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Palliative Care in Lung Cancer: ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Palliative Care in Lung Cancer*

ACCP Evidence-Based Clinical Practice Guidelines (2nd Edition)

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Goals/objectives: **To review the scientific evidence on symptoms and specific complications that are associated with lung cancer, and the methods available to palliate those symptoms and complications.**
Methods: **MEDLINE literature review (through March 2006) for all studies published in the English language, including case series and case reports, since 1966 using the following medical subject heading terms: bone metastases; brain metastases; cough; dyspnea; electrocautery; hemoptysis; interventional bronchoscopy; laser; pain management; pleural effusions; spinal cord metastases; superior vena cava syndrome; and tracheoesophageal fistula.**
Results: **Pulmonary symptoms that may require palliation in patients who have lung cancer include those caused by the primary cancer itself (dyspnea, wheezing, cough, hemoptysis, chest pain), or locoregional metastases within the thorax (superior vena cava syndrome, tracheoesophageal fistula, pleural effusions, ribs, and pleura). Respiratory symptoms can also result from complications of lung cancer treatment or from comorbid conditions. Constitutional symptoms are common and require attention and care. Symptoms referable to distant extrathoracic metastases to bone, brain, spinal cord, and liver pose additional problems that require a specific response for optimal symptom control. There are excellent scientific data regarding the management of many of these issues, with lesser evidence from case series or expert opinion on other aspects of providing palliative care for lung cancer patients.**
Conclusions: **Palliation of symptoms and complications in lung cancer patients is possible, and physicians who provide such care must be knowledgeable about these issues.**

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Key words: bone metastases; brain metastases; cough; dyspnea; electrocautery; hemoptysis; interventional bronchoscopy; laser; pain management; pleural effusions; spinal cord metastases; superior vena cava syndrome; tracheoesophageal fistula

Abbreviations: APC = argon plasma coagulation; CI = confidence interval; NSAID = nonsteroidal antiinflammatory drug; NSCLC = non-small cell lung cancer; OR = odds ratio; PCI = prophylactic cranial irradiation; PDT = photodynamic therapy; RCT = randomized controlled trial; SCLC = small cell lung cancer; SVC = superior vena cava; TEF = tracheoesophageal fistula; WBRT = whole-brain radiation therapy

The histologic type, biological behavior, and the anatomic location of lung cancer within the thoracic cage determine the type and severity of respiratory symptoms manifested by patients with lung cancer. Pulmonary symptoms that may require palliation include those caused by the primary cancer itself (dyspnea, wheezing, cough, hemoptysis, chest pain),[1–7] or locoregional metastases within the thorax (superior vena cava [SVC] syndrome, tracheoesophageal fistula [TEF], pleural effusions, ribs, and pleura).[8–18] Respiratory symptoms can also result from complications

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of lung cancer treatment (such as radiation- and chemotherapy-induced lung toxicity, airway stenosis and necrosis, fistula formation, hemoptysis from neovascularization).[13,14,16,19–27] Comorbid conditions (such as COPD, heart failure, pulmonary embolism, prior lung resection, malnutrition) cause or contribute to respiratory symptoms. Constitutional symptoms (depression, fatigue, insomnia, anorexia-cachexia syndrome) are common and require attention and care. Symptoms referable to distant extrathoracic metastases to bone, brain, spinal cord and liver pose additional problems that require a specific response for optimal symptom control.

Pharmacologic (noninvasive) approaches to alleviating the above-mentioned respiratory symptoms from lung cancer are discussed in this chapter and elsewhere in the guidelines. However, a significant number of patients have respiratory symptoms as the result of mechanical (anatomic) effects of lung cancer, such as major airway obstruction, postobstructive pneumonia, fistulae between airways and other intrathoracic organs, pleural effusion, and paralysis of diaphragm and vocal cords. In such patients, pharmacologic (noninvasive) therapies may be inadequate to palliate respiratory symptoms. Several invasive techniques are available to benefit this selected group of patients and will be discussed in the appropriate section of this chapter.

Methods and Materials

The key words for various palliative care topics, as listed in above-mentioned "Key words" section, were searched using Ovid MEDLINE and PubMed from 1966 through March 1, 2006. Randomized controlled trials (RCTs) were especially sought for all such topics; where this type of study was available, it is clearly identified as such in the appropriate section of this chapter. For many of the topics, evidence is of substantially less quality, and it typically consists of case series of varying size. This has led to recommendations that are based on publications describing clinical experience with varying sizes of patient population. The sections that discuss approaches to treatment of airway obstruction and hemoptysis, as well as palliation of malignant pleural effusion are examples where the evidence-based literature pertaining to palliative therapy is limited.

Results

Pain Control

Studies reveal that adults with lung cancer have more symptoms than patients with other types of cancer.[28] Pain is a common symptom in lung cancer patients, yet inadequate pain management is prevalent, harmful to patients, and costly.[29] A comprehensive document for the management of cancer pain was developed and published in 1994 as part of a response to Public Law 101–239 (the Omnibus Reconciliation Act of 1989), under the aegis of the Agency for Health Care Policy and Research. The name subsequently was changed to the Agency for Healthcare Research and Quality.[30] The document on cancer pain management was updated in October 2001.[31]

In 2005, the American Pain Society revised and updated their recommendations for improving the quality of cancer pain management, and subsequently published guidelines on this topic.[32] The comments in this section are adapted from these resources. The scope of these efforts is beyond what can be discussed in detail in this document, and the reader is referred to these resources for additional information. In their 2005 recommendations, the American Pain Society calls caregivers' attention to five areas of pain management: (1) recognize and treat pain promptly; (2) involve the patients and families in the pain-management plan; (3) improve treatment patterns by eliminating inappropriate practices and providing multimodal therapy; (4) reassess and adjust the pain management plan as needed, focusing not only on pain intensity but on functional status and side effects as well; and (5) monitor the processes and outcomes of pain management, using national performance indicators.[32]

The potential causes of cancer pain are multiple and can include tumor progression and related pathology (*eg*, nerve damage), surgery and other procedures used for treatment and diagnosis, toxic side effects of chemotherapy, and radiation. Approximately 75% of patients with advanced cancer have pain. Failure to relieve pain leads to unnecessary suffering. Decreased activity, anorexia, and sleep deprivation caused by pain can further weaken already debilitated patients.

Effective management of pain from cancer can be achieved in most patients. Clinical trials[33–35] indicate that patients consider pain management effective if it decreases the pain intensity 33 to 50%, such that a clinician's goal and/or promise to the patient of "no pain" is ill founded and unnecessary. Proper management of a patient's pain involves more than analgesia, and the program of pain control for any one patient must be individualized. Approaches that may augment analgesia include cognitive/behavioral strategies, physical modalities, palliative radiation and antineoplastic therapies, nerve blocks, and palliative and ablative surgery. Studies[1,36–40] reveal that palliative chemotherapy in advanced lung cancer can have a modest increase in survival, and often has the additional benefit of improving pain and other symptoms. Any analgesic medication program should be kept as simple as possible, both with regard to the frequency and route of administration. Oral medications are preferred, because of convenience and

cost-efficacy. If the patient cannot take medications by mouth, rectal and transdermal routes should be considered because they are relatively noninvasive. IM routes of administration should be avoided because of the associated pain and inconvenience, and also because of unreliable absorption.

A nonsteroidal antiinflammatory drug (NSAID) or acetaminophen should be used unless there is a contraindication (*eg*, increased risk of cardiovascular events and GI bleeding with NSAID medications). If pain persists or becomes worse, an opioid should be added and not substituted. Using opioids and acetaminophen or NSAIDs often provides more analgesia than can be accomplished by either class of drug alone. Further, the use of acetaminophen or NSAIDs may have a dose-sparing effect for opioids, which can provide the benefit of fewer side effects from the opioids. When pain persists despite this approach, the dose of opioids should be increased or a more potent agent chosen. The World Health Organization ladder has been shown to be an effective method to ensure the rational titration of therapy for cancer pain (Fig 1).

Morphine is the most commonly used opioid for moderate or severe pain. It is available in a wide variety of dosage forms that include immediate and controlled-release preparations. Morphine is relatively inexpensive. Transdermal and rectal routes of administration can be used for most patients who cannot take medications by mouth. Morphine, hydrocodone, and oxymorphone suppositories are available. Fentanyl is the opioid most frequently used for transdermal administration. Meperidine should not be used because it has a short duration of action and its metabolite normeperidine is toxic and causes CNS stimulation with dysphoria, agitation, and seizures.

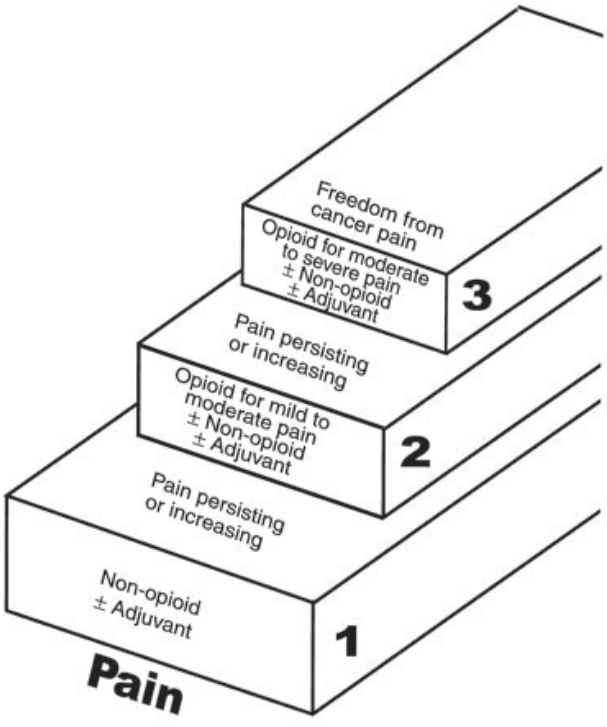

FIGURE 1. The World Health Organization three-step analgesic ladder.

Both the cancer patient and family members may shun the use of opioids because of a fear of addiction. Physicians must educate both the patient and the family about pain and how it is to be managed as part of the treatment plan. Effective pain control begins by asking the patient about pain. An easily administered pain rating scale should be used for assessment of pain, both at the time of initial presentation and periodically at regular intervals during the course of the disease. The most common pain scales are numeric (0 to 10 pain intensity), simple descriptive in nature (no pain, mild, moderate, severe), and a visual analog scale. Quality pain management requires a comprehensive assessment of the patient's pain, described as learning the "who", "how," and "when" of the pain.[29] Focusing only on pain intensity is insufficient and can lead to poor pain relief.

Analgesic medications should be administered around-the-clock with a long-acting opioid, with extra doses of an immediate-release opioid on an as-needed basis for breakthrough pain because this approach helps to prevent recurrence of pain. A written pain-management plan should be given to patients with cancer pain and their families. Constipation is a side effect of opioid medications, and should be anticipated, treated prophylactically, and monitored constantly. Mild constipation can be managed by an increase in fiber consumption and a mild laxative such as milk of magnesia. Bulk-forming laxatives such as fiber supplements should be avoided. Unless there are contraindications, cathartic agents should be administered on a regular schedule.

Ketamine is a parenteral general anesthetic that has been used in subanesthetic doses to relieve pain, particularly in opioid-tolerant patients. In the absence of large controlled trials providing recommended dosing schedules, clinicians with limited experience in using ketamine should seek expert consultation to develop an appropriate treatment and patient-monitoring plan.[41]

Adjuvant drugs may be used to enhance the efficacy of opioids. Corticosteroids produce effects that include mood elevation, relief of inflammation, and reduction of cerebral or spinal cord edema when there is intracranial metastasis or spinal cord compression. Anticonvulsants such as phenytoin, carbamazepine, and clonazepam are used to manage neuropathic pain. Tricyclic antidepressants are used

as an adjuvant to analgesics for the management of neuropathic pain. They augment the effects of opioids and have innate analgesic properties. Their mood-elevating properties may be helpful as an adjuvant to strict analgesics. Other adjunctive pharmacologic approaches include neuroleptics such as the major tranquilizers, hydroxyzine, bisphosphonates, and calcitonin for bone metastases.

There are many different nonpharmacologic methods to manage pain, many of which are very simple, effective, and inexpensive. Nonpharmacologic methods to manage pain include cutaneous stimulation techniques (heat and cold applications), accupuncture, psychosocial methods of care, and pastoral care. For patients with intractable and persistent pain despite use of all modalities that are known and familiar to the practitioner, referral to a clinic that specializes in the management of pain should be considered. Pain-control specialists can help to select additional methods that may improve the overall palliation of pain.

