brain metastasis may produce headache, nausea and vomiting, focal neurologic symptoms or signs, seizures, confusion, and personality changes. The lung is the primary site of approximately 70% of cancers that initially present with symptomatic brain metastases.[36]

The most common site of palpable lymphadenopathy is the supraclavicular fossa, which can be in-



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volved in 15 to 20% of cases during the course of the disease. Identifying an enlarged lymph node or subcutaneous nodule due to metastatic lung cancer is extremely helpful in facilitating both diagnosis and staging. Fine-needle aspiration can be performed quickly at the bedside or as an outpatient with little morbidity and with a high sensitivity.[37]

*Standardized Evaluation for Systemic Metastases*

Carbone et al[11] and Feinstein and colleagues[38–42] have explored the relationship between symptoms at presentation and prognosis in a large cohort of consecutive lung cancer patients. Patients with the best prognosis were either asymptomatic or had symptoms referable only to the primary tumor. In patients either with systemic symptoms of anorexia, weight loss, and fatigue or with symptoms attributable to metastatic disease, prognosis was especially poor. The relationship between systemic symptoms and prognosis was conserved with standard staging of lung cancer. Within any individual tumor stage, there was a gradient of worsening prognosis in patients who presented with anorexia, weight loss, and fatigue. The biological association between systemic symptoms and worse prognosis was not entirely clear, although, intuitively, patients with systemic symptoms would be clinically suspected of having extensive disease.

Hooper and colleagues[43,44] used a cluster of clinical factors, including symptoms, signs, and standard laboratory tests, to screen patients for metastatic disease. Included within these clinical factors were weight loss and anemia. They found that abnormalities in these factors were associated with radiographic evidence of metastatic disease. The more abnormalities noted in the clinical assessment, the more likely that metastases would be detected. They also found that patients with no abnormalities in these clinical factors were extremely unlikely to have evidence of metastatic disease found on a CT scan. Silvestri et al[45] adapted the criteria of Hooper et al[43,44] (Table 2) and retrospectively asked whether they would be a useful screen for detecting adrenal metastases. As with the work by Hooper et al,[43,44] if no clinical abnormalities were noted, adrenal metastases were not found by CT scan; the more clinical abnormalities that were found, the more likely it was that adrenal metastases would be found. Both the work by Silvestri et al[45] and a study by Quinn and coworkers[46] pointed out that abnormalities in the clinical assessment would often not be helpful in identifying the site of metastases. However, the recognition of abnormalities in the clinical screen strongly suggested the presence of metastases.

Silvestri et al[45] also considered whether clinical evaluation would be useful in identifying which patients with lung cancer would have extrathoracic metastases detected by CT scanning of the brain or abdomen or by radionuclide bone scans.[47] They performed a metaanalysis[47] of all studies in lung cancer patients that provided data on both radiographic studies and the clinical factors adapted from the criteria of Hooper et al.[43,44] Consistent with earlier work, this metaanalysis showed that patients with clinical abnormalities were often found to have metastatic disease. However, if no abnormalities were noted in the clinical assessment, patients were very unlikely to have evidence of metastatic disease on CT scans of the brain or abdomen or on radionuclide bone scans. These authors concluded that performing an assessment of various clinical factors through a thorough history and physical examination, and standard laboratory tests would be a useful screen for identifying patients with a higher likelihood of metastatic disease.

### Recommendation

**2. It is recommended that all patients with known or suspected lung cancer give a thorough history and undergo a thorough physical examination and standard laboratory tests as a screen for metastatic disease.** Grade of recommendation, 1B

## Paraneoplastic Syndromes

Paraneoplastic syndromes are a group of clinical disorders that are associated with malignant diseases

**Table 2—*Features of a Standardized Evaluation for Systemic Metastases**

| Symptoms | Signs | Laboratory Tests |
|---|---|---|
| Constitutional: weight loss > 10 lb | Lymphadenopathy (> 1 cm) | Hematocrit < 40% in men |
| Musculoskeletal: focal skeletal pain | Hoarseness, superior vena cava syndrome | Hematocrit < 35% in women |
| Neurologic: headaches, syncope, seizures, extremity weakness, or recent change in mental status | Bone tenderness, hepatomegaly (> 13-cm span), focal neurologic signs, papilledema, and soft tissue mass | Elevated alkaline phosphatase, γ-glutamyltransferase, or serum glutamicoxaloacetic transaminase level |

*Modified from references 42 and 44.



