Chronic Cough Due to Lung Tumors
ACCP Evidence-Based Clinical Practice Guidelines
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Goals/objectives: To review the scientific evidence on cough associated with tumors in the lungs.
Methods: MEDLINE literature review (through March 2004) for all studies published in the English language, including case series and case reports, since 1966 using the medical subject heading terms “cough” and “lung neoplasms.”
Results: Primary bronchogenic carcinoma is the most common lethal neoplasm in the United States. Malignancies that arise in other organs will often metastasize to the lungs. Any form of cancer involving the lungs may be associated with cough. However, cough is far more likely to indicate involvement of the airways than the lung parenchyma because of the location of cough receptors. Cough is present in > 65% of patients at the time lung cancer is diagnosed, and productive cough is present in > 25% of patients. While cough as a presenting symptom of lung cancer is common, many studies have shown that lung cancer is the cause of chronic cough in ≤ 2% of all patients who present with a chronic cough.
Conclusions: Bronchoscopy is usually indicated when there is suspicion of airway involvement by a malignancy. Conversely, bronchoscopy usually should not be performed to assess a cough for the possibility of lung cancer when there is little risk for lung cancer (nonsmokers) and when there are normal findings on a plain chest radiograph. If the lung cancer can be removed surgically, cough will usually abate. Radiation therapy, chemotherapy (especially with gemcitabine), and endobronchial treatment methods likely will improve cough caused by lung cancer. Centrally acting narcotic antitussive agents are usually administered for the control of cough caused by lung cancer when other treatment methods fail. (CHEST 2006; 129:147S–153S)

Key words: ablative methods; antitussives; brachytherapy; bronchoscopy; chemotherapy; electrocautery; endobronchial treatment; laser; lung cancer; metastatic carcinoma (to lungs); radiation therapy; surgery; stents
Abbreviation: NSCLC = non-small cell lung cancer

Primary bronchogenic carcinoma is the most common lethal malignancy in the United States, with > 172,000 new cases expected in 2003. Moreover, malignancies that arise in other organs will often metastasize to the lungs. As the entire blood flow must traverse the lungs during a normal circuit, malignant cells that enter the bloodstream may become entrapped in the pulmonary capillaries. Far less frequently, the bronchial arterial supply gives rise to metastases from other primary organ sites into the conducting airways. Any form of cancer involving the lungs may be associated with cough. However, cough is more likely to indicate involvement of the airways than the lung parenchyma because of the location of cough receptors. Adenocarcinoma of the lung usually occurs in the periphery of the lung, and it may not cause cough as an early symptom. Cancer cell types that are centrally located in the airways (ie, squamous cell carcinoma and small cell undifferentiated lung cancer) are more likely to cause cough at the time of presentation. Carcinoid tumors, mucoepidermoid carcinoma, and adenoid cystic carcinoma usually arise in the more central conducting airways, and cough is often a presenting symptom for these less common airway neoplasms.
Bronchoalveolar cell carcinoma, a type of primary lung cancer that is parenchymal in location, accounts for 2 to 4% of all primary lung cancers. This cell type may be confused with pneumonia because of its airspace opacification pattern that is apparent on a chest radiograph. While cough that is productive of large amounts of thin sputum is the paradigm often used to characterize the clinical presentation of patients with bronchoalveolar cell carcinoma, most patients with this type of lung cancer have a nonproductive cough.7

A MEDLINE literature review was conducted (through March 2004) for all studies published in the English language, including case series and case reports, since 1966 using the medical subject heading terms “cough” and “lung neoplasms.” The focus of this section is to review the management of cough associated with tumors in the lung. While hemoptysis means that the patient has coughed up blood, this section will not focus on the management of hemoptysis. For those readers who wish to read more about hemoptysis, see the review article by Jean-Baptiste.8

**Clinical Features of Cancer as a Cause of Cough**

Smoking tobacco causes 90% of primary lung cancers. Thus, heavy cigarette smokers who have a new onset of cough, a change in the characteristics of a preexisting cough, and the presence of hemoptysis (usually a small volume, often only streaks) should promote consideration of cancer as the cause of cough. Among other important points in a person’s medical history that lead to a higher index of suspicion for primary lung cancer are passive cigarette smoke exposure; exposure to asbestos, radon, and selected other carcinogens; COPD; and a family history of lung cancer. A personal history of cancer in another body site raises the possibility of metastatic involvement by a malignancy. Shure19 found completely obstructing lung cancers in the central airways (segmental or larger) in 36 of 81 endobronchial lesions (44%) with no radiographic signs of obstruction. The chest radiograph findings were normal in 13 patients (16%). All 13 patients had risk factors for and symptoms suggestive of bronchogenic carcinoma. Thus, for a smoker who has both cough and hemoptysis that persist after antimicrobial treatment for bronchitis, bronchoscopy is indicated even when the chest radiograph finding is normal.