Recommendations

1. All lung cancer patients and their families must be reassured that pain can be relieved safely and effectively. All patients should be questioned regularly about their pain, using the patient's self-report of pain and a simple rating scale as the primary source of assessment. Grade of recommendation, 1A

2. For all patients, individualize medications that are used to control pain. Administer medications regularly and treat pain appropriately. Document the effectiveness of pain management at regular intervals during treatment. Grade of recommendation, 1A

3. For all patients with mild-to-moderate pain, manage the pain initially with acetaminophen or an NSAID, assuming there are no contraindications to their use. Use opioids when pain is more severe or when it increases. Grade of recommendation, 1B

4. For any patient, if it is anticipated that there will be a continuous need for opioid medication, meperidine is not recommended. It has a short duration of action, and its metabolite normeperidine is toxic and can cause CNS stimulation resulting in dysphoria, agitation, and seizures. Grade of recommendation, 1B

5. For patients whose pain is not controlled by pure analgesic medications, adjunctive medications such as tricyclic antidepressants, anticonvulsants, and neuroleptic agents will often augment the effects of pure analgesic medications. Grade of recommendation, 1C

6. For all patients, administer medications by mouth because of convenience and cost-effectiveness. In patients with lung cancer who cannot take pain medications by mouth, rectal and transdermal administration are recommended. Administration of analgesics by the IM route is not recommended because of pain, inconvenience, and unreliable absorption. Grade of recommendation, 1C

7. For all patients receiving opioids, because constipation is common, anticipate it, treat it prophylactically and constantly monitor it. Grade of recommendation, 1B

8. Encourage all patients to remain active and to care for themselves whenever possible. Avoid prolonged immobilization whenever possible. Grade of recommendation, 1B

9. In patients who have pain associated with muscle tension and spasm, it is recommended that complimentary methods for pain relief such as cutaneous stimulation techniques (heat and cold applications), acupuncture, psychosocial methods of care, and pastoral care be incorporated into the pain-management plan, but not as a substitute for analgesics. Grade of recommendation, 1C

10. For patients with advanced lung cancer, provide palliative radiation therapy to control pain. Palliative chemotherapy to decrease pain and other symptoms is recommended, even though the increase in survival may be only modest. Grade of recommendation, 1B

11. In patients with lung cancer who have pain unresponsive to standard methods of pain control, referral to a specialized pain clinic or palliative care consultant is recommended. Grade of recommendation, 1C

Palliation of Dyspnea

Dyspnea is the subjective experience of difficult, labored, and uncomfortable breathing. Dyspnea and cough are the most commonly reported symptoms in lung cancer, with 15% of patients having dyspnea at diagnosis and 65% at some point during their illness.[42,43] A prospective cohort study[44] of seriously ill, hospitalized adults in five teaching hospitals in the United States reported that among 939 patients with stage III or IV non-small cell lung cancer (NSCLC), severe dyspnea was recorded in 32%. Near death, 90% of patients with NSCLC have dyspnea. It is more common in men, older patients, and those with lower quality of life scores, and the incidence of dyspnea is higher when pain and anxiety are high.[45,46] Because of its frequency, clinicians should routinely assess the lung cancer patient for dyspnea. The intensity of the dys-

pnea can be discerned by the patient using a modified Borg scale of 0 to 10. Often patients will modify their activities to reduce the sensation of dyspnea, such that a report of intensity alone disguises the advancing dyspnea. It behooves the clinician also to ask what activities the patient has curtailed because of dyspnea.[47] The causes of dyspnea in patients with lung cancer can be classified into five broad groups: (1) the result of direct involvement of the respiratory system by lung cancer; (2) the result of indirect respiratory complications caused by lung cancer (such as postobstructive pneumonia and pleural effusion); (3) the result of specific therapies to treat lung cancer (such as radiation- and chemotherapy-induced lung toxicity, and anemia); (4) the result of respiratory complications that occur more frequently in these patients (such as pulmonary embolism and lung infections); and (5) comorbid conditions (such as COPD, heart failure, prior lung resection, and malnutrition).

Regardless of the stage of lung cancer, dyspnea usually impacts the patient's physical, social, and psychological well being. Anxiety, fear of impending death, and pain caused by lung cancer are among the factors that contribute to the subjective symptoms of dyspnea. A prospective study of 100 terminally ill cancer patients (49 patients with lung cancer) observed that dyspnea, measured on visual analog scale, was significantly associated with anxiety ($p = 0.001$).[48] From the perspectives of the patient and health-care providers, dyspnea can be perceived as panic, chest congestion and tightness, and suffocation. One study[46,49] of 52 patients with lung cancer noted that both physical and emotional sensations were associated with descriptions of breathlessness, such as the feeling of being unable to get enough breath, or of panic or impending death. Increased anxiety has been connected with worse dyspnea in patients with obstructive lung disease, chronic pulmonary disease, and/or cancer.[50–52] One study[46] of 120 patients with stage I-IV lung cancer observed no difference in dyspnea based on cancer stage, cell type, or performance status. However, pain and anxiety scores were higher in patients with high dyspnea scores.

The treatment of dyspnea should follow a stepwise approach, starting with treatment of the specific cause of the dyspnea if it can be identified (*eg*, pleural effusion, obstructed major airway, SVC syndrome, pericardial effusion and/or tamponade, carcinomatous lymphangitis, congestive heart failure, pulmonary embolism, and COPD and/or asthma).[47,53] If the specific cause cannot be identified, or if moderate-to-severe dyspnea persists despite attempted palliation of the cause, nonpharmacologic treatments should be considered. If these are not or only partly successful, pharmacologic therapies should be added to the treatment plan.

Nonpharmacologic Treatments

Nonpharmacologic treatments start with patient self-care strategies and coping strategies. Self-care strategies are particularly helpful in the patient who has coexisting COPD, and include simple measures such as body position (*eg*, leaning forward with arms and shoulders supported), pursed-lip breathing, paced breathing during activity (*eg*, inhale at the pause on the step while climbing stairs, exhale with the next step), and diaphragmatic breathing. Coping strategies can include practicing desensitization to the symptom, learning relaxation techniques (guided imagery, self-hypnosis, meditation/prayer, music therapy), and energy conservation techniques.[54]

Complementary methods for the control of dyspnea often include intervention by allied health personnel. A multicenter RCT of 119 patients with small cell lung cancer (SCLC) or NSCLC or with mesothelioma, who had completed first-line treatment and reported dyspnea, used various strategies. These included breathing control, activity pacing, relaxation techniques, and psychosocial support, in addition to standard management and treatment available for dyspnea. The group assigned to intervention by nurses improved significantly at 8 weeks in breathlessness, performance status, and physical and emotional status compared to the control group.[55,56] Similarly, using these techniques within specialist palliative care settings in a "breathlessness clinic" demonstrated a significant improvement in breathlessness, functional capacity, activity levels, and distress levels in lung cancer patients.[57]

Patient and family education about dyspnea and its treatments is the foundation of successful treatment. In patients with advanced disease, families should be educated about controlling the impact of things such as ambient weather and the indoor environment and its effect on the patient's perception of dyspnea. Patients with dyspnea at rest or with minimal activity often prefer an open and cool room with a clear line of sight to the outside. They also can receive benefit from a fan blowing on their face or a cool compress applied to the forehead, both mediated by the trigeminal nerve.[47]

The American College of Chest Physicians is in the process of developing evidence-based clinical practice guidelines for the management of dyspnea in advanced lung disease, including lung cancer. The reader is referred to the American College of Chest Physicians journal *CHEST* for this resource currently not yet published.

Oxygen: Supplemental oxygen is perhaps the most commonly prescribed therapy to relieve dyspnea in patients with lung cancer.[58] Significant involvement

of the respiratory system by lung cancer or underlying obstructive airways disease usually produces or aggravates dyspnea and hypoxemia. A limited number of studies have shown the beneficial effects of supplemental oxygen therapy. A prospective, double-blind, crossover trial[59] assessed the effects of supplemental oxygen on the intensity of dyspnea in 14 patients with advanced cancer. Patients were randomized to receive either oxygen or air delivered at 5 L/min by mask. Dyspnea was evaluated with a visual analog scale. The results showed that 12 patients consistently preferred oxygen to air; and patients reported little or no benefit from air compared with moderate to much benefit from oxygen.[59]

Regardless of the oxygenation status, supplemental oxygen therapy should be considered if patients with lung cancer experience dyspnea. Multiple blood gas analyses should be avoided to justify oxygen therapy. Percutaneous oximetry should suffice to assess adequate oxygenation. Providing supernormal oxygenation in patients with lung disease has shown an increase in exercise tolerance by relieving or decreasing the sensation of dyspnea, likely by suppressing the carotid body response.[60]

Pharmacologic Treatments

Pharmacologic treatments for dyspnea caused by lung cancer have included bronchodilators, corticosteroids, anxiolytics, antidepressants, and opioids. One retrospective study[58] at a medical center specializing in cancer assessed the resource utilization associated with the management of dyspnea caused by lung cancer in 45 patients. The most common therapies administered in the emergency department were oxygen (31%), β_2-agonists (14%), antibiotics (12%), and opioids (11%).[58]

Inhaled Bronchodilators and Corticosteroids: Standard bronchodilators such as β_2-agonists, anticholinergics, and aerosolized corticosteroids are commonly prescribed to lung cancer patients who also have underlying COPD or asthma. There is no evidence that the presence of lung cancer induces bronchospastic disease. However, the onset of lung cancer in patients with underlying obstructive lung diseases usually aggravates symptoms of preexisting obstructive lung disease. There are not many studies to prove a beneficial effect of bronchodilators in patients with lung cancer. However, a prospective study[48] of 100 terminally ill cancer patients (49 patients with lung cancer) observed that the potentially correctable causes of dyspnea included bronchospasm (in 52%) and hypoxia (in 40%). It is important to ensure that bronchodilator therapy is optimized if the patient has obstructive airways disease. Inhaled furosemide also has been studied in patients with obstructive airways disease and in those with terminal dyspnea, and has been shown to improve airflow and exercise tolerance.[61]

Systemic Corticosteroids: The role for systemic corticosteroids is limited for relieving dyspnea from lung cancer. As is the case with bronchodilator therapy, patients with obstructive airways disease may benefit from systemic corticosteroids to decrease mucus production and inflammatory changes in the airway mucosa. It is also important to recognize that patients with lung cancer who are actively receiving specific therapy, such as radiotherapy and/or chemotherapy, may experience varying degrees of dyspnea.[62] This may reflect pulmonary toxicity to such therapies. Pulmonary parenchymal toxicity leading to dyspnea may require discontinuation of tumor-specific therapies and administration of systemic corticosteroids.

Analgesics: Dyspnea has been shown to be more severe in patients with severe pain.[46,50] Dyspnea caused or aggravated by cancer-induced pain may respond to nonnarcotic analgesic therapy. However, dyspnea due to pain caused by bony metastases, malignant pleural effusions, or fatigue is unlikely to respond to conventional analgesic therapy. Such circumstances require more aggressive pain control, including palliative radiotherapy for skeletal metastasis. In patients with dyspnea caused by milder pain and discomfort, nonnarcotic analgesics should be tried for a brief period.

Anxiolytics and Antidepressants: Anxiety can aggravate the sensation of dyspnea, but studies of anxiolytics used to treat dyspnea, including benzodiazepines, phenothiazines and buspirone, have not shown benefit over placebo. Similarly, although antidepressants such as nortriptyline, desipramine, paroxetine, and selective serotonin reuptake inhibitors can be used to treat depression, their use to treat dyspnea is not supported.[48]

Opioid Treatment: Opioids are frequently used to alleviate dyspnea in patients with advanced lung cancer, advanced obstructive airway disease, and cardiac failure.[63] A wide variety of opioid analgesics have been used to control both dyspnea and pain in patients with cancer of the lung and other organs. They include hydrocodone, acetaminophen with codeine, morphine, oxycodone, hydromorphone, and others. Opioids have been used orally, parenterally, and by aerosol, although the latter technique has not produced reliable results.[64] It is unclear if all opioids

are equally efficacious in decreasing dyspnea perception in patients with lung cancer. In a study[46] of 104 patients with lung cancer, opioids administered to treat pain did not decrease dyspnea, although one study[65] showed an improvement in dyspnea when a subcutaneous dose of morphine 50% above the pain-relief dose was administered.

An open, uncontrolled study[63] evaluated the role of oral morphine to relieve dyspnea in 15 patients with advanced malignancy receiving standard care and noted that regular, titrated oral morphine may improve dyspnea but can cause significant short-term adverse effects. The relief of dyspnea is usually noted within 24 h, and the relief stays at a plateau with continued opioid therapy.[63]

A metaanalysis[66] of 18 RCTs revealed a statistically significant positive effect of opioids on breathlessness. Oxygenation and carbon dioxide did not change in the 11 studies that included those variables. Some patients withdrew because of nausea, vomiting, and/or constipation. The effect of nebulized opioids was not different from placebo. A subsequent RCT[67] also showed significant improvement in refractory dyspnea using a sustained-release, low-dose, oral morphine.

Continuous IV infusion of morphine has been used in patients with terminal lung cancer with severe dyspnea, unrelieved by oxygen, nonnarcotic drugs, or intermittent bolus narcotics.[68] Even when patients achieve good dyspnea relief, the major side effect is sedation. Health-care providers, the patient, and family should be cognizant of the possibility of severe hypoventilation and hypercarbic respiratory failure and death. This side effect has been described also with inhaled morphine.[69] Nonetheless, the ethical principle of "double effect" supports the palliative use of opioids to relieve symptoms such as dyspnea and pain.[47]

Invasive Approaches to Palliation of Dyspnea

Airway Obstruction: Primary lung cancer or metastatic malignancy in the thoracic cage can lead to airway obstruction as a result of tumor growth inside the airway lumen (intraluminal or intramural), airway wall (luminal or mural), or outside the airway lumen (extraluminal or extramural).[70–73] Central airway obstruction refers to significant obstruction of the trachea and main bronchi. Patients with this complication are more likely to have significant dyspnea and hemoptysis, at times life threatening, and require urgent therapy. Onset of stridor and its progression indicates the possibility of impending airway obstruction. The obstruction caused by the neoplasm can be aggravated by associated factors such as excessive mucous secretion and formation of mucous plugs, and blood and blood clots in the airway lumen. Palliative bronchoscopy plays a major role in such situations.

Clinical evaluations including imaging techniques and flow-volume curves may indicate the degree of airway obstruction. However, bronchoscopy is the singularly important technique for the diagnosis as well as therapy of airway obstruction. Bronchoscopic visualization usually determines the nature and severity of the obstruction and helps determine the appropriate diagnostic and therapeutic procedures.

Almost all bronchoscopic therapies are palliative in patients with lung cancer involving the major airways. A small number of patients with *in situ* lung cancer who cannot undergo resection because of comorbid conditions may get cured with endobronchial therapies. Bronchoscopic relief of disabling dyspnea is the most beneficial effect of the procedure. The next important symptom that can be treated by bronchoscopy is hemoptysis. Cough relief by bronchoscopy is less satisfactory because none of the palliative therapies will totally eradicate the tumor that is responsible for the cough.

The type of bronchoscopic therapy should be determined by the type and severity of respiratory symptoms, and the overall condition of the patient. The types of bronchoscopic therapy include endotracheal intubation, bronchoscopic debulking of intraluminal tumor, balloon dilatation, laser therapy, electrocautery, cryotherapy, argon plasma coagulation (APC), endobronchial irradiation (brachytherapy), or airway stent insertion (Table 1).[74] Some patients require a combination of techniques to obtain complete and lasting relief of symptoms.[75] All of these therapeutic techniques will provide significant relief of dyspnea and hemoptysis in the majority of patients.[76] While most of the techniques provide rapid relief of these symptoms, some procedures take a longer time and repeated applications. Expertise in these specialized techniques is imperative.

