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DIAGNOSIS AND MANAGEMENT OF LUNG CANCER, 3RD ED: ACCP GUIDELINES

Symptom Management in Patients With Lung Cancer

Diagnosis and Management of Lung Cancer, 3rd ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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Background: **Many patients with lung cancer will develop symptoms related to their disease process or the treatment they are receiving. These symptoms can be as debilitating as the disease progression itself. To many physicians these problems can be the most difficult to manage.**
Methods: **A detailed review of the literature using strict methodologic review of article quality was used in the development of this article. MEDLINE literature reviews, in addition to Cochrane reviews and other databases, were used for this review. The resulting article lists were then reviewed by experts in each area for quality and finally interpreted for content.**
Results: **We have developed recommendations for the management of many of the symptom complexes that patients with lung cancer may experience: pain, dyspnea, airway obstruction, cough, bone metastasis, brain metastasis, spinal cord metastasis, superior vena cava syndrome, hemoptysis, tracheoesophageal fistula, pleural effusions, venous thromboembolic disease, depression, fatigue, anorexia, and insomnia. Some areas, such as dyspnea, are covered in considerable detail in previously created high-quality evidence-based guidelines and are identified as excellent sources of reference. The goal of this guideline is to provide the reader recommendations based on evidence supported by scientific study.**
Conclusions: **Improved understanding and recognition of cancer-related symptoms can improve management strategies, patient compliance, and quality of life for all patients with lung cancer.**
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Abbreviations: ACCP = American College of Chest Physicians; ATC = around the clock; EAPC = European Association for Palliative Care; EBRT = external beam radiotherapy; EORTC QLQ-C30 = European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire; FBT = fentanyl buccal tablet; INFS = intranasal fentanyl spray; LINAC = linear accelerator; MPE = malignant pleural effusion; NRS = numerical rating scale; NSAID = nonsteroidal anti-inflammatory drug; NSCLC = non-small cell lung cancer; OTFC = oral transmucosal fentanyl citrate; PICO = population, intervention, comparator, outcome; QOL = quality of life; RCT = randomized controlled trial; RDQ = Roland-Morris disability questionnaire; RTOG = Radiation Therapy Oncology Group; SBRT = stereotactic body radiotherapy; SCC = spinal cord compression; SCLC = small cell lung cancer; SIGN = Scottish Intercollegiate Guidelines Network; SRS = stereotactic radiosurgery; SVC = superior vena cava syndrome; TEF = tracheoesophageal fistula; TPC = tunneled pleural catheter; VAS = visual analog scale; WBRT = whole-brain radiation therapy; WHO = World Health Organization

Summary of Recommendations

Pain Control

2.13.1. In patients with lung cancer who experience chronic pain, it is suggested that thorough assessment of the patient and his or her pain should be performed (Grade 2C).

Remark: A patient-reported pain scale should be the principal tool to assess their pain.

Remark: Visual analog scales (VASs), numerical rating scales (NRSs) and verbal rating scales are also suggested tools for rating pain.

2.13.2. In patients with lung cancer who experience chronic pain, the use of the World Health

Organization (WHO) analgesic ladder to plan treatment is suggested (Grade 2C).

2.13.3. In patients with lung cancer who are being treated at all stages of the WHO analgesic ladder, it is recommended that acetaminophen and/or a nonsteroidal antiinflammatory drug (NSAID) be prescribed unless contraindicated (Grade 1A).

2.13.4. In lung cancer patients with chronic pain who are taking NSAIDs and who are at high risk of gastrointestinal bleeding it is recommended that they take either misoprostol 800 mcg/day, standard dose proton pump inhibitors, or double-dose histamine H2 antagonists (Grade 1A).

2.13.5. In patients with chronic neuropathic pain due to cancer, treatment with an anticonvulsant (eg, pregabalin, gabapentin or carbamazepine) or a tricyclic antidepressant (eg, amitriptyline or imipramine) is recommended (Grade 1A).

2.13.6. In patients with chronic pain due to lung cancer, the use of ketamine, lidocaine 5% plasters, and cannabinoids is not recommended (Grade 1A).

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2.13.7. In lung cancer patients with mild to moderate chronic pain (score 3-6 on a VAS or NRS), it is recommended that codeine or dihydrocodeine be added to acetaminophen and/or NSAID (Grade 1C).

2.13.8. In lung cancer patients with severe chronic pain, oral morphine is recommended as first-line treatment (Grade 1C).

2.13.9. In lung cancer patients with severe chronic pain, oxycodone or hydromorphone are recommended as alternatives when there are significant side effects or lack of efficacy with oral morphine (Grade 1A).

2.13.10. In lung cancer patients with severe chronic pain due who are able to swallow, transdermal fentanyl is not recommended for first-line use (Grade 1C).

2.13.11. In lung cancer patients with stable, severe, chronic cancer pain who have difficulty swallowing, nausea and vomiting, or other adverse effect from oral medications, transdermal fentanyl is recommended as an alternative to oral morphine (Grade 1B).

2.13.12. In lung cancer patients with severe chronic pain, it is suggested that the prescription of methadone as an alternative to oral morphine be confined to a specialist in palliative care units with experience in methadone prescription, because of difficulties with dose prediction, adjustment, and drug accumulation (Grade 2C).

2.13.13. In lung cancer patients with severe chronic cancer pain, treatment with systemic strong opioids is recommended (Grade 1C).

Remark: The oral route of administration is recommended on the grounds of convenience and cost.

2.13.14. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who cannot swallow or who suffer excessive nausea and vomiting, the parenteral, transcutaneous or transmucosal route of administration is recommended (Grade 1C).

2.13.15. In the management of pain in lung cancer patients unable to take oral opioids, it is suggested that the subcutaneous route to administer continuous infusion of strong opioids, is equally effective as the intravenous route (Grade 2C).

2.13.16. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids, dose titration using either immediate release or sustained release oral morphine is suggested (Grade 2B)**.**

Remark: The recommended starting dose is oral morphine 30 mg/24 h in patients not previously treated with opioids, and 60 mg/24 h in those already taking an opioid at step 2 of the WHO ladder. Where immediate release oral morphine is used, the four-hourly dose is used to treat episodes of uncontrolled pain and in this context may be used up to hourly. The total dose administered in 24 h is used to calculate ongoing opioid requirements. Where sustained release morphine is used, the total estimated daily dose is prescribed as once-daily or twice-daily oral morphine.

2.13.17. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who experience breakthrough pain, parenteral morphine or transmucosal fentanyl citrate are recommended (Grade 1B)**.**

Remark: Oral transmucosal fentanyl citrate, fentanyl buccal tablet and transnasal fentanyl spray are all effective formulations for breakthrough pain.

Remark: In patients with severe chronic cancer pain who experience a lack of effective analgesia, or uncontrollable side effects, or both, it is appropriate to switch to an alternative strong opioid, or route of administration, or both, though evidence of benefit from this approach is lacking.

Airway Obstruction

4.1.1. In lung cancer patients with inoperable disease and symptomatic airway obstruction, therapeutic bronchoscopy employing mechanical debridement, brachytherapy, tumor ablation or airway stent placement is recommended for improvement in dyspnea, cough, hemoptysis and overall quality of life (QOL) (Grade 1C)**.**

Symptom Management for Cough

5.4.1. In all lung cancer patients with troublesome cough, evaluation for other treatable causes of cough in addition to cancer-related etiologies is recommended (Grade 1C)**.**

5.4.2. In all lung cancer patients with troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough (Grade 1B)**.**

5.4.3. In all lung cancer patients with troublesome cough attributed to chemotherapy or radiation-induced pneumonitis, anti-inflammatory therapy with corticosteroids is recommended (Grade 1C)**.**

Remark: Macrolides can be considered as steroid-sparing agents.

Palliation of Bone Metastasis

6.7.1. In patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief (Grade 1A)**.**

Remark: A single fraction of 8 Gy is equally effective for immediate relief of pain and more cost-effective than higher fractionated doses of external radiation therapy.

6.7.2. In patients with lung cancer who have painful bone metastases, bisphosphonates are recommended in addition to external beam radiation therapy for pain relief (Grade 1A)**.**

6.7.3. 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 (Grade 1C)**.**

Remark: Intramedullary nailing is the preferred approach, especially for the femur or the humerus.

Remark: Radiotherapy should follow the orthopedic management 2-4 weeks later.

6.7.4. In patients with lung cancer who have vertebral compression fractures causing pain, vertebral augmentation procedures are recommended to reduce pain (Grade 1A)**.**

Palliation of Brain Metastasis

7.6.1. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/day is recommended during the course of definitive therapy with a rapid taper as allowed by neurologic symptoms (Grade 1B)**.**

7.6.2. In lung cancer patients with significant brain edema, neurologic symptoms, or large space occupying brain metastasis (> 3 cm), surgical resection is recommended if they are surgical candidates (Grade1B)**.**

7.6.3. In lung cancer patients with 1 to 3 brain metastases, stereotactic radiosurgery alone is the recommended initial therapy (Grade 1A)**.**

Remark: With a low burden of disease, the benefit gained by delaying whole brain radiation therapy outweighs the potential risk.

7.6.4. In patients with 5 or more brain metastases, whole brain radiation is the recommended therapy (Grade 1A)**.**

Palliation of Spinal Cord Compression

8.4.1. In patients with lung cancer that have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended (Grade 1C)**.**

8.4.2. In patients with lung cancer and epidural spinal cord metastases, who are not symptomatic, prompt treatment with high-dose dexamethasone and radiotherapy is recommended (Grade 1B)**.**

8.4.3. In lung cancer patients with symptomatic, radiographically confirmed epidural spinal cord compression and good performance status, it is recommended that neurosurgical consultation be sought and, if appropriate, surgery should be performed immediately and followed by radiation therapy (Grade 1B)**.**

Palliation of Superior Vena Cava Syndrome

9.1.1. In patients with superior vena cava (SVC) obstruction from suspected lung cancer, definitive diagnosis by histologic or cytologic methods is recommended before treatment is started (Grade 1C)**.**

9.1.2. In patients with symptomatic SVC obstruction due to small cell lung cancer (SCLC), chemotherapy is recommended (Grade 1C)**.**

9.1.3. In patients with symptomatic SVC obstruction due to non-small cell lung cancer (NSCLC), radiation therapy and /or stent insertion are recommended (Grade 1C)**.**

Remark: When using stenting for the management of SVC obstruction, consideration of necessary anticoagulation as it relates to future management of the patient must be considered.

9.1.4. In patients with SCLC or NSCLC with SVC obstruction who fail to respond to chemotherapy or radiation therapy, vascular stents are recommended (Grade 1C)**.**

Management of Hemoptysis

10.1.1. In all lung cancer patients with large volume hemoptysis, securing the airway with a single-lumen endotracheal tube is recommended. Bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as argon plasma coagulation, Nd:YAG laser, and electrocautery for visible central airway lesions (Grade 1C)**.**

10.1.2. In all lung cancer patients with non-large volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding. For visible central airway lesions, endobronchial management options are recommended. For distal or parenchymal lesions, external beam radiotherapy is recommended (Grade 1C)**.**

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

Management of Airway-Esophageal Fistulas

11.1.1 In patients with tracheoesophageal fistulas, double stenting of the esophagus and airway or esophageal stenting is recommended with self-expanding metallic stents (Grade 1B)**.**

Remark: When primary esophageal stenting is to be used, airway compromise must be considered prior to placing the stent. If a concern exists, an airway stent should be placed prior to esophageal stenting.

Management of Malignant Pleural Effusions

12.4.1. In patients with a symptomatic recurrent malignant pleural effusion (MPE) with documented re-expandable lung, tunneled pleural catheters or chemical pleurodesis are recommended (Grade 1C)**.**

Remark: In patients with a limited life span, serial thoracentesis can be considered.

12.4.2. In patients with a symptomatic recurrent MPE with lung trapping, tunneled catheters are recommended for symptomatic relief and improvement in QOL (Grade 1C)**.**

12.4.3. In lung cancer patients with a suspected MPE and in whom the diagnosis of stage IV disease is not confirmed, thoracoscopy is recommended instead of a tunneled catheter due to its diagnostic as well as therapeutic benefit (Grade 1C)**.**

12.4.4. In patients with a MPE, graded talc is the pleural sclerosant that is recommended due to its efficacy and safety profile (Grade 1C)**.**

12.4.5. In lung cancer patients with a malignant effusion, thoracoscopy with talc poudrage is recommended instead of talc slurry through a bedside chest tube for pleurodesis (if there are no contraindications to thoracoscopy) (Grade 1C).

Management of Depression, Fatigue, Anorexia, and Insomnia

14.1.1. In patients recently diagnosed with lung cancer, it is recommended that comprehensive biopsychosocial assessment be performed soon after the diagnosis is made and at key transition points (completion of treatment, disease progression, and new symptom onset) thereafter for the remainder of life (Grade 1C).

14.1.2. In lung cancer patients that identify psychologic and physical symptoms causing distress or interfering with their QOL, it is recommended that these symptoms are addressed by appropriately trained individuals (Grade 1C).

14.1.3. In lung cancer patients with depression, anxiety, excessive daytime sedation and fatigue, medications such as antidepressants, anxiolytics and psychostimulants are recommended to decrease the morbidity associated with these symptoms (Grade 1C).

14.1.4. In lung cancer patients with psychologic symptoms, a comprehensive symptom management plan is recommended. This should include non-pharmacologic interventions integrated with medication management, which may be offered as a single treatment modality (Grade 1C).

14.1.5. In lung cancer patients with insomnia, sedating antidepressants (which target both sleep and mood) are recommended over sedative-hypnotics (which only improve sleep) (Grade 1C).

14.1.6. In lung cancer patients with the subjective experience of breathlessness, interventions specifically designed to manage this symptom using psychologic coping and physical adaptation are recommended (Grade 1C).

Remark: Targeted interventions for breathlessness, more effectively decrease distress and improve satisfaction with care than usual care provided during medical follow-up office visits.

14.1.7. In lung cancer patients with psychologic distress, it is suggested that one of several psychologic interventions have demonstrated benefit (including psycho-education, deep breathing, progressive muscle relaxation, guided imagery, cognitive behavioral therapy and supportive psychotherapy) (Grade 2C).

Remark: There is limited evidence to support selection of one intervention over another based on characteristics of the target symptom, patient, or disease status.

Remark: We suggest that psychologic interventions to relieve distress are chosen based on patient preference, available skill-set of the health care team, and the available evidence from lung cancer studies.

14.1.8. It is suggested that educational programs responsible for preparing health care professionals to care for persons with cancer should include specific training in psychologic and physical symptom management of symptoms that are frequently associated with cancer diagnosis, treatment and survivorship (Grade 2C).

14.1.9. It is suggested that health care systems providing care to persons with cancer should develop and support integrated programs in psychologic and physical symptom management which are accessible to all (Grade 2C).

Symptoms of lung cancer are often the presentation of the disease. Once the appropriate radiographic images, laboratory testing, and pathologic specimens are collected, treatment will begin. The treatment of the cancer itself will not always relieve the symptoms that patients endure as part of their disease. This symptom control article of the third edition of the American College of Chest Physicians (ACCP) Lung Cancer Guidelines replaces the article entitled "Palliative Care" from the previous editions of the ACCP Lung Cancer Guidelines.[58] The most difficult aspect of managing patients with lung cancer can often be the symptoms that they experience. These symptoms can be due to the primary site of the cancer, due to metastatic disease, a result of the treatment they have received, or manifestations of their underlying comorbidities. Presenting symptoms, such as pain, cough, dyspnea, or hemoptysis, are often brought by the patient to the treating physician. Patients can have further complications, including those of brain, bone, or spinal cord metastasis or superior vena cava (SVC) syndrome. Constitutional symptoms, such as depression, cachexia, and insomnia, may not be addressed unless the treating physician recognizes them as a morbidity of the patient's disease. The development of tracheoesophageal fistulas (TEFs), airway stenosis, or radiation lung toxicity can develop throughout the treatment phase of cancer. Symptoms are part of the entire manifestation of lung cancer in patients; it

remains important, though, to not only identify the obvious symptoms but also recognize the less apparent symptoms to provide the best management for patients with lung cancer.

The recommendations in this article are derived from the best available evidence. Many of the data are derived from observational studies or systematic reviews of observational studies. The strength of the recommendation is reflective of the quality of the data. Because of the palliative nature of many of the interventions discussed in the article, randomized trials may not even be considered ethical. The authors of the article recognize the limitations of the data and have attempted to provide practical guidance for the readers that is informed by the best available evidence.

