Palliative Procedures in Lung Cancer

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Abstract

Keywords

- palliative treatment
- superior vena cava (SVC) syndrome
- hemoptysis
- osseous metastasis
- interventional radiology

Palliative care aims to optimize comfort and function when cure is not possible. Image-guided interventions for palliative treatment of lung cancer is aimed at local control of advanced disease in the affected lung, adjacent mediastinal structures, or distant metastatic sites. These procedures include endovascular therapy for superior vena cava syndrome, bronchial artery embolization for hemoptysis associated with lung cancer, and ablation of osseous metastasis. Pathophysiology, clinical presentation, indications of these palliative treatments, procedural techniques, complications, and possible future interventions are discussed in this article.

Objectives: Upon completion of this article, the reader will be able to identify the indications and contraindications for placing a stent in the superior vena cava in the setting of lung cancer, the palliative interventional treatment for hemoptysis, and the indications and contraindications of the treatment of bone metastasis in lung cancer.

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Interventional radiologists have made many advances in endovascular and ablative techniques tailored to cancer care. These techniques today play an integral role in multi-modality cancer treatment. Much of the interventional radiology (IR) literature has focused on curative techniques or prolonged survival; however, these interventional techniques can also improve quality of life. This article addresses particular endovascular and ablative therapies

that provide palliation to the advanced lung cancer patient.

Palliative Treatment of the Superior Vena Cava Syndrome

Superior vena cava (SVC) syndrome is defined as obstruction of the SVC, either by thrombus within the lumen or by compression from surrounding mass effect. SVC syndrome was first described in 1757 in a patient with a thoracic aortic aneurysm causing obstruction of the SVC. The SVC is a thin-walled low-pressure vein, making it intrinsically prone to mechanical obstruction. In addition, its location adjacent to the right upper lobe and mediastinal lymph nodes makes SVC syndrome much more common in the setting of intrathoracic malignancy. The severity of SVC syndrome depends on the presence and degree of a collateral venous system. The azygous system is the most common pathway for decompression of an SVC obstruction, and when an adequate collateral system is in place, symptoms can be minimal despite complete SVC obstruction. In most patients, however, collaterals are insufficient. This leads to elevated venous pressures in the veins that drain the head, neck, and upper extremities, usually involving not only the SVC but also the brachiocephalic, subclavian, and jugular veins.

Symptoms can be gradual or acute. Dyspnea is the most common presenting symptom, with a frequency of 50%.¹

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Other symptoms include chest pain, cough, dysphagia, cyanosis, and hoarseness. Swelling of the upper extremity and face is found in 40 to 45% of patients.² Neurologic symptoms such as headaches and cognitive dysfunction may occur, and when severe, they can lead to syncope, seizures, coma, and death secondary to cerebral venous hypertension. Rapid growth within the mediastinum or acute thrombosis of the SVC can present emergently, leading to airway compromise, laryngeal edema, or venous congestion. Although SVC syndrome can be an oncologic emergency, most cases present with progressive symptoms over months.

SVC obstruction occurs in ~15,000 patients per year.¹ The most common cause of SVC syndrome is malignancy (85 to 97% of cases),³ and the most common malignancy causing SVC syndrome is lung cancer.⁴ The development of SVC syndrome is estimated in ~3 to 15% of patients with bronchogenic carcinoma.⁴ More specifically, small cell lung cancer is implicated in ~38% of cases⁴ (despite only representing 10 to 15% of all new lung cancers), likely related to its more central predilection and high rate of mediastinal node involvement. The mean survival in SVC syndrome caused by malignancy is 6 to 7 months.