Endotracheal Intubation: Endotracheal intubation is recommended in a patient who faces impending death because of tracheal obstruction and no therapeutic bronchoscopy is available. As soon as dyspnea is relieved and optimal oxygenation is accomplished, bronchoscopic visualization should be performed to assess the proper placement of the endotracheal tube and the extent of airway obstruction. Endotracheal intubation is useful in both luminal and extraluminal obstructions.[77–80] The risk of bleeding during endotracheal intubation and the difficulty of intubation should be recognized. Therapeutic endotracheal intubation is temporary, and plans should be made for more permanent relief of symptoms.

Table 1—*Palliative Bronchoscopic Therapies

Therapy	Type of Lesion	Type of Bronchoscope	Rapidity of Positive Result	Repeatability of Therapy	Complications
Mechanical debridement	Intraluminal or submucosal	Rigid or flexible	++++	+++	Hemorrhage
Laser	Intraluminal	Rigid or flexible	++++	++++	Hemorrhage, fistula
APC	Intraluminal	Rigid or flexible	++++	++++	Hemorrhage, fistula
Brachytherapy	Intraluminal or submucosal	Flexible	+	+	Hemorrhage, fistula
Cryotherapy	Intraluminal	Rigid or flexible	++	+++	Necrotic tissue may obstruct airway lumen
Balloon dilatation	Intraluminal or submucosal	Rigid or flexible	++++	++++	Minimal
PDT	Intraluminal	Flexible	++	+++	Necrotic tissue; therapy may obstruct airway lumen
Electrocautery	Intraluminal	Rigid or flexible	+++	++++	Hemorrhage, fistula
Stent	Intraluminal or compression	Rigid or flexible	++++	+++	Stent migration, extrinsic granulation tissue, infection, stent malfunction

*Adapted from Prakash.[358] + = least effective therapeutic response; ++ = modest rate of therapeutic response; +++ = excellent therapeutic response; ++++ = most rapid or repeatable therapeutic response.

Bronchoscopic Debridement: Bronchoscopic debridement (resection) of intraluminal tumor can quickly relieve airway obstruction and resultant dyspnea. In many patients, this technique alone may suffice to relieve dyspnea. The rigid bronchoscope is much quicker than the flexible bronchoscope in accomplishing this task. The most important advantage of the rigid bronchoscope is that the instrument itself can be used as a tumor-debulking instrument, much like coring an apple. The other important advantages of the rigid bronchoscope include the ability to secure and maintain the airway, delivery of oxygen and anesthetic gases, and the ability to employ other therapeutic techniques. One retrospective study[77] evaluated the role of urgent rigid bronchoscopy, including Nd-YAG laser resection or stenting, in patients with acute respiratory failure from malignant central airways obstruction. Airway obstructions were caused by lung cancer in 14 patients. Urgent therapeutic bronchoscopy permitted immediate discontinuation of mechanical ventilation in $>$ 52% of these patients (including 19 patients with benign lesions).[77] A study[73] of 143 patients who underwent 309 stent procedures of which 67% were for malignant disease observed that 82% required urgent or emergency intervention, and 77% had compromise of more than three fourths of the airway lumen. Flexible bronchoscopic debridement requires longer time because of the limitation of the ancillary instruments to adequately resect the tumor. Bronchoscopic debridement is best suited for intraluminal tumor growth and not applicable for therapy of extrinsic compression. Rigid bronchoscopy is best accomplished under general anesthesia or deep IV sedation. The major complication of simple bronchoscopic debridement is the bleeding associated with tumor resection.

Balloon Dilatation: Bronchoscopic balloon dilatation has a limited role in the treatment of major airway obstruction by malignant tumors.[81,82] This technique is a preparatory procedure to dilate the obstructed airway prior to placement of stents. Balloon dilatation through either the flexible or rigid bronchoscope is best suited for stenoses that are short in length.[83] Complications are few; excessive dilatation has the potential to cause airway rupture.

Laser: Bronchoscopic laser therapy is useful in relieving obstruction caused by intraluminal lesions. It has no role in treatment of obstruction caused by extraluminal tumors. Either rigid or flexible bronchoscopy can be used for application of laser energy, even though the former accomplishes this more quickly.[84] Rigid bronchoscopy is recommended for the management of large tumors in the trachea and mainstem bronchi. Once the laser accomplishes the coagulation of the tumor, a rigid bronchoscope itself or large forceps can be deployed to rapidly remove the obstructing tissue. If significant bleeding is encountered during the procedure, a rigid bronchoscope can provide quick control of this problem by tamponading the bleeding source as well as permitting suctioning of large quantities of blood from the airway. Currently, various types of lasers are available for treatment of endobronchial tumors. These include Nd-YAG, potassium titanyl phosphate, and CO_2 laser units. The Nd-YAG laser is the most commonly employed type of laser to treat malignant

lesions of major airways. Immediate relief of airway occlusion and obstructive symptoms can be expected in > 90% of patients. Laser therapy also helps in preparing the airway for insertion of airway stents as well as brachytherapy catheters. Complications from laser therapy include endobronchial fire, severe hemorrhage, perforation of the airway, pneumothorax, and pneumomediastinum.[85–88]

Electrocautery: Electrocautery application through either a rigid or flexible bronchoscope employs alternating electrical current to produce coagulation and vaporization of endobronchial lesions.[89–94] The result from electrocautery technique is similar to that achieved with laser therapy. Immediate relief of dyspnea can be achieved with electrocautery in 55 to 75% of patients.[90,93,95–97] A prospective study[98] evaluated the impact of bronchoscopic electrosurgery on the need for bronchoscopic Nd-YAG laser in patients with symptomatic airway lesions and observed that of the 47 bronchoscopic electrosurgery procedures, 42 procedures (89%) were successful in alleviating the obstruction, thus eliminating the need for laser. All procedures were performed in the outpatient bronchoscopy suite with the patient under conscious sedation (morphine and midazolam) and topical anesthesia with 2% lidocaine.[98] The advantages of electrocautery include less-expensive equipment (compared to laser) and the ease of use through flexible or rigid bronchoscope. Complications are similar to those encountered in laser ablation, and inadvertent delivery of electrical shock to the operator or patient.

APC: APC applies a technique to achieve noncontact electrocoagulation of viable tissue. APC utilizes electrically conductive argon plasma as a medium to deliver high-frequency current via a flexible probe to coagulate tissue. APC devitalizes tissue gradually by producing temperatures that coagulate and desiccate tissue. One retrospective study[99] of 60 patients with bronchogenic carcinoma (n = 43), metastatic tumors of airways (n = 14), or benign bronchial disease (n = 3) employed APC therapy via flexible bronchoscopy to control hemoptysis, symptomatic airway obstruction, or both obstruction and hemoptysis. Patients with endoluminal airway lesions had an overall decrease in mean obstruction of 18 ± 22%. All patients with obstructive lesions had symptom improvement, and symptom control was maintained during a median follow-up period of 53 days.[99] The advantages of APC include low cost (compared to laser), noncontact mode of therapy, easy portability of equipment, and ease of use. The noncontact feature of APC allows rapid coagulation with minimal manipulation of and mechanical trauma to the target tissue. Complications are similar to those described for laser and electrocautery.

Cryotherapy: Cryotherapy employs cryoprobes through either a rigid or flexible bronchoscope to apply extremely cold temperatures to tumor tissue so that malignant cells are devitalized and killed by repeated cycles of cold application followed by thawing. Nitrous oxide or liquid nitrogen is most commonly used to produce temperatures of − 80°C.[100–102] As is the case with laser and electrocautery, cryotherapy can be used to treat only intraluminal tumors. Subjective improvements have been observed in > 75% of patients with malignant airway lesions.[103,104] In a study[105] of 476 consecutive patients with obstructive airway tumors treated by cryotherapy, significant improvements in hemoptysis, cough, and dyspnea were observed in 76%, 69%, and 59%, respectively. In this study,[105] the overall complication rate was 3.5% and included bleeding, pneumothorax, respiratory distress, and cardiac events. Repeat bronchoscopy is needed for continued therapy in many patients. Cryotherapy equipment is less expensive and easier to use than laser therapy. The major disadvantage of treating large tumors in major airways is that cryotherapy requires repeated applications and far more time to relieve obstruction. Therefore, cryotherapy is not an ideal technique to acutely relieve dyspnea caused by major airway lesions.

Brachytherapy: Brachytherapy is the term used to describe intraluminal radiation therapy to treat malignant tumors within the airways. The flexible bronchoscope is used to insert and place the brachytherapy catheter into the affected airway lumen. Brachytherapy can be used to treat airway obstruction caused by intraluminal, luminal, as well as extraluminal cancer located immediately adjacent to the airway.[106–110] Usually, brachytherapy is aimed at palliating malignant airway lesions in patients who have already received a maximum dose of external-beam radiation. Brachytherapy can also be used as a stand-alone therapy or as complimentary or combined therapy following external beam radiation therapy, airway debulking (laser, mechanical removal), or after airway stent placement. Even though earlier experience demonstrated that brachytherapy alone resulted in adequate symptomatic relief in a considerable number of patients,[11,12,111–115] current evidence indicates that brachytherapy as a complimentary therapy provides better relief of dyspnea and other symptoms than brachytherapy alone.[112,116–123] Relief from dyspnea can be expected in > 60% of patients and can last for weeks to months. A phase II study[124] involving 30 patients with stage-III NSCLC treated with 60 Gy x-ray therapy also used brachytherapy and reported palliation rates of 80% for dyspnea and 43% for

cough. One prospective study[123] of 342 patients with endobronchial tumors treated by the combination of external-beam radiation therapy (30 to 60 Gy) and concomitant brachytherapy during weeks 1, 3, and 5 observed a response rate of 85% for cough and 86% for dyspnea. Major complications of brachytherapy include fistula formation between the airways and other thoracic structures in up to 8% of patients. The risk of massive hemoptysis increases dramatically when a fraction size of 15 Gy is used.[121]

Photodynamic Therapy: Photodynamic therapy (PDT) consists of deploying tumor-tagging compounds such as hematoporphyrin derivative and porfimer sodium. When tumor cells thus tagged are exposed to the light of the proper wavelength, chemical reactions cause death of malignant cells through production of toxic radicals. Patients with small (< 3 cm^2) epithelial cell malignancies are most likely to benefit from this therapy.[125] Complete response lasting for > 12 months has been observed in 50% of patients.[126,127] The effectiveness of PDT for symptom palliation, and survival benefit has been evaluated in patients with advanced inoperable bronchogenic cancer and endobronchial luminal obstruction. Among 100 such patients, 82% had received prior chemotherapy and/or radiotherapy. On an average, endoluminal obstruction diminished from 86 to 18%. This study suggests that PDT is effective in palliation of inoperable advanced lung cancer in a subset of patients. One study[128] has reported on the therapeutic efficacy of combined brachytherapy and PDT in patients with bulky endobronchial lung cancer. Another study[129] of 37 consecutive cases of inoperable cancer, either primary or metastatic to lung, used porfimer sodium as a primer before PDT and observed 32 complete or partial responders and five treatment failures.

When PDT alone is used, however, the relief from obstruction is slow[130]; because of this slow response, there is no major role for PDT in the treatment of obstructing lesions of central airways. In locally advanced and symptomatic lung cancer, PDT with or without radiotherapy can contribute to the relief of airway obstruction and hemoptysis, but it has not exhibited a survival advantage when compared with current treatments, such as Nd-YAG laser therapy or radiotherapy alone.[131] Complications from PDT include phototoxicity, hemoptysis, and obstruction of bronchi by thick necrotic material.

Stents: Airway prostheses or stents made of metal, silicone, or other materials can be used to relieve airway obstruction caused by malignant tumors.[132–137] Stent therapy is indicated in both intraluminal and extraluminal major airway obstructions. Stent therapy is more effective in patients with tracheal or main bronchial obstruction than in those with airway diseases that involve lobar and more distal bronchi. Either silicone or metallic stents can be used to treat malignant airway lesions. Malignancy involving the main carina is best treated with silicone stents designed for this anatomic location.[138] Uncovered metallic stents are not recommended in patients with malignant airway lesions because the growth of cancer through the wire mesh negates the benefits of stent placement.[139] After bronchoscopic debridement of tumor and laser therapy, stent placement should be considered to maintain long-term airway patency. Even though bronchoscopy is frequently used to deploy airway stents, tracheobronchial stent insertion can be accomplished using fluoroscopic guidance alone.[140]

In a report[136] on clinical experience over a 10-year period with 307 Gianturco metal stents placed via the flexible bronchoscope in 162 patients (144 primary lung tumors, 18 secondary malignancy), the average survival following stent insertion was less for primary lung cancer than for secondary disease (103 days vs 431 days, $p < 0.001$). In a study[141] of 22 patients with severe malignant strictures, 34 airway stents were implanted as a temporary measure before patients received irradiation or chemotherapy. Significant improvements of dyspnea and partial oxygen pressure were observed; and in 50% of patients, the stents were removed after successful tumor-specific therapy.[141] In another study,[77] among 34 patients with inoperable malignant airway stenosis, covered metallic stents were implanted on emergency basis in 19 patients (56%) because of life-threatening airway obstruction. Immediate relief of dyspnea was achieved in 82% of the patients, and significant improvements were observed in airway diameter, vital capacity, and peak expiratory flow.[77]

All silicone stents require rigid bronchoscopy for their insertion, manipulation, and removal,[142–144] whereas metal stents can be inserted with the aid of flexible bronchoscopy and/or fluoroscopic guidance. Frequently, multiple stents and multiple procedures will be necessary to maintain a satisfactory airway.[73] Complications from silicone stents include migration of stent and inspissations of thick mucus within the stent lumen. Metallic stents are more likely to promote growth of granulation tissue.

