Palliative Interventions for Pain in Cancer Patients

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ABSTRACT

Pain is a debilitating problem that is common to most patients with cancer at some time during the course of their disease. Conventional therapies such as opiate analgesics and radiation therapy provide suboptimal and limited relief. Novel image-guided interventions have made a significant impact in the management of this difficult problem. This article reviews some of the most promising image-guided techniques for relieving bone and visceral pain in patients suffering from cancer.

KEYWORDS: Pain control, palliation, radiofrequency ablation, osteoplasty, embolization, nerve block

Objectives: Upon completion of this article, the reader should be able to describe five image-guided interventions for palliation of bone or visceral pain in patients suffering from cancer.

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Pain is one of the most common and most feared consequences of cancer. About half of all patients with cancer and more than 70% of patients with advanced cancer report pain at some stage of their disease.¹ Moreover, 75% of those sufferers describe their pain as moderate to very severe. Although cancer pain is considered multifaceted, the most common types of pain in patients with advanced cancer are bone and visceral pain.² Over the last two decades, several image-guided interventions have evolved for treatment of bone and visceral pain in cancer patients. These techniques include radiofrequency ablation (RFA) of metastatic bone tumors, percutaneous cementoplasty with or without RFA of metastatic bone tumors, embolization of hypervascular bone tumors, celiac ganglion block, and splanchnic nerve block.

PALLIATION OF PAINFUL BONE TUMORS

More than 60% of patients with cancer develop bone metastasis, and autopsy studies of patients who die of breast, prostate, or lung cancer have shown that as many as 85% have bone metastases at the time of death.^{3,4} Although most bone metastases are not painful, osseous metastases are the most common cause of cancer-related pain and can result in considerable morbidity, affecting mobility, quality of life, and performance status.

External-beam radiation therapy has made a significant impact in the management of osseous metastases and has become the standard of care. However, published results of radiation therapy for painful bone metastases have shown a suboptimal frequency of response and durability of relief.⁵ The onset of pain relief is not immediate; most patients who have a

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response experience relief 10 to 14 days after the start of treatment. Radiation therapy contributes little to bone strengthening; any bone-strengthening effect usually occurs 2 to 4 months after treatment and can be preceded by a period of transient osteoporosis that increases the risk for pathological fracture.^{6,7} Furthermore, patients with recurrent pain at a previously irradiated site may not be eligible for further radiation therapy. The advent of the image-guided techniques addresses several of these limitations of radiation therapy.

Before any image-guided interventions can be performed, three major issues must be addressed. First, adequate imaging of the affected site is essential for planning the procedure. Because plain radiographs, although helpful, are rarely adequate, cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is necessary for evaluating the extent of disease and the proximity of the lesion to vital structures. Second, the location and severity of the pain must be determined by physical examination and validated pain scales, respectively. The Brief Pain Inventory and Memorial Pain Assessment Cards are two commonly used pain scales. In addition to scoring the pain, the Brief Pain Inventory can be used to assess the extent to which the patient's pain interferes with daily activities. Third, the patient's use of opioid analgesics must be inventoried; it can be translated into a morphine-equivalent dose for outcome analysis and future comparisons.

Radiofrequency Ablation of Painful Bone Metastases

Percutaneous RFA has gained acceptance over the past decade as the primary treatment for extraspinal osteoid osteomas, replacing the once-popular practice of removing these lesions surgically.⁸ More recently, RFA has been applied to treatment of painful bone metastases, with promising early results.⁹⁻¹³ Currently, RFA is reserved for patients with painful osteolytic bone metastases who are not suitable candidates for or have not benefited from other standard forms of therapy. To be considered a suitable candidate for RFA treatment, the patient's pain must originate from a solitary site of metastatic disease in bone and rate 4 or higher on a pain scale of 0 to 10. No maximum tumor size has been determined. Tumors that are in contact with hollow viscera or neural elements should not be treated with RFA. Lesions in weightbearing bones may be treated only if there is no risk of an impending fracture. Patients who have been stabilized with metallic hardware and have tumor recurrence at the surgical site are not eligible for RFA. Hypervascular bone metastases > 3 or 4 cm are a treatment challenge for RFA but a relative contraindication. Preablation arterial embolization can be performed to address the problem of perfusion-mediated

tissue cooling, thereby making the subsequent ablation more effective.