1.0 Methods

This article on symptom control consists of sections covering a broad range of topics. As such, many sections were written by multiple authors in several specialties. This article is not designed as an update to the previous editions of the ACCP Lung Cancer Guidelines but instead a new document using newer methodologic techniques. To consistently format the searches, we used the population, intervention, comparator, outcome (PICO) format. The list of questions generated previous to each search can be seen in Table S1. The process for selection of the writing team, drafting of the PICO questions, and the process of reviewing the literature is described in more detail by Lewis et al,[1] "Methodology for Development of Guidelines for Lung Cancer," in the ACCP Lung Cancer Guidelines.

The writing team searched Ovid MEDLINE, Google Scholar, CINAHL, PsycInfo, Cochrane, Embase, Web of Science, and review of references. Searches extended back more than 10 years in all reviews. Upon completion of the searches, we first performed a title review of those materials. This was followed by an abstract review, and then articles were selected for full text review by one of the article authors. MeSH terms and key words were searched with no limiters of language or article type, as we suspected many of the data were observational. Data were then abstracted and the text and recommendations written.

The data and recommendations were reviewed, discussed, revised, and approved at the ACCP Lung Cancer Guidelines panel meeting as described in detail in the methodology article of these guidelines.[1] The entire article, including the data, text, and recommendations, then underwent several additional layers of peer review and approval as described for the ACCP Lung Cancer Guidelines.[1]

2.0 Pain Control

Pain is common in patients with cancer and is the symptom most feared by them.[2] It can be defined various ways, but the definition used in the preparation of this section is that adopted by the Scottish Intercollegiate Guidelines Network (SIGN) in its 2008 guideline on control of pain in adults with cancer[3] and defined by the international association for the study of pain: "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[4]

The 2008 SIGN guideline on cancer pain in adults[4] is the single publication most influential on the preparation of this section. Its scope and detail are considerably greater than is possible to encompass within this section. Since its publication, there have been a number of well-conducted and highly relevant systematic reviews published. These include 17 systematic reviews commissioned by the European Association for Palliative Care (EAPC) as supporting evidence for its 2012 guidelines on opioids for cancer pain.[5] Together with accompanying articles, these reviews compose the entire July 2011 issue of the journal *Palliative Medicine*.

2.1 Assessment of Cancer Pain

A patient's experience of pain is multidimensional and is influenced by its physical causes and effects, its functional impact, and psychosocial and spiritual factors. A thorough assessment of the patient and his or her pain is an essential first step in pain management. For readers seeking an evidence-based and more detailed approach to the assessment of cancer pain, the SIGN guideline on cancer pain in adults is recommended.[3]

2.1.1 How Should Cancer Pain Be Assessed?: Pain is assessed by a combination of careful history taking and physical examination supplemented by the use of pain-assessment tools and targeted investigations as required. The assessment should yield a complete description of the cause, type, severity, and impact of the pain.

2.1.2 Who Should Assess Cancer Pain?: In general, health-care professionals underestimate the severity of a patient's pain, whereas family and caregivers tend to overestimate it. If a patient is able to communicate, then he or she should be the principal assessor of his or her pain.

2.1.3 Pain Assessment Tools: A variety of tools have been developed to assess pain. These produce inconsistent results when compared with one another.[6,7] As a consequence, the EAPC recommends standardization of pain-assessment tools to visual analog scales (VASs), numerical rating scales (NRSs), and verbal rating scales.[8] These tools have the advantage that they remain valid when assessing pain in the very elderly, the dying, and those with cognitive impairment.[9]

2.2. Management of Cancer Pain

2.2.1 The WHO Pain Ladder: In the mid-1980s the World Health Organization (WHO) campaigned for

a systematic approach to the relief of pain in patients with cancer, using the so-called analgesic ladder (Fig 1).[10] The WHO analgesic ladder has been adopted worldwide. The principles of the WHO cancer pain relief program are:

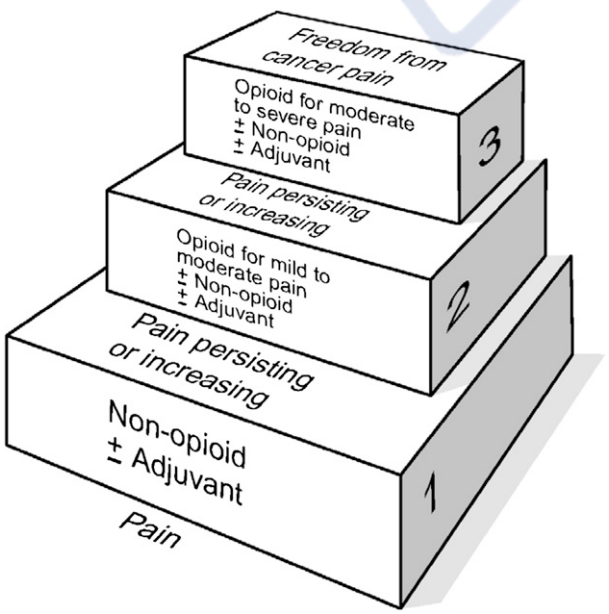
- A detailed assessment of pain severity and causes is required
- The patient is started on the appropriate step of the analgesic ladder, using medications given regularly, by mouth wherever possible
- Medications for breakthrough pain and constipation are prescribed
- Acetaminophen and/or nonsteroidal antiinflammatory drugs (NSAIDs) are used at all steps of the analgesic ladder
- Adjuvant drugs should be considered and the class of medication chosen according to the type of pain
- Morphine is the strong opioid of choice

The correspondence between pain scores as assessed by VASs and categorization into mild, moderate, and severe, as required by the WHO ladder, is summarized in Fig 2.[11,12]

Giving patients appropriate education about their pain, and a role in its management, has been shown to improve pain experience.[11] Multidisciplinary involvement in pain management is also beneficial.

The WHO pain ladder deliberately refers to drug classes rather than individual medications, in order to promote its applicability in differing health-care systems. One of its original purposes was to encourage the prescription of strong opioids, the use of which might otherwise have been limited by fears surrounding addiction and illegal use. Strong opioids used in palliative care include: morphine, diamorphine, buprenorphine, hydromorphone, fentanyl, oxycodone, and methadone.

Figure 1. [Section 2.2.1] World Health Organization analgesic ladder. (Reprinted with permission from World Health Organization.[10])



Although the ladder has been reported to lead to "good" pain relief in up to three-fourths of patients,[13] its use has generated controversy,[14] particularly over the role of weak opioids at step 2 of the ladder. Weak opioids used in palliative care of cancer pain include codeine and dihydrocodeine. There is no evidence to support or reject the recommendation of the WHO that weak opioids are preferred to NSAIDs.[15] Concerns exist that for patients with rapidly worsening pain, prescription of a weak opioid at step 2 may simply delay the start of adequate pain relief at step 3. Removing step 2 and proceeding directly to step 3 has been the subject of randomized controlled trials (RCTs).[16,17] It appears to be possible to proceed directly to strong opioid use, with reductions in the number of changes in drugs and doses and in pain scores in some patients but at the expense of a higher incidence of side effects. A recent systematic review performed to support the EAPC guidelines explored the evidence in this area and made a weak negative recommendation against a removal of step 2 in the WHO ladder.[18]

2.2.2 The WHO Pain Ladder in Practice: Effective use of the pain ladder starts with a complete patient assessment. Analgesia is prescribed according to pain severity, as detailed in Figures 2 and 3.The type of pain, and its cause, will determine whether any adjuvant analgesics are required—for example, anticonvulsants for neuropathic pain. Regular review of pain severity, response to treatment, and side effects is required to determine whether to move up or down the ladder. Regular analgesia around the clock (ATC) is essential for chronic cancer pain. In patients requiring strong opioids, the daily opioid requirement is adding the total dose of ATC and breakthrough opioid administered. The daily dose is usually administered as a long-acting preparation (for example, twice-daily slow-release morphine). A separate prescription is required for breakthrough pain. The dose of short-acting opioid prescribed for breakthrough pain is conventionally calculated as equivalent to one-sixth of the daily opioid requirement, and immediate-release morphine sulfate is commonly used for this purpose. For breakthrough pain, both the use of oral morphine and the use of the one-sixth rule for dosing are being increasingly challenged (see the section on breakthrough pain). No pain is predictably unresponsive to opioids, although the response in neuropathic pain may be incomplete.

FIGURE 2. [Section 2.2.1] Categorization of pain and appropriate analgesia.

WHO Analgesic Ladder Step	Score on Numerical Rating Scale (out of 10)	Analgesics of Choice
1 (mild pain)	<3	Paracetamol and NSAIDs
2 (mild to moderate pain)	3-6	Weak opioids (e.g. codeine or dihydrocodeine) plus Paracetamol and NSAIDs
3 (severe pain)	>6	Strong opioids (e.g. morphine, alfentanil, fentanyl, diamorphine, hydromorphone or oxycodone) plus Paracetamol and NSAIDs

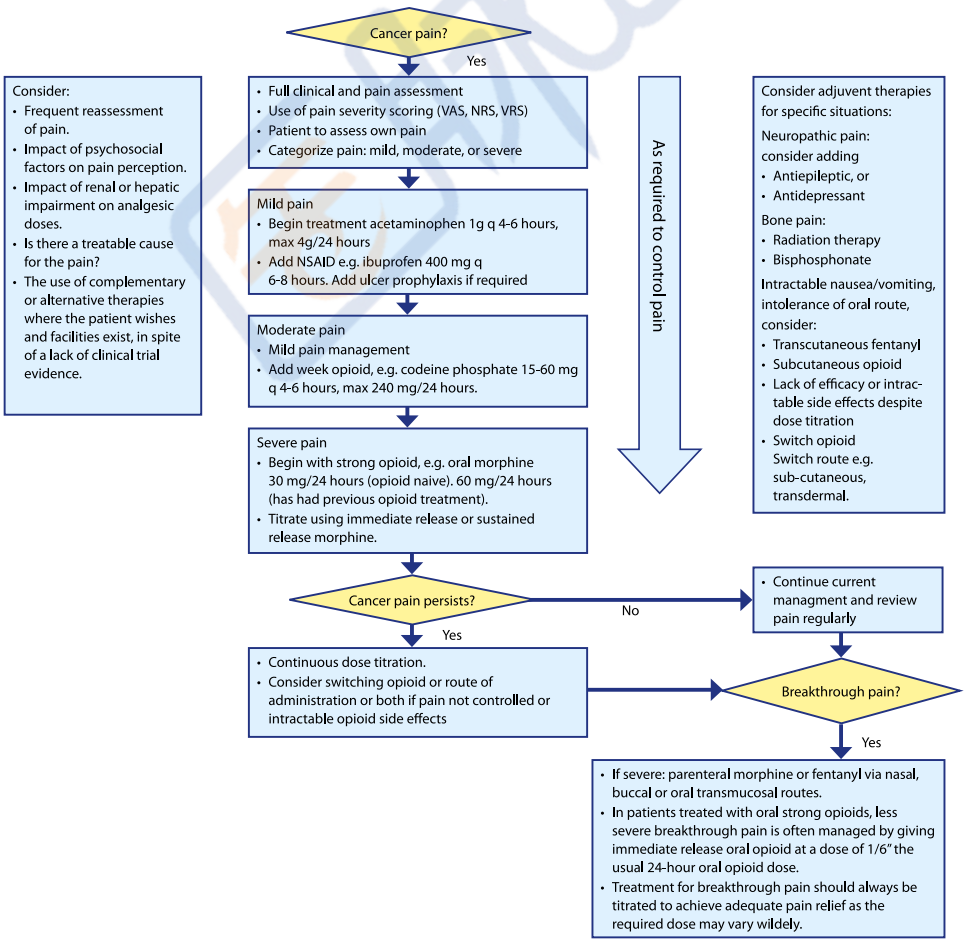
NSAID = non-steroidal anti-inflammatory drug; WHO = World Health Organization. (Reprinted with permission from the Scottish Intercollegiate Guidelines Network (SIGN).[12]

2.3 Nonopioid Medication

Nonopioid drugs can be used at all steps of the WHO pain ladder. They may act synergistically with opioids, reducing the required opioid dose and potentially the opioid side effects.

2.3.1 Acetaminophen and NSAIDs: NSAIDs are effective for cancer pain, and there is no clear evidence to prefer any one NSAID over another, either for efficacy or safety.[15] Combinations of NSAID plus an opioid offer a small but statistically significant superiority in efficacy compared with either agent alone, although the possibility that this effect could also be achieved by increasing the dose of either drug administered alone cannot be discounted. Patients receiving NSAIDs should be prescribed ulcer prophylaxis

FIGURE 3. [Section 2.2] Pain management algorithm created by guideline authors. NRS = numerical rating scale; NSAID = nonsteroidal antiinflammatory drug; VAS = visual analog scale; VRS = verbal rating scale.



in the form of misoprostol 800 μg/d, standard-dose proton pump inhibitors, or double-dose histamine H2 antagonists.[7,19] Acetaminophen was shown to be effective in improving cancer pain and well-being when added to the regimen of patients already receiving strong opioids in a single small RCT.[20]

2.3.2 Anticonvulsants: Anticonvulsants are used as adjuvants to opioids for the treatment of cancer pain, particularly if the pain is neuropathic in character. Three systematic reviews,[21-23] and one RCT published after these reviews,[24] provide evidence on which to base recommendations. The systematic reviews contained studies involving patients with chronic neuropathic pain of various causes and were not confined to patients with cancer. Carbamazepine, gabapentin, phenytoin, and pregabalin all appear more effective than placebo in reducing neuropathic pain. Serious side effects are no more common with these agents than with placebo, but minor side effects are very common. In an RCT, 120 patients with severe cancer-related neuropathic pain were randomized to treatment with placebo, pregabalin, amitriptyline, or gabapentin; patients treated with pregabalin had a significantly greater reduction in pain score when compared with each other group.[24] Lamotrigine is unlikely to be of benefit and is not recommended.[22]

2.3.3 Ketamine: Ketamine is an anesthetic agent used by pain relief specialists for the relief of pain resistant to conventional analgesics. It was the subject of a Cochrane systematic review in 2009.[25] This included two small RCTs totaling 30 patients, together with 32 case reports. There is insufficient evidence upon which to base a recommendation.

2.3.4 Lidocaine 5% Plaster: Topical lidocaine 5% plaster has been used to treat peripheral neuropathic pain of noncancer etiology. No RCTs were identified investigating its use in patients with cancer. A single retrospective case series was identified[26] in which 18 patients with cancer were treated with lidocaine plasters for neuropathic pain. The available evidence is not sufficient to permit any recommendation to be made.

2.3.5 Cannabinoids: Cannabinoids such as tetrahydrocannabinol have been studied for their use in noncancer and cancer pain. In an RCT of extracts of tetrahydrocannabinol, tetrahydrocannabinol plus cannabidiol, and placebo, 177 patients with cancer pain who experienced inadequate analgesia despite strong opioid administration were randomized. The combination of tetrahydrocannabinol/cannabidiol, but not tetrahydrocannabinol alone, achieved a significant reduction in pain NRS when compared with placebo. There was a statistically significant reduction in memory and concentration scores seen with tetrahydrocannabinol/cannabidiol compared with placebo. The evidence is not considered sufficiently strong to make a recommendation with respect to cannabinoids.[27]

2.4 Opioid Drugs

Opioid drugs are typically used at levels 2 and 3 of the WHO analgesic ladder. Weak opioids, such as codeine or dihydrocodeine, are used at level 2 and morphine or alternative strong opioids at level 3.

2.4.1 Mild to Moderate Pain (Step 2 of the WHO Ladder, Score 3-6 out of 10 on a VAS): 2.4.1.1 Choice of Opioid—Codeine or dihydrocodeine are appropriate analgesics to use at step 2 of the ladder.[7] There is evidence to support their addition to acetaminophen, an NSAID, or a combination of acetaminophen plus NSAID. There is no evidence to support the superiority of one weak opioid over another provided therapeutic doses are administered. There is insufficient evidence to make any recommendation concerning tramadol, which was the subject of a systematic review published in July 2011.[18]

2.4.2 Severe Pain (Step 3 of the WHO Ladder, Score 7-10 out of 10 on a VAS): 2.4.2.1 Choice of Opioid—Morphine, oxycodone, hydromorphone, methadone, fentanyl, and alfentanil are used in the United States for the treatment of severe cancer pain. There have been recent developments in the range of medications, their formulations, and their routes of administration, making the field more complex for the nonspecialist. Since patients are increasingly cared for in the community, and since strong opioids are powerful in their wanted and unwanted effects, the availability of clear guidance on opioid administration for health professionals is increasingly important.