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that are not directly related to the physical effects of primary or metastatic tumors.[48,49] Paraneoplastic syndromes may occur in 10% of patients with bronchogenic carcinoma.[2,3] The extent of paraneoplastic symptoms is unrelated to the size of the primary tumor, and in some cases can precede the diagnosis of malignant disease. At other times they may occur late in the illness, or herald the first sign of recurrence. The exact mechanism by which paraneoplastic syndromes occur is not fully understood in all cases, but in many cases it appears to be related to either the production of biologically active substances by the tumor itself (*eg*, polypeptide hormones or cytokines) or in response to the tumor (*eg*, antibodies). Although a wide variety of paraneoplastic syndromes have been associated with lung cancer (Table 3), the most commonly recognized include endocrine, joint, and neurologic abnormalities.

**Table 3—*Paraneoplastic Syndromes Associated With Lung Cancer**

| |
|---|
| Endocrine syndromes |
| SIADH production |
| Nonmetastatic hypercalcemia |
| Cushing syndrome |
| Gynecomastia |
| Hypercalcitonemia |
| Elevated levels of LSH and FSH |
| Hypoglycemia |
| Hyperthyroidism |
| Carcinoid syndrome |
| Neurologic syndromes |
| Subacute sensory neuropathy |
| Mononeuritis multiplex |
| Intestinal pseudo-obstruction |
| LEMS |
| Encephalomyelitis |
| Necrotizing myelopathy |
| Cancer associated retinopathy |
| Skeletal syndromes |
| Hypertrophic osteoarthropathy |
| Clubbing |
| Renal syndromes |
| Glomerulonephritis |
| Nephrotic syndrome |
| Metabolic syndromes |
| Lactic acidosis |
| Hypouricemia |
| Systemic syndromes |
| Anorexia and cachexia |
| Fever |
| Collagen-vascular syndromes |
| Dermatomyositis |
| Polymyositis |
| Vasculitis |
| Systemic lupus erythematosus |
| Cutaneous |
| Acquired hypertrichosis languinosa |
| *Erythema gyratum repens* |
| Erythema multiforme |
| Tylosis |
| Erythroderma |
| Exfoliative dermatitis |
| *Acanthosis nigricans* |
| Sweet syndrome |
| Pruritus and urticaria |
| Hematologic |
| Anemia |
| Leucocytosis and eosinophilia |
| Leukemoid reactions |
| Thrombocytosis |
| Thrombocytopenic purpura |
| Coagulopathies |
| Thrombophlebitis |
| Disseminated intravascular coagulation |

*LSH = lutein-stimulating hormone; FSH = follicle-stimulating hormone. Modified from references 1 and 11.

### *Common Endocrine Paraneoplastic Syndromes Associated With Lung Cancer*

*Hypercalcemia:* The incidence of hypercalcemia in patients with lung cancer ranges from 2 to 6% at presentation to 8 to 12% throughout the course of the disease. Symptoms include nausea, vomiting, abdominal pain, constipation, polyuria, thirst, dehydration, confusion, and irritability. Squamous cell carcinoma is most frequently associated with hypercalcemia. Although bone metastases may be found in patients with lung cancer and hypercalcemia, most commonly humoral mechanisms account for the hypercalcemia.[50,51] Bioassays have suggested that there are increased levels of parathyroid hormone (PTH)-like activity in lung cancer patients with hypercalcemia.[52] Increased levels of urinary cyclic adenosine monophosphate have been reported in lung cancer patients, which is consistent with an increased PTH effect.[53] However, serum immunoreactive PTH levels are low to undetectable in patients with lung cancer and hypercalcemia.[54] A protein with PTH-like activity has been purified from lung cancer cell lines.[55,56] Increased bone resorption as the explanation for hypercalcemia has been attributed to this PTH-related protein (PTH-rP) released from lung cancer cells.[50] Serum levels of PTH-rP may be a valuable indicator of survival in lung cancer patients. Hiraki et al[57] found in a small group of patients with lung cancer and hypercalcemia that elevated circulating levels of PTH-rP were associated with shorter survival times. Increased serum PTH-rP levels were also associated with a higher likelihood of bony metastases. The authors speculated that PTH-rP, besides increasing bone resorption, might also play a role in facilitating bone metastases.

*Syndrome of Inappropriate Antidiuretic Hormone Production:* Hyponatremia, the most obvious sign of syndrome of inappropriate antidiuretic hormone