RFA is performed while the patient is under conscious sedation or regional or general anesthesia. CT is the preferred imaging modality for guiding placement of the electrode. The electrode can penetrate the lytic component of the bone metastasis; however, at times a guide needle may be necessary for coaxial placement of the electrode. "Insulated" guide needles are now available and can prevent skin burn at the needle insertion site should the active tip of the electrode stay in contact with the guide needle during the ablation. Depending on the lesion size, one or more ablations are performed, with emphasis on treating the tumor-to-bone interface.

Immediately after the procedure, the patient's pain will increase as a result of the ablation. We prefer to admit our patients so we can administer patient-controlled analgesia and observe them overnight. Others have used epidural anesthesia for the duration of the procedure and recovery period. By day 1 following the procedure, the patient's pain intensity should return to its pretreatment level (i.e., baseline) or lower, and the patient may be discharged with oral pain medication. Significant decreases of pain intensity may be expected 1 week following the procedure. Potential complications include hemorrhage, infection, nerve damage, and fracture. To date, only a few adverse events have been reported after RFA of painful bone metastases, including incomplete hemiplegia, radiculopathy, second-degree skin burn at the grounding-pad sites, transient bowel and bladder incontinence with treatment of a sacral lesion, and acetabular fracture 6 weeks following RFA.^{11,14}

Dupuy et al first reported the application of RFA for painful osseous metastasis in 10 patients.⁹ Pain relief, measured by the Memorial Pain Assessment Card, was attained in 9 of 10 patients. None of the patients experienced major complications. Callstrom et al reported their initial experience with 12 adult patients who had a single, painful osteolytic metastasis and in whom radiation therapy or chemotherapy had failed.¹⁰ The patients were treated with percutaneous image-guided RFA. The authors reported significantly decreased pain scores and a decrease in the interference of pain with daily activities as determined by the Brief Pain Inventory. No severe adverse events were reported. The authors suggested the mechanism of pain relief was probably multifactorial and likely included (1) inhibition of pain transmission as a result of the physical destruction of adjacent sensory nerve fibers involving the periosteum; (2) decreased stimulation of sensory nerve fibers by mechanical decompression of tumor volume; (3) destruction of tumor cells that produce nerve-stimulating cytokines; and (4) inhibition of osteoclast activity.¹⁰ These early promising results provided the impetus for a

multicenter study that was completed in March 2002.¹¹ Overall, 43 patients with severe bone pain were treated with RFA under conscious sedation or general anesthesia. The median number of ablations per lesion was 3 (range, 1 to 14 ablations), with an average time per ablation of 11.7 minutes (range, 1.1 to 52.5 minutes). The mean total ablation time was 49.5 minutes (range, 8.0 to 218.9 minutes). Procedure-related pain was treated with epidural or intravenously administered opioid analgesics, and the patients were observed for a period of 4 to 24 hours, depending on the size of the treated lesion and the degree of postprocedure pain. Significant pain relief was achieved in 41 (95%) of 43 patients. There were significant decreases in mean pain score, interference with daily activities, and opioid use. Adverse events were encountered in three patients and included a second-degree skin burn at the grounding-pad site, transient bowel and bladder incontinence after treatment of a sacral lesion, and a fracture of the acetabulum 6 weeks following RFA of an acetabular lesion. The authors concluded that RFA of metastases involving bone provides significant and durable pain relief for cancer patients who have failed standard treatments.¹⁵

Considering the risk of neural injury after RFA of vertebral body tumors, Dupuy et al conducted ex vivo and in vivo animal studies evaluating temperature distribution in the spinal canal.¹³ The authors reported diminished heat transmission by cortical and, to a lesser extent, cancellous bone in comparison to soft tissues. They concluded, therefore, that radiofrequency thermal ablation can be performed safely in the vertebral body without cytotoxic temperature elevation in the spinal canal, as long as preserved cancellous or cortical bone separates the lesion from the neural elements. The authors acknowledged the lack of neurological or histological testing to determine the effects of treatment in the animals treated in this study. More recently, Nour et al evaluated MRI-guided radiofrequency thermal ablation of the lumbar vertebrae in a porcine model.¹⁶ The animals were monitored for a maximum of 14 days after the procedure. A careful histopathological assessment of the treated vertebrae and adjacent neural elements was conducted after each animal was sacrificed. Interestingly, ablations performed away from the neural elements did not cause any neural injury, but when a radiofrequency probe was placed directly over the posterior cortex, RFA treatment resulted in paraplegia. Histopathological analysis demonstrated focal demyelination and diffuse axonal edema in the vertical tracts of the white matter of the spinal cord. There was degeneration and necrosis in the anterior and posterior horn neurons. Furthermore, pedicular ablations resulted in radiculopathy in two animals. Even though symptoms of radiculopathy resolved with time, histopathological examination showed mild axonal edema in the ipsilateral