2.4.2.2 Oral Morphine—Morphine remains the first-line opioid for oral use in severe cancer pain.[28] In their updated Cochrane review, Wiffen and McQuay[28] found that the RCT evidence for morphine was small, given its importance as a cancer medicine. Morphine appears effective in controlling cancer pain and has predictable side effects, including nausea, constipation, and drowsiness. Clinical trial evidence of the superiority of other strong opioids either in efficacy or side effects is lacking. Morphine given orally has poor and variable bioavailability, but dose titration permits an effective dose to be identified in most cases.

2.4.2.3 Oxycodone—The efficacy and tolerability of oral oxycodone are similar to those of oral morphine and hydromorphone,[29,30] with no difference in pain control or adverse effects noted in a well-conducted systematic review of high-quality evidence conducted in 2009.[30] Transdermal fentanyl patches provide controlled-release administration of fentanyl over 72 h.

In a well-conducted systematic review published in 2011, Tassinari and colleagues[17] found only low- or very low-quality trials investigating the first-line use of transdermal fentanyl and made a weak recommendation against its use in opioid-naive patients (black box warning).The side-effect profile of transdermal fentanyl differs from that of sustained-release oral morphine, with a difference in favor of transdermal fentanyl for constipation and urinary retention and in favor of sustained-release oral morphine for nausea, diarrhea, and sweating.[31] In a systematic review of 32 cohort studies performed in China, Yang and colleagues[32] found that constipation, nausea, vertigo/somnolence, and quality of life (QOL) were all improved in patients receiving transdermal fentanyl when compared with sustained-release oral morphine. This review did not, however, contain any blinded RCTs.

Transdermal fentanyl patches are not suitable for patients whose pain is unstable, because of their slow onset and very long duration of action. They may be considered in patients who cannot swallow or those with intractable nausea and vomiting.

2.4.2.4 Methadone—Two recent systematic reviews were found examining the role of oral methadone for the management of cancer pain.[33,34] No RCTs comparing methadone with placebo in cancer pain were found. The available evidence suggests that methadone is effective for cancer pain and may be equally effective to oral morphine for first-line use but that there is a propensity to sedation and drug accumulation unless there is close monitoring of the patient. A dose ratio of no less than 4:1 for morphine:methadone should be used. It is recommended that methadone is only prescribed by specialists in palliative medicine with experience in its use because of its unpredictable dosing and accumulation.

2.5 Routes of Administration for Opioids

Opioids are available for the treatment of cancer pain by a variety of routes, including oral, IV, subcutaneous, rectal, transdermal, sublingual/buccal, transnasal, epidural, intrathecal, and IM. The oral route is preferred for first-line use because of convenience and cost. Administration via parenteral, transdermal, or transmucosal routes is advantageous in patients who cannot swallow or have excessive nausea and vomiting. A systematic review carried out to inform the European Palliative Care Research Collaborative's opioid guidelines project considered evidence on differing routes of administration of opioids for cancer pain.[35] The IM route is not used in palliative care on comfort grounds. The greatest level of evidence was found for the subcutaneous route, with one systematic review and three RCTs being analyzed. There was no difference between subcutaneous and IV opioids in efficacy, safety, or side effects. Since the risk of complications is lower with subcutaneous administration, it is preferred.

Comparison between transdermal and subcutaneous or IV administration is complicated because the opioids used are usually different, so it is not only the route of administration that is being compared. Changes in dose via the transdermal route are slow to take effect, and this route is suitable only for patients with chronic pain that is stable.

Transnasal and buccal opioids are primarily indicated for breakthrough, not chronic, pain and are discussed separately. The evidence for spinal opioids in cancer pain is weak,[36] and it is not possible to make any recommendation concerning their use.

2.6 Titration of Strong Opioid Doses

Strong opioids are used at step 3 of the WHO ladder. It is conventional to introduce immediate-release morphine sulfate, given on a 4-h schedule, with the dose adjusted on the basis of regular pain assessments until adequate analgesia is achieved. The evidence for opioid titration schemes was reviewed in 2011 for the EAPC guidelines.[37] Only two RCTs were identified, one comparing IV vs immediate-release oral morphine and one comparing immediate-release with sustained-release oral morphine. The authors recommended that at step 3 of the WHO ladder, oral morphine 30 mg/24 h in divided doses is prescribed for opioid-naïve patients and oral morphine 60 mg/24 h for patients already prescribed weak opioids. There is no evidence supporting titration with immediate-release in preference to sustained-release morphine. There is no evidence upon which to base a recommendation on the frequency of dose adjustments during dose titration.

2.7 Breakthrough Pain

Breakthrough pain in cancer treatment has been defined as a transient flare of severe pain in the setting of chronic pain managed with opioid drugs.[38] It is common, being reported by two out of three patients surveyed,[38] and has a number of characteristics[39]:

- It usually is sudden, with a median interval from onset to peak intensity of 3 min (range, 1 s to 30 min)
- It is moderate to severe in severity
- It is of short duration (median, 30 min; range, 1-240 min)
- A precipitant, such as movement or end-of-dose failure, is identifiable in about two-thirds (62%) of episodes
- It is associated with more intense and more frequent background pain

- It is associated with greater functional impairment and worse mood and anxiety

Breakthrough pain is conventionally managed by prescribing as-required short-acting strong opioid in a dose equivalent to one-sixth of the daily ATC opioid dose. The ATC dose is then titrated by totaling the breakthrough doses administered in the preceding 24 h and adding all or a proportion of this dose to the ATC dose for the following day. The breakthrough dose is then increased in proportion. Immediate-release oral morphine has a time to peak effect of 20-30 min and a plasma elimination half-life of 2.2 h.[40] An ideal agent for treating breakthrough pain would have an onset and duration of effect similar to those of the pain itself, reaching peak effect after 1 to 2 min and lasting 30 to 60 min.

Various formulations of transmucosal fentanyl are available for the treatment of breakthrough pain. These include oral transmucosal fentanyl citrate (OTFC), fentanyl buccal tablet (FBT), and intranasal fentanyl spray (INFS). OTFC is a fentanyl-impregnated lozenge on a handle, which is applied to the buccal mucosa. As the lozenge dissolves, approximately 25% is absorbed through the mucosa, and a further 25% is absorbed via the GI tract after swallowing. FBT uses an effervescence reaction to promote the absorption of fentanyl transmucosally. Approximately 48% of the administered dose is absorbed via the buccal mucosa. INFS contains a phosphate-buffered solution of the drug that in pharmacokinetic studies has an approximate bioavailability of 90%. The time to maximum plasma concentration for each preparation is as follows: OTFC, 91 min; FBT, 47 min; INFS, 13 min.[41,42] RCTs of opioids as rescue medication were the subject of a well-conducted systematic review.[43] Eight studies were identified describing the use of transmucosal and parenteral opioids in the management of breakthrough cancer pain. Transmucosal fentanyl preparations appear safe, tolerable, and effective provided the dose is titrated to achieve adequate analgesia. Most studies found no relationship between ATC dose and the dose of rescue opioid, providing no support for the conventional approach described above. There was no evidence to support the superiority of one transmucosal fentanyl preparation over another.

2.8 Opioid Prescribing in Patients With Renal Impairment

Worsening renal function occurs frequently in patients with lung cancer requiring palliative care, owing to the effects of age, disease, treatment, or dehydration. Renal impairment increases the possibility of opioid toxicity. A recent systematic review was identified[44] that was carried out as part of the European Palliative Care Research Collaborative's opioid guidelines project. The review aimed to examine the evidence for the safe and effective use of opioids for the relief of cancer pain in patients with renal impairment. Fifteen clinical studies were identified, but no RCTs were included. The evidence was considered of very low quality. The direct clinical evidence from opioid prescribing for cancer pain in patients with renal impairment is insufficient to permit a recommendation to be made but does suggest that the risk profile is different for various opioids. From data on pharmacokinetics, extrapolation from studies in noncancer pain, and clinical experience, fentanyl, alfentanil, and methadone are identified, with caveats, as being the least likely to cause harm. If morphine is used, either increasing the dosing interval or reducing the total dose can minimize the side effects. The SIGN guidelines on cancer pain discuss opioid prescribing in renal impairment in more detail than can be provided here and are recommended for guidance on individual opioids in this situation.[7]

2.9 Switching Between Opioids

The term opioid switching is used to describe a change to a different opioid, with or without a changed route of administration, in order to try to overcome either a failure to achieve adequate analgesia, or intolerable side effects, or both. It should only be contemplated after adequate dose titration and attempts to address predictable side effects of the first-line opioid.

Four systematic reviews were identified.[45-48] The evidence quality is very low. There were no RCTs. Eleven uncontrolled studies describing outcomes in 280 patients[45] examined a variety of different opioids and routes of administration and often reported relatively low pre-switch opioid doses. Improvement in pain and reduction in side effects were reported in the majority of patients, but a lack of blinding and the possibility of publication bias limit the generalizability of the results.

In the absence of any good evidence, it is appropriate to consider switching opioids in a patient with uncontrolled pain and/or intolerable opioid side effects that persist after adequate dose titration and management of the initial side effects.

2.10 Management of Opioid-Induced Side Effects

The principal side effects of opioid use are constipation, nausea/vomiting, and drowsiness. Of these, constipation is the only side effect to which tolerance does not usually develop.

2.11 Nonpharmacologic Treatments

2.11.1 Complementary Therapies for Cancer Pain: Complementary therapies have increased in popularity for patients with cancer pain, but the evidence

for their benefit is weak or nonexistent. In general, patients report a positive experience, but any impact on pain or well-being is short lived.

2.11.2 Acupuncture: A 2011 Cochrane review considered the evidence for acupuncture as a treatment of cancer pain.[49] Three RCTs, including one of high quality, found positive results in favor of acupuncture when compared with placebo procedures or medication, but problems with blinding and other methodologic issues led the authors to conclude that no recommendation could be made.

2.11.3 Aromatherapy and Massage: A systematic review was identified examining the role of aromatherapy and massage in cancer pain.[50] There is evidence for a beneficial effect of massage on anxiety, although it is unclear whether aromatherapy has any additional effect. There is conflicting evidence for any impact of massage on physical symptoms, with three trials (117 participants) finding a reduction in pain. There is insufficient evidence upon which to base any recommendation.

2.11.4 Reflexology, Reiki, and Healing/Therapeutic Touch: Partner-administered reflexology reduced pain intensity in patients with cancer in an RCT (n = 86).[51] A systematic review of 66 studies investigating the role of so-called biofield therapies (Reiki, healing touch, therapeutic touch)[52] found moderate evidence for the reduction in pain intensity in patients with cancer. These studies suggest that touch therapies may have a role in treating cancer pain, and there is a need for further research.

2.11.5 Music: A Cochrane review of music for the treatment of all types of pain[53] contained only one English-language study examining its effect in cancer pain,[54] involving 15 patients. There is insufficient evidence upon which to base a recommendation.

2.11.6 Transcutaneous Electrical Nerve Stimulation and Transcutaneous Spinal Electroanalgesia: A Cochrane review of the evidence for transcutaneous electrical nerve stimulation for cancer pain found two RCTs meeting the eligibility criteria, involving 64 patients. Neither study found any evidence that transcutaneous electrical nerve stimulation is superior to placebo for treating cancer pain.

2.12 Summary

In conclusion, the appropriate tools for the assessment of pain should always be used. Understanding the WHO pain ladder and use of the SIGN guidelines are recommended tools for practitioners. Consultation with pain and palliative medicine specialists for more complex programs of pain management should be considered.

2.13 Recommendations

2.13.1. In patients with lung cancer who experience chronic pain, it is suggested that thorough assessment of the patient and his or her pain should be performed (Grade 2C).

Remark: Patient-reported pain scale should be the principal tool to assess their pain.

Remark: VASs, NRSs and verbal rating scales are also suggested tools for rating pain.

2.13.2. In patients with lung cancer who experience chronic pain, the use of the WHO analgesic ladder to plan treatment is suggested (Grade 2C).

2.13.3. In patients with lung cancer who are being treated at all stages of the WHO analgesic ladder, it is recommended that acetaminophen and/or a NSAID be prescribed unless contraindicated (Grade 1A).

2.13.4. In lung cancer patients with chronic pain who are taking NSAIDs and who are at high risk of gastrointestinal bleeding it is recommended that they take either misoprostol 800 mcg/day, standard dose proton pump inhibitors, or double-dose histamine H2 antagonists (Grade 1A).

2.13.5. In patients with chronic neuropathic pain due to cancer, treatment with an anticonvulsant (eg, pregabalin, gabapentin or carbamazepine) or a tricyclic antidepressant (eg, amitriptyline or imipramine) is recommended (Grade 1A).

2.13.6. In patients with chronic pain due to lung cancer, the use of ketamine, lidocaine 5% plasters, and cannabinoids is not recommended (Grade 1A).

2.13.7. In lung cancer patients with mild to moderate chronic pain (score 3-6 on a VAS or NRS), it is recommended that codeine or dihydrocodeine be added to acetaminophen and/or NSAID (Grade 1C).

2.13.8. In lung cancer patients with severe chronic pain, oral morphine is recommended as first-line treatment (Grade 1C).

2.13.9. In lung cancer patients with severe chronic pain, oxycodone or hydromorphone are recommended as alternatives when there are significant side effects or lack of efficacy with oral morphine (Grade 1A).

2.13.10. In lung cancer patients with severe chronic pain due who are able to swallow, transdermal fentanyl is not recommended for first-line use (Grade 1C).

2.13.11. In lung cancer patients with stable, severe, chronic cancer pain who have difficulty swallowing, nausea and vomiting, or other adverse effect from oral medications, transdermal fentanyl is recommended as an alternative to oral morphine (Grade 1B).

2.13.12. In lung cancer patients with severe chronic pain, it is suggested that the prescription of methadone as an alternative to oral morphine be confined to a specialist in palliative care units with experience in methadone prescription, because of difficulties with dose prediction, adjustment, and drug accumulation (Grade 2C).

2.13.13. In lung cancer patients with severe chronic cancer pain, treatment with systemic strong opioids is recommended (Grade 1C).

Remark: The oral route of administration is recommended on the grounds of convenience and cost.

2.13.14. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who cannot swallow or who suffer excessive nausea and vomiting, the parenteral, transcutaneous or transmucosal route of administration is recommended (Grade 1C).

2.13.15. In the management of pain in lung cancer patients unable to take oral opioids, it is suggested that the subcutaneous route to administer continuous infusion of strong opioids, is equally effective as the intravenous route (Grade 2C).

2.13.16. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids, dose titration using either immediate release or sustained release oral morphine is suggested (Grade 2B).

Remark: The recommended starting dose is oral morphine 30 mg/24 h in patients not previously treated with opioids, and 60 mg/24 h in those already taking an opioid at step 2 of the WHO ladder. Where immediate release oral morphine is used, the four-hourly dose is used to treat episodes of uncontrolled pain and in this context may be used up to hourly. The total dose administered in 24 h is used to calculate ongoing opioid requirements. Where sustained release morphine is used, the total estimated daily dose is prescribed as once-daily or twice-daily oral morphine.

2.13.17. In lung cancer patients with severe chronic cancer pain treated with systemic strong opioids who experience breakthrough pain, parenteral morphine or transmucosal fentanyl citrate are recommended (Grade 1B).

Remark: OTFC, FBT and transnasal fentanyl spray are all effective formulations for breakthrough pain.

Remark: In patients with severe chronic cancer pain who experience a lack of effective analgesia, or uncontrollable side effects, or both, it is appropriate to switch to an alternative strong opioid, or route of administration, or both, though evidence of benefit from this approach is lacking.

3.0 Dyspnea

The topic of dyspnea had been reviewed as part of the second edition of the ACCP Evidenced-Based Clinical Practice Guidelines 2007.[58] The methods of literature review with more comprehensive methodologic techniques identified three sources as excellent references on the topic of dyspnea management.

The first is the Vancouver Island Health Authority End of Life Symptom Guidelines of 2008.[55] The information was compiled using the CINAHL, MEDLINE (1996 to March 2006) and Cochrane Database of Systematic Reviews, American College of Physicians Journal Club, Database of Abstracts of Reviews of Effects (DARE), and the Cochrane Central Register of Controlled Trials (CCTR) databases, limiting to reviews/systematic reviews, clinical trials, case studies, and guidelines/protocols using respiratory terms in conjunction with palliative/hospice/end of life/dying.