Surgery: Surgical resection of malignant tracheobronchial tumors should be considered when unusual types of malignant tumors are encountered. The types of tumors that are amenable to resection and anastomosis include carcinoid, cylindroma, and mucoepidermoid tumors. The length of involvement of trachea or major bronchus

should be short enough for the surgeon to resect the tumor so that the anastomotic site is free of malignant cells. Malignancy involving the main carina is usually deemed advanced and thus unresectable. Such patients, if symptomatic, benefit from the bronchoscopic techniques described above. In recent years, surgical resection and reconstruction of the main carina is being performed in patients who can tolerate surgery.[145–147]

Recommendations

12. For all lung cancer patients who complain of dyspnea, it is recommended that they be evaluated for potentially correctable causes, such as localized obstruction of a major airway, a large pleural effusion, pulmonary emboli, or an exacerbation of coexisting COPD or congestive heart failure. If one of these problems is identified, treatment with appropriate methods is recommended. Grade of recommendation, 1C

13. For all lung cancer patients whose dyspnea does not have a treatable cause, opioids are recommended. Also recommended are other pharmacologic approaches such as oxygen, bronchodilators, and corticosteroids. Grade of recommendation, 1C

14. For all lung cancer patients with dyspnea, it is recommended that nonpharmacologic and noninterventional treatments be considered, such as patient and family education, breathing control, activity pacing, relaxation techniques, fans, and psychosocial support. Grade of recommendation, 2C

Palliation of Cough

Cough is a frequent and distressing symptom in patients with lung cancer. Cough can be dry or associated with sputum production. Involvement of any part of the respiratory system can lead to cough. Among the initial symptoms of lung cancer, cough is present in $> 65\%$ and productive cough in $> 25\%$ of patients.[148] Cough can be the presenting or leading symptom of lung cancer. It is more likely among patients with lung cancer originating in the airways. As in the treatment of dyspnea, the principal cause of the cough needs to be identified and treated appropriately (such as pleural involvement by the tumor, and infection). Other factors can contribute, such as esophageal reflux, coexisting COPD, or congestive heart failure, and should be addressed.[7]

Even if complete cessation of cough is not possible, significant control of cough may help patients enjoy cough-free periods. In late stage cancer when no specific therapy can address the cancer itself, control of bothersome cough becomes a problem. The following commentary is a brief summary of methods available to manage cough in the setting of lung cancer; a more detailed review was recently published as part of the American College of Chest Physicians evidence-based clinical practice guidelines for cough.[7]

Pharmacologic Agents

Cough Suppressants: Nonopioid cough suppressants may work in a small group of patients with advanced lung cancer. Occasionally, even opioid-resistant cough may respond to agents such as the peripherally acting nonopioid drug benzonatate.[149]

Bronchodilators: Bronchospasm can cause or contribute to cough. If the patient with lung cancer also has underlying bronchospastic obstructive airways disease, then standard bronchodilator therapy may help alleviate the cough.

One study[150] tested the role of inhaled sodium cromoglycate in 20 patients with NSCLC and cough resistant to conventional treatment. The patients were randomized to receive, in a double-blind trial, inhaled sodium cromoglycate or placebo. The results showed that inhaled sodium cromoglycate reduced cough in all patients with NSCLC.

Opioids: Opioids are the best cough suppressants in patients with lung cancer. Codeine is the most widely used opioid for cough suppression. In advanced stages of lung cancer, standard nonopioid cough suppressants may not control the cough. Intractable or troublesome cough should be treated with opioid agents. Caution should be exercised in prescribing graduated doses of these drugs because of the risk of respiratory depression and hypoventilation.

A double-blind RCT[151] regarding the treatment of nonproductive cough was performed in 140 adults with primary lung cancer or metastatic cancer of the lungs. The therapeutic efficacy and the tolerability of a 7-day treatment with levodropropizine drops (75 mg tid) were evaluated in comparison with dihydrocodeine drops (10 mg tid). Efficacy was assessed on the basis of cough severity scores, number of night awakenings due to cough, and overall estimate of antitussive efficacy. Tolerability was evaluated by laboratory results, vital signs, and any adverse event occurring during the clinical trial, including the presence or absence of somnolence. Subjective cough severity was significantly reduced during treatment with levodropropizine and dihydrocodeine, the antitussive effect, and its time profile being similar for both drugs. Also, according to the investigator's evaluation, both levodropropizine and

dihydrocodeine produced a significant decrease in cough severity. Concurrently with the relief of cough, the number of night awakenings was decreased significantly by both drugs, with no difference between the two treatments. No change in laboratory test values was considered clinically relevant, and vital signs were not clinically affected. The number of patients reporting adverse events was similar in the levodropropizine (n = 6) and dihydrocodeine (n = 4) group. However, the percentage of patients with somnolence in the group receiving levodropropizine (8%) was significantly lower as compared with that of the dihydrocodeine group (22%). These results confirm the antitussive effectiveness of levodropropizine and suggest a more favorable benefit/risk profile when compared to dihydrocodeine.[151] However, levodropropizine is not available for use in the United States.

Corticosteroids: There are no studies on steroids specifically for cough in lung cancer. If cough is caused by radiation-induced lung problems, then high-dose corticosteroid therapy may relieve a significant degree of cough.

Lidocaine: There are no studies on the role of inhaled lidocaine on cough in patients with lung cancer.

Chemotherapy: Newer agents such as gemcitabine and cisplatin-based chemotherapy have been studied with regard to their specific effects on cough frequency and severity among patients with NSCLC. Gemcitabine reduces cough in 44% of subjects so treated, and moderate or severe cough was improved in 73%.[152,153] Treatment of SCLC patients with chemotherapy is reported to improve cough in 7 to 80%.[154–156]

Nonpharmacologic Treatment of Cough

Surgery: No systematic studies have addressed the effect of surgical resection of NSCLC on the specific symptom of cough, but clinical experience suggests that cough will improve when the cancer is resected. Palliative ipsilateral high intrathoracic vagotomy immediately below the origin of the recurrent laryngeal nerve was reported in a small case series[157] to improve cough when an exploratory thoracotomy was done but the cancer was not resectable.

Radiation Therapy: Two RCTs in the United Kingdom were designed to assess the effect of different external-beam radiation programs on specific symptoms, including cough.[158,159] The first study[158] was a comparison of a two-dose schedule (8.5 Gy each) to longer conventional external-beam multifractionated treatment; and the second study[159] was a comparison of two 8.5-Gy fractions to a single 10-Gy fraction. Relief of cough occurred in 48 to 95% of patients treated with one or another of these schedules.

Endobronchial Treatment Methods: Laser and electrocautery methods of endobronchial treatment are usually offered for the purpose of palliating dyspnea or hemoptysis. However, various series[91,111–113,116,122,160,161] that have reported on cough have noted improvement in 51 to 90% of patients. All such reports are case series; there are no RCTs that have specifically analyzed cough as an outcome variable for such methods of palliating symptoms. Brachytherapy is the one endobronchial treatment modality that specifically includes a mention of cough palliation.[106,111–113,116,122]

Recommendations

15. For all lung cancer patients who have troublesome cough, it is recommended that they be evaluated for treatable causes. Grade of recommendation, 1B

16. For all lung cancer patients who have troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough. Grade of recommendation, 1B

Palliation of Bone Metastases

Metastatic lung cancer to bone is a manifestation of stage IV disease; thus, cure essentially is not possible, and care for the patient will be palliative in nature. Elimination or reduction of pain is the primary goal of treatment. There are no randomized prospective studies that directly compare radiation to pharmacotherapy for the management of pain due to bony metastases. If a metastasis occurs in a weight-bearing bone, prophylactic surgical stabilization should be considered before a pathologic fracture occurs.

Pain caused by bone metastases has multiple causes. Periosteal inflammation and elevation is the most common mechanism behind the pain from bone metastases. Lung cancer metastases to bone are predominantly lytic. After controlling pain with pharmacologic methods, treatment should be directed at managing the inflammation. External-beam radiation should therefore be considered as the initial nonpharmacologic method. This technique uses energy to diminish the local inflammatory response and thereby eliminates the source of the pain. Other nonpharmacologic methods to manage pain

from bone metastases include radioactive isotope infusion, supportive measures for pain management, and direct local management (such as surgery and nerve blocks).

A majority of patients with symptomatic bone metastases obtain some pain relief with a low-dose, brief course of palliative radiation therapy. One half of the responding patients may experience complete pain relief.[162] For short-term improvement in bone pain, 8 Gy in a single fraction is as effective as higher doses.[158,159] Single-fraction radiotherapy is less expensive than multiple-fraction radiotherapy, and it is more convenient from the patient's perspective. A systematic review and metaanalysis[163] of 11 randomized trials involving 3,435 patients treated with single-fraction radiotherapy vs multiple fraction radiotherapy was conducted in 2005. Although the trials included patients with painful bony metastases from multiple primary sites, the majority were from prostate, breast, and lung cancers. Lung cancers compromised 19.9% of the total. The overall response for relief of pain was 60% for patients treated with a single fraction, and 59% for patients treated with multiple fractions. Complete pain relief was accomplished in 34% of patients treated with a single fraction vs 32% for those treated with multiple fractions (odds ratio [OR], 1.11; 95% confidence interval [CI], 0.94 to 1.30). Although a single dose of radiation is effective, the duration of pain relief is less than with higher fractionated doses of radiation therapy. Retreatment was needed in 21.5% vs 7.4% for patients treated with multiple fractions (OR, 3.44; 95% CI, 2.67 to 4.43).[163] The pathologic fracture rate was 3% among patients treated with a single fraction, compared to 1.6% for those treated with multiple fractions (OR, 1.82; 95% CI, 1.06 to 3.11). If large fields are required, local inflammation and edema may be a problem with a high single dose. A high single dose is appropriate for small extremity fields, provided internal organs are not included, and for patients whose expected survival is only a few months.

Bisphosphonates have assumed an important role in the treatment of patients with bone metastases, especially since the introduction of zoledronic acid. Bisphosphonates prevent bone resorption at sites of bone remodeling. In three large randomized phase III trials[164] with $>$ 3,000 patients, 4 mg of zoledronic acid administered during a 15-min infusion was found to be a very effective treatment for bone metastases in patients with lung cancer, prostate cancer, and other solid tumors. Zoledronic acid is generally well tolerated, but it can be associated with increases in serum creatinine that require monitoring of renal function.[164] Zoledronic acid has also been shown to prevent skeletal related events (pathologic fractures, spinal cord compression, hypercalcemia, or pain requiring surgery).[165] In a multicenter RCT comparing zoledronic acid to placebo, there were 378 patients with NSCLC among the 773 subjects with solid tumors that had metastasized to bones. The incidence of skeletal related events was significantly reduced among patients treated with zoledronic acid ($p = 0.039$).[166]

Adjunctive therapy with disodium pamidronate has demonstrated good therapeutic response by itself, but more importantly when it is used in combination with radiotherapy for bony metastases. Response rates of 92% were seen in a randomized study[167] with external-beam radiation and pamidronate, vs radiation alone (83%), pamidronate alone (85%), or pamidronate in combination with chemotherapy (87%).

IV radioisotope infusion can also be used to manage pain from bony metastases, and it is especially useful for patients with widespread bony metastases. In a systematic review, Bauman et al[168] identified six randomized phase III trials, two randomized phase II trials, and one randomized crossover trial of ^{89}Sr. Another three randomized phase III trials and two randomized phase II trials of ^{153}Sm were part of their review, as were additional randomized trials of rhenium, ^{117m}Sn, and ^{32}P. As is true for most issues regarding the palliative management of a specific problem, the study groups contained mixtures of primary organ sites of the cancers. In these studies, only 5 to 10% of the patients had primary lung cancer, with the majority of other patients having breast or prostate primary sites. In most of these studies, pain relief in existing sites of metastases was significantly longer for patients treated with radiopharmaceuticals. This led to the conclusion that single-agent radiopharmaceuticals (^{89}Sr and ^{153}Sm) should be considered as a possible option for the palliation of multiple sites of bone pain from metastatic cancer, when pain control with conventional analgesic regimens is unsatisfactory, and when activity on a bone scan of the painful lesions is demonstrated.[168]

Pathologic fractures may occur when lung cancer metastasizes to bones. Fracture of long bones significantly impairs functional status and quality of life. The femur is at special risk because of its role in weight bearing, and surgical intervention may be needed. Other bones that may require palliative surgical intervention include the tibia, hip (proximal femur plus acetabulum), vertebrae, and the humerus.

Prophylactic surgery is recommended for the following situations when long bones are involved: persistent or increasing local pain despite the completion of radiation therapy; a solitary well-defined lytic lesion circumferentially involving $>$ 50% of the

cortex; involvement of the proximal femur associated with a fracture of the lesser trochanter; and diffuse involvement of a long bone.[169] Contraindications to surgical treatment of metastatic disease to long bones include a survival expectancy < 4 weeks and a poor general condition that is an obstacle to a safe operation.[170]

No randomized, prospective, controlled trials have compared surgery alone, surgery plus radiation therapy, or radiation therapy alone for metastatic long bone disease. Generally, however, postoperative radiotherapy is recommended regardless of the type of surgical procedure chosen for bony metastases.[171] All series that have analyzed operative intervention have included metastatic bone disease from multiple primary organ sites, with breast cancer as the most common. Lung cancer usually is the second most common primary site in reported series. A retrospective study[170] of 60 patients compared adjuvant surgery plus radiation therapy (35 sites) to 29 sites that were treated with surgery alone. Univariate analysis revealed that combined therapy ($p = 0.02$) and prefracture functional status ($p = 0.04$) were the only predictors of patients achieving a good functional status after surgery. On multivariate analysis, only postoperative radiation therapy was significantly associated with attaining a good level of function after surgery ($p = 0.02$).[170]

Intramedullary nailing is generally regarded as the preferred operative approach to deal with metastatic long bone disease. Standard total joint arthroplasty of the proximal femur is very useful for pathologic fractures of the femoral head and neck and for intertrochanteric fractures that have metastases in the neck and head of the femur.[171] Operative intervention for metastatic fractures of long bones provides a good functional result in approximately 80 to 85% of patients; a good analgesic effect is accomplished in nearly all patients.

In summary, pain relief is complete after radiotherapy for bony metastases in only one-third of patients. An approach to the management of bony metastases that is multifactorial (radiotherapy, bisphosphonates, and radioisotopes) coupled with analgesics is recommended. Because such combination approaches are usually successful, older methods of treatment (calcitonin, percutaneous ethanol injection into metastatic lesions, and embolization of the bone tumor vasculature) have not been reported extensively in recent years.