nerve roots. The axons in all tracts within the white matter of the cord remained intact. The investigators also reported a close correlation between the lesion size measured on T2-weighted images and the pathology specimen. T2-weighted images also demonstrated that peripherally located vertebral thermal lesions continued to grow into the adjacent soft tissues or the spinal cord, despite the presence of intact cortical bone. The authors concluded that the safety of the procedure depends on the location of ablation within the vertebra.¹⁶ These results contradict earlier reports that suggested intact cortical bone protects against thermal damage to the adjacent neural elements. Gronemeyer et al reported on the use of CT-guided RFA of painful spinal metastases in 10 patients.¹² Lesions ranged in size from 1.5 to 9 cm and involved the thoracic spine, lumbar spine, or sacrum. The procedures were performed under local anesthesia alone to allow intraoperative assessment of the neural status. Four of 10 patients also underwent vertebroplasty 3 to 7 days after RFA. At follow-up, 9 of 10 patients reported an average pain reduction of 74.4% (range, 30 to 100%). Neurologic function was preserved in 9 patients and improved in 1. One patient reported worsening of pain (16.6% over baseline). There were no other complications.

Based on the available data, we can conclude that RFA is a feasible and safe treatment for painful bone metastases outside the spinal column. Preliminary data suggest that RFA is effective in providing significant and prolonged pain relief for patients in whom other standard therapies have failed. The evidence on the safety of RFA in the spinal column is limited and contradictory. Other studies are needed to further investigate the safety and limitations of RFA in treatment of vertebral metastases. There may be a role for the placement of thermistors near temperature-sensitive tissues adjacent to the ablation site to increase the safety of the procedure.

Percutaneous Osteoplasty of Painful Bone Metastases

Vertebroplasty has become a well-accepted treatment for painful benign and malignant lesions within the spine. The mechanism of pain relief associated with cement injection is poorly understood. It is thought that the injection of cement results in stabilization of microfractures in the trabecular bone. Moreover, the exothermic reaction created during the polymerization of the polymethylmethacrylate may have a direct cytotoxic effect on the tumor cells and interosseous sensory nerve fibers.¹⁷ The percutaneous injection of bone cement into bony lesions outside the spinal column is not as well described but has been performed in the acetabulum, pelvis, femur, humerus, and facial bones.^{14,18-20}

In 1995, Cotten et al described the effects of percutaneous injection of acrylic cement into lytic lesions

of the acetabulum in 11 patients with inoperable metastatic bone disease or myeloma.¹⁹ The patients all received radiation therapy an average of 21 days following osteoplasty. The presence of bone cement does not preclude radiotherapy: Polymethylmethacrylate does not alter the mechanism of action of radiation on tumor cells and its integrity is not degraded by radiation.²¹ Percutaneous osteoplasty was performed under conscious sedation by using a 10-gauge needle that was guided fluoroscopically into the target lesion. The average amount of bone cement injected was 15 mL. Pain was relieved in 82% of patients within hours to days and all patients, including four who were bedridden, experienced improvement in walking within 1 to 5 days. Ninety-one percent of patients experienced transitory side effects that subsequently resolved: immediate postprocedural increase in hip pain, low-grade fever ($<39^{\circ}\text{C}$), and renal insufficiency. There were three complications, involving leakage of cement into the acetabular fossa of two patients and into the joint space in one patient. None of the leaks was clinically significant or required additional procedures. One patient developed a fracture of the acetabulum 1 month following the procedure. The authors concluded that, although still experimental, percutaneous osteoplasty provided durable pain relief (mean follow-up, 7.2 months). They also theorized that percutaneous osteoplasty and radiotherapy could be complementary treatments, radiation causing tumor cell destruction and injection of bone cement providing stabilization and the potential for improved function.