The second reference is more specific to COPD, but the guidelines for the assessment and management recommendations for dyspnea are very strong.[56] The third is "an integrative review of systematic reviews related to the management of breathlessness in respiratory illnesses." Although not specific to lung cancer, this comprehensive review gives excellent information on the management of breathlessness.[57]

The symptom of breathlessness creates significant worsening to a patient's QOL. Dyspnea can also greatly impede patients receiving either chemotherapy or radiation therapy as part of the management of their disease. A comprehensive evaluation of treatable causes, including COPD, cardiac disease, airway obstruction, pleural disease, hematologic conditions, nutritional deficits, and neuromuscular conditions, must be addressed in a prompt and comprehensive fashion. The guidelines above outline several approaches to evaluating patients with dyspnea.

4.0 Management of Airway Obstruction

Patients with symptomatic central airway obstruction can benefit from therapeutic bronchoscopy using mechanical debridement, tumor ablation, or airway stent placement. Our search for evidence supporting this benefit included only studies that used validated questionnaires to assess improvement in symptoms or QOL. Please refer to Kvale and colleagues[58] for a more comprehensive review of therapeutic options.

Multiple prospective randomized trials of different dose/fractionation schedules have shown that thoracic palliative external beam radiotherapy (EBRT) can alleviate thoracic symptoms in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) who are not candidates for curative therapy. Studies suggest that higher dose/fractionation EBRT regimens (ie, 30 Gy/10 fraction equivalent or greater) are associated with modest improvements in survival and total symptom score, primarily in patients with good performance status. Please refer to Rodrigues and colleagues[59] for a more comprehensive review of therapeutic options. A recurring theme in this report[59] involves personalizing the radiotherapy dose to the individual patient's needs. As such, patients who have a poor performance status or extensive disease burden may benefit more from a shorter fractionation schedule (eg, 20 Gy in five fractions, 17 Gy in two weekly fractions, 10 Gy in one fraction).

In asymptomatic patients, there is currently no randomized or meta-analysis-based evidence to recommend endobronchial brachytherapy alone or in conjunction with other palliative therapies (eg, external radiotherapy, chemotherapy, bronchoscopy with laser) in the routine initial palliative management of endobronchial obstruction resulting from lung cancer.[59] In general, proximal airway obstruction is more amenable to endobronchial interventions, and distal obstruction (lobar or segmental bronchi) lends itself more to radiotherapy approaches. Two randomized trials assessed the palliative effect of endobronchial brachytherapy alone on patients with inoperable symptomatic airway obstruction in comparison with either EBRT alone or EBRT plus brachytherapy.[60,61] Improvement in dyspnea was found in the combined EBRT/brachytherapy arm only in one trial and lasted for 3 months. The other trial showed that either EBRT or brachytherapy produced good levels of symptom relief (cough, hemoptysis, and dyspnea) with EBRT performing better at the expense of more acute morbidity. The rate of fatal hemoptysis in both trials was alarmingly high and ranged between 7% and 15%.

Additional retrospective and prospective studies asked the same question about brachytherapy and found variable but consistently high degrees of improvement in dyspnea, cough, hemoptysis, obstructive pneumonia, and QOL.[62-66] The incidence of fatal hemoptysis and radiation-induced stenosis ranged from 1% to 11% and 0% to 11%, respectively.

Studies on ablative therapies in the airways for palliation purposes are scant. A study on bronchoscopic use of laser in the airways of 27 patients with malignant airways obstruction demonstrated an improvement in dyspnea, FVC, FEV_1, and Karnofsky performance status score, but only in patients with partial and not totally occluded airways, with two death occurring related to the procedure.[67] Photodynamic therapy, used in 133 patients with obstructive airway lesions, led to improvement in dyspnea in 74% of patients and in hemoptysis in 99% of patients.[68] The morbidity rate was 15%, with a 3% incidence of photosensitivity reaction. Similarly, endobronchial cryotherapy was used in a similar patient cohort and yielded less frequent improvement in dyspnea, cough, and hemoptysis (50%, 51%, and 21% of patients, respectively) but with no reported adverse events.[69]

Airway stents can reestablish luminal patency and provide symptomatic relief when airways are compromised by an extrinsic compression. Stents were the focus of seven retrospective and prospective studies evaluating a variety of airway stents, including metallic, silicone, and hybrid.[70-76] The studies demonstrated that airway stent placement improved dyspnea in 80% to 90% of patients, with an associated morbidity rate of 1% to 36%, including hemoptysis, stent migration, retention of secretions, tumor ingrowth or overgrowth, and granulation tissue formation.

Evidence on the palliative role of multimodality therapeutic bronchoscopy comes from two prospective studies with objective measures. The first study, by Oviatt et al,[77] evaluated 37 patients with malignant airway obstruction and demonstrated an increase in patients' 6-min walk test distance by 100 m, FEV_1 by 448 mL, and FVC by 416 mL at 30 days compared with baseline, as well as significant improvement in composite dyspnea and QOL scores. The rate of complications range from 3% to 8%, with one mortality related to asphyxiation due to an obstructed stent at 30 days postprocedure. A second smaller study evaluated 20 similar patients and demonstrated that therapeutic bronchoscopy led to improvement in dyspnea in 85% of participants, but only 65% of them had an improvement in QOL.[78] Figure 4 provides a schematic summary of the most appropriate interventional procedures for endoluminal, extrinsic, and mixed diseases of the airway.

4.1 Recommendation

4.1.1. In lung cancer patients with inoperable disease and symptomatic airway obstruction, therapeutic bronchoscopy employing mechanical

FIGURE 4. [Section 4.0] Interventional techniques for management of airway obstruction or hemoptysis in patients with lung cancer.

Tumor Location:	Endoluminal		Extrinsic	Mixed	
Clinical Problem	Airway Obstruc	Hemop-tysis	Airway Obstruc	Airway Obstruc	Hemop-tysis
Laser					
o Nd:YAG	+	+	-	+	+
o Nd:YAP	+	+	-	+	+
o Ho:YAG	+	+	-	+	+
o KTP	-	-	-	-	-
o CO2	-	-	-	-	-
Electrocautery	+	+	-	+	+
Argon Plasma Coagulation	+	+	-	+	+
Cryotherapy (contact)	+	+	-	+	+
Photodynamic Therapy	+/-	-	-	+/-	-
Brachytherapy	+	-	+	+	-
Mechanical Debridement	+	+	-	+	+
Rigid Bronchoscopy	+	+	+	+	+
Balloon Dilatation	+/-	-	+	+/-	-
Stenting	+	-	+	+	-

+, indicated; −, not indicated; ±, equivocal. Obstruc = obstruction. Airway obstruction may manifest as dyspnea, cough, wheeze, atelectasis, or collapse and can be as extreme as respiratory failure. In both airway obstruction and hemoptysis, airway security should be a priority and may require an invasive artificial airway or rigid bronchoscopy. This table reflects only airway obstruction due to malignant causes. Interventional bronchoscopy requires a multidisciplinary team and is based on the availability of the technology and the appropriate experience and skill of the operator. These procedures should only be performed at centers with experience. Ho:YAG = holmium yttrium-aluminum-garnet; KTP = potassium-titanyl-phosphate; Nd:YAP = neodymium-doped yttrium-aluminum-perovskite.

debridement, brachytherapy, tumor ablation or airway stent placement is recommended for improvement in dyspnea, cough, hemoptysis and overall QOL (Grade 1C)**.**

5.0 Palliation of Cough

Cough is a frequent symptom in patients with lung cancer and may arise from any part of the respiratory system. It can exacerbate dyspnea and lead to decreased QOL. Among the initial symptoms of lung cancer, cough is present in 25% to 84% and is productive in 25% of patients.[79,80] It is often underrecognized by health-care professionals, leaving the symptom unaddressed, and can profoundly impair QOL,[79] especially in long-term survivors.[81] Cough tends to cluster with and augment other symptoms, such as dyspnea and fatigue.[79,82,83] Unfortunately, there are only small studies and few high-quality data on its treatment.[84,85] Cough can be the presenting or leading symptom of lung cancer. It is more likely among patients with tumors involving the airways. Despite appropriate oncologic therapy, cough may continue to persist and remains distressing.[86] As in the patient without cancer, cough is often multifactorial. The underlying cause of cough needs to be identified and treated appropriately in conjunction with oncologic therapy, while minimizing toxicity or adverse events.[85,87,88] Cough can be directly related to malignancy (such as airway involvement, fistulous tract, postobstructive collapse, or pneumonia, lymphangitic disease, or pleural disease—solid or effusive), secondary to treatment of malignancy (infection secondary to superinfection or architectural disturbance, such as after radiofrequency ablation, chemotherapy-induced pneumonitis, radiation-induced pneumonitis, or postoperative), comorbidities (such as postnasal drip, esophageal reflux, coexisting COPD, or congestive heart failure), or active smoking. Although with limited data and clinical practice based upon mostly experience and preference for opioids, systematic reviews have resulted in a guideline suggesting a pyramidal approach to cough management.[89]

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 cough becomes a distressing problem.[58,90] The following is a brief summary of methods available to manage cough in the setting of lung cancer; a more detailed review was published as part of the ACCP evidence-based clinical practice guidelines for cough.[91]

5.1 Pharmacologic Agents

5.1.1 Nonopioid Cough Suppressants: Nonopioid cough suppressants may work in a small group of patients with advanced lung cancer. Opioid-resistant cough may respond to agents such as the peripherally acting nonopioid drug benzonatate.[92]

5.1.2 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. Clinical experience shows that bronchodilators may also help in the postinfectious phase plagued by prolonged cough due to bronchospasm and airway inflammation. With malignant airway involvement, clinical experience has shown that inhaled steroids can provide relief from cough. The role of inhaled sodium cromoglycate was studied in 20 patients with NSCLC and cough resistant to conventional treatment. The patients were randomized in a double-blind trial, and results showed that inhaled sodium cromoglycate reduced cough in all patients with NSCLC vs placebo.[93]

5.1.3 Antibiotics: Concurrent infections during the management of lung cancer should be addressed. These may include common bacteria, viruses, or opportunistic fungi and should be treated as indicated. There are no randomized studies looking at anti-infectives in the setting of lung cancer. However, infections with opportunistic fungi or *Pneumocystis* can occur and should be considered in the workup of cough, as these could be life threatening. Macrolides are known to serve as effective immunomodulators in chronic lung disease[94] and can be considered as steroid-sparing agents in inflammatory conditions, such as chemotherapy-induced or radiation-induced pneumonitis. This has not been studied in a randomized fashion in patients with lung cancer with or without treatment-related toxicities.

5.1.4 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.

Dextromethorphan has been shown to be more effective than codeine in controlling cough, including in patients with lung cancer.[95] Codeine has been shown to have an effective dose-response relationship.[96] Cough frequency in patients with advanced cancer is reduced with hydrocodone.[97] A double-blind RCT regarding the treatment of nonproductive cough was performed in 140 adults with primary lung cancer or metastatic cancer of the lungs. The therapeutic efficacy of levodropropizine drops (75 mg tid) vs dihydrocodeine drops (10 mg tid) was assessed on the basis of cough severity scores, number of night awakenings due to cough, and overall estimate of antitussive efficacy. Subjective cough severity and night awakenings were both significantly reduced during treatment with levodropropizine and dihydrocodeine, with no difference between the two treatments. However, somnolence in the levodropropizine group was significantly lower than that of the dihydrocodeine group (8% vs 22%). This suggests a more favorable risk/benefit profile for levodropropizine; however, it is not available for use in the United States.[98]

5.1.5 Corticosteroids: There are no studies on steroids specifically for cough in lung cancer. If cough is caused by malignant airway involvement or chemotherapy-induced or radiation-induced pneumonitis, then high-dose corticosteroid therapy may relieve a significant degree of cough. This is based upon clinical experience. Inhaled or nebulized steroids can also be effective. Macrolides, as immunomodulators, may serve as adjunctive or steroid-sparing therapy; however, this has not been studied in this population.[92]

5.1.6 Local Anesthetics: There are no studies on the role of inhaled lidocaine on cough in patients with lung cancer; there have been only case reports in patients without cancer. Benzonatate has been shown to control cough effectively in patients with lung cancer when opioids were ineffective.[92]

5.1.7 Chemotherapy: 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%.[98,99] Treatment of patients with small cell lung cancer (SCLC) with chemotherapy is reported to improve cough in 7% to 80%.[100-102] Patients with NSCLC who progressed on standard chemotherapy were treated with erlotinib vs placebo, with 44% of patients expressing improved cough based upon validated QOL measures.[103] Targeted therapy should be

considered in the appropriate patient. More detail on chemotherapy treatment can be found in the articles by Socinski et al[104] (stage IV NSCLC) and Jett et al[105] (SCLC) in these guidelines.

5.2 Nonpharmacologic Treatment of Cough

5.2.1 Smoking Cessation: Ongoing cigarette smoking may lead to ongoing cough, and smoking cessation should be a routine part of patient interactions. This may include counseling, behavioral therapy, or group sessions. Nicotine replacement should be considered in the appropriate patient. In an intention-to-treat analysis of the Lung Health Study participants, cough was significantly reduced in intermittent and sustained quitters over a 5-year period.[106] A population-based study in Japan showed that cough is less prevalent in former smokers as compared with current smokers.[107] A more detailed discussion and recommendations regarding smoking cessation and cough can be found in the article about tobacco dependence by Leone and colleagues[108] in the ACCP Lung Cancer Guidelines.

5.2.2 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. However, cough has been reported to persist for 1 year after pulmonary resection and lymph node dissection, with gastroesophageal reflux as a compounding cause.[109] QOL studies have noted cough to worsen for >5 years after surgical resection in 44% of patients.[81] Palliative ipsilateral high intrathoracic vagotomy immediately below the origin of the recurrent laryngeal nerve was reported in a small case series to improve cough when an exploratory thoracotomy was done but the cancer was not resectable.[110]

5.2.3 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. The first study was a comparison of a two-dose schedule (8.5 Gy each) to longer conventional external-beam multifractionated treatment,[111] and the second study 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.[112] In a study looking at stereotactic body radiotherapy (SBRT) for stage I NSCLC, QOL questionnaires showed no significant difference in cough up to 12 months after treatment.[113] However, others have shown a 54% improvement in cough with palliative radiation for NSCLC.[114] Alternatively, EBRT combined with endobronchial brachytherapy has been shown to relieve cough in 72% of 117 patients with endobronchial tumor and extrabronchial extension,[115] whereas endobronchial brachytherapy alone relieves cough in 77% of patients.[116]

5.3 Summary

Overall, there are limited data in a limited number of studies applying to patients with lung cancer with cough. Considerations must be made including cost, convenience, toxicity, and treatment interactions. QOL questionnaires can provide validated standardized tools to assess cough during and after treatment. An escalating or multimodality approach can be implemented depending on individual patient evaluation.

5.4 Recommendations

5.4.1. In all lung cancer patients with troublesome cough, evaluation for other treatable causes of cough, in addition to cancer-related etiologies is recommended (Grade 1C)**.**

5.4.2. In all lung cancer patients with troublesome cough without a treatable cause, it is recommended that opioids be used to suppress the cough (Grade 1B)**.**

5.4.3. In all lung cancer patients with troublesome cough attributed to chemotherapy or radiation-induced pneumonitis, anti-inflammatory therapy with corticosteroids is recommended (Grade 1C)**.**

Remark: Macrolides can be considered as steroid-sparing agents.

6.0 Palliation of Bone Metastases

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects. The presence of bone metastases represents stage IV disease; thus, cure essentially is not possible. Still, the end points defining palliative care can vary greatly. 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 several 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).

6.1 Radiation Therapy

A majority of patients with symptomatic bone metastases obtain some pain relief with a low-dose, brief course of palliative radiation therapy. Three meta-analyses have been performed comparing different radiotherapy fraction schemes. For short-term improvement in bone pain, a single fraction is as effective as multiple fractions.[117-119] Single-fraction radiotherapy is less expensive than multiple-fraction radiotherapy, and it is more convenient from the patient's perspective.