Recommendations

17. For patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief. A single fraction of 8 Gy is as effective as higher fractionated doses of external radiation therapy for immediate relief of pain. Grade of recommendation, 1A

18. For patients with lung cancer who have pain due to bone metastases, higher fractionated doses of radiation therapy provide a longer duration of pain relief, less frequent need for retreatment, and fewer skeletal-related events than does a single fraction. Grade of recommendation, 1A

19. For patients with lung cancer who have painful bone metastases, bisphosphonates are recommended together with external radiation therapy for pain relief. Grade of recommendation, 1A

20. For patients with lung cancer who have painful bone metastases refractory to analgesics, radiation, and bisphosphonates, radiopharmaceuticals are recommended for pain relief. Grade of recommendation, 1B

21. In patients with lung cancer who have painful bone metastases to long and/or weight-bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status, surgical fixation is recommended to minimize the potential for a fracture. Intramedullary nailing is the preferred approach, especially for the femur or the humerus. Grade of recommendation, 1C

Palliation of Brain Metastases

Brain metastases are more common from lung cancer than from any other primary site. Brain metastases from NSCLC occur in approximately one third of patients.[172] They are the presenting clinical problem in 10% of SCLC patients at the time of diagnosis, and the reported cumulative incidence in SCLC at 2 years is > 50%.[173] If patients with brain metastases are not treated, neurologic deterioration occurs quickly.[174,175] Brain metastasis has generally been considered as one manifestation of the terminal stage of cancer. This view holds true in many cases. However, patients with limited numbers of metastatic lesions have a considerably longer survival, particularly when the systemic cancer is controlled. The methods available to treat patients with metastatic lung cancer to the brain include the following: (1) systemic glucocorticoids, used to ameliorate the brain edema that typically accompanies intracranial metastases; (2) whole-brain radiation therapy (WBRT); (3) surgical resection of the metastasis; (4) stereotactic

radiosurgery; (5) chemotherapy; and (6) a judicious combination of these treatments.

Corticosteroids: Systemic glucocorticoids are known to improve neurologic function only for a short time (maximum, 1 month).[176] Two thirds of patients will have improvement in neurologic signs and symptoms with the use of glucocorticoids.[177] Dexamethasone is the most commonly used glucocorticoid because it has minimal mineralocorticoid activity as compared with other steroids. Conventional dosing with dexamethasone for brain tumor edema is ≥ 16 mg/d.[178–180] When dexamethasone is used in these doses for > 1 month, serious side effects are common.[181] Two consecutive, randomized, double-blind, prospective, controlled trials of patients with brain metastases and Karnofsky scores ≤ 80 compared dexamethasone at 8 mg/d or dexamethasone at 4 mg/d to dexamethasone at 16 mg/d.[182] Lower doses of dexamethasone were equally effective for improvement in quality of life as compared with patients treated with 16 mg/d, with significantly fewer toxic side effects (cushingoid facies, peripheral edema, steroid-induced myopathy) than in the 16 mg/d group ($p < 0.03$). One other study[183] (nonrandomized and nonblinded) also reported on the effect of lower doses of dexamethasone; there were similar benefits from lower doses and fewer toxic side effects. In a small pilot study,[184] 12 patients with intracranial metastases were initially administered 24 mg of dexamethasone IV q6h for 48 h, and then randomized to receive either 4 mg dexamethasone po q6h for approximately 2 weeks during brain irradiation or no further dexamethasone during the radiotherapy. Withholding steroids during the radiotherapy did not result in pronounced deterioration of general performance status or neurologic function at the conclusion of treatment or in reduction in overall survival. A multiinstitutional, prospective trial is needed to perform adequate statistical evaluation of patients regarding the role of steroid therapy in managing intracranial metastases. Until such a study is done, the consensus of opinion holds that dexamethasone at 16 mg/d should be administered for 4 weeks, during the time of WBRT, and that it should then be rapidly tapered and discontinued.

WBRT: Because of the frequency with which brain metastases occur in patients with SCLC, prophylactic cranial irradiation (PCI) is routinely indicated in patients with limited-stage disease who achieve either a complete or a near-complete response in the thorax following combined radiation and chemotherapy. In seven RCTs[185,186] of PCI for SCLC patients, the survival advantage at 3 years was 5.4%, and brain metastases were reduced by 25.3% at 3 years in patients who had achieved a complete remission with chemotherapy. Quality of life data were not collected in any of these trials, but it is likely that there was some improvement in quality of life. When intracranial metastases are known to be present with small cell lung cancer, WBRT is again the primary method for palliating symptoms.

Patients with multiple intracranial metastases from NSCLC are generally treated with WBRT. Median survival with this approach is 3 to 7 months, depending on prognostic factors.[187] Oligometastatic disease (fewer than three metastases) may be treated with surgical resection or radiosurgery followed by WBRT. Four randomized controlled trials[188] have compared PCI with no PCI in NSCLC patients who were treated with the intent to cure. While PCI did reduce the incidence of brain metastases in three of these trials, none of them was associated with a survival advantage of PCI over no PCI.[188] There were no good quality of life data in any of the trials, and toxicity was poorly reported.

Surgical Resection of Brain Metastases: Currently, there are three treatment options available for patients with a known NSCLC and a solitary intracranial metastasis: surgical resection, external-beam WBRT, and stereotactic radiosurgery[189] (see chapter on "Special Treatment Issues") Most often, some combination of these methods of treatment is preferable. Almost all studies of patients with solitary intracranial metastases that have compared two or more methods of treatment have included patients with tumors from a variety of primary sites, not solely lung cancer. Lung cancer is almost always the most common primary site in these studies; SCLC is usually an exclusion criterion. Whereas data analyses are done on the group as a whole, it is reasonable to apply the conclusions to the subset of NSCLC patients with solitary intracranial metastases.

Two randomized, prospective, controlled trials[190,191] have demonstrated a better outcome for a combination of WBRT plus surgical resection of a solitary metastasis over WBRT alone. Surgery is appropriate for a solitary metastasis in patients with good functional status and a surgically accessible lesion. Median survival for the patients treated with combination therapy was significantly better in both studies as compared with WBRT alone. A third randomized trial[192] failed to show a survival benefit from surgery, but more patients with active systemic disease were included in this study. In one[191] of the two studies that showed a significant difference in median survival for the combined approach, the differences were most pronounced for patients with stable extracranial disease.

The rationale for adding WBRT to surgical resection in the setting of a solitary brain metastasis is based on the notion that micrometastases cannot

reliably be detected with current technology. A randomized, prospective, controlled trial[193] that compared postoperative WBRT plus surgical resection to surgery alone demonstrated that recurrence of tumor anywhere in the brain was less frequent in the WBRT group than in the observation group (18% vs 70%, $p < 0.001$). The time to any brain recurrence was also significantly longer in the WBRT group. Overall survival was not different between the two groups; thus, postoperative radiotherapy prevented death due to neurologic causes, but death due to systemic cancer was more frequent.

There are no significant differences among various conventional radiation therapy fractionation schemes (20 Gy in 5 fractions, 30 Gy in 10 fractions, 40 Gy in 20 fractions). A common dose of radiation therapy used is 30 Gy administered at 3 Gy per fraction in 10 fractions. A more protracted schedule is used for patients who have limited or no evidence of systemic disease, or those who have undergone resection of a single brain metastasis, because these patients have the potential for long-term survival or even cure.[194,195] Because of the potential side effects of WBRT in the long-term survivors, the role of WBRT also has been questioned because there has been no overall survival benefit when combined with other treatment modalities. However, the concept of omitting WBRT after focal therapy (*ie*, surgery or radiosurgery), in the hopes of decreasing the number of patients with cognitive decline after radiation therapy, leads to decreased control of intracranial metastases and is not associated with a survival advantage. Treatment with WBRT that uses 3 Gy daily fractionation is not associated with a substantial increase in the long-term risk of dementia.[196]

Stereotactic Radiosurgery: Stereotactic radiosurgery utilizes a stereotactic fixation system and noncoplanar convergent beams that create a very sharp peripheral dose fall-off along the edge of the target. Thus, the surrounding normal tissues are spared while the radiation kills the tumor cells; accordingly, a single large fraction of ionizing radiation can be administered, making this method of treatment an attractive alternative to treat lesions whether surgically accessible or not. Stereotactic radiosurgery is usually restricted to lesions < 3 cm in diameter. Larger lesions, particularly those in the posterior fossa, are a relative contraindication for radiosurgery. The most recent randomized study was to test the role of radiosurgery with or without WBRT.[197] Patients with one to three newly diagnosed brain metastases were randomly allocated either WBRT alone or WBRT followed by a stereotactic radiosurgery boost. There was a survival advantage in the WBRT and stereotactic radiosurgery group for patients with a single brain metastasis. In addition to the survival benefit for patients with a single brain metastasis, data from this study also showed improved performance in all patients with one to three brain metastases who had radiosurgery boost, with or without previous craniotomy and within reasonable size constraints. Thus, WBRT and stereotactic radiosurgery should also be considered for patients with two or three brain metastases.[197] Stereotactic radiosurgery is of special value for patients with a single surgically inaccessible lesion and for patients who are unable to tolerate surgery.

Sneed et al[198] found from a retrospective review that median survival did not differ for patients with brain metastases who were treated with stereotactic radiosurgery alone or stereotactic radiosurgery followed by WBRT (8.2 months vs 8.6 months). When WBRT was added to stereotactic radiosurgery, however, there was a reduction in progression of brain metastases. With the addition of WBRT, only 7% of patients needed salvage brain therapy as compared with 37% if stereotactic radiosurgery was administered by itself ($p < 0.00001$).

No randomized, prospective trials have compared stereotactic radiosurgery to surgery. Many studies[199–203] of stereotactic radiosurgery for patients with intracranial metastases have reported similar median survival times to surgery as reported by others. A retrospective study[204] has demonstrated equal local tumor control rates and equal neurologic death rates between surgery and stereotactic radiosurgery. A prospective but nonrandomized study[205] of patients with lung cancer (both SCLC and NSCLC) demonstrated significantly longer median survival for stereotactic radiosurgery plus WBRT over WBRT alone (10.6 months and 9.3 months vs 5.7 months, $p < 0.0001$). A randomized study[206] of WBRT alone vs WBRT plus stereotactic radiosurgery in patients with two to four intracranial metastases showed significantly improved local control with a trend toward increased survival for WBRT plus stereotactic radiosurgery. Stereotactic radiosurgery can be performed after brain recurrence in patients who previously have had WBRT, surgical excision of a metastasis, or both. Median survival in a case series of lung cancer patients whose brain metastases were treated with stereotactic radiosurgery alone was 13.9 months, 14.5 months for stereotactic radiosurgery plus WBRT, and 10 months for patients treated with stereotactic radiosurgery for recurrent brain metastases.[207]

It is thought that surgical resection is preferred when rapid relief of increased intracranial pressure is needed. The general trend is toward less invasive treatment but improved intracranial tumor control.

Although there has been no randomized study for direct comparison of the local tumor control using surgical resection or radiosurgery, many institutions use radiosurgery for oligometastatic (up to three to four) brain metastases without WBRT. This is because of the potential for long-term side effects of WBRT.

Chemotherapy: The notion that chemotherapeutic agents do not cross the blood-brain barrier is no longer thought to be true for patients with cancers metastatic to the brain, and evidence has indicated that chemotherapeutic agents that are active elsewhere also may be associated with a response of metastatic brain lesions.[208–210] Platinum-based doublet therapy has been reported to produce a 20 to 21% overall objective intracranial response.[211] Another study[212] that included a variety of platinum-based doublet chemotherapy treatment arms after WBRT reported a median survival for the chemotherapy arm of 58.1 weeks vs 19 weeks in the no-chemotherapy arm ($p < 0.001$). Temozolomide is able to cross the blood-brain barrier, and it has been studied as a monotherapeutic agent for treatment of brain metastases. In a study[213] of 134 patients with brain metastases, 82% of whom had lung cancer, response rates for temozolomide plus WBRT were 53% vs 33% for WBRT alone ($p = 0.039$). More data are needed from randomized, prospective trials of chemotherapy for brain metastases before firm recommendations can be made.

In summary, there are many different options for brain metastases based on prognostic factors developed by the Radiation Therapy Oncology Group.[214] Steroids only are recommended for hospice care; WBRT for multiple brain metastases for those with a poor prognosis; for patients with a limited number of metastases in a favorable prognostic group, surgical resection for symptomatic lesions or radiosurgery with or without WBRT can be offered. Newer chemotherapy agents are showing some promise in the treatment of patients with brain metastases from lung cancer.

Recommendations

22. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/d is recommended during the course of definitive therapy with a rapid taper and discontinuation within 6 weeks of completion of definitive therapy (either surgery or radiation therapy). Grade of recommendation, 1B

23. Patients with NSCLC and an isolated solitary brain metastasis should be considered for a curative resection of the lung primary tumor as long as a careful search for other distant metastases or mediastinal lymph nodes has been performed and results are negative. Grade of recommendation, 1C

24. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis should be undertaken (as well as resection of the primary tumor). Resection of the isolated solitary brain metastases should be followed by WBRT. Grade of recommendation, 1B

Palliation of Spinal Cord Compression

Spinal cord compression by epidural tumor is an important complication for many patients with lung cancer, with an estimated frequency of 5% based on autopsy data.[215] Spinal cord compression can be classified anatomically as intramedullary, leptomeningeal, and extradural. No studies focus on functional results of treating intramedullary or leptomeningeal compression of the spinal cord; paraplegia and death occur rapidly in almost all such cases, and treatment is merely supportive. Epidural spinal cord compression is defined as compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass. The minimum radiologic evidence for cord compression is indentation of the theca at the level of clinical features, which include any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction.