The first-line therapy today for acute malignant SVC syndrome is endovascular stenting of the SVC, usually in combination with radiation and/or chemotherapy^{5,6} (→Fig. 1). Several studies report immediate technical success rates from stenting in 90 to 100%, with primary patency of ~70 to 80% at 6 months. Secondary patency is ~95% at 6 months.^{4,5,7-12} Stent placement and angioplasty (with or without thrombolysis) should be considered in patients with acute and severe symptoms necessitating immediate treatment because radiation treatment and chemotherapy may not resolve symptoms quickly enough. In this patient population, the life expectancy is only 3 to 10 months.¹³ The goal of treatment is palliation with symptomatic relief as soon as possible. Success rates with radiation therapy (RT) alone are >70%.¹⁴ Clinical improvement may not be seen in up to 4 weeks with RT therapy alone, however, and recurrence is common. Chemotherapy regimens are typically used to treat SVC syndrome caused by small cell lung cancers and lympho-

ma; however, myelosuppression, infection, alopecia, nausea and vomiting, and stomatitis are common side effects of chemotherapy treatment. Response rates with chemotherapy are best in small cell cancers (60% within 7 days⁷); non-small cell lung cancer, however, is much less sensitive to chemotherapy.

SVC syndrome is a clinical diagnosis confirmed with imaging studies. Initial evaluation includes a detailed lung cancer history and physical examination. Laboratory testing should include hemoglobin, platelet, prothrombin time, international normalized ratio (INR), and partial thromboplastin time (PTT). On chest radiography, a growing right-sided mediastinal or hilar mass is seen in most lung cancer patients. Upper extremity and neck venous ultrasound with Doppler can definitively diagnose the presence of venous obstruction and collateral vascularity. Contrast computed tomography (CT) or magnetic resonance (MR) imaging can further delineate the point of obstruction and the size and character of the obstructing mass, as well as evaluate any additional structures the tumor has invaded.

Before placing an SVC stent, one must know the extent and location of stenosis or obstruction. A superior vena cavogram is therefore crucial, and the presence and extent of collateral circulation should be evaluated before intervention. Thrombosis often occurs after a significant narrowing is reached, and clot lysis or removal is sometimes necessary to relieve symptoms and to permit optimal stenting. Catheter-directed lysis can allow passage of a wire across an otherwise completely occluded vein and eliminate nonocclusive thrombus. The patient should not have any contraindications to thrombolysis including brain metastases. The thrombolytic agent is delivered directly into the thrombus by infusion catheters centered in the thrombus. Angioplasty of SVC occlusion alone often results in rapid recurrence. Pressure measurements of the SVC and right atrium may also be helpful; however, the treatment decision for palliative therapy is based on the patient's clinical findings regardless of the pressure readings.

The right common femoral vein is the most commonly used approach for accessing SVC anatomy prior to stent

Figure 1 A 65-year-old woman with superior vena cava (SVC) syndrome secondary to metastatic lung cancer. (A) Chest radiograph shows a right upper lobe Pancoast tumor with postobstructive right upper lobe collapse. (B) Venography demonstrates abrupt transition at the distal left brachiocephalic vein, slitlike narrowing at the site of tumor compression, and delayed venous drainage of the SVC. (C) Successful deployment of a 14 mm × 80 mm self-expanding stent with sequential balloon angioplasty. (D) Completion superior vena cavogram with excellent flow from the right internal jugular vein through the SVC with no delayed venous drainage. The patient's head and neck swelling resolved within 2 days.

placement. The internal jugular veins or peripheral veins in the arms may also be used to cross a tight stenosis or occlusion, and occasionally a through-and-through wire may be needed to provide adequate support for a catheter or stent delivery system to cross a lesion.¹⁵

Commonly used stents include the Wallstent (Boston Scientific, Natick, MA), the Memotherm (Bard, Salt Lake City, UT), and several self-expanding nitinol stents including the SMART (Cordis, Miami Lakes, FL), Protégé (EV3), and Epic (Boston Scientific) stents.^{16–18} The Gianturco Z-stent (Cook, Inc., Bloomington, IN) and the Palmaz stent (Cordis, Miami Lakes, FL) have been well documented in the literature but are currently used less often.^{9,10} The Wallstent is a self-expandable stent composed of surgical-grade stainless-steel alloy filaments. The 16-mm diameter Wallstents are the most frequently reported in the literature.¹⁹ When stents >16 mm have been used, complication rates were shown to be increased significantly due to wall rupture and increased pulmonary edema.⁴ Total encasement of the SVC by tumor, however, may limit the expansion of the Wallstent. The role of concomitantly stenting of one or both of the innominate veins in SVC syndrome is case dependent.