The findings of these meta-analyses were confirmed in a collection of studies that have shown comparable results between single-fraction radiotherapy and multiple-fraction radiotherapy[120-124]; Radiation Therapy Oncology Group (RTOG) 97-14[121] was the most prominent of these trials. In this trial, there were 455 patients who received 8 Gy in a single fraction and 443 patients who received 30 Gy in 10 fractions. This study did not include patients with lung cancer; all patients had either breast cancer or prostate cancer. The results can still be considered applicable to patients with lung cancer. Grade 2 to 4 acute toxicity was more frequent in the 30-Gy arm (17%) than in the 8-Gy arm (10%) (difference = 7%; 95% CI, 3-12; $P = .002$). Late toxicity was rare (4%) in both arms. The overall response rate was 66%. Complete and partial response rates were 15% and 50%, respectively, in the 8-Gy arm compared with 18% and 48% in the 30-Gy arm ($P = .6$). At 3 months, 33% of all patients no longer required narcotic medications. The incidence of subsequent pathologic fracture was 5% for the 8-Gy arm and 4% for the 30-Gy arm. The retreatment rate was statistically significantly higher in the 8-Gy arm (18%) than in the 30-Gy arm (9%) ($P < .001$). In a subsequent analysis of this trial,[125] a Markov model was used to evaluate the cost-effectiveness of 30 Gy in 10 fractions compared with 8 Gy in one fraction. The expected mean cost and quality-adjusted survival in months for patients receiving 8 Gy in one fraction and 30 Gy in 10 fractions was $998 and 7.2 months and $2,316 and 9.5 months, respectively. The incremental cost-effectiveness ratio was $6,973/quality-adjusted life year. The results were sensitive to the usefulness of the posttreatment state for both single- and multiple-fraction treatment. Thus, single-fraction treatment was the less expensive treatment in the treatment of patients with bone metastasis treated on this randomized trial.

6.2 Bisphosphonates

Bisphosphonates (pamidronate and zoledronic acid) have assumed an important role in the treatment of patients with bone metastases. Bisphosphonates prevent bone resorption at sites of bone remodeling. In three large randomized phase 3 trials with > 3,000 patients, 4 mg of zoledronic acid administered during a 15-min infusion was found to be a very effective treatment of 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.[126] Zoledronic acid has also been shown to prevent skeletal-related events (pathologic fractures, spinal cord compression [SCC], hypercalcemia, or pain requiring surgery).[127] In a multicenter RCT comparing zoledronic acid to placebo, there were 378 patients with NSCLC among the 773 subjects with solid tumors with bone metastasis. The incidence of skeletal-related events was significantly reduced among patients treated with zoledronic acid ($P = .039$).[128]

A randomized trial[129] was performed to compare the long-term (25 month) safety and efficacy of zoledronic acid with pamidronate in patients with bone lesions without lung cancer (advanced breast carcinoma or multiple myeloma). Patients (n = 1,648) were randomized to receive 4 mg or 8 mg (later reduced to 4 mg) zoledronic acid as a 15-min infusion or to receive 90 mg pamidronate as a 2-h infusion every 3 to 4 weeks for 24 months. After 25 months of follow-up, zoledronic acid reduced the overall proportion of patients with a skeletal-related event and reduced the skeletal morbidity rate similar to pamidronate. Compared with pamidronate, zoledronic acid (4 mg) reduced the overall risk of developing skeletal complications (including hypercalcemia) by an additional 16% ($P = .030$). Thus, zoledronic acid appears to have solidified its role in the management of bone metastasis.

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[130] identified six randomized phase 3 trials, two randomized phase 2 trials, and one randomized crossover trial of a strontium isotope (^{89}Sr). Another three randomized phase 3 trials and two randomized phase 2 trials of a samarium isotope (^{153}Sm) were part of their review, as were additional randomized trials of rhenium, Tin (^{117m}Sn), and phosphorus (^{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 cancer as primary sites. In most of these studies, pain relief in existing sites of metastases was significantly longer for patients treated with radiopharmaceuticals. The radioisotopes can have significant bone marrow suppression. Based on current evidence, no recommendation can be made regarding the use of these agents in the management of patients with lung cancer.

6.3 Surgery

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

Prophylactic surgery is recommended for the following situations when long bones are involved[131]:

- 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
- Diffuse involvement of a long bone

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.[132] No randomized, prospective, controlled trials have compared surgery alone, surgery plus radiation therapy, or radiation therapy alone for metastatic long bone disease. Postoperative radiotherapy is commonly recommended regardless of the surgical procedure for bony metastases.[133] 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 is usually the second most common primary site in reported series. A retrospective study[132] 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 ($P = .02$) and prefracture functional status ($P = .04$) 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 ($P = .02$).[132]

Intramedullary nailing is generally regarded as the preferred operative approach to address 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.[133] 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 the majority of patients. Radiotherapy should be performed 2 to 4 weeks following the orthopedic procedure. The typical schedule is 30 Gy in 10 fractions, although The British Association of Surgical Oncologists guidelines recommends 20 Gy in 5 fractions.[295]

6.4 Vertebral Fracture

The natural history of malignant vertebral compression fractures in the cancer setting is presumably different from those seen with osteoporotic fractures. Factors contributing to the poor outcome with conservative treatment in patients with cancer include continued bone loss due to tumor invasion, poor nutritional status, immobilization, prolonged steroid use, gonadal ablation, chemotherapy, and radiotherapy. Vertebral augmentation procedures have been shown by retrospective and prospective randomized studies to be effective in treating symptomatic vertebral compression fractures. Advantages of vertebral augmentation procedures include immediate pain relief, avoiding delays in chemoradiation, outpatient care in the majority of cases, biopsy of tissue, vertebral height restoration, and potential antitumor effect of bone cement. The Cancer Patient Fracture Evaluation study[134] was an RCT that enrolled patients who had cancer and one to three painful vertebral compression fractures. Patients (N = 134) were randomly assigned to kyphoplasty or nonsurgical management (control group). The primary end point was back-specific functional status measured by the Roland-Morris disability questionnaire (RDQ) score at 1 month. The mean RDQ score in the kyphoplasty group changed from 17.6 at baseline to 9.1 at 1 month (mean change, −8.3 points; 95% CI, −6.4 to −10.2; $P < .0001$). The mean score in the control group changed from 18.2 to 18.0 (mean change, 0.1 points; 95% CI, −0.8 to 1.0; $P = .83$). At 1 month, the kyphoplasty treatment effect for RDQ was −8.4 points (95% CI, −7.6 to −9.2; $P < .0001$). Currently, there is good evidence to recommend kyphoplasty in the management of painful vertebral compression fractures. The role, and the relationship/timing with palliative radiotherapy, needs to be further investigated.

6.5 Stereotactic Body Radiotherapy

SBRT has emerged as a new option in the multidisciplinary management of metastases located within

or adjacent (paraspinal) to vertebral bodies/spinal cord. SBRT provides an attractive option to deliver high dose per fraction radiation, and therefore a high biologic equivalent dose, typically in one to five fractions. The goal of SBRT for spinal metastases is to improve on existing rates of clinical response and tumor control and to reduce the retreatment rate by increasing the biologic equivalent dose. For previously irradiated spinal metastases, the focal nature of SBRT provides an otherwise unavailable noninvasive treatment option. Thus, the goals of spinal SBRT parallel those of brain radiosurgery.[135] Several nonrandomized studies have shown very promising results.[136-138] The RTOG is currently investigating a single fraction of SBRT for spinal metastasis (16 Gy) vs standard single-fraction radiotherapy (8 Gy). SBRT is an emerging technology that requires further studies to identify which patients will benefit from this therapy as well as optimization of the technique and radiotherapy dose delivered. There is insufficient evidence upon which to base any recommendations.

6.6 Summary

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. The use of orthopedic therapy is needed in patients who are risk for a pathologic fracture. Balloon kyphoplasty and SBRT appear to be promising technologies; their role still needs to be investigated further to optimize the therapy of patients with bone metastasis from lung cancer.

6.7 Recommendations

6.7.1. In patients with lung cancer who have pain due to bone metastases, external radiation therapy is recommended for pain relief (Grade 1A)**.**

Remark: A single fraction of 8 Gy is equally effective for immediate relief of pain and more cost-effective than higher fractionated doses of external radiation therapy.

6.7.2. In patients with lung cancer who have painful bone metastases, bisphosphonates are recommended in addition to external beam radiation therapy for pain relief (Grade 1A)**.**

6.7.3. 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 (Grade 1C)**.**

Remark: Intramedullary nailing is the preferred approach, especially for the femur or the humerus.

Remark: Radiotherapy should follow the orthopedic management 2-4 weeks later.

6.7.4. In patients with lung cancer who have vertebral compression fractures causing pain, vertebral augmentation procedures are recommended to reduce pain (Grade 1A)**.**

7.0 Palliation of Brain Metastases

An estimated 20% to 40% of patients with cancer will develop metastatic cancer to the brain. Lung cancer accounts for approximately 50% of all brain metastasis. Historically, survival was poor (< 6 months), and systemic failure was believed to be the major cause of death. Long-term toxicities were not an issue; thus short, cost-effective, outpatient treatments constituted the primary therapy. Recently, a series of prospective clinical trials have changed the management of brain metastasis and moved the long-term sequela associated with treatment to the forefront of the discussion.

The methods available to treat patients with metastatic lung cancer to the brain include: (1) systemic corticosteroids, 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 (SRS); (5) chemotherapy; and (6) a judicious combination of these treatments.

7.1 Corticosteroids

Patients with brain metastasis can have significant cerebral edema that can cause headache, nausea, vomiting, seizure, and even death. Systemic glucocorticoids are known to improve neurologic function only for a short time (maximum, 1 month).[139] 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 has a maximum dose of 16 mg/d. The primary difficulty with corticosteroids is the side effects that patients experience (cushingoid facies, peripheral edema, gastrointestinal bleeding, psychosis, and steroid-induced myopathy, among others).[140] Therefore, patients should only be on corticosteroids if they are symptomatic.

7.2 Whole-Brain Radiation Therapy

WBRT has long been a standard treatment of patients with brain metastases. The philosophy is simple: "do not miss." Therefore, the intention is to treat the cancer cells not seen in addition to the ones that appear on MRI or CT scan; the "whole brain" is treated. A trial by Horton et al[141] compared WBRT plus supportive care (oral prednisone) vs supportive care alone. Median survival in the prednisone-alone arm was 10 weeks compared with 14 weeks in the combined arm. The proportion of patients with an improvement in performance status was similar in the prednisone-alone and the combined WBRT and prednisone arms. This trial subsequently changed the standard of care for patients with brain metastasis. RTOG 6901 established 30/10 (Gy/fraction) as a standard approach. Despite numerous studies[142-150] testing numerous combinations of dose and fractionation (10/1, 12/2, 20/5, 30/6, 30/10, 35/15, 18/3 + 18/3 split, 37.5/15, 40/15, 50/20, 50/23, and 54/34 bid), the outcomes remain the same (and as poor) as the standard established by RTOG 6901 (30/10).

7.3 Surgical Resection of Brain Metastases

Two subsequent trials by Patchell et al[151] examined the relationship between WBRT and neurosurgical resection for patients with solitary brain metastasis. In the first trial, 84 patients were randomized to either WBRT alone or resection followed by WBRT. The radiotherapy dose was 39 Gy in 13 fractions. The results for this trial showed that the addition of resection to radiation dramatically increased survival from 40 weeks to 45 weeks ($P < .01$). Patchell and colleagues[152] then designed a second trial to answer the reverse question, if the benefit of resection is increased by the addition of WBRT. In this trial, 95 patients with solitary resected brain metastasis were randomized to either WBRT or observation. The investigators for this trial were concerned about the long-term survival for this patient population; thus, the radiotherapy was 50.4 Gy in 28 fractions. In this trial of selected patients, the addition of WBRT to resection increased control of cancer within the brain but had no effect on survival. Because of the potential side effects of WBRT in long-term survivors, the role of WBRT 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, resection or SRS), 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.[153]

7.4 Stereotactic Radiosurgery

SRS operates by directing highly focused beams of ionizing radiation with great precision to ablate intracranial tumors. SRS uses 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 they are surgically accessible or not. SRS was first developed at the Karolinska Institute of Stockholm, Sweden. In 1968, they developed the Gamma Knife, a device exclusively for SRS, which consisted of radioactive sources of cobalt-60 (Co-60) placed in a kind of helmet with central channels for irradiation using gamma rays. In order to achieve a high degree of precision, the patient's head was attached to a rigid frame of reference, called a stereotactic frame, which was inserted into the metal helmet.

A linear accelerator (LINAC) may also be used to deliver radiosurgery. These systems differ from the Gamma Knife in a variety of ways. The Gamma Knife produces gamma rays from the decay of Co-60 with an average energy of 1.25 MeV. A LINAC produces x-rays from the impact of accelerated electrons striking a high "Z" target (usually tungsten). A LINAC therefore can generate any number of energy x-rays, although usually 6 MeV photons are used. The Gamma Knife has approximately 200 sources arrayed in the helmet to deliver a variety of treatment angles. On an LINAC, the gantry moves in space to change the delivery angle. Both can move the patient in space to also change the delivery point. Both systems use a stereotactic frame attached to the patient's head to restrict movement. The CyberKnife is a specific type of LINAC-based system; it delivers similar submillimeter accuracy without the use of a stereotactic frame. This precision is accomplished via an image guidance system that uses kilovolt images before the delivery of each individual beam delivery. Although all of these systems are extremely precise, the radiation to the surrounding normal brain is not zero; the more lesions that are treated, the greater the radiation dose to the surrounding normal brain tissue. Furthermore, no platform has demonstrated superiority to another; correct application by the treating physicians is the primary aspect of SRS. There is therefore insufficient evidence upon which to make a recommendation between the available technologies.

The role of SRS in addition to WBRT was addressed by the RCT study RTOG 9508.[154] Three hundred thirty-three patients with one to three newly diagnosed brain metastases were randomly allocated to either WBRT or WBRT followed by SRS boost. Patients were stratified by number of metastases and status of extracranial disease. Univariate analysis showed that there was a survival advantage in the WBRT plus SRS group for patients with a single brain metastasis (median survival time, 6.5 vs 4.9 months; $P = .0393$). Patients in the WBRT plus SRS group were more likely to have a stable or improved Karnofsky Performance Status score at 6 months' follow-up than were patients allocated to WBRT alone (43% vs 27%, respectively; $P = .03$). By multivariate analysis, survival improved in patients with a recursive partitioning analysis class 1 ($P < .0001$) or a favorable histologic status ($P = .0121$). This trial was essentially a question of either immediate SRS or delayed SRS (for salvage); given the equality between the two treatment arms, the benefits associated with SRS emphasize the importance of aggressive management of intracranial metastasis. Therefore, WBRT and SRS became a standard treatment of patients with a single unresectable brain metastasis and strongly considered for patients with two or three brain metastases.

A collection of trials[155,156] was then designed to ask the reverse question: does WBRT add to SRS? The most insightful trial was performed by Chang et al.[157] Patients with one to three newly diagnosed brain metastases were randomly assigned to SRS with or without WBRT. The primary end point was neurocognitive function objectively measured as a significant deterioration (5-point drop compared with baseline) in Hopkins Verbal Learning Test—Revised, for total recall at 4 months. After 58 patients were recruited (n = 30 in the SRS alone group, n = 28 in the SRS plus WBRT group), the trial was terminated by the data monitoring committee according to early stopping rules on the basis that there was a high probability (96%) that patients randomly assigned to receive SRS plus WBRT were significantly more likely to show a decline in learning and memory function (mean posterior probability of decline, 52%) at 4 months than patients assigned to receive SRS alone (mean posterior probability of decline, 24%). An overall survival benefit was also identified in the patients who received SRS alone, although this may have been the result of more liberal use of salvage therapy. It is recommended that immediate SRS be offered to patients with one to three brain metastases. WBRT should be considered to be used as part of therapy as needed.

Although there has been no randomized study for direct comparison of local tumor control using surgical resection or radiosurgery, many institutions have integrated the results of these clinical trials into the following clinical pathway:

1. Patients are evaluated to determine if they would benefit from neurosurgical therapy. Specifically, consideration of patients with significant edema, neurologic symptoms, large metastasis (>3 cm), or resectable solitary lesions with radio-resistant histology (melanoma, renal cell cancer, and sarcoma). Patients who have a gross total resection with no evidence of residual intracranial disease can be observed. All other patients have radiotherapy tailored to their individual needs.
2. For patients without neurosurgical indications/availability/options, radiotherapy is the primary treatment.
    a. For patients with five or more brain metastasis, WBRT is the recommended therapy. With the increased number of lesions, the patient is at significant risk to have occult disease not visualized on imaging studies. Therefore, it is important to treat the disease not seen more than the disease seen. SRS can be used if progression is identified.
    b. For patients with one to three brain metastases, SRS alone is the appropriate initial therapy. With a low burden of disease, the benefit gained by delaying WBRT outweighs the potential risk. This approach emphasizes treating only the disease that is seen but does require rigorous surveillance with MRI.
    c. For patients with four brain metastasis, the combination of SRS and WBRT individualized to the patient.