Early detection of epidural metastases with compression of the spinal cord and prompt treatment appears to favorably affect outcome. Back pain is usually present for weeks or months before the onset of neurologic dysfunction. Approximately 60% of cancer patients with the new onset of back pain but with a normal neurologic examination will have spinal metastases that can be detected by radiologic studies.[216] Because the consequences of cord compression are so severe (paraplegia with its attendant complications and altered functional status), sagittal T1-weighted MRI of the entire spine should be done initially in known lung cancer patients with the new onset of back pain. This is the most rapid and cost-effective means of diagnosing spinal cord compression; other studies such as plain films, bone scans, or CT myelograms should be bypassed because they delay the process of a definitive diagnosis.[217]

Corticosteroids: There is good evidence to support the use of high-dose dexamethasone (96 mg/d) for patients with malignant extradural spinal cord compression.[218] This recommendation was based on a systematic review of studies that compared high-

dose dexamethasone to no dexamethasone in malignant spinal cord compression treated with radiation therapy alone. In an RCT,[219] 81% of patients in the high-dose dexamethasone treatment arm who were ambulatory before treatment remained ambulatory after treatment, compared with 63% in the control arm. In patients who are paretic or paraplegic before treatment, there is a lesser likelihood that gait function will be regained, but the addition of dexamethasone appears to improve the probability of regaining the ability to ambulate. A review of the evidence in 2004 led to the conclusion that the optimal dose of dexamethasone was not known.[218]

Significant side effects occur in 11% of those who receive high-dose dexamethasone. High-dose dexamethasone is recommended, however, as an adjunct to radiation therapy and/or surgery to retain or restore ambulation after treatment. The amount of dexamethasone may need to be reduced in the setting of uncontrolled diabetes mellitus or other intolerance of higher-dose therapy.

Radiation Therapy: The evidence for radiation therapy for patients with spinal metastases but no epidural spinal cord compression is fair, and radiation therapy without surgery should be the first line of treatment for patients who are ambulatory and do not have compression of the spinal cord. A combination of high-dose steroids plus radiation should be administered for patients who are not paretic and who are ambulatory.[220]

In a systematic review[163] of three RCTs, 1.9% of 1,102 patients with bony spinal metastases treated with a single fraction of radiotherapy had spinal cord compression, vs 1.4% of 1,104 patients treated with multiple fractions ($p = 0.3$). Among the 739 patients with spinal metastases, cord compression was again not significantly different in the single-fraction groups (5.6%) vs the multiple-fraction groups (4%) [$p = 0.3$].[163] Stereotactic radiosurgery is a combination of stereotactic localization of the treatment site so that multiple radiation beams of equal intensity can deliver a high dose of radiation without exposing normal tissues to excessive doses. In the few centers where stereotactic approaches are utilized, one or two treatment sessions with 8 to 18 Gy are given.[221,222] Most lesions that do not compress the spinal cord can be managed with nonoperative aggressive treatment aimed at shrinking tumor size and halting growth of the tumor.[163]

Surgery: Until recently, surgical intervention was limited to specific indications that included spinal instability, progressive neurologic deterioration from bony collapse and compression, intractable pain, and failure of conservative treatment.[220] Posterior laminectomy alone was once the surgical intervention of choice, but it was associated with a high rate of spinal instability and inferior ambulatory outcomes compared with radiation therapy alone. An anterior approach to the vertebral body with removal of tumor, immediate circumferential decompression of the spine, and reconstruction with stabilization of the spine has the advantage of maintaining the structural integrity of the spine and removing the bulk of bony disease. Reconstruction (cement or prosthesis) is often needed.[223] In several case series,[224–226] a minimally invasive approach with vertebroplasty or kyphoplasty has been satisfactory, and this is most often done by interventional radiologists. Patchell et al[227] performed a randomized multi-institutional nonblinded study of patients with spinal cord compression caused by metastatic cancer that has led to a recent change in the approach to patients with metastatic epidural spinal cord compression. Surgery followed by radiation was compared to radiotherapy alone. Both treatment groups received radiotherapy in 10 3-Gy fractions. Using the ability to walk after treatment as the primary end point, 84% (42 of 50 patients) of the surgery group were ambulatory after treatment compared to 57% (29 of 51 patients) in the radiation group ($p = 0.001$) [OR, 6.2; 95% CI, 2.0 to 19.8]. In addition, the ability to ambulate was sustained for a longer period of time in the surgery group than the radiation group (122 days vs 13 days, $p = 0.003$), with additional benefits for the surgery group that included maintenance of continence, muscle strength, functional ability, survival time, reduction in the use of corticosteroids, and opioid requirements. Thus, patients with metastatic epidural spinal cord compression and generally good performance status should be treated with direct surgical decompression followed by radiation because this will allow most patients to remain ambulatory for the rest of their lives. Good performance status patients with metastatic epidural spinal cord compression who are treated only with radiation and no surgical decompression will become paraplegic for a substantial portion of the rest of their lives, and they will not live as long if surgical intervention is not done initially.[227] However, there are also patients who have symptomatic cord compression who are not going to be surgical candidates due to the extent of their other disease (such as performance status) relative to the extent of surgery required.

Recommendations

25. For cancer patients with lung cancer who have the new onset of back pain, sagittal T1-weighted MRI of the entire spine is recom-

mended for diagnostic purposes. Other diagnostic studies such as plain radiographs, bone scans, or CT myelograms are not recommended. Grade of recommendation, 1C

26. For patients with lung cancer and epidural spinal cord metastases who are not paretic and ambulatory, prompt treatment with high-dose dexamethasone and radiotherapy is recommended. Grade of recommendation, 1B

27. When there is symptomatic radiographically confirmed compression of the spinal cord, neurosurgical consultation must be sought and, if appropriate, surgery should be performed immediately and should then be followed by radiation for patients with metastatic epidural spinal cord compression and generally good performance status. Grade of recommendation, 1A

Hemoptysis

Hemoptysis (expectoration of blood) is the presenting symptom in 7 to 10% of lung cancer patients. Approximately 20% will have hemoptysis some time during their clinical course, with 3% having terminal massive hemoptysis.[2,4,6,228] In contrast to other respiratory symptoms, hemoptysis is usually interpreted as serious by patients.[229] Hemoptysis is more likely in malignant lesions involving the airways than in cancers located in the peripheral lung parenchyma. The mechanisms responsible for hemoptysis include growth of new blood vessels (neovascularization) in and around the neoplasm, exfoliation of surface tumor with exposure of underlying blood vessels, tumor necrosis, trauma from cough and iatrogenic procedures (such as bronchoscopy), and formation of airway-vascular fistula. Minor episodes of hemoptysis do not usually require bronchoscopic therapy. However, significant hemoptysis may call for interventional procedures including therapeutic bronchoscopy, bronchial or pulmonary angiography followed by therapeutic embolization, and surgery. For patients with significant hemoptysis caused by a surgically resectable tumor, surgical resection of the bleeding lobe or the entire lung may be appropriate.

Massive hemoptysis, which most commonly requires intervention, has a broad definition as expectoration of at least 200 mL of blood in 24 h. Massive hemoptysis due to lung cancer has a much poorer prognosis than hemoptysis of other etiologies. The mortality rate of massive hemoptysis may be as high as 59 to 100% in patients with bronchogenic carcinoma.[230] Surgery, a more definitive therapeutic modality, is not on the algorithm for intervention because most lung cancer patients with massive hemoptysis have advanced disease and are already nonsurgical candidates. When surgical therapy is deemed futile or not feasible, less-invasive forms of therapy are considered.

Treatment of significant or massive hemoptysis requires securing and maintaining an adequate airway and optimal oxygenation.[231–233] This usually necessitates endotracheal intubation, and a single-lumen cuffed endotracheal tube is generally more beneficial than a double-lumen endotracheal tube. Selective right or left mainstem intubation can be performed to protect the nonbleeding lung. Double-lumen endotracheal tubes are more difficult to place and position, have smaller lumens, and do not permit a therapeutic bronchoscope to be passed through each side of the tube. This makes it difficult to further control and/or suction the airways.[234] Since blood clot formation obstructing the airways is the most common cause of respiratory insufficiency from massive hemoptysis, it is essential to place an endotracheal tube with a larger diameter so that bronchoscopic suctioning and removal of large obstructing clots can be accomplished quickly.

Bronchoscopy is used for both diagnostic and therapeutic purposes in patients with massive hemoptysis.[235] Bronchoscopic visualization will provide the following information: anatomic site and side of bleeding, nature of the bleeding source, severity of bleeding, and therapeutic feasibility. When no direct source of bleeding is found, as in bleeding from a peripheral tumor, bronchoscopic management begins with tamponade of the segment by tightly inserting the tip of the bronchoscope into the bronchus, followed by bronchoscopic instillation of iced saline solution to constrict the blood vessels.[236,237] This alone may stop the bleeding in many patients. If the bleeding is brisk, instillation of vasoactive agents like epinephrine is unlikely to help. Bronchial blockade balloons can be used to tamponade the bronchus. It may be necessary to leave the balloons in place for 24 to 48 h to allow tamponade of hemoptysis.[238–242] A study[242] reported that of the 57 patients who had persistent endobronchial bleeding despite bronchoscopic wedging technique, cold saline solution lavage, and instillation of regional vasoconstrictors, bronchoscopy-guided topical hemostatic tamponade therapy using oxidized regenerated cellulose mesh immediately arrested hemoptysis in 56 of 57 patients (98%). All patients thus treated remained free of hemoptysis for the first 48 h.

If these measures are unsuccessful, consideration should be given to bronchial artery embolization to temporize the bleeding. Most reports[243–246] of bronchial artery embolization are limited by the few cases of lung cancer managed in almost all studies.

Bronchoscopically visualized lesions that are responsible for the bleeding can be treated with one of

the following techniques described above, namely Nd-YAG laser coagulation, electrocautery, or APC. Nd-YAG laser coagulation has shown a therapeutic response rate of 60%.[84,247] Electrocautery should produce similar results, but its use to control hemoptysis has thus far been anecdotal. APC has provided resolution of hemoptysis in 100% of patients with a 3-month follow-up.[99] Cryotherapy, PDT, and stent insertion have no role in the treatment of massive hemoptysis.

When bronchoscopy reveals that insignificant or nonmassive hemoptysis is caused by a bronchoscopically visible or invisible, unresectable lung cancer, external beam radiation should be the next consideration.[162] Bronchoscopic techniques should be available if bleeding increases or becomes massive.

Recommendation

28. For all lung cancer patients with large-volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as APC, Nd-YAG laser, and electrocautery. Grade of recommendation, 1C

Malignant Pleural Effusions

Malignant pleural effusions occur in 7 to 15% of lung cancer patients.[248–250] In the United States, > 156,000 new cases of malignant pleural effusion are estimated to occur each year, with lung and breast cancers responsible for 75% of them.[251] The discussion and recommendations in this section apply to malignant pleural effusion caused by lung cancer and cancers from other sites with the exception of malignant mesothelioma.

Dyspnea is the most common presenting symptom when a malignant pleural effusion is present, and > 50% of patients with malignant pleural effusion have dyspnea.[252] Other symptoms caused by malignant pleural effusion include orthopnea, cough, chest discomfort, and pain. The mechanism of dyspnea with pleural effusions is unclear. Mechanical factors influencing the chest wall, depression of the ipsilateral diaphragm, mediastinum and its contents, pleural space, and the lung itself all may contribute to the dyspnea.[8,251,253–258] Palliation of a malignant pleural effusion is to relieve dyspnea and respiratory distress. Removal and prevention of reaccumulation of malignant pleural effusion does not treat or cure the underlying malignancy. Complete success of palliation is dependent on the long-term relief of symptoms related to the malignant effusion, with absence of fluid reaccumulation on chest radiographs until death.[251]

It is essential to recognize that there are multiple causes of dyspnea in patients with lung cancer, and removal of the pleural fluid may or may not provide adequate relief of dyspnea. If the lung is trapped because of parenchymal or pleural disease, there will be minimal relief of dyspnea and the lung will not re-expand after thoracentesis. The steps in the diagnosis of malignant pleural effusion are discussed in another section. (See "Initial Diagnosis of Lung Cancer" chapter in this guideline.)

Once the presence of symptomatic pleural effusion is confirmed by clinical examination and appropriate imaging techniques, therapeutic thoracentesis should be performed in virtually all dyspneic patients with malignant pleural effusions to determine its effect on dyspnea, as well as the rate and degree of reaccumulation of pleural fluid.[251] If bilateral pleural effusions are present, the larger accumulation is drained first. In patients with massive effusions and resultant respiratory distress, immediate hospitalization for chest tube drainage is prudent. If the initial thoracentesis provides relief of dyspnea and the lung re-expands on a postprocedure chest radiograph, reaccumulation of fluid can be managed by one or more of the following techniques (Table 2): (1) intermittent therapeutic thoracentesis; (2) insertion of a chest tube to completely evacuate the pleural fluid; (3) chest tube drainage followed by chemical pleu-

Table 2—*Intrapleural Pleurodesis Agents and Their Reported Complete Response Rates*

Pleurodesis Agent	Success, %	Dose*
Talc (poudrage or slurry)	60–95	2.5 to 10 g
Tetracycline	45–70	500 mg, or 20 to 35 mg/kg†
Doxycycline	50–75	500 mg†
Bleomycin	54–70	15 to 240 U (usual, 1 U/kg)
Chemotherapy agents‡	35–100	Varied
Quinacrine (mepacrine)	65–86	500 mg†
Corynebacterium parvum	60–76	3.5 to 14 mg
Other chemical agents§	30–95	Varied
Pleural catheter	85–95	Drainage‖
Surgical pleurodesis	75–100	Thoracoscopy, thoracotomy

*Wide variation in dosages reported in publications.

†Sometimes in repeated doses.

‡Agents other than bleomycin have included doxorubicin, adriamycin, cisplatin, cytarabin, mitomycin C, 5-fluorouracil, etoposide, mitoxantrone, combined intrapleural, IV chemotherapy, and pulmonary irradiation, and others.

§Minocycline, fibrinolytic agents (streptokinase and urokinase), fibrinogen solution, saline solution, silver nitrate, iodoprovidone, interleukin-2, ß-interferon, tumor necrosis factor, methylprednisolone, collagen powder, batimastat (matrix metalloproteinase inhibitor).