Cytologic examination of spontaneously expectorated or induced sputum may provide a definitive diagnosis of lung cancer. However, bronchoscopy is usually indicated when there is suspicion of airway involvement by a malignancy. Shure19 found completely obstructing lung cancers in the central airways (segmental or larger) in 36 of 81 endobronchial lesions (44%) with no radiographic signs of obstruction. The chest radiograph findings were normal in 13 patients (16%). All 13 patients had risk factors for and symptoms suggestive of bronchogenic carcinoma. Thus, for a smoker who has both cough and hemoptysis that persist after antimicrobial treatment for bronchitis, bronchoscopy is indicated even when the chest radiograph finding is normal.

The findings from a bronchoscopic inspection of the airways may guide the choice of treatment options, some of which are likely to improve the cough and often the associated dyspnea. The accom-
panying postobstructive pneumonia may be more easily understood by the findings at bronchoscopy, and relief of the pneumonia may follow specific treatment that is aimed at relieving the obstruction.

Conversely, bronchoscopy usually will not reveal a malignancy when there is little risk for lung cancer (nonsmokers) and normal findings on a plain chest radiograph. Two prospective descriptive studies\textsuperscript{13,20} have provided information about the role of bronchoscopy in this setting. Chest radiographs had positive predictive values of 36\% and 38\%, respectively, for airway cancers and a negative predictive value of 100\%. Bronchoscopy had positive predictive values of 50\% and 89\%, respectively, in the two studies, and a negative predictive value of 100\%. Bronchoscopy may be indicated to complete the assessment of cough in nonsmokers with normal chest radiograph findings to diagnose bacterial suppurrative disease and other nonmalignant airway diseases. However, a patient who smokes cigarettes who has a new cough or a changing character to the cough that persists for months should almost always stimulate a bronchoscopic examination, even when the chest radiograph findings are negative.\textsuperscript{21,22}

**Recommendations**

1. In a patient with cough who has risk factors for lung cancer or a known or suspected cancer in another site that may metastasize to the lungs, a chest radiograph should be obtained. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, E/A

2. In patients with a suspicion of airway involvement by a malignancy (eg, smokers with hemoptysis), even when the chest radiograph findings are normal, bronchoscopy is indicated. Level of evidence, low; benefit, substantial; grade of recommendation, B

**Treatment of Cough Caused by Cancer**

**Surgery**

Surgery to remove non-small cell lung cancer (NSCLC) is the treatment of choice for patients with stage I and II NSCLC, assuming that comorbid diseases (eg, COPD and heart disease) do not create a prohibitive risk. If cough was caused by a NSCLC that can be surgically removed, clinical experience suggests that the cough will typically cease. However, there are no studies that have systematically addressed the incidence of cough cessation after surgical resection of lung cancer. Palliative, ipsilateral to the primary, high intrathoracic vagotomy immediately below the origin of the recurrent laryngeal nerve was reported to substantially alleviate cough in almost all of the 18 patients who underwent exploratory thoracotomy but who had unresectable cancers.\textsuperscript{23}

**Radiation Therapy**

For patients with more advanced NSCLC (stages III and IV), external beam radiation and/or chemotherapy are usually offered as treatment. Chest pain and hemoptysis are more effectively palliated than cough and dyspnea.\textsuperscript{24} Two multicenter randomized prospective controlled trials\textsuperscript{25,26} that were conducted in the United Kingdom were designed to assess the effects of different external beam radiation programs to the thoracic inlet and mediastinum on the relief of specific symptoms that are related to an intrathoracic tumor. In the first study,\textsuperscript{25} 369 patients were allocated to receive either two 8.5-Gy fractional doses (total dose, 17 Gy) administered 1 week apart or a conventional multifractionated regimen of either 30 Gy in 10 fractions or 27 Gy in 6 fractions (a biologically equivalent dose). In the second study,\textsuperscript{26} 235 patients were allocated to receive a single 10-Gy dose or two 8.5-Gy fractional doses. Cough was present at baseline in 93\% of patients in the first study,\textsuperscript{25} and in 95\% of patients in the second study.\textsuperscript{26} Significant relief of cough, as judged by the patients and their clinicians through a questionnaire technique, was achieved in 74\% of patients for the multifractionated program and 82\% of patients in the two-fraction program in the first study,\textsuperscript{25} and in 48\% of patients in the two-fraction program and 56\% of patients in the single-fraction program in the second study.\textsuperscript{26} Palliation of cough lasted for a median of 70 to 78 days in the first study,\textsuperscript{25} and for 56 to 61 days in the second study.\textsuperscript{26} Radiofrequency ablation has also been suggested as treatment for larger tumors that cause cough, but precise data are not available regarding the improvement of this symptom by such a treatment method.\textsuperscript{27}