For patients with brain metastases, prospective clinical trials have changed management of the disease. Management of the long-term treatment-related sequela is a significant concern of the treating oncologist. Future questions currently being investigated involve both the use of adjuvant SRS for resected brain metastasis and the role of SRS for increasing number of intracranial metastasis.

7.5 Chemotherapy

Cytotoxic chemotherapy has traditionally been considered ineffective for brain metastasis because of poor penetration across the blood-brain barrier. However, there have been several attempts to determine if combined chemotherapy plus radiotherapy would be of some benefit. Temozolomide (a novel alkylating agent) is able to cross the blood-brain barrier, and it has been studied as a monotherapeutic agent for treatment of brain metastases. In a meta-analysis[158] of four trials totaling 280 patients comparing WBRT

with or without temozolomide, chemoradiotherapy had a better objective response, worse grade 3 toxicity, and no improvement in survival. Individual trials investigating WBRT with or without thalidomide,[159] motexafin gadolinium,[160] topotecan,[161] and bromodeoxyuridine[145] have shown similar results. Currently, no evidence exists to suggest that chemotherapy should be combined with WBRT.

7.6 Recommendations

7.6.1. In patients with lung cancer who have symptomatic brain metastases, dexamethasone at 16 mg/day is recommended during the course of definitive therapy with a rapid taper as allowed by neurologic symptoms (Grade 1B)**.**

7.6.2. In lung cancer patients with significant brain edema, neurologic symptoms, or large space occupying brain metastasis (>3 cm), surgical resection is recommended if they are surgical candidates (Grade 1B)**.**

7.6.3. In lung cancer patients with 1 to 3 brain metastases, SRS alone is the recommended initial therapy (Grade 1A)**.**

Remark: With a low burden of disease, the benefit gained by delaying who brain radiation therapy outweighs the potential risk.

7.6.4. In patients with 5 or more brain metastases, whole brain radiation is the recommended therapy (Grade 1A)**.**

8.0 Palliation of Spinal Cord Compression

SCC is one of the most dreaded complications of metastatic cancer. Its natural history, if untreated, is usually one of relentless and progressive pain, paralysis, sensory loss, and sphincter dysfunction. At presentation, 90% of patients have pain (local and/or radicular), and up to 50% of patients may be unable to walk and have sensory and/or bladder/bowel dysfunction.[162,163] Patients with paralysis either at presentation or after treatment have a much shorter life expectancy than ambulatory patients.[164-166] In addition, the deterioration is devastating for patients and their families and is difficult to manage medically.[167-169]

The definition[170] of SCC is a combination of clinical features and radiographic features:

- Clinical features: Any or all of the following: pain (local or radicular), weakness, sensory disturbance, and/or evidence of sphincter dysfunction.
- Radiographic features: Compression of dural sac and its contents (spinal cord and/or cauda equina) by a tumor mass. Minimum radiographic evidence is indentation of the theca at the level of clinical features.

SCC can be classified anatomically as intramedullary, leptomeningeal, and extradural. The pathophysiology of extradural compression includes several mechanisms, such as continued growth of bone metastases into epidural space, blockage of neural foramina by a paraspinal mass, destruction of vertebral bone (causing a collapse and displacement of bony fragments into epidural space), and vascular obstruction of epidural venous plexus. Any of the mechanisms can lead to spinal cord edema, ischemia, and ultimately permanent damage if not treated emergently.

The consequences of cord compression are so severe that sagittal T1-weighted MRI with or without gadolinium of the entire spine should be done initially in patients with known lung cancer with the new onset of back pain or focal neurologic deficit. A study[171] from the Netherlands referred to the time patterns of referrals for radiotherapy to treat SCC. In this analysis of 443 patients with SCC, 30% of the referrals took place on a Friday. Thus, referring physicians need to be encouraged to expedite their workup.

8.1 Corticosteroids

If there is a significant clinical suspicion of SCC, steroids should be administered prior to radiographic confirmation. If the MRI is found to be negative, de-escalation of treatment can occur rapidly. A randomized trial[172] demonstrated improved ambulation with administration of steroids (96 mg/d); 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 lower likelihood that gait function will be regained, but the addition of dexamethasone appears to improve the probability of regaining the ability to ambulate. Similar to patients with brain metastases, the use of this high-dose dexamethasone can be associated with significant toxicity (11%). A retrospective study from the Norwegian Radium Hospital[173] reviewed their experience treating patients with high-dose dexamethasone (96 mg IV daily, tapered over 14 days) in 28 consecutive patients. The toxicity profile was found to be significant: 29% side effects, 14% serious (one fatal ulcer, one rectal bleeding, one GI perforation, one sigmoid perforation) with high-dose dexamethasone therapy.

Another randomized trial from Rotterdam[174] compared different bolus doses of dexamethasone (Arm

A, 10 mg IV vs Arm B, 100 mg IV), both followed by dexamethasone 16 mg/d. A trend for improved neurologic status (Arm A, 8% vs Arm B, 25%; P = not significant) was identified, but overall no difference in pain management, ambulation, or bladder function was demonstrated. High-dose dexamethasone is recommended as an adjunct to radiation therapy and/or surgery to restore ambulation after treatment. The amount of dexamethasone needs to be reduced in the setting of uncontrolled diabetes mellitus or other intolerance of higher-dose therapy.

8.2 Surgery Plus Radiotherapy vs Radiotherapy Alone

Surgery is indicated when there is spinal cord instability or bony retropulsion causing the cord compression,[170] although there are no data comparing this to no intervention. Surgery is also suggested in patients with paralysis for <2 days based on a prospective trial.[175] Significant morbidity is associated with surgical intervention for SCC.

The Bluegrass Neuro-Oncology Consortium[175] performed a randomized trial comparing surgery plus radiotherapy vs radiotherapy alone. The population studied included patients with paraplegia ≤ 48 h. Thirty-two patients were unable to walk at enrollment, equally divided between the two arms. The radiotherapy consisted of 30 Gy in 10 fractions. The trial was designed to accrue 200 patients but closed early (N = 101 patients) because of an early stopping rule. Multiple end points in this trial reached statistical significance (Fig 5).

In this trial, the RT arm results were significantly worse than what would have been expected based on other prospective RT trials. This trial took 10 years to accrue 101 patients, suggesting the results may apply to only a minority of patients with SCC. The radiotherapy arm also had higher nonneurologic morbidity, suggesting that insufficient stratification factors were used. These prospective data need to be considered when making clinical decisions.

FIGURE 5. [Section 8.2] Impact of surgical decompression of spinal cord impingement.

Outcome	S + RT	RT
% symptomatically better	62%	19%
Ability to Walk (%)	84%	57%
Continence (days)	156	17
Length of response (days)	122	13
Overall Survival (days)	126	100

Results are outcomes from a randomized controlled trial of 101 patients with symptomatic spinal cord compression from metastatic cancer.[174] RT = radiotherapy; S = surgery.

A group from Germany performed a match pair analysis[176] of 108 patients receiving surgery plus steroids plus radiotherapy for metastatic cord compression vs 216 patients (1:2 match) from a database of 2,300 patients treated with radiotherapy alone. The matching was based on 11 potential prognostic factors. The outcomes demonstrated no difference between the two groups in terms of ambulation, regained ambulation, 1-year local control, 1-year overall survival, or complications. The authors suggest that another randomized trial is needed that stratifies patients based on the identified 11 prognostic factors.

8.3 Radiation Therapy

Radiation therapy is a mainstay for the treatment of SCC. Multiple trials have investigated the optimal radiotherapy dose. It was found to be similar to what has already been discussed for the management of bone metastasis. The standard of care is 30 Gy in 10 fractions (30/10), and shorter fractionation schedules (20/5 or 8/1) are typically reserved for those patients with poor performance status and progressive disease refractory to systemic chemotherapy. They are typically avoided in newly diagnosed patients who are chemotherapy naïve or in the postoperative setting. Accurate prognostic factors as well as end points that focus on patient function are urgently needed in this setting.[176-183]

8.4 Recommendations

8.4.1. In patients with lung cancer that have new onset of back pain, sagittal T1-weighted MRI of the entire spine is recommended (Grade 1C)**.**

8.4.2. In patients with lung cancer and epidural spinal cord metastases, who are not symptomatic, prompt treatment with high-dose dexamethasone and radiotherapy is recommended (Grade 1B)**.**

8.4.3. In lung cancer patients with symptomatic radiographically confirmed epidural SCC and good performance status, it is recommended that neurosurgical consultation be sought and, if appropriate, surgery should be performed immediately and followed by radiation therapy (Grade 1B)**.**

9.0 Palliation of SVC Obstruction

SVC syndrome has a characteristic and often striking clinical presentation, which can be life threatening. It is caused by invasion/compression of the SVC by a mass in the right lung, lymph nodes, mediastinal structures, or thrombosis within the SVC. Obstruction of

the SVC is usually caused by malignancies, 72% of which are due to lung cancer (22% SCLC and 50% NSCLC). Impending obstruction of the SVC may be identified by CT imaging before development of symptoms associated with SVC obstruction.[184,185] In approximately 60% of the cases, SVC compression is the presenting symptom for the diagnosis of lung cancer.

The mechanism responsible for SVC syndrome is simple to explain. If the SVC becomes obstructed, blood flows through multiple smaller collaterals to the azygos vein or the inferior vena cava. These venous collaterals dilate over several weeks so that the upper body venous pressure is markedly elevated initially but decreases over time.[186,187] Thus, SVC syndrome includes symptoms such as neck swelling, swelling of one or both arms, and swelling of the face and eyelids; dyspnea is often present. Headache from cerebral venous hypertension is common with SVC syndrome, along with hoarseness of the voice and cyanosis, which are less frequent. Cerebral edema may occur and be severe, with coma as a possible result. Cardiac output may be diminished transiently by acute SVC obstruction. However, within a few hours, the increased venous pressure forces blood through collaterals so that a steady state of blood return is once again achieved. Evidence of hemodynamic compromise is usually a result of mass effect on the heart itself rather than the SVC compression. Signs and symptoms of SVC obstruction are usually more of a nuisance than of clinical consequence. In a review of 1,986 cases of SVC obstruction, only one documented death was found from epistaxis.[188] SVC syndrome is no longer considered a medical emergency; still, prompt expedited care is warranted.[189]

The medical management for SVC syndrome involves elevation of the head to decrease the hydrostatic pressure and cerebral edema. If the cerebral edema is severe, loop diuretics can be considered. Systemic corticosteroids are usually administered to relieve swelling associated with radiation therapy, although data to support the efficacy of steroids are missing.[190] A meta-analysis of two randomized studies and 44 nonrandomized studies failed to identify a benefit associated with corticosteroid administration.[191] Furthermore, their use may impact the ability to obtain histology in cases in which the first biopsy is found to be insufficient.

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. Patients with SCLC are managed well with chemotherapy.[192] A histologic diagnosis is also needed for patients with NSCLC because the choice of appropriate antineoplastic drugs is different from the treatment of SCLC and would include the use of radiotherapy. Similar to the use of corticosteroids, the use of radiation prior to a biopsy may obscure the histologic diagnosis.[193] Reported response rates for relief of SVC obstruction in NSCLC are 59% (chemotherapy), 63% (radiation therapy), and 31% for synchronous chemoradiation.[193] Relapses after treatment with chemotherapy and/or radiation therapy are seen in 19% of patients with NSCLC.[193]

Symptom relief from SVC syndrome is more rapidly achieved by vascular stenting. Headache may disappear immediately, and swelling of the face and arms are reported to abate within 24 h and 72 h, respectively.[194,195] Overall response rates of about 95% with stent insertion are reported from a variety of case series, with an 11% recurrence rate.[191,196] 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.[197] It is also important to remember that since stent placement does not impact the outcomes of histologic assessment, stents can be placed in patients with significant respiratory distress without impacting the overall management of the cancer. 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.[198] 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.

The severity of symptoms is important in determining the urgency of intervention. This has not been well characterized in existing studies because of the lack of a classification scheme. Furthermore, the severity of symptoms of SVC syndrome changes over time. For example, important time points might be at the time of presentation, at the time of initiation of treatment, or after the treatment has been finished. The Thoracic Group at Yale University[199] has developed a classification system as well as a treatment algorithm. Although this lacks prospective data, the manuscript offers an algorithm for clinicians to consider.

9.1 Recommendations

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

histologic or cytologic methods is recommended before treatment is started (Grade 1C).

9.1.2. In patients with symptomatic SVC obstruction due to SCLC, chemotherapy is recommended (Grade 1C).

9.1.3. In patients with symptomatic SVC obstruction due to NSCLC, radiation therapy and/or stent insertion are recommended (Grade 1C).

Remark: When using stenting for the management of SVC obstruction, consideration of necessary anticoagulation as it relates to future management of the patient must be considered.

9.1.4. In patients with SCLC or NSCLC with SVC obstruction who fail to respond to chemotherapy or radiation therapy, vascular stents are recommended (Grade 1C).

10.0 Management of Hemoptysis

Hemoptysis (expectoration of blood) is the presenting symptom in 7% to 10% of patients with lung cancer. Hemoptysis is more likely caused by malignant lesions involving the airways than 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, or 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 as a broad definition the 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 causes. The mortality rate of massive hemoptysis may be as high as 59% to 100% in patients with bronchogenic carcinoma.[200] Surgery, a more definitive therapeutic modality, is not on the algorithm for intervention because most patients with lung cancer with massive hemoptysis have advanced disease and are already not surgical 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.[201-203] 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.[204,205] 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.[206] 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.[207] 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.

A study[208] 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[209-211] 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 several

techniques, including Nd-YAG laser photocoagulation, electrocautery, or argon plasma coagulation. Nd-YAG laser coagulation has shown a therapeutic response rate of 60%.[212-214] Electrocautery should produce similar results, but its use to control hemoptysis has thus far been anecdotal. Argon plasma coagulation provided control of hemoptysis in 100% of patients with a 3-month follow-up.[215] Cryotherapy, photodynamic therapy, and stent insertion have no role in the treatment of massive hemoptysis. There is insufficient evidence upon which to make a recommendation of therapeutic approach between technologies.

Hemoptysis that is not massive in patients with unresectable lung cancer can be treated with EBRT, whether it is caused by a bronchoscopically visible or invisible tumor. Most of the reported studies include hemoptysis with other pulmonary symptoms. EBRT has played a major role in the palliative therapy of NSCLC. One prospective study of palliation randomized 409 patients to either 30 Gy in 10 fractions or 40 Gy in 20 fractions. The median survival time was 6 months, with no significant differences between the groups. Approximately 60% of patients had their symptoms relieved.[216]

To reduce the time spent in radiation therapy departments, hypofractionated regimens have been evaluated for palliation. One study reported regimens of 42 to 44 Gy in 5.5- to 8.8-Gy fraction weekly doses. The authors reported objective remission in 49% and an increased performance status in 42%, with an additional 42% having stable performance status. They reported increased side effects, however, in regimens using 8.8-Gy fractions.[217]

The British Medical Research Council reported on a randomized trial comparing 17 Gy in 8.5-Gy fractions, one fraction per week, vs 30 Gy in 10 fractions over 2 weeks. There was no difference in survival or palliation of symptoms. In general, hemoptysis was palliated the best, with 81% to 86% having relief of this symptom.[110]

Endobronchial brachytherapy has been used for palliation of intraluminal tumor symptoms, including hemoptysis, obstruction with resultant postobstructive pneumonia, atelectasis, dyspnea, and cough. A meta-analysis was attempted of 13 randomized trials investigating endobronchial brachytherapy but in the end could not be performed because of the heterogeneity of the patients and treatments.[218] Another review of 29 trials reported that high dose rate brachytherapy combined with EBRT resulted in better symptom relief when compared with EBRT alone.[219] However, the rate of fatal hemoptysis ranged from 7% to 22%. A collection of retrospective studies suggest that the toxicity can be minimized with close monitoring of patients resulting in an effective treatment with very few complications.[220-222]

Across various institutions, bronchial artery embolization provides 73% to 99% immediate control and 10% to 55% recurrence rates; however, these findings were in mixed populations that include lung cancer only on a small scale.[223,224] In a single-center experience of 128 arterial embolizations (eight lung metastasis, seven lung cancers) for hemoptysis, there was 98% clinical success and 40% recurrence.[225] In general, success rates have improved over the years, with improvements in angiography and embolization techniques.