Complete resolution of the SVC syndrome occurs in 68 to 100%¹⁹ of patients treated with a metallic stent. Immediate relief of disabling headaches is usually noted; facial edema improves within 1 to 2 days, and upper extremity edema typically resolves within 2 to 3 days.

Complications of SVC recanalization are mostly related to bleeding secondary to the use of thrombolytics. Kee et al¹³ reported a 10% complication rate with the combined use of stents and thrombolysis to treat SVC stenosis. Migration of an SVC stent is a rare complication and can be minimized by ensuring adequate stent length on either side of the stenosis with an adequate diameter. Increase in venous return after stent placement can occasionally result in cardiac failure or pulmonary edema. Other complications include recurrent laryngeal nerve paralysis, pulmonary emboli, and SVC wall perforation with cardiac tamponade; SVC perforation is most commonly associated with intrastent angioplasty.

The role of anticoagulation after SVC stent placement is controversial.^{19,20} Patients are often anticoagulated during the procedure due to the thrombogenicity of the metallic stent and slow venous flow. Although many interventionalists use heparin during stent placement, the use of postprocedure anticoagulation varies considerably.

Palliation of Massive Hemoptysis

Although pulmonary tuberculosis is still the most common cause of hemoptysis in the world, lung cancer, bronchiectasis, chronic obstructive pulmonary disease, and cystic fibrosis are the most frequent causes of hemoptysis in North America. Malignancy is responsible for ~30% of cases.²¹ Up to 30% of lung cancer patients reportedly develop hemoptysis, of which 10% can be defined as massive. The incidence of lung cancer was estimated at 226,160 new cases in 2012²² leading to an estimated 7000 cases of massive hemoptysis due to lung cancer per year.²²

Massive hemoptysis is a life threatening emergency, with an all-cause mortality rate ranging from 50 to 85% (without immediate intervention).²³ In patients with lung cancer, hemoptysis continues to be associated with a high mortality rate despite bronchial artery embolization (42 to 92%).²³ Embolization of the bleeding vessels causing hemoptysis, however, frequently provides symptomatic palliation with immediate improvement in or resolution of bleeding.

Hemoptysis in lung cancer is caused by enlargement and abnormal angiogenesis of the arteries supplying the tumor (→Fig. 2). The small vessels within the tumor are fragile, irregular, and tortuous, and prone to hemorrhage. The most common feeding vessels are supplied from the bronchial or intercostal arteries, with numerous anatomical variants. Bronchial artery embolization (BAE) to treat hemoptysis was first reported by Rémy et al in 1977²⁴ and has since become an established treatment for massive and recurrent hemoptysis. Embolization causes mechanical occlusion of the bleeding arteries, followed by platelet aggregation and activation of the clotting system, providing stasis of life-threatening bleeding into the airways that can cause asphyxiation and death.

Indications for BAE include massive or recurrent hemoptysis. Massive hemoptysis is variably defined as the production of 200 to 600 mL of blood in a 24-hour period. Recurrent hemoptysis is defined as three or more episodes of 100 mL of blood per day within a week. If there is no contraindication to thoracotomy, surgical resection as definitive therapy for pulmonary hemorrhage is indicated, although surgical mortality rates have been particularly high (up to 35%)²⁵ when surgical resections are performed emergently. BAE is most commonly performed in patients who are deemed nonsurgical candidates. Other indications for BAE include preoperative BAE in surgical candidates and recurrent hemoptysis in patients who have had prior BAE procedures. The initial management of a patient with acute massive hemoptysis is airway protection to prevent aspiration of blood and resultant asphyxiation. The patient's respiratory status and hemodynamics should be evaluated and optimized. Multidisciplinary planning and coordination between various services including pulmonary medicine, thoracic surgery, and IR is vital.