‖Duration of drainage has varied from 2 days to 6 mo; pleuroperitoneal catheters have been left in place for prolonged periods.

rodesis; (4) long-term chest tube drainage; (5) pleuroperitoneal shunting; (6) surgical pleurodesis; or (7) systemic therapy. The American Thoracic Society and the British Thoracic Society have published guidelines on the management of malignant pleural effusion.[8,251]

Therapeutic Thoracentesis: Repeated thoracentesis using topical anesthetic may suffice in some patients. In such patients, if the need for repeated procedures is too frequent, discomfort and inconvenience may persuade the patient to seek more definitive therapy. Repeated thoracentesis also increases the risk of pneumothorax, loculated effusions, and empyema. Ultrasound-guided thoracentesis is reported to be safer and to reduce the risk of pneumothorax. The volume of fluid removed with the initial thoracentesis should be no more than 1 to 1.5 L, stopping earlier should the patient experience dyspnea, chest pain, or cough. Removal of larger amounts of pleural fluid may be associated with re-expansion pulmonary edema, particularly if there is coexisting endobronchial obstruction.[251] Interventional bronchoscopy to open the obstructed airway before the thoracentesis may minimize the risk of re-expansion pulmonary edema and help assess for the presence of a trapped lung at the time of the diagnostic or therapeutic thoracentesis.[259,260] Repeated therapeutic thoracentesis is an option for patients with poor performance status or with advanced disease, and a very short life expectancy.[8,251]

Chest Tube Drainage: If repeated thoracentesis is not an option, insertion of a chest tube to drain the pleural fluid can be considered. This procedure can be accomplished under topical anesthesia and mild IV sedation. After the pleural space is completely drained of fluid, and if fluid does not reaccumulate, then the tube can be removed. Currently, however, chest tube drainage is almost always followed by intrapleural instillation of a chemical agent to produce pleurodesis (see below). Since the recurrence rate at 1 month after fluid drainage alone is close to 100%, chest tube drainage without pleurodesis is not recommended.[8]

Long-term Indwelling Pleural Catheters: One of the options is to place a smaller tunneled long-term pleural drainage catheter to drain the fluid on a long-term basis.[261–267] This technique is effective in controlling recurrent and symptomatic malignant effusions in selected patents. After the placement of the catheter under fluoroscopic or CT guidance, the patient is instructed to drain the fluid from the collecting bag. In a randomized and controlled study,[268] long-term indwelling pleural catheter was compared with doxycycline pleurodesis via a standard intercostal tube. Spontaneous pleurodesis was observed in 42 of the 91 patients in the catheter group. A late failure rate (*ie*, accumulation of pleural fluid) of 13% was reported, compared with 21% for the doxycycline group. The complication rate was higher (14%) in the catheter group and included local cellulitis and tumor seeding of the catheter tract. A retrospective analysis[265] of 250 sequential tunneled long-term pleural drainage catheter insertions in 223 patients during a 3-year period observed complete symptom control in 39%, partial relief in 50% of the procedures, and no relief in 4%. Spontaneous pleurodesis occurred in 103 of the 240 successful procedures (43%). Catheters stayed in place for a median period of 56 days.[265]

Chemical Pleurodesis: This technique involves drainage of pleural fluid by chest tube followed by intrapleural instillation of a sclerosant. Various agents have been used to bring about pleurodesis (Table 2). The overall complete response rate to chemical pleurodesis is 64%.[251,269] Further analysis according to the type of agent used reveals that sclerosant agents as a group are associated with a 75% complete response rate. Antineoplastic agents are less often successful, with a reported complete response of 44%.[269,270] However, some reports[271,272] indicate a success rate $>90\%$ for antineoplastic agents such as bleomycin and the antiparasitic (antimalarial) drug quinacrine. Interferon α or β, biological response modifiers, have been administered intrapleurally to treat malignant pleural effusions, with reported success rates ranging from 21 to 100%.[270,273–276] Intrapleural corticosteroid has been used to delay reaccumulation of malignant pleural effusion. However, a double-blind, randomized, placebo-controlled trial[277] in 67 patients comparing methylprednisolone to saline solution showed that intrapleural methylprednisolone did not delay reaccumulation of symptomatic pleural effusion compared to placebo.

Tetracycline derivatives, quinacrine, silver nitrate, iodopovidone, and other talc preparations such as facial talc have been used to produce pleurodesis.[278] All chemical pleurodesis and intrapleural therapy agents that are available have common as well as their own unique complications and constraints for use, which should be reviewed before a specific agent is chosen. In a study[279] of 49 patients who were enrolled into a randomized study, malignant pleural effusion was initially drained by chest tube, and 25 patients received 5 g of talc diluted to a total volume of 50 mL with saline solution, 24 patients received 20 mL of 0.5% silver nitrate through the chest tube, and

the results indicated that silver nitrate is as effective as talc for producing a pleurodesis.

Talc Pleurodesis: Talc remains the most effective agent for pleurodesis. Asbestos-free talc is an inexpensive agent now commonly used to treat malignant pleural effusions. The two favored methods of intrapleural talc administration are talc poudrage and talc slurry. Talc poudrage is accomplished under thoracoscopic guidance, and the technique consists of complete pleural fluid drainage, complete collapse of the lung, followed by spraying talc (approximately 5 g) evenly over the pleural surfaces. A 24 to 32F chest tube is inserted for progressive suction and re-expansion of lung. Talc slurry is prepared by thoroughly mixing talc (5 g) with normal saline solution (50 to 250 mL). The slurry is instilled through the chest tube, which then is clamped for 1 h afterwards. This is followed by drainage of the pleural fluid, and the chest tube is removed when the 24-h tube drainage is $<$ 100 to 150 mL. Intrapleural topical anesthetic (lidocaine), systemic analgesia, and sedation are recommended before talc pleurodesis is performed.

An overall success rate (complete and partial response) for talc pleurodesis is $>$ 90% (range, 88 to 100%).[269,280–285] The Cochrane Database Systemic Review (metaanalysis)[286] of 36 RCTs with 1,499 subjects (1980 to June 2002) reported that compared to different sclerosants, talc was most efficacious for pleurodesis. The relative risk of death was 1.19 (95% CI, 0.08 to 1.77) for talc compared to bleomycin, tetracycline, mustine and tube drainage alone based on six studies of 186 subjects.[286] However, the risk of respiratory failure as a result of talc pleurodesis has been debated.[282,287–292] Also debated is the difference in results and complications following talc poudrage and talc slurry therapy. One prospective study[293] of video-assisted thoracoscopic talc poudrage was no better than talc slurry. Another prospective, randomized trial[294] also compared thoracoscopy with talc insufflation to thoracostomy and talc slurry in patients with malignant pleural effusions. The results showed no difference between patients with successful 30-day outcomes (78% vs 71%). This study also noted that both methods of talc delivery are similar in efficacy. However, respiratory failure was observed in 8% of patients who underwent thoracoscopy with talc insufflation, and in 4% of patients who received talc slurry, and accounting for six deaths and five deaths, respectively.[294] The etiology and incidence of respiratory complications from talc pleurodesis need further exploration.

Pleuroperitoneal Shunting: This is an alternative technique to manage malignant pleural effusions refractory to chemical pleurodesis.[294–300] It may also benefit patients with trapped lung, particularly those with lungs trapped by visceral pleural carcinomatosis.[300] All studies of pleuroperitoneal shunting are case series. The device consists of a valved chamber containing two unidirectional valves, with fenestrated pleural and peritoneal catheters attached at either end. The insertion of the shunt is facilitated by thoracoscopy or a minithoracotomy. The device is pressure activated but many patients with malignant pleural effusions lack the ability to actively utilize the pumping device, which must be pushed at least 100 times or so daily to overcome the positive peritoneal pressure. In a report[301] on 368 patients who were treated for malignant pleural effusions, 160 patients (44%) had a pleuroperitoneal shunt inserted. Follow-up in 88% of patients showed a median survival of 7.7 months. Shunt complications occurred in 21 patients (15%), and included shunt occlusion, skin erosion, infection, breakage of a shunt limb, and malignant seeding at the site of shunt insertion.[301] Some of the complications require revision or shunt removal. The presence of pleural infection, multiple pleural loculations, and inability to compress the pump chamber are contraindications to pleuroperitoneal shunting.

Intrapleural Fibrinolysis: In patients who have dyspnea due to multiloculated malignant effusions that are resistant to simple drainage, instillation of an intrapleural fibrinolytic agent has been recommended.[8,302,303] Reports have shown that instillation of intrapleural streptokinase or urokinase with multiloculated or septated malignant effusions, leads to increased pleural fluid drainage and radiographic improvement and palliation of symptoms. The published studies on the topic have included small numbers of patients. In one study,[302] 10 consecutive patients with malignant multiloculated pleural effusions were administered intrapleural streptokinase, 250,000 IU bid, after the standard chest tubes failed to drain the effusions. All 10 patients responded to between 500,000 and 1,500,000 IU of streptokinase, and radiographic improvement was seen in all. There were no hemorrhagic or allergic complications. One patient died of unrelated septicemia.[302]

Systemic Therapy: The treatment of choice for malignant effusions due to SCLC is systemic chemotherapy. Many patients will respond with resolution of pleural effusions and the associated dyspnea.[304] There is little role for administration of external radiation therapy to the pleural surfaces. If the malignant pleural effusion is caused by mediastinal lymphadenopathy as in lymphoma, mediastinal radiation may be useful.[305] Combined intrapleural and

IV chemotherapy, and pulmonary irradiation have been tried to treat malignant pleural effusion.[306]

Surgical Pleurodesis: Thoracoscopic drainage of pleural fluid followed by pleural decortication/abrasion and instillation of chemical agents is perhaps the most definitive invasive procedure to prevent reaccumulation of malignant pleural effusion. However, these procedures should be reserved for patients who have failed to respond to other forms of treatment.[283,307–315] In the comparison of thoracoscopic vs medical pleurodesis, the Cochrane Database Systemic Review (metaanalysis) of 36 randomized controlled trials with 1499 subjects (1980 to June 2002) reported that thoracoscopic pleurodesis was more effective. The relative risk of nonrecurrence of effusion is 1.19 (95% CI, 1.04 to 1.36) in favor of thoracoscopic pleurodesis compared with tube thoracostomy pleurodesis utilizing talc as the sclerosant based on two studies with 112 subjects.[286] Currently, thoracoscopic drainage of pleural fluid with talc poudrage is an effective and popular technique controlling malignant effusions with a success rate $> 90\%$.[314,316,317]

Palliation of Pleurodesis-Associated Complications

Pleurodesis is not innocuous, and the discussion above describes some of the complications associated with the procedure. The most commonly reported adverse effects are pain and fever.[269] Intrapleural instillation of sclerosing agents is associated with chest pain and discomfort in up to 40% of patients.[318,319] Preinstillation of lidocaine and premedication with analgesics and sedative should be considered to alleviate anxiety and pain associated with pleurodesis.[8]

Paramalignant Pleural Effusion: Paramalignant effusions are pleural effusions that are not the direct result of malignant involvement of the pleura but are still related to the primary tumor.[251] Common causes include postobstructive pneumonia complicated by parapneumonic effusion; chylothorax due to obstruction of the thoracic duct, pulmonary embolism and infarction, radiation therapy, and chemotherapy. In addition, patients with lung cancer may also have pleural effusions that are due to concurrent nonmalignant disorders (congestive heart failure, renal failure, hypoproteinemia). Definitive and palliative therapy should address the cause of the pleural effusion.

Recommendations

29. In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. Grade of recommendation, 1C

30. In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. Grade of recommendation, 1B

Palliation of SVC Obstruction

Obstruction of the SVC is usually caused by malignancies, the majority of which are due to lung cancer.[320] Typically, the lung cancer spreads by lymph node metastases into the right paratracheal or precarinal lymph nodes, although some cancers cause obstruction of the SVC by direct extension. Impending obstruction of the SVC may be identified by CT imaging before development of symptoms associated with SVC obstruction.[321] At the time of diagnosis, SVC obstruction is present in 10% of patients with SCLC and 1.7% of patients with NSCLC.[322]

While SVC obstruction may not be symptomatic, SVC syndrome develops in 10% of patients with right-sided malignant intrathoracic lung cancers.[323] SVC syndrome includes symptoms that may be severe and debilitating, including neck swelling, swelling of one or both arms, and swelling of the face and eyelids. Collateral veins of the neck and anterior chest wall become engorged, and dyspnea is often present. Headache from cerebral venous hypertension is common with SVC syndrome; hoarseness of the voice and cyanosis are less frequent. Typically, lifestyle is significantly impaired with SVC syndrome.

Obstruction of the SVC with SVC syndrome has historically been considered a medical emergency. Systemic corticosteroids are usually administered to relieve swelling associated with radiation therapy, although data to support the efficacy of steroids are missing.[320] A randomized trial is needed to discern the value of steroid therapy when radiation is administered. In the era when treatment for SVC syndrome was considered an emergency, SCLC patients were administered chemotherapy and NSCLC patients were administered external-beam radiation. Since the outcome of treatment is not related to the duration of symptoms, emergency treatment is no longer believed to be needed.[324,325]

As the need for emergent treatment is no longer considered mandatory, it is prudent to obtain a histologic diagnosis before treating patients with SVC syndrome. SCLC patients are managed well with chemotherapy.[326] After treatment with chemotherapy, objective and subjective responses of SVC syndrome are seen in 68% and 77% of SCLC patients, respectively.[327] Whereas chemotherapy for SCLC may improve the symptoms associated with

SVC syndrome, radiation therapy is usually a part of treating SCLC with SVC obstruction. Relief of SVC symptoms is nearly equal for SCLC patients treated with either chemotherapy (77%) or radiation therapy (78%) or both chemotherapy and radiation therapy (83%).[322] In one nonrandomized observational study,[18] patients with SCLC and SVC syndrome undergoing concurrent treatment with chemotherapy and radiation therapy had paradoxically improved 5-year survival (15 ± 7%) compared with SCLC patients without SVC syndrome (9 ± 2%; $p = 0.008$). Similarly, a metaanalysis[328] of SCLC patients with SVC obstruction showed a median survival of 16.1 months compared to 13.7 months for SCLC patients without SVC obstruction. Relapse of SVC syndrome after treatment for SCLC occurs in 17%.[322]

A histologic diagnosis is also needed for patients with NSCLC because the choice of appropriate antineoplastic drugs is different from the treatment of SCLC. Reported response rates for relief of SVC obstruction in NSCLC are 59% (chemotherapy), 63% (radiation therapy), and 31% for synchronous chemoradiation.[322] Relapses after treatment with chemotherapy and/or radiation therapy are seen in 19% of patients with NSCLC.[322]

Symptom relief from SVC syndrome is more rapidly achieved by stenting.[326] Headache may disappear immediately,[329] and swelling of the face and arms are reported to abate within 24 h and 72 h, respectively.[330,331] Overall response rates of 94 to 95% with stent insertion are reported from a variety of case series, with an 11% recurrence rate.[322] Multiple authors of case series[332–346] of stenting advocate for stents as the initial treatment of SVC syndrome because symptom relief is more rapid and there is a low incidence of complications. The need to place a stent soon after the onset of SVC syndrome is not clearly established, however, because chemotherapy and/or radiation therapy are almost always offered in the setting of symptomatic SVC obstruction. Stent placement also has been demonstrated to be effective in relieving symptoms in patients who fail to respond to radiation therapy.[344]

It is sometimes necessary to enlarge the vascular lumen by way of balloon angioplasty in order to properly place a stent. Occasionally it may not be possible to insert a stent because a tumor has grown directly into the SVC.[329] When thrombosis occurs as a complication of SVC syndrome, local thrombolytic therapy may be of value to re-establish patency and subsequently to allow insertion of a stent. The use of thrombolytics and anticoagulants after stenting patients with SVC obstruction is associated with an increased frequency of complications attributable to bleeding. The need for long-term anticoagulation has not been established.