Surgery for massive hemoptysis is associated with increased morbidity and mortality. In a 10-year single-center experience, there was 16% mortality in patients with massive hemoptysis managed surgically. Mortality was associated with blood aspiration into the contralateral lung and pneumonectomy. However, this included 68 patients largely representing active or history of TB or bronchiectasis, with only four patients with carcinoma.[226]

10.1 Recommendations

10.1.1. In all lung cancer patients with large volume hemoptysis, securing the airway with a single-lumen endotracheal tube is recommended. Bronchoscopy is recommended to identify the source of bleeding, followed by endobronchial management options such as argon plasma coagulation, Nd:YAG laser, and electrocautery for visible central airway lesions (Grade 1C)**.**

10.1.2. In all lung cancer patients with non-large volume hemoptysis, bronchoscopy is recommended to identify the source of bleeding. For visible central airway lesions, endobronchial management options are recommended. For distal or parenchymal lesions, EBRT is recommended (Grade 1C)**.**

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

11.0 Management for Airway-Esophageal Fistulas

TEFs are an uncommon complication of lung cancer. The largest study evaluating patients with malignant tracheoesophageal and bronchoesophageal fistulas demonstrated and incidence of 0.16% in 5,714 patients with lung cancer and 14.75% in patients with tracheal cancer.[227] Patients typically present with coughing and shortness of breath secondary to aspiration of food,

saliva, and contamination of the airways by gastric contents. Recurrent respiratory infections and malnutrition lead to their rapid deterioration with reduced survival of 1 to 6 weeks with supportive management alone.[228] Patients with lung cancer with TEFs are considered inoperable. Curative resection of the involved tracheal-bronchial and/or esophageal segments in face of a malignancy should not be considered, as most of these patients are at the end stage of their lung cancer, and palliative management should be emphasized.

New interventions for the management of lung cancer with combination therapy including chemoradiation and bevacizumab, an antiangiogenesis agent, may lead to an increased risk for the development of TEF. A phase 2 clinical trial, using bevacizumab and chemoradiation, was terminated early due to the increased incidence of TEF development in the treated patients.[229] Antiangiogenic agents may also cause impaired wound healing in radiation-injured tissue.

The goal of therapeutic intervention for patients with TEFs should be to palliate their symptoms of dyspnea, cough, dysphagia, and airway infections and to maintain oral intake and relieve any pain, to ultimately improve their QOL. Preventing further contamination of the airways will improve coughing and shortness of breath and reduce the occurrence of airway infections. The most accepted therapeutic intervention is airway stenting. A study of 35 consecutive patients who presented with TEF were evaluated with the European Organization for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire (EORTC QLQ-C30) and the Quality of Life Questionnaire-esophageal module. The patients self-selected the mode of therapy that they underwent, being given the options of: supportive care (n = 9), gastrostomy (n = 9), or airway stenting (n = 17). A follow-up questionnaire for health-related QOL was completed by the 27 patients who were still alive 2 weeks postintervention or postassessment. They identified that the gastrostomy group compared with the control group had lower emotional function, whereas the stenting group, as compared with the control group, had improvement in dyspnea, dysphagia, eating, cough, respiratory problems, and dry mouth, with significantly higher scores in emotional and social function, thus supporting the use of stenting and not using gastrostomy in the management of patients with TEFs.[230]

The American College of Gastroenterology's evidence-based guidelines identify that the role of esophageal stents in malignant disease in patients with unresectable cancer is to ameliorate symptoms. The majority of TEFs referred to in this guideline are related to esophageal cancer, with a small percentage of lung cancer-related disease. The evidence from reported prospective case series suggests the use of self-expanding metallic stents over plastic stents. In these same series, occlusion rates of 70% to 100% are reported with complication rates of 10% to 30%.[231] The largest study, with 61 patients with lung cancer, had an initial success rate of occlusion of the TEF of 80% (n = 49). Approximately one-third of the patients developed recurrence of the fistulas. The overall survival of patients with successful closure of the fistula was greater than those without or with incomplete closure (15 vs 6 weeks, $P < .05$).[232]

Herth et al[233] performed a prospective evaluation of airway stenting vs esophageal stenting vs double stenting of the airway and esophagus in112 patients (74% with advanced lung cancer and 26% with esophageal cancer). The decision regarding stent placement was made based on the location of the stenosis by the operator. Sixty-five patients (58%) had airway stents, 37 (33%) had esophageal stents, and 10 (9%) had double stenting as their primary intervention. An EORTC QLQ-C30 was administered to all patients prior to stenting and again 6 weeks postprocedure. During the follow-up period, 21% of patients had recurrence of the fistulas (17 airway, six esophageal, and one double) requiring a second stent insertion. Survival in the patients who received only airway stent placement was significantly lower than in either the esophageal or double-stent group (airway stent, 219 days vs 263 days in the esophageal stent group and 253 days in the double-stent group; F-test, $P = .023$). Overall health and QOL demonstrated marked improvement in the post- vs pre-stent scores (paired t test, $P < .001$). This study was not designed to compare the benefits of double stenting vs esophageal stenting alone.[233]

The technique of double stenting is often used with the failure of a single-lumen stent. Several case series suggest higher initial success rates with fewer recurrences of fistulas with double stenting as compared with single stenting.[234-236] Double stenting of the airway and esophagus (with self-expanding metallic stents) appears to provide the best palliation of symptoms, improvement of QOL, and survival. The airway stent should be placed prior to the esophageal stent to minimize the risk of airway compromise if the esophageal stent is placed first.

After airway stenting patients may be able to eat soft foods and drink, but maintaining fluid status and nutritional adequacy is very difficult. The use of percutaneous gastrostomy tubes to provide fluid and caloric support can be considered. There is no evidence in support of or counter to this consideration.

11.1 Recommendation

11.1.1. In patients with TEFs, double stenting of the esophagus and airway or esophageal stenting

is recommended with self-expanding metallic stents (Grade 1B)**.**

Remark: When primary esophageal stenting is to be used, airway compromise must be considered prior to placing the stent. If a concern exists, an airway stent should be placed prior to esophageal stenting.

12.0 Management of Malignant Pleural Effusions

Malignant pleural effusion (MPE) accounts for 22% of all pleural effusions, and in the United States > 150,000 new cases are diagnosed annually.[237] Carcinoma of any organ can metastasize to the pleura, and when malignant cells are detected in the pleural fluid or in pleural tissue they denote dissemination and poor prognosis. Median survival after the diagnosis of MPE is 4 to 6 months, depending on type of neoplasm.[238]

During the course of disease, 25% of patients with lung cancer and > 90% with mesothelioma develop symptomatic MPE.[239] Although therapeutic thoracentesis provides effective symptom relief, most MPEs recur within a month, and therefore simple thoracentesis should not be the treatment of choice for those with a good performance status (Karnofsky score > 30 or Eastern Cooperative Oncology Group score ≥ 1).[240,241] In fact, repeated thoracentesis carries a risk of pneumothorax and empyema and impedes success with subsequent drainage procedures or thoracoscopy because of pleural adhesions.[238]

Dyspnea presents in 21% to 78.6% of patients with advanced lung cancer. Of these patients, 10% to 63% grade their dyspnea as moderate-severe.[242,243] Dyspnea is the most common symptom associated with MPEs.[244] Higher dyspnea scores have been correlated with lower QOL, and this is a common cause for both referral to palliative care and consideration of palliative sedation.[245]

Dyspnea attributable to recurrent malignant effusions in patients with lung cancer may be effectively palliated by eradication of the pleural space or minimizing the fluid reaccumulation into the hemithorax. Commonly used management strategies have included drainage followed by instillation of a sclerosant or, alternatively, insertion of a semipermanent tunneled pleural catheter (TPC). With respect to the former, the chest cavity may be drained surgically via thoracoscopy or at the bedside with a simple chest tube. Both techniques may be used as conduits for instillation of a sclerosant into the pleural space. Despite there being multiple strategies for palliation, their efficacy and safety have yet to be compared in a well-designed RCT.

12.1 Comparison of Sclerosants to Induce Pleural Symphysis

Malignant effusions may be effectively managed by complete drainage of fluid and administration of intrapleural sclerosant. For successful pleurodesis, the underlying lung must re-expand and pleural apposition must occur. Pleurodesis can be performed by instilling a sclerosant into the pleural space via intercostal tube or small-bore catheter or by thoracoscopic talc poudrage.[246-248] Commonly used sclerosants are talc, tetracycline derivatives, and bleomycin (Fig 6).[237,238,248]

12.2 Mode of Administration of Sclerosants

A recently updated Cochrane Review from 2010 compared the efficacy of various sclerosant agents both with respect to immediate effects and recurrence rates.[249] Based on 10 RCTs including 308 patients, the most effective pleurodesis agent was found to be talc, with a pooled estimate of the relative risk for successful pleurodesis of 1.34 (95% CI, 1.16-1.55). Compared with bleomycin, the relative risk of effective pleurodesis was 1.23 (95% CI, 1.00-1.50). These data were derived from the analysis of five RCTs involving 147 patients. Data from three additional RCTs evaluated efficacy of talc and tetracyclines (n = 103) and again found talc to be superior (relative risk, 1.32; 95% CI, 1.01-1.72).

The routine use of talc for pleurodesis has been limited by concerns regarding safety. ARDS following

Figure 6. [Section 12.1] Sclerosants for chemical pleurodesis.

Sclerosant	Dose	Dilution	Success Rate (%)	Side effects	Complications
Talc Slurry via tube	2–5g	50-100ml	90%	Chest pain, fever	ARDS
Talc Poudrage via Pleuroscopy	2-5g	None	>90%	Chest pain, fever	None
Tetracycline	1–1.5g[a]	50-100ml	67%	Chest pain, fever	None
Bleomycin	60 IU	50-100ml	61%	Chest pain, fever	None
Doxycycline	0.5-1g	50-100ml	76%	Chest pain, fever	Anaphylaxis
Minocycline	300mg	100ml	80%	Chest pain, fever	None

[a]20 mg/kg.

talc slurry has been reported from the United Kingdom and the Americas, where nongraded talc (50% talc with particle size < 15 μm) is used.[250,251] Maskell and colleagues[252] demonstrated that patients who underwent pleurodesis with nongraded talc had greater alveolar-arterial oxygen gradient at 48 h compared with those who received graded talc (particle size > 15 μm). In a multicenter trial of 558 patients with MPE who underwent thoracoscopic talc poudrage using graded talc, there was no occurrence of deaths, ARDS, or pneumonitis.[253]

The Cochrane Systematic Review of patients who underwent pleurodesis supports the use of intrapleural sclerosants to prevent recurrence, with talc as the sclerosant of choice.[249] The concern regarding safety of talc is not supported by the evidence from the Cochrane Review or the aforementioned RCT, particularly when graded talc is used.[249,253]

Talc may be instilled into the pleural space either during thoracoscopy or via a chest tube (Fig 7). These techniques are often referred to as talc poudrage or talc slurry. A recent systematic review by Tan and colleagues[254] reported significant reduction in malignant effusion recurrence following talc poudrage compared with slurry. The largest single RCT of talc slurry and poudrage, the phase 3 Intergroup study, showed similar outcomes for patients randomized to receive talc poudrage or slurry, although patients who underwent thoracoscopy reported greater comfort and safety. Malignant effusions due to lung cancers were more effectively palliated with talc poudrage.[255] Stefani and colleagues[256] randomized 109 patients to talc poudrage vs slurry and also demonstrated better immediate (87.5% vs 73%) and lifelong pleurodesis successes (82% vs 62%) in favor of talc poudrage.

The additional advantage of talc administered via thoracoscopy is the ability to inspect the pleural space and perform biopsies when appropriate. The diagnostic accuracy of thoracoscopy exceeds 90% for lung cancer.[257] For cases in which the clinical situation requires both a diagnostic procedure as well as intervention to prevent pleural fluid reaccumulation, thoracoscopy and poudrage is the preferred technique and should be considered if patients have good performance status.

The main outcome reported in the majority of the literature that addresses mode of sclerosant administration is the rate of pleurodesis rather than QOL or dyspnea scores. This rate may be considered as a marker of efficacy of palliation, considering the strong correlation between dyspnea, impairment of QOL, and pleural fluid accumulation in lung cancer.

12.3 TPCs for Palliation

As stated above, no head-to-head comparison has ever been performed between thoracoscopy and talc poudrage and an indwelling TPC. Tremblay and colleagues[258,259] did attempt to retrospectively compare a subgroup of patients with TPCs considered fit for surgery from his database to patients from the Intergroup trial.[255] He found that TPC compared favor-

FIGURE 7. [Section 12.2] Treatment options for malignant pleural effusion.

Treatment Option	Indication	Considerations
Observation	Asymptomatic small effusion SCLC, lymphoma, breast cancer, cancers readily responsive to systemic therapy	Majority of effusions recur during course of treatment but time to recurrence difficult or impossible to predict
Therapeutic thoracentesis	Recurrent effusion and poor PS, short expected (<2 months) survival Performed in outpatient setting, obviating hospitalization	High recurrence rate Complicated by iatrogenic pneumothorax, and pleural space infection 1-1.5 liters per session: multiple sessions usually necessary to remove all fluid
Chest tube and intrapleural instillation of sclerosant (Figure 5)	Symptomatic large effusions Recurrent effusions	> 60% success rate Poor alternative to talc poudrage Alternative to pleurodesis via pleuroscopy
Talc poudrage via pleuroscopy	Recurrent symptomatic effusions	Success rate 90% Available expertise
Long-term indwelling pleural catheter	Intractable effusion Recurrent effusion with poor PS Trapped lung	Catheter related infection and obstruction Tumor seeding in mesothelioma
Pleuroperitoneal shunt	Intractable effusion Trapped lung Failed pleurodesis, in good health with long survival	Shunt-related complications: infection and occlusion
Pleural abrasion and pleurectomy	Failed pleurodesis, in good health with long survival	Surgical procedure with risk of morbidity - Usually 100% effective
Radiotherapy	Mediastinal lymph node metastasis from lymphoma and SCLC.	Contraindicated in NSCLCas adverse effects of radiation pneumonitis outweigh benefit
Chemotherapy	SCLC, Lymphoma, breast cancer	Receptor analysis in breast cancer allows hormonal manipulation. Tissue chemosensitivity studies can be performed as indicated.

NSCLC = non-small cell lung cancer; PS = performance status; SCLC = small cell lung cancer.

ably with medical thoracoscopy, with no procedure-related deaths and similar symptom control and side effect profiles (pleurodesis rate, 70% for TPC, 78% for thoracoscopy and talc poudrage, and 71% for talc slurry). The late recurrence rate (at 30 days) was 33% for poudrage and 22% for talc slurry, whereas < 10% of patients with TPCs required further interventions.

A TPC is inserted in an ambulatory setting via tunneled technique and provides access to the pleural space for fluid drainage when symptoms recur. In a well-designed systematic review of 12 observational studies on TPC for palliation of malignant effusions, 96% of patients derived symptomatic relief.[260] Unfortunately, the reporting of improvement of dyspnea was not uniform, and the majority of studies included were large case series. Two studies, including a total of 46 patients, performed formal assessment of QOL, and all patients studied demonstrated improvement. The reported rate of pleurodesis in the 943 patients studied was 46%; however, this included patients with nonexpanding lungs despite drainage. The duration of the catheter remaining in situ was 52 days. A subsequent procedure was required in only 5% of patients (n = 652) among those in whom the need for further intervention was noted. Reporting of complications varied significantly across studies, although in general major complications were rare. Empyema and cellulitis rates were 2.8% and 3.4%, respectively, and 8.5% of catheters required removal because of complication. Disease extension along the catheter tract developed in 0.8% of patients, and an additional 5.9% required chest tube insertion for a symptomatic pneumothorax.