Before a BAE procedure in a stable nonemergent case, any coagulopathy should be corrected prior to intervention to decrease further bleeding risk during and after the procedure. All medications that prolong bleeding should be stopped. Acceptable coagulation parameters include platelet levels of at least 70,000, an INR of ≤ 1.5 , and an activated PTT of no more than twice that of the control.²¹ In emergent cases, fresh-frozen plasma or platelet transfusion can be given to correct any existing coagulopathy during the procedure. A sputum sample should be sent for culture and sensitivity including bacteria, mycobacterium, and fungi despite known lung cancer, because the infections can be additive.

Preprocedure diagnostic imaging should always include a chest radiograph. If clinically feasible, a chest CT is very helpful to obtain prior to the procedure; this can be used to assess the size of the lung mass in addition to the extent and location of bleeding. Bronchoscopy before BAE can also help

Figure 2 A 72-year-old man with stage IIIB lung cancer and massive hemoptysis. (A) Contrast-enhanced computed tomography with large right upper lobe mass. (B, C) Right intercostobronchial angiogram, early and delayed phases, demonstrates enlarged abnormal vessels feeding a hypervascular mass with a pseudoaneurysm. (D) Postembolization with 300- to 500- μ m microspheres demonstrates complete stasis of flow to the hypervascular mass.

lateralize and possibly localize the site of bleeding, which can make the BAE procedure more efficient with a faster time to embolization of the bleeding artery. Bronchoscopy may not be helpful in massive hemorrhage, however, because extensive blood in the bronchial tree may obscure the original site of bleeding. When bronchoscopy was performed early in the patient's management, Saumenchet et al²⁶ identified the source of hemorrhage on bronchoscopy in 91% of cases compared with only 50% when performed later. In cases of massive hemoptysis requiring emergent embolization, performing bronchial artery embolization without bronchoscopy may be more prudent.

A brief neurologic examination should be performed before the procedure to establish a baseline. This examination should be repeated intermittently throughout the procedure and in the postprocedural setting to assess for inadvertent embolization of the spinal artery. Inadvertent embolization of the radiculomedullary arteries that can arise from the bronchial arteries can lead to spinal cord ischemia. This complication has been described to occur in 1.4 to 6.5% of BAEs.^{27,28}

Diagnostic ascending and descending thoracic aortograms are performed to identify the bronchial arteries and systemic collaterals. The bronchial artery is then selected, commonly with a reverse-curved catheter such as a Mikaelsson, Simmons I, or SOS Omni catheter, although a Cobra or Headhunter catheter can also be used. Microcatheter systems can be placed coaxially through larger 4F or 5F catheters to allow for further stability and safety during embolization.

The bronchial arteries arise from the thoracic aorta at the fifth to sixth thoracic vertebral level. The left main stem bronchus can also be used as a fluoroscopic landmark to locate the bronchial arteries. In ~60% of patients,²⁹ there is a single right bronchial artery, and multiple bronchial arteries are more common on the left. The catheter is directed laterally to select the right bronchial artery and more anteriorly to select the left bronchial artery. The target bronchial artery should be identified, and any angiographic abnormalities should be documented. The selective arteriograms should be reviewed meticulously for the presence of spinal artery branches. The spinal arteries can arise from intercostal

(the right common intercostobronchial artery trunk) and subclavian artery branches, and they have a characteristic “hairpin” loop. Embolization must be performed distal to the origin of the spinal artery to prevent spinal infarct. Any bronchial artery to pulmonary artery or pulmonary vein shunts must also be identified because particles can pass through a bronchial artery to pulmonary artery shunt and cause small pulmonary emboli. Particles that pass through a bronchial artery to pulmonary vein shunt can cause fatal systemic emboli to the heart or brain.

Abnormal angiographic findings that indicate the potential source of bleeding include tortuosity and enlargement of the selected bronchial artery, hypervascularity, aneurysms, extravasation, and bronchial artery to pulmonary artery or pulmonary vein shunting. In hemoptysis caused by lung cancer, all abnormal bronchial arteries and systemic arteries parasitized by tumor (especially in previously embolized patients) should be embolized regardless of whether or not active contrast extravasation is noted.