Recommendations

31. In patients with SVC obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started. Grade of recommendation, 1C

32. In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended. Grade of recommendation, 1C

33. In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who fail to respond to chemotherapy or radiation therapy. Grade of recommendation, 1C

Palliation of Malignant Tracheoesophageal Fistula

Tracheoesophageal fistulas (TEFs) are uncommon complications of lung cancer. TEFs are more common with esophageal cancers than primary lung cancers. Because patients with TEF have repeated aspiration of food, gastric contents, and saliva into the lungs, they have cough, shortness of breath, and recurrent pneumonia with the potential for sepsis. These phenomena lead to a markedly reduced survival of 1 to 7 weeks. Patients frequently lose weight and become dehydrated because they cannot tolerate oral intake. Even with abstinence from eating and drinking most patients have difficulty with controlling their own secretions.

Curative resection of the involved tracheal-bronchial and/or esophageal segments in face of a malignancy is inappropriate; most such patients are near the end of their lives and palliation should be the primary treatment objective. Likewise, esophageal bypass procedures can be considered, but they have very high morbidity and mortality rates and are inappropriate as palliative tools in advanced lung cancer. The goals of therapy are to restore patency of the trachea, bronchi, and/or esophagus to prevent spillage of further material into the lung and ensure that the patient receives nutrition and fluid.

Double stenting of the tracheobronchial tree and the esophagus appears to be the procedure that yields the best overall results for symptomatic relief for patients with this condition. All reports are case series; there are no controlled trials that study any of these endoscopic treatment methods.

Clinical series have attempted either esophageal

or tracheobronchial stenting with mixed results. Most reports[347–351] with higher success rates use a double-stenting technique. If stents are not placed into both the esophagus and the trachea at the same operative setting, the tracheal stent should be placed first because an esophageal stent alone may compress the trachea and lead to respiratory distress or failure. The addition of percutaneous enterogastric tube placement can ensure proper nutrition and fluid management for patients with a TEF. Patients may be able to eat soft foods once double stenting is performed, but maintaining adequacy of fluid status and nutrition is often difficult.

Recommendation

35. For patients with malignant TEF or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. Grade of recommendation, 1C

Depression, Fatigue, and Other Symptoms

Lung cancer patients can have a variety of symptoms from the time of the diagnosis through the treatment and possible progression of their disease, and each needs to be addressed. Two studies in newly diagnosed patients revealed that fatigue, pain, loss of appetite, coughing, and insomnia were common.[28] A study[28] of patients with advanced disease admitted to a palliative medicine service revealed that they had a median of nine symptoms, with pain, dyspnea and anorexia being the most common. All of these symptoms can impact their quality of life and therefore need to be addressed. This is best done by gathering information about symptoms directly from the patient because family caregivers tend to rate the symptom distress as more severe than the patient, and physicians tend to underrate the severity.[28]

Depression is common and can be persistent in lung cancer patients. A study[352] of self-rated depression in 987 patients with inoperable lung cancer revealed that 33% had depression before entering a palliative medicine treatment trial, and it persisted in 50% of them. SCLC patients had a threefold-greater prevalence of depression. Functional impairment was the most important risk factor for depression.

The caregiver must guard against assuming that the patient receiving a diagnosis of lung cancer is in itself depressing, and therefore miss assessing the patient for depression.[353] Various screening tools can be used to identify patients in need of specific treatment. The Hospital Anxiety and Depression Scale is commonly used.[354] Clinicians sometimes feel that there is insufficient time for medications to improve the depression in a patient with advanced lung cancer who may have an abbreviated life span. However, randomized studies reveal an improvement of symptoms with antidepressants. Cognitive, behavioral and psychosocial interventions also show benefit.[355]

Fatigue is a common symptom among patients with lung cancer as well, particularly those with advanced disease.[356] One study[357] of 227 cancer patients and 98 control subjects reported that the prevalence of severe fatigue was 15% among patients with recently diagnosed breast cancer, 16% among patients with recently diagnosed prostate cancer, 50% among patients with inoperable NSCLC, and 78% among patients receiving specialist inpatient palliative care. Fatigue was significantly associated with the severity of psychological symptoms (anxiety and depression) and with the severity of pain and dyspnea.[357]

Fatigue and anemia commonly coexist and can be treated with RBC transfusions and/or erythropoietic agents, including epoetin alfa and darbepoetin. Studies[355] reveal that patients with hemoglobin ≤ 10 g/dL treated with either of these agents revealed an improvement in fatigue and quality of life.

Insomnia is common in many patients with a chronic illness, including lung cancer, and is associated with other symptoms that can decrease quality of life. Treatment includes modalities used for the treatment of chronic insomnia, including addressing symptoms that are disturbing the patient's sleep (*eg*, pain, dyspnea), instructing the patient in proper sleep hygiene and behavior modification techniques (*eg*, guided imagery, relaxation), and supplementing them with the periodic use of a hypnotic agent chosen to address the patient's insomnia complaint.

Anorexia cachexia syndrome is characterized by loss of appetite, weight loss, wasting of muscle mass and adipose tissue, anemia and asthenia. It is a common problem in advanced cancer and can impact quality of life and survival. Various pharmacologic treatments have been tried, including the use of megestrol acetate and cannabinoids.[355]

Recommendation

36. It is recommended that all patients with lung cancer be evaluated for the presence of depression and, if present, treated appropriately. Grade of recommendation, 1C

Conclusion

The majority of patients with lung cancer will have one or more symptoms or complications from met-

astatic disease. These symptoms will severely alter the patient's quality of life. It is important for clinicians who care for lung cancer patients to be familiar with these many different symptoms and complications of the disease, and to utilize the many available methods that are designed to palliate these problems and improve the patient's life quality.

Summary of Recommendations

1. All lung cancer patients and their families must be reassured that pain can be relieved safely and effectively. All patients should be questioned regularly about their pain, using the patient's self-report of pain and a simple rating scale as the primary source of assessment. Grade of recommendation, 1A

2. For all patients individualize medications that are used to control pain. Administer medications regularly and treat pain appropriately. Document the effectiveness of pain management at regular intervals during treatment. Grade of recommendation, 1A

3. For all patients with mild-to-moderate pain, manage the pain initially with acetaminophen or an NSAID, assuming there are no contraindications to their use. Use opioids when pain is more severe or when it increases. Grade of recommendation, 1B

4. For any patient, if it is anticipated that there will be a continuous need for opioid medication, meperidine is not recommended. It has a short duration of action, and its metabolite normeperidine is toxic and can cause CNS stimulation resulting in dysphoria, agitation, and seizures. Grade of recommendation, 1B

5. For patients whose pain is not controlled by pure analgesic medications, adjunctive medications such as tricyclic antidepressants, anticonvulsants, and neuroleptic agents will often augment the effects of pure analgesic medications. Grade of recommendation, 1C

6. For all patients, administer medications by mouth because of convenience and cost-effectiveness. In patients with lung cancer who cannot take pain medications by mouth, rectal and transdermal administration are recommended. Administration of analgesics by the IM route is not recommended because of pain, inconvenience, and unreliable absorption. Grade of recommendation, 1C

7. For all patients receiving opioids, because constipation is common, anticipate it, treat it prophylactically, and constantly monitor it. Grade of recommendation, 1B

8. Encourage all patients to remain active and to care for themselves whenever possible. Avoid prolonged immobilization whenever possible. Grade of recommendation, 1B

9. In patients who have pain associated with muscle tension and spasm, it is recommended that complimentary methods for pain relief such as cutaneous stimulation techniques (heat and cold applications), acupuncture, psychosocial methods of care, and pastoral care be incorporated into the pain-management plan, but not as a substitute for analgesics. Grade of recommendation, 1C

10. For patients with advanced lung cancer, provide palliative radiation therapy to control pain. Palliative chemotherapy to decrease pain and other symptoms is recommended even though the increase in survival may be only modest. Grade of recommendation, 1B

11. In patients with lung cancer who have pain unresponsive to standard methods of pain control, referral to a specialized pain clinic or palliative care consultant is recommended. Grade of recommendation, 1C

12. For all lung cancer patients who complain of dyspnea, it is recommended that they be evaluated for potentially correctable causes, such as localized obstruction of a major airway, a large pleural effusion, pulmonary emboli, or an exacerbation of coexisting COPD or congestive heart failure. If one of these problems is identified, treatment with appropriate methods is recommended. Grade of recommendation, 1C

13. For all lung cancer patients whose dyspnea does not have a treatable cause, opioids are recommended. Also recommended are other pharmacologic approaches such as oxygen, bronchodilators, and corticosteroids. Grade of recommendation, 1C

14. For all lung cancer patients with dyspnea, it is recommended that nonpharmacologic and noninterventional treatments be considered, such as patient and family education, breathing control, activity pacing, relaxation techniques, fans, and psychosocial support. Grade of recommendation, 2C

15. For all lung cancer patients who have troublesome cough, it is recommended that they be evaluated for treatable causes. Grade of recommendation, 1B

16. For all lung cancer patients who have troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough. Grade of recommendation, 1B

17. For patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief. A single fraction of 8 Gy is as effective as higher fractionated doses of external radiation therapy for immediate relief of pain. Grade of recommendation, 1A

18. For patients with lung cancer who have pain due to bone metastases, higher fractionated doses of radiation therapy provide a longer duration of pain relief, less frequent need for retreatment, and fewer skeletal-related events than does a single fraction. Grade of recommendation, 1A

19. For patients with lung cancer who have painful bone metastases bisphosphonates are recommended together with external radiation therapy for pain relief. Grade of recommendation, 1A

20. For patients with lung cancer who have painful bone metastases refractory to analgesics, radiation and bisphosphonates, radiopharmaceuticals are recommended for pain relief. Grade of recommendation, 1B

21. In patients with lung cancer who have painful bone metastases to long and/or weight-bearing bones and a solitary well-defined lytic lesion circumferentially involving > 50% of the cortex and an expected survival > 4 weeks with satisfactory health status, surgical fixation is recommended to minimize the potential for a fracture. Intramedullary nailing is the preferred approach, especially for the femur or the humerus. Grade of recommendation, 1C

22. In patients with lung cancer who have symptomatic brain metastases, dexamethasone, 16 mg/d, is recommended during the course of definitive therapy with a rapid taper and discontinuation within 6 weeks of completion of definitive therapy (either surgery or radiation therapy). Grade of recommendation, 1B

23. Patients with NSCLC and an isolated solitary brain metastasis should be considered for a curative resection of the lung primary tumor as long as a careful search for other distant metastases or mediastinal lymph nodes has been carried out and is negative. Grade of recommendation, 1C

24. In patients with no other sites of metastases and a synchronous resectable N0,1 primary NSCLC, resection or radiosurgical ablation of an isolated brain metastasis should be undertaken (as well as resection of the primary tumor). Resection of the isolated solitary brain metastases should be followed by WBRT. Grade of recommendation, 1B

25. For patients with lung cancer who have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended for diagnostic purposes. Other diagnostic studies such as plain radiographs, bone scans, or CT myelograms are not recommended. Grade of recommendation, 1C

26. For patients with lung cancer and epidural spinal cord metastases who are not paretic and ambulatory, prompt treatment with high-dose dexamethasone and radiotherapy is recommended. Grade of recommendation, 1B

27. When there is symptomatic radiographically confirmed compression of the spinal cord, neurosurgical consultation must be sought and, if appropriate, surgery should be performed immediately and followed by radiation for patients with metastatic epidural spinal cord compression and generally good performance status. Grade of recommendation, 1A

28. For all lung cancer patients with large-volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as APC, Nd-YAG laser, and electrocautery. Grade of recommendation, 1C

29. In lung cancer patients with symptomatic malignant pleural effusions, thoracentesis is recommended as the first drainage procedure for symptom relief. Grade of recommendation, 1C

30. In lung cancer patients with symptomatic pleural effusions that recur after thoracentesis, chest tube drainage and pleurodesis are recommended. Grade of recommendation, 1B

31. In patients with SVC obstruction from suspected lung cancer, definitive diagnosis

by histologic or cytologic methods is recommended before treatment is started. Grade of recommendation, 1C

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33. In patients with symptomatic SVC obstruction due to NSCLC, stent insertion and/or radiation therapy are recommended. Stents are also recommended for SCLC or NSCLC symptomatic patients with SVC obstruction who fail to respond to chemotherapy or radiation therapy. Grade of recommendation, 1C

35. For patients with a malignant TEF or bronchoesophageal fistula, stenting of esophagus, airway, or both should be considered for symptomatic relief. Attempts at curative resection or esophageal bypass of the involved airway and/or the esophagus are not recommended. Grade of recommendation, 1C

36. It is recommended that all patients with lung cancer be evaluated for the presence of depression and, if present, treated appropriately. Grade of recommendation, 1C

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