In a prospective 12-month study in which patients with symptomatic MPE were asked to choose between TPC and talc slurry, 34 received TPC and 31 talc slurry. Total hospital days were significantly fewer in patients who received TPC than those who received talc slurry (7 vs 18 days), fewer patients with TPC required subsequent pleural procedures (14% vs 32%), and more patients with TPC reported immediate (within 7 days) improvements in QOL and dyspnea.[261]

In the case of patients with nonexpanding lungs, insertion of a TPC is the only option for palliation from dyspnea related to recurrent malignant effusions. A survey of patients with nonexpanding lungs demonstrated that nearly 50% were either very or moderately satisfied with their symptomatic relief following insertion of a TPC.[262]

We recognize the limitations posed by the lack of high-quality RCTs for tunneled catheters as well as the need for a well-designed RCT comparing tunneled catheters to thoracoscopy with pleurodesis. Our recommendations are based on the best available evidence. In addition, we acknowledge that many of the studies cited were inclusive of malignant effusions from primary tumors other than lung cancer. In general, lung cancer represented approximately 30% of patients studied and the largest single included tumor cell type, and the overall results were reflective of the subgroup with lung cancer. In general, about 95% of all patients with malignant effusion describe symptomatic benefit.[260] TPCs provide a less invasive means to reduce dyspnea and subsequently positively impact on QOL.

12.4 Recommendations

12.4.1. In patients with a symptomatic recurrent MPE with documented re-expandable lung, TPCs or chemical pleurodesis are recommended (Grade 1C)**.**

Remark: In patients with a limited lifespan, serial thoracentesis can be considered.

12.4.2. In patients with a symptomatic recurrent MPE with lung trapping, tunneled catheters are recommended for symptomatic relief and improvement in QOL (Grade 1C)**.**

12.4.3. In lung cancer patients with a suspected MPE in whom the diagnosis of stage IV disease is not confirmed, thoracoscopy is recommended instead of a tunneled catheter due to its diagnostic as well as therapeutic benefit (Grade 1C)**.**

12.4.4. In patients with a MPE, graded talc is the pleural sclerosant that is recommended due to its efficacy and safety profile (Grade 1C)**.**

12.4.5. In lung cancer patients with a malignant effusion, thoracoscopy with talc poudrage is recommended instead of talc slurry through a bedside chest tube for pleurodesis (if there are no contraindications to thoracoscopy) (Grade 1C)**.**

13.0 Management of Venous Thromboembolic Disease

The ACCP has published Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. This document is very comprehensive. For recommendations as they relate to cancer, refer to "Patients with Cancer in the Outpatient Setting," by Kahn and colleagues.[263]

14.0 Management of Depression, Fatigue, Anorexia, and Insomnia

Patients with lung cancer experience a variety of symptoms from the time of diagnosis, through treatment,

and throughout the remainder of life. Symptoms may wax and wane, persist throughout the course of the disease, or present only during one phase of the illness trajectory, such as cognitive decline related to late effects of WBRT. Distressing symptoms often present in clusters (ie, depression, anxiety, and fatigue; or fatigue, depression, dyspnea, and difficulty sleeping). There is a difference between the mere presence of symptoms and the degree of symptom bother (distress) and symptom interference (impact on QOL and functional status). Both curative and palliative lung cancer treatments (surgery, chemotherapy, and radiation therapy) may relieve, temporarily exacerbate, or cause new distressing symptoms, such as fatigue and cognitive dysfunction. Suicidal ideation has not been well studied in patients with lung cancer, but the findings for patients with cancer in general demonstrate a higher risk of suicide among patients with cancer than the general population, especially those people with cancer who are male, older, depressed, feeling hopeless, suffering from unrelieved pain, physically dependent, lack social support, or have evidence cognitive impairment.[264] Akechi and colleagues[265] found pain at baseline, declining physical function, and depressive disorder predicted suicidal ideation in a sample of Japanese individuals with unresectable lung cancer.

According to Cooley et al,[266] the most common symptoms identified in newly diagnosed patients are fatigue, pain, insomnia, and depression, with difficulty breathing and coughing becoming problematic at 3 and 6 months. Wang and colleagues[267] studied patients with NSCLC receiving chemotherapy and radiation therapy and reported prevalence rates of 25% for fatigue and 20% for pain, insomnia, or dyspnea at the beginning of treatment. At the completion of chemotherapy or radiation therapy, 63% of the patients reported two or more moderate to severe symptoms, with fatigue ranking as the most severe symptom during the entire course of treatment. Graves and colleagues[268] found 62% of patients with lung cancer in ambulatory settings reported a significant level of distress, and Hopwood and Stephens[269] found one-third of patients with inoperable lung cancer reported significant levels of depression before treatment, with depression persisting through treatment of more than one-half. Another key finding of the Hopwood and Stephens[269] study is that patients with SCLC report depression three times more often than people with NSCLC.

Functional impairment is the most important risk factor for depression, with pretreatment physical symptom burden, fatigue, and clinician-rated performance status also independently predictive of depression. In a population of patients with lung cancer treated with curative resection, Uchitomi et al[270] found a small percentage of individuals (5%-8%) whose depression did not abate the first year after surgery. Predictors of psychologic distress at 1 year were a diagnosis of depression after the diagnosis or 1 month after surgery and lower educational level. Buchanan and MacIvor[271] demonstrated that a patient's personal anxiety and perception of familial anxiety increased as performance status decreased. Importantly, the mere presence of increased anxiety or worry did not inhibit patients from sharing their feelings with their support network.

The symptoms of patients with lung cancer need to be assessed and addressed to maximize both QOL and functional status. Patient-reported information should be given the highest weight in determining symptom burden, because family caregivers and clinicians may overestimate or underestimate distress. Broberger and colleagues[272] found that patients and caregivers have higher concordance predicting which symptoms might cause distress than on which symptoms the patient is currently experiencing. Caregiver and health-care professional assessment should not substitute for a patient's self-report, but collateral information can be useful in completing a comprehensive biopsychosocial clinical assessment, especially when patients are reluctant to speak up secondary to communication, personality style, mood disorder, cognitive dysfunction, or other communication barriers. Tools used to measure distressing symptoms among individuals with lung cancer include the Distress Thermometer, SupportScreen, Hospital Anxiety and Depression scale, Rotterdam Symptom Checklist, and health-related QOL scales such as the EORTC-QLQ-C30, Lung Cancer Symptom Scale, Functional Assessment of Chronic Illness Therapy Measurement System, and the Medical Outcome Study Short Form-36.

In addition to the significant symptom burden found among patients with lung cancer at all stages of illness, mention must be made of studies identifying extensive symptom burden among patients' caregivers.[273] Badr and Taylor's[274] study of couples coping with lung cancer suggested "engaging in relationship maintenance during…[the early treatment period]… may help mold more resilient relationships and facilitate adjustment as the disease progresses." Family members and significant others not only assist patients through the illness experience but also take on additional roles and functions and experience high levels of fatigue and worry as a result of the patient's diagnosis and treatment. Since patients rely on their caregivers for optimal well-being, attention to caregiver distress should be considered part of comprehensive patient care.

Patterns of distress can be anticipated, but only individual assessment of patients and caregivers provides an accurate understanding of a particular

patient's or caregiver's concerns. Therefore, systematic, comprehensive, evidence-based assessment of distress experienced by patients and caregivers should be conducted at critical points in the cancer trajectory (new diagnosis, completion of treatment, relapse, and so forth) in order to accurately understand symptom burden, treat distress, and link people with appropriate resources. Diagnosis and relief of distress is recognized as a necessary and integral component of health care for a patient with cancer.[275-277] The American College of Surgeons' Commission on Cancer has established universal distress screening, monitoring, and treatment as a standard of care for all people being treated for cancer with expected implementation to begin in 2013 and full compliance by 2015.[277]

The term "supportive care" encompasses multidisciplinary efforts to optimize overall physical, psychosocial, spiritual, and cultural functioning and should be a core component of cancer care at all stages of illness, regardless of prognosis.[278] Palliative care, as defined by the WHO, is "the active total care of patients whose disease is not responsive to curative treatment."[279] "Individuals with lung cancer should have access to supportive and palliative care, as needed, throughout the course of their illness. Further, interventions which improve illness-related symptoms should not artificially separate psychologic and physical aspects of symptoms but ideally, facilitate an integrated approach to symptom relief which matches the patients' and families' needs, wishes and circumstances."[280]

A 2011 Cochrane Review of noninvasive interventions for improving well-being and QOL in patients with lung cancer identified a profound need for "high-quality care to support patients and reduce symptoms as much as possible."[280] Nursing programs and interventions to manage breathlessness and some psychotherapeutic, psychosocial, and educational interventions have been shown to help improve QOL among patients with lung cancer. Specifically, counseling may improve coping with emotional distress, and reflexology may reap immediate short-term relief. The link between emotions and physical health provided a theoretical basis for many of the studies that demonstrated the power of supportive interventions to improve both psychologic and physical functioning.[280] Psychologic benefits identified by the 2011 Cochrane Review and other researchers included decreased anxiety and depression, increased understanding of one's illness, and enhanced sense of meaning. Improved physical symptoms included decreased dyspnea, decreased fatigue, decreased pain, and improved sleep. No matter the intervention, the importance of a supportive and empathic relationship with an appropriately trained professional seems to be central to an intervention's success. This need for relationship-centered care presents challenges for delivering services to large numbers of individuals in a cost-effective manner.

Nursing interventions to improve the subjective experience of breathlessness had a modest effect on breathlessness sensation, performance status, functional ability, and depression. Interventions required specialized training and targeted one specific troubling symptom among the array of complex symptoms usually experienced by patients with lung cancer.[280] Importantly, improvement in patient's feelings about breathlessness may explain some of the improvement in actual physical expression of the symptom, highlighting a relationship between psychologic and physiologic distress. Both the Corner et al[281] and Bredin et al[282] studies suggest that patients benefit psychologically and physically from opportunities to master self-care skills.

McCorkle and colleagues[283] demonstrated the benefit of specialized nursing interventions delivered in home-care settings for delaying progression of symptom distress, patient dependency, and reduced health perceptions and found that effective symptom management decreased the likelihood of a hospital admission. However, once admitted, patients in the treatment arm of the McCorkle et al[283] study required longer hospital stays than control subjects. Moore and colleagues[284] showed how a specialized clinic-based nursing program could increase patient satisfaction, decrease dyspnea, and improve emotional functioning. Chan et al's[285] brief educational program combining symptom management with relaxation therapy improved subjective breathlessness, fatigue, anxiety, and functional ability. The McCorkle et al, Moore et al, and Chan et al studies each highlight the benefits of supportive care beyond what is available during routine medical visits.

As demonstrated by Linn and colleagues,[286] patients with lung cancer who participate in counseling sessions report benefits in depression intensity, life satisfaction, and self-esteem. Unfortunately, these benefits were not maintained over time. Caregivers who participated in telephone counseling to improve caregiver coping[287] did not demonstrate significant benefit for themselves, but the patients of the caregivers did report improvements in pain, physical well-being, lung cancer symptoms, depression, and self-efficacy in coping with symptoms. Wilkie and colleagues[288] used a video coaching intervention to improve communication about and self-monitoring of pain among people with lung cancer. Unfortunately, improvements in pain communication and monitoring did not result in improvement in actual pain symptoms.

Surprisingly, studies to date demonstrate only limited support for the benefit of exercise programs to enhance vigor or subjective QOL of patients with

lung cancer. Wall[289] found significant differences in overall strength for patients with lung cancer enrolled in preoperative exercise training during two postoperative measurement periods. Litterini and Fieler[290] were able to demonstrate improvements in fatigue, QOL, physical strength, and functioning in a small group of patients with lung cancer within 1 year after a twice-weekly, 10-week, individualized physical therapy-directed exercise program. Other researchers[291] did not find a positive impact from early exercise interventions over usual care.

In two small studies of the effect of reflexology on anxiety and pain in patients with cancer (including 30 patients with lung cancer), Stephenson et al[51,292] found an immediate decrease in anxiety[292] and a decrease in both anxiety and pain[51] for patients who received reflexology. One cannot discern from these studies how long the immediate posttreatment benefit lasts, but the study raises the possibility that this complementary intervention might hold promise for patients with lung cancer.

Much research is needed to improve the quality of evidence for determining which factors impact distress among patients with lung cancer and which interventions most effectively target symptoms across the age, socioeconomic, cultural, and illness spectrum of lung cancer. Since most people with lung cancer experience declining health and, ultimately, terminal illness and death, interventions must be delivered in a timely fashion to rapidly target acute symptoms with enough flexibility to match the patient's evolving needs throughout the remainder of the patient's life. Across intervention types, studies demonstrating biopsychosocial benefits for symptom management shared one or more of the following features: increased understanding of one's illness; facilitation of meaning-making; opportunities for active coping; promotion of self-care skills; and provision of a supportive, therapeutic atmosphere for expression and exploration of feelings.[280] Universal access to appropriate symptom management interventions will require expansion of training programs across health-care disciplines (medicine, nursing, psychology, and social work) and extensive resource development to ensure integration of supportive care programs into the "usual care" offered to patients with lung cancer.

In two studies using the National Comprehensive Cancer Network Guidelines on Fatigue as a model, Borneman and colleagues[293] identified barriers to pain and fatigue management. Notably, patients believed physicians would initiate discussion of fatigue if it was clinically important, health-care professionals did not document fatigue assessments, and few referrals were generated to supportive care staff specializing in fatigue management. In a subsequent study, Borneman and colleagues[294] demonstrated that a feasible and patient-accepted psychoeducational intervention addressing fatigue could improve QOL in physical and psychologic domains for patients with lung cancer.

14.1 Recommendations

14.1.1. In patients recently diagnosed with lung cancer it is recommended that comprehensive biopsychosocial assessment be performed soon after the diagnosis is made and at key transition points (completion of treatment, disease progression, and new symptom onset) thereafter for the remainder of life (Grade 1C)**.**

14.1.2. In lung cancer patients that identify psychologic and physical symptoms causing distress or interfering with their QOL, it is recommended that these symptoms are addressed by appropriately trained individuals (Grade 1C)**.**

14.1.3. In lung cancer patients with depression, anxiety, excessive daytime sedation and fatigue, medications such as antidepressants, anxiolytics and psychostimulants are recommended to decrease the morbidity associated with these symptoms (Grade 1C)**.**

14.1.4. In lung cancer patients with psychologic symptoms, a comprehensive symptom management plan is recommended. This should include non-pharmacologic interventions integrated with medication management, which may be offered as a single treatment modality (Grade 1C)**.**

14.1.5. In lung cancer patients with insomnia, sedating antidepressants (which target both sleep and mood) are recommended over sedative-hypnotics (which only improve sleep) (Grade 1C)**.**

14.1.6. In lung cancer patients with the subjective experience of breathlessness, interventions specifically designed to manage this symptom using psychologic coping and physical adaptation are recommended (Grade 1C)**.**

Remark: Targeted interventions for breathlessness, more effectively decrease distress and improve satisfaction with care than usual care provided during medical follow-up office visits.

14.1.7. In lung cancer patients with psychologic distress, it is suggested that one of several psychologic interventions have demonstrated benefit (including psycho-education, deep breathing, progressive muscle relaxation, guided imagery,

cognitive behavioral therapy and supportive psychotherapy) (Grade 2C)**.**

Remark: There is limited evidence to support selection of one intervention over another based on characteristics of the target symptom, patient, or disease status.

Remark: We suggest that psychologic interventions to relieve distress are chosen based on patient preference, available skill-set of the health care team, and the available evidence from lung cancer studies

14.1.8. It is suggested that educational programs responsible for preparing health care professionals to care for persons with cancer should include specific training in psychologic and physical symptom management of symptoms frequently associated with cancer diagnosis, treatment and survivorship (Grade 2C)**.**

14.1.9. It is suggested that health care systems providing care to persons with cancer should develop and support integrated programs in psychologic and physical symptom management which are accessible to all (Grade 2C)**.**

15.0 Conclusion

Symptom management in lung cancer is a very broad topic. The strict methodologic techniques used to write the overall lung cancer guidelines were at many times difficult to apply to the body of literature regarding symptom management. The largest volume of literature addressing symptom management is case reports and series, which we as clinicians have extrapolated and used to guide our management of patients. These guidelines looked at the literature, using only that which has stronger scientific validity, narrowing the recommendations down to that which has the strongest support.

As we prolong the lives of patients with lung cancer, a greater number of clinical problems related to the disease and treatments used to treat it will be seen. The article itself is very long and still only covers some topics superficially. A comprehensive review of this subject could fill an entire textbook on its own.

The recommendations are designed to be tools for practitioners. The topics were chosen to keep treating physicians aware of the potential problems that present as plainly as hemoptysis or an intractable cough or as subtly as a major depression, all of which can contribute to a diminished QOL for our patients.

With newer treatment options arising for patients, a variety of different problems will arise. Subsequent guidelines will be important to keep practitioners aware of these problems and modalities to address them.

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