**Chemotherapy**

Some studies\textsuperscript{28} of newer chemotherapeutic agents like gemcitabine and cisplatin-based combination chemotherapy have concentrated on specific symptoms, including cough. Cough was assessed by the patients, using a visual analog scale, with improvement defined as two consecutive cycles of improvement over baseline. Most of the symptom control was achieved during the first three cycles of treatment. More patients benefit by the reduction of tumor-related symptoms from gemcitabine chemotherapy than is suggested by the objective response rate. Cough, in particular, was improved for 2 to 5
months by gemcitabine alone in 44% of all subjects with cough, and in 73% of those with moderate or severe cough.\textsuperscript{29,30} This relief of cough by gemcitabine monotherapy, which has a much lower toxicity profile than platinum-based chemotherapy programs in combination with other agents, is comparable to the reported frequency of cough relief with external radiation.\textsuperscript{29}

A review of multiple randomized trials of both palliative radiotherapy and chemotherapy was performed to assess the impact of anticancer treatments on quality of life in patients with advanced NSCLC. In almost all of the studies cited, patients completed questionnaires as the method of assessing a reduction of cough frequency or severity. Objective methods, such as cough counting by the patient or an observer, are not reported. The subjective rate of palliation of local symptoms is high, with cough controlled in 50 to 70% of patients.\textsuperscript{31} The control of symptoms seems to be best among patients with good overall performance status, small losses of body weight, and age < 70 to 75 years, although some studies\textsuperscript{31} have supported the use of chemotherapy in patients with poor prognostic features. Cough associated with small cell lung cancer improves in 7 to 80% of patients with chemotherapy for small cell lung cancer.\textsuperscript{32–34}

Endobronchial Treatment Methods To Relieve Cough

Central airway obstruction (ie, significant obstruction of the trachea and main bronchi) can cause life-threatening dyspnea and hemoptysis, and intractable cough.\textsuperscript{35} Cough can be palliated by endobronchial treatment methods, but the relief of cough is seldom a reason to offer such treatment if dyspnea or hemoptysis are not also present.

Immediate relief of airway occlusion and many of the symptoms it causes can be expected with endobronchial treatment approaches in 73 to 90% of patients.\textsuperscript{36,37} All endobronchial therapeutic techniques have the potential to provide significant relief of cough and dyspnea, but relief of cough is more troublesome because it is rare that any endobronchial treatment method will totally eradicate the tumor. While cough is improved from 51 to 90% in various series that have reported on this symptom,\textsuperscript{38–45} many patients will require some other form of treatment such as centrally acting narcotic antitussive agents to control cough. Nearly all reports on endobronchial treatment methods are case series; randomized prospective controlled trials of such treatment methods are lacking. Brachytherapy is the one endobronchial treatment method in which the relief of cough is often specifically mentioned.\textsuperscript{35,39–43} Reports\textsuperscript{36,38} of other endobronchial treatment methods (eg, laser, electrocautery, or stents) have referred to the relief of symptoms globally, but they generally do not specifically mention the percentage of patients who have cough that is relieved by these treatment methods.

Recommendations

3. For patients with stage I and II NSCLC, surgery to remove the NSCLC is the treatment of choice. If cough was caused by a NSCLC that can be surgically removed, the cough will typically cease. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. For patients with more advanced NSCLC (stages III and IV), external beam radiation and/or chemotherapy should usually be offered. Level of evidence, good; benefit, intermediate; grade of recommendation, A

5. For patients with dyspnea or hemoptysis due to endobronchial tumors, cough may also be present. Endobronchial methods should be considered for the palliation of these symptoms, but cough alone is seldom a reason to offer such treatment. Level of evidence, fair; benefit, small; grade of recommendation, C

Pharmacotherapy of Cough

Cough may persist in the setting of lung cancer, despite all other treatments that are directed at the cancer and the associated symptom of cough. When cough persists, most patients will be offered pharmacologic therapy that is designed to control cough. The use of various protussive and antitussive pharmacologic agents is evaluated extensively elsewhere in these guidelines.

When a comorbid disease that causes cough is present together with lung cancer, pharmacologic treatment of the comorbid disease may provide relief from the cough. Thus, the use of bronchodilators and corticosteroids for the treatment of chronic bronchitis and asthma, for example, may improve cough in a patient who also has lung cancer. There are no data to support this approach, but it is an approach that is commonly used by clinicians. Therapy with bronchodilators and corticosteroids likely will not improve cough if the cough is caused by the cancer itself.