Embolization can be performed with a variety of embolic agents. Polyvinyl alcohol (PVA) particles (300 to 500 μm) are most commonly used for bronchial artery embolization. Embospheres (Merit Medical, South Jordan, UT), spherical PVA particles (Cook, Bloomington, IN), and Gelfoam (Upjohn, Kalamazoo, MI) pledgets in conjunction with PVA particles may also be used. Proximal embolization with coils or balloons should be avoided because these vessels would become inaccessible for later embolization procedures secondary to their placement in a proximal location. Numerous collateral vessels are often recruited after proximal coil embolization, which also results in a predisposition for further rebleeding. Small particles (<200 μm) and liquid agents such as glue or alcohol are contraindicated secondary to the risk of spinal artery infarct and bronchial wall necrosis. Postembolization angiography should confirm complete occlusion of the bleeding vessel.

Common postprocedure symptoms include fever, leukocytosis, pleuritic chest pain, and dysphagia lasting up to 1 week. This postembolization syndrome is treated supportively. The most dreaded complication is ischemic or contrast-induced transverse myelitis resulting in paralysis. For this reason, only nonionic contrast media should be used, and the volume used should be monitored carefully. Additional complications include pulmonary infarction, bronchial wall or nontarget tissue necrosis, and iatrogenic aortic dissection.

Palliation of Painful Skeletal Metastasis

Osseous metastasis is common in advanced lung cancer, and when left untreated is associated with a median survival of only 3 months.³⁰ Osseous metastases can cause intractable pain, pathologic fracture, neurologic deficits, and decreased mobility. Approximately 50% of patients with osseous metastasis develop poorly controlled pain.^{31,32} The etiology of pain caused by osseous metastases is thought to be multifactorial and includes osteoclast-mediated bone remodeling, loss of mechanical strength of the affected bone, and corresponding activation of sensory nerves. The production of nerve-stimu-

lating tumor-derived products such as cytokines, vasoactive peptides, and growth factors also play a role in the etiology of bone pain. Reduced tumor burden and reduced osteolysis are thought to be the causes for decreased pain following RT, with likely a similar mechanism of action for decreased pain in osseous ablation.³²

Palliation of painful bone metastases consists of a combined multi-treatment approach. This combination includes local radiation, chemotherapy, surgery, image-guided percutaneous ablation, hormonal therapy, radiopharmaceuticals, bisphosphonates, and analgesics. The current standard of care for focal painful osseous metastases is external-beam RT and surgery. Surgery is indicated for osseous metastases causing a recent or impending pathologic fracture; however, many of these stage IV lung cancer patients with osseous metastasis are nonsurgical candidates. Chemotherapy and hormone therapy are not as effective in the treatment of painful lesions. Bisphosphonate therapy may be a helpful adjunct, but there are inherent side effects such as osteonecrosis of the jaw and atypical femur fractures. The intervention discussed here includes percutaneous image-guided ablation of osseous metastasis, which can effectively palliate painful localized metastases.

In the assessment of a patient with painful bone metastasis for possible percutaneous ablation, careful examination of the character, severity, and cause of pain should be performed. The location and severity of pain should be assessed on physical examination. Palliative ablation is indicated in patients with at least moderate pain who have failed oral analgesic therapy. Patients should ideally have pain localized to one or two sites that correspond to the osseous metastatic foci on cross-sectional imaging. Percutaneous ablation is contraindicated in patients with diffuse painful skeletal metastases because it is difficult to localize the source of pain and select an appropriate lesion to treat. Optimal lesions for ablation are osteolytic, mixed osteolytic with osteoblastic lesions, or primarily soft tissue metastases.