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(SIADH) production, has been reported to occur in a wide incidence of lung cancer patients. Elevated antidiuretic hormone (ADH) levels and impaired water handling are found in possibly 30 to 70% of patients with lung cancer,[50] but the production of excess ADH does not always produce symptoms.[58–60] Only 1 to 5% of lung cancer patients have symptoms that are attributable to the SIADH production. Manifestations of SIADH production include confusion, unexplained seizures, decreased level of consciousness, and coma. Biochemically, the SIADH production is defined as low serum sodium and a dilute plasma osmolality along with a higher, or "inappropriate," urine osmolality, in the presence of continued urinary sodium excretion. The SIADH production is mainly associated with small cell lung cancer, although other malignant tumors of the lung may rarely be associated with this syndrome.[58,61,62] Although a variety of hormones, including atrial natriuretic peptide, have been implicated as possibly contributing to the hyponatremia found in lung cancer patients, hormone assays performed under controlled settings have shown that elevated plasma ADH levels are consistently found in these patients and seem to explain the impaired ability to excrete a water load.[63] The excess levels of ADH have been reported to originate from either ectopic production by lung cancer cells[59] or inappropriate peripheral baroreceptor stimulation of ADH release from the hypothalamus.[63] The syndrome resolves promptly (within 3 weeks) with the initiation of combination cytotoxic chemotherapy in 80% of patients with small cell lung cancer, but commonly recurs with tumor progression.[64]

*Cushing Syndrome:* Ectopic production of adrenocorticotropic hormone (ACTH) by small cell lung cancer cells is the most common explanation for Cushing syndrome.[50] ACTH is the most commonly produced ectopic hormone in lung cancer patients. It is not unusual to find increased serum levels of ACTH in patients with lung cancer; it may be detectable in up to 50% of patients with lung cancer.[65] However, some patients with Cushing syndrome may have normal basal ACTH levels.[66] In these patients, precursors of ACTH, such as proopiomelanocortin, may be elevated, suggesting that Cushing syndrome could develop due either to ectopic production or to aberrant processing of ACTH by small cell lung cancer cells.[50] Clinical manifestations of Cushing syndrome, which include weakness, muscle wasting, drowsiness, confusion, possible psychosis, dependent edema, moon facies, hypokalemic alkalosis, and hyperglycemia, are found in only a very small proportion of lung cancer patients. Cushing syndrome has been described in 1 to 5% of patients with small cell carcinoma,[67,68] but this may be an overestimate. In a 2005 report[66] of the National Institutes of Health experience with Cushing syndrome, only 3 of the 90 cases were attributed to small cell lung cancer. Most commonly, Cushing syndrome occurred in patients with pulmonary carcinoid (35 of 90 patients). Resection of the primary tumor, if possible, will effectively treat Cushing syndrome. Most patients with Cushing syndrome due to small cell lung cancer present with extensive stage disease and have a poor response to chemotherapy.[50]

### *Digital Clubbing and Hypertrophic Osteoarthropathy*

Digital clubbing is an enlargement of the terminal segments of the fingers and/or toes due to proliferation of connective tissue beneath the nail matrix. Quantitative indexes of the nail profile angle, hyponychial angle and phalangeal depth ratio can be determined to assist in identifying clubbing.[69] Hypertrophic osteoarthropathy (HOA) is a systemic disorder, which involves both a painful symmetrical arthropathy, usually of the ankles, wrists, and knees, and periosteal new bone formation in the distal long bones of the limbs. Histologic features of HOA include vascular hyperplasia, edema, and excessive fibroblast and osteoblast proliferation.[70]

Clubbing and HOA may be associated with any cell type of lung cancer, although they are associated most frequently with squamous cell carcinoma and adenocarcinoma, and least frequently with small cell lung carcinoma. The exact mechanism responsible for the development of clubbing and HOA is unknown. In the past, explanations included neurogenic, hormonal, and vascular mechanisms.[71] More recently, the overexpression of vascular endothelial growth factor (VEGF) has been implicated as contributing to the pathogenesis of clubbing and HOA. In the case of a young woman with lung cancer and HOA, serum VEGF levels were initially elevated; after resection of the cancer, the serum VEGF levels fell and HOA remitted. Histochemical studies of the resected tumor showed increased VEGF messenger RNA expression, suggesting ectopic production by the lung cancer cells.[70]

Clubbing is much more common than HOA. In one study[72] of 111 consecutive patients with pathologically proven lung cancer, clubbing was present in 32 patients (29%). The phenomenon was significantly more common among women than men (40% vs 19%, respectively), and in patients with non-small cell lung cancer than in those with small cell lung cancer (35% vs 4%, respectively).[72] HOA is seen in $< 5\%$ of patients with non-small cell lung cancer.[73]



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Small cell lung cancer is a rarer cause of HOA; in one series,[74] it accounted for only 1% of the patients with HOA. Anecdotal observations indicate that clubbing and HOA may resolve with successful treatment of the primary tumor, particularly surgical resection of a non-small cell lung cancer.