The pharmacologic agents that are available when cancer is the cause of cough include the following two classes of antitussive drugs: (1) those with central activity (ie, opioids and nonopioids); and (2) those with peripheral activity, the action of which can be
direct or indirect. Not all of the drugs to manage cough are available throughout the world. Antitussive drugs that have been studied extensively include codeine, hydrocodone, and dextromethorphan. Each of these agents has been demonstrated to be effective and has a good safety profile. The drugs that have been specifically studied in the setting of cancer and improvement in cough related to the cancer are hydrocodone, dihydrocodeine, levodropropizine, sodium cromoglycate, and benzonatate. While each of these agents has been shown to be effective and safe primarily in case series of variable size, we are unaware of any randomized, prospective, double-blind, placebo-controlled trials of pharmacologic agents to control cough in the specific setting of lung cancer.

Opioids appear to be the best cough suppressants in patients with lung cancer. Dihydrocodeine and hydrocodone are the most widely used opioids. In a phase II dose-titration study of 25 patients with advanced cancer who have cough, 5 mg of hydro-codone was administered twice daily. The dose was increased daily until there was an improvement of ≥ 50% in the frequency of cough and then was maintained for 3 consecutive days. The median best response was 70% in cough frequency, which was achieved with a median hydrocodone dose of 10 mg/d (range, 5 to 30 mg/d). A double-blind randomized trial in 140 patients with lung cancer compared levodropropizine drops (75 mg tid) to dihydrocodeine drops (10 mg tid for 7 days). The subjective severity of cough was significantly reduced with the use of both drugs, which had similar antitussive effects and duration of cough suppression. Adverse effects were infrequent in both groups, but the degree of somnolence was lower in the group treated with levodropropizine (8%) than among those treated with dihydrocodeine (22%). Levodropropizine is not available in the United States.

It is well-known that placebo administration can be associated with significant suppression of cough, especially in patients with acute cough due to upper respiratory infections. This issue should be considered not only when evaluating investigations on the suppressant effects of a single active drug, but also in studies comparing two active drugs, such as the report on levodropropizine and dihydrocodeine. However, to our knowledge, there have been no studies documenting the magnitude of the placebo effect on chronic cough due to pulmonary neoplasms.

Moroni et al hypothesized that inhaled sodium cromoglycate might reduce cough associated with lung cancer. Sodium cromoglycate had previously been reported to be effective for treating cough due to angiotensin-converting enzyme inhibitors, possibly because of the inhibition of afferent unmyelinated C-fiber activation. A role for C-fibers in cancer-related cough, both from the release of bradykinin by neoplastic cells and from the mechanical stimuli of the endings of the C-fibers caused by distortion by the cancer, was postulated. In a prospective, double-blind, placebo-controlled trial, a statistically significant reduction in cough was observed in all patients with advanced lung cancer who were treated with sodium cromoglycate. This study enrolled only 20 patients, and the results have not been repeated in a larger group of patients with lung cancer.

There have been few studies of benzonatate as a peripherally acting antitussive in the setting of pulmonary malignancies. In a case series, benzonatate effectively controlled cough in 80% of 21 patients with malignant pulmonary involvement, and it was effective for cough associated with lung cancer that was unresponsive to treatment with opioids in another small case series of three patients.

In summary, when considering other treatment methods to control cough caused by lung cancer, clinicians are left to use a variety of pharmacologic agents in an effort to relieve cough. There is little scientific rigor in most studies of pharmacologic approaches to cough suppression, and the efficacy of these pharmacologic methods is variable in the reported series.

**Recommendation**

6. For patients with cough and lung cancer, the use of centrally acting cough suppressants such as dihydrocodeine and hydrocodone is recommended. Level of evidence, low; benefit, intermediate; grade of recommendation, C

**Summary of Recommendations**

1. In a patient with cough who has risk factors for lung cancer or a known or suspected cancer in another site that may metastasize to the lungs, a chest radiograph should be obtained. Level of evidence, expert opinion; benefit, substantial; grade of recommendation, EA

2. In patients with a suspicion of airway involvement by a malignancy (eg, smokers with hemoptysis), even when the chest radiograph findings are normal, bronchoscopy is indicated. Level of evidence, low; benefit, substantial; grade of recommendation, B
3. For patients with stage I and II NSCLC, surgery to remove the NSCLC is the treatment of choice. If cough was caused by a NSCLC that can be surgically removed, the cough will typically cease. Level of evidence, low; benefit, substantial; grade of recommendation, B

4. For patients with more advanced NSCLC (stages III and IV), external beam radiation and/or chemotherapy should usually be offered. Level of evidence, good; benefit, intermediate; grade of recommendation, A

5. For patients with dyspnea or hemoptysis due to endobronchial tumors, cough may also be present. Endobronchial methods should be considered for the palliation of these symptoms, but cough alone is seldom a reason to offer such treatment. Level of evidence, fair; benefit, small; grade of recommendation, C

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