Diagnostic evaluation includes platelet and coagulation testing. Prior CT imaging is required for planning and assessment of the anatomy around the lesion of interest. The most useful imaging modality to use during the ablation procedure is CT. CT imaging can be used to assess the location of the probe with respect to the targeted lesion and adjacent structures. Multidetector CT may be used to reconstruct images during the procedure to allow careful evaluation of the ablation zone in multiple planes. Ultrasound (US) can also be used with radiofrequency and microwave ablations because these modalities can produce localized gas, enabling evaluation of the ablation zone by appraising the extent of echogenicity produced by the gas bubbles surrounding the ablated lesion. Although both CT and US can be used for ablation, there are distinct advantages with utilizing CT particularly during cryoablation because the ice ball can be more easily visualized with better spatial resolution as compared with US. US also has limited penetrance in cortical bone, therefore impairing accurate assessment of the extent of ablation. In addition, the gas bubbles noted on US may be misleading in determining the actual extent of ablation.

Thermal ablation treatment methods include radiofrequency (RF), cryotherapy, microwave ablation, laser ablation, and MR imaging–guided extracorporeal-focused US (MRgFUS). Other percutaneous treatment options include alcohol ablation. The type of energy or material delivered, image-guidance methods, and patient and operator experience vary among these methods. These differences can be used to tailor each technique to a particular patient or lesion. This is often based on lesion location, patient tolerance, and goals of therapy. We discuss the three most common palliative ablative techniques: RF ablation, cryoablation, and microwave ablation.

RF ablation has shown excellent palliation of painful bone metastases.^{33–35} Although there is the potential for incomplete tumor ablation at the margins of overlapping treatment areas or at the periphery of treatment margins, the goals of palliative treatment differs from that of obtaining complete tumor-free margins, and bone pain has been shown to be improved significantly in these patients. Patients may experience significant pain during and immediately after RF ablation; however, this is temporary and can be managed with narcotics. Other complications with RF ablation include fever, second-degree grounding pad burns, and damage to adjacent nontarget tissues.

Cryoablation is another common palliative ablative technique. Insulated cryoprobes are used to deliver room-temperature high-pressure argon gas to the lesion. Rapid gas expansion at the distal tip of the cryoprobe causes rapid cooling (Joule-Thompson effect) to temperatures as low as -100°C within a few seconds. Cryoablation is effective in treating complex metastases while preserving adjacent critical structures. An advantage of cryoablation over other ablation techniques is the ability to visualize the developing “ice ball” at the ablation margin (► **Fig. 3**). A recent study by Callstrom et al³² includes a total of 69 treated tumors (ranging

in size from 1 to 11 cm) with mean score for worst pain in a 24-hour period prior to cryoablation of 7.1 out of 10. This pain decreased to a mean score of 1.4 out of 10 during a follow-up period of 24 weeks ($p < 0.0001$).

Microwave ablation technology uses 14.5- to 17-gauge antennae to deposit electromagnetic microwaves (at least 900 MHz) to produce heat-based tissue ablation.³⁶ Microwaves are thought to be less influenced by variable tissue impedance and perfusion-mediated tissue cooling, potentially reaching higher intratumoral temperatures. This characteristic is thought to create larger, more uniform ablation zones with shorter ablation times.³⁶

Possible future treatments for bone metastases include MR imaging–compatible ablation devices and MRgFUS. Potential complications include skin burns and injury to heat-sensitive structures such as nerves and bowel. Laser ablation may also be used to transmit infrared light energy into a tumor to produce heat and coagulative necrosis. A potential advantage of laser ablation equipment is MR imaging compatibility.

Palliative osseous ablation techniques are safe and effective in alleviating painful skeletal lung metastasis and have been found to improve the quality of life for these patients following treatment.

Conclusion

Image-guided percutaneous ablation of bone and soft tissue tumors offers a safe and effective treatment approach. The treatment of lung cancer patients with osseous metastatic disease greatly depends on appropriate tumor selection, with specific consideration of adjacent anatomy and symptomatology. Image-guided ablative therapies have proven to be effective in the treatment of patients who have not responded to conventional treatments and those that are poor candidates for surgery or RT.

Figure 3 Cryoablation treatment for local control of right iliac bone solitary metastasis. (A) Noncontrast computed tomography at the time of ablation demonstrates an osteolytic expansile mass in the right iliac bone. (B) Four cryoprobes were placed in the mass, creating a well-delineated ice ball extending beyond the visible tumor.

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