### *Neurologic Syndromes*

A variety of poorly understood neurologic syndromes may occur in patients with lung cancer.[46] The diagnosis of a neurologic paraneoplastic syndrome is made once other causes, such as electrolyte imbalance, metastatic disease, cerebral and spinal vascular disease, infections, and treatment toxicity, are excluded. The neurologic syndromes include the Lambert-Eaton myasthenic syndrome (LEMS), limbic encephalopathy, polyneuropathy, cerebellar degeneration, retinopathy, opsoclonus-myoclonus, and autonomic neuropathy.[75,76] In LEMS, which is the most widely recognized of these disorders, patients present with the gradual onset of proximal lower extremity weakness; proximal upper extremity weakness is usually less noticeable. The syndrome may be worse in the morning and improve during the day. Although extraocular muscle involvement is uncommon, ptosis is often found.[77] Paraneoplastic neurologic syndromes have been associated almost exclusively with small cell lung cancer. These syndromes have been reported to affect 4 to 5% of lung cancer patients,[75] but the incidence is probably lower. In 1991, Elrington et al[78] reported that in a prospective survey of 150 consecutive cases of small cell lung cancer only two patients (1%) had LEMS and one patient (< 1%) had a polyneuropathy. A 2005 study[76] of 432 consecutive patients with small cell lung cancer showed similar results. LEMS was found in seven patients (1.6%), polyneuropathy in two patients (< 1%), subacute cerebellar degeneration in one patient (< 1%), and limbic encephalitis in three patients (< 1%).[76] The severity of the neurologic symptoms is unrelated to tumor bulk; in fact, the syndromes seem to be found more often in patients with limited disease, and in some patients a primary malignant lesion may be undetected before death despite disabling symptoms.[76,78–80]

The neurologic syndromes associated with lung cancer seem to develop through autoimmune mechanisms. Nearly all of the paraneoplastic neurologic syndromes are associated with the presence of type 1 antineuronal nuclear antibodies (also known as *anti-Hu antibodies*).[81] The Hu antigen is normally found in neurons, but, because the developing CNS is sequestered from the immune system by the blood-brain barrier, healthy adults do not have anti-Hu antibodies. Small cell lung cancers express Hu antigen, and up to 20% of patients with small cell lung cancer have detectable circulating levels of anti-Hu antibodies, although paraneoplastic neurologic syndromes will not develop in all of these patients.[76,82] In patients with LEMS, IgG antibodies directed against the P/Q voltage-gated presynaptic calcium channel interfere with Ca++-dependent neurotransmitter release.[83,84] At autopsy, lymphocytic inflammatory infiltrates in patients with paraneoplastic neurologic syndromes are found in areas of the nervous system that correspond to the neurologic deficits, supporting the concept that the autoantibodies play a key role in the pathogenesis of the neurologic syndromes. Lymphocytic infiltrates have also been found around the primary tumor, suggesting that the immune response may actually limit progression of the underlying small cell lung cancer.[85]

The response of the neurologic paraneoplastic syndrome to effective chemotherapy in patients with small cell lung cancer is variable.[86,87] Sustained improvements in the neurologic symptoms have been reported, although this is less commonly seen in patients with motor or sensory neuropathies.[88] In a small series[89] of patients with small cell lung cancer, the overall prognosis was more favorable in those patients with LEMS than in those without it.

## Recommendation

**3. It is recommended that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone.** Grade of recommendation, 2C

## Summary

Most patients with lung cancer will be symptomatic at presentation. A minority of patients presents with symptoms related to the primary tumor, but most patients present with either nonspecific systemic symptoms, including anorexia, weight loss, and fatigue, or specific symptoms indicating metastatic disease. Asymptomatic patients and patients with symptoms related to the primary tumor have better 5-year survival rates than those patients with systemic symptoms or symptoms indicating metastatic disease. The initial evaluation of the patient with known or suspected lung cancer should include an assessment of symptoms, signs, and laboratory test results in a standardized manner as a screen for identifying those patients with a higher likelihood of metastatic disease.



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Paraneoplastic syndromes, which occur in up to 10% of patients with lung cancer, are a group of clinical disorders that are associated with malignant diseases not directly related to the physical effects of primary or metastatic tumors. These syndromes may be due to the production of biologically active substances, such as polypeptide hormones, antibodies, or cytokines. Paraneoplastic symptoms are unrelated to the size of the primary tumor, in some cases can precede the diagnosis of malignant disease, and at other times may occur late in the illness or may herald the first sign of recurrence.

## Summary of Recommendations

**1. It is recommended that patients with known or suspected lung cancer receive timely and efficient care**. Grade of recommendation, 1B

**2. It is recommended that all patients with known or suspected lung cancer give a thorough history, and undergo a thorough physical examination and standard laboratory tests as a screen for metastatic disease**. Grade of recommendation, 1C

**3. It is recommended that patients with lung cancer and a paraneoplastic syndrome not be precluded from potentially curative therapy on the basis of these symptoms alone.** Grade of recommendation, 2C

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# Initial Evaluation of the Patient With Lung Cancer: Symptoms, Signs, Laboratory Tests, and Paraneoplastic Syndromes *

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