The results of this initial study were confirmed in 1998 when Weill et al reported an 83% pain relief response rate following bone cement injection into painful periacetabular lesions.²² Sixty-one percent of patients experienced "total" or "clear" improvement, which were defined, respectively, as disappearance of pain (without analgesic medication) even while walking and a $\geq 50\%$ reduction in analgesic dose or replacement by a non-narcotic medication. Improvement in pain was seen within the first 72 hours. Although there was no clear correlation between the degree of filling of the lesion and pain response, the authors hypothesized that cement distribution may be related to response. The cement distribution took on the appearance of a "neo-acetabular roof" in 10 patients. All 10 patients experienced pain relief, and 90% demonstrated total or clear improvement. Complications were related to cement leaks toward either the joint space or the adjacent soft tissues or veins. Of the 9 reported leaks, only 2 were symptomatic: worsening of pain secondary to cement contact with sciatic nerve and an intra-articular cement fragment requiring surgical removal. In 2003, Hierholzer et al performed percutaneous osteoplasty in five patients with severe bone pain caused by metastatic disease to the pelvis, ilium, or femur.¹⁸ All patients

experienced rapid pain relief and none required pain medication for the duration of follow-up (range, 6 to 24 weeks). There were no reported complications and all patients were discharged on the first postprocedural day. The authors concluded that percutaneous osteoplasty was a powerful additional tool for pain palliation.

Currently, focus has turned to using the combination of RFA followed by percutaneous osteoplasty in the treatment of bony metastases (Fig. 1). It is thought that the coagulative necrosis provided by RFA promotes even distribution of the bone cement and that injecting bone cement into ablated tissue provides stabilization and prevents subsequent fracture.^{12,23} The initial data consisted of small case reports; Gronemeyer et al reported on their results in four patients with painful spinal tumors,¹² and Schaefer et al used the combination therapy to treat a pathological fracture in the tibial plateau of a patient with metastatic melanoma.²³ The four patients who underwent combination therapy for their spinal lesions reported that they felt more secure during movement, and the patient with the tibial plateau fracture was able to walk without pain on the first day following the procedure.

In 2004 and 2005, published results of two series provided data on the largest number of patients treated with both RFA and percutaneous osteoplasty to date. In 2004, Nakatsuka et al evaluated the feasibility, safety, and efficacy of combined treatment with RFA followed by bone cement injection in 17 patients with 23 malignant bone lesions.¹⁴ Seventeen lesions were located within the spine, three in the iliac bone, two in the sacrum, and one in the ischium. Pain relief was assessed using a visual analogue scale (VAS) score, and MRI imaging was performed 1 week following the procedure to evaluate local tumor effects. The technical success rate was 96%; one osteoblastic lesion was impermeable to the RF probe. In the 13 patients who complained of pain, relief was achieved in all patients within the first week, with a significant decrease in VAS score, from 8.4 to 1.1. Tumor necrosis, as inferred by the lack of enhancement on MR imaging, was observed in 71%, and lesions ≤ 5 cm exhibited a significantly larger necrosis rate than those ≥ 5 cm. Major complications occurred in four patients (24%) and consisted of incomplete hemiplegia in three patients who had tumor involvement of the posterior cortex of the treated vertebral body and radiculopathy in one patient who had tumor involvement of the pedicle. Interestingly, the complications in the study of Nakatsuka et al mirror those reported by Nour et al.¹⁶ In their porcine model, pedicular RFA was associated with radiculopathy and axonal edema, and RFA over the posterior cortex of the vertebral body resulted in paraplegia and demyelination. Nakatsuka et al concluded that combination therapy is both feasible and effective for the treatment of malignant bone neoplasms but that safety depends on tumor location.¹⁴

Figure 1 A 68-year-old woman with a history of non-small cell lung cancer had severe pain at the site of a lytic metastasis in the distal left femur that required moderate to high doses of opiate analgesics. She underwent radiation therapy with no benefit. (A) Axial computed tomography (CT) image of the left distal femur demonstrates the lytic lesion involving the medullary cavity. The cortex is intact. There is no risk of impending fracture. (B) Axial CT image demonstrates placement of the guide needle within the tumor for subsequent radiofrequency ablation and injection of bone cement. (C) Anteroposterior and lateral radiographs of the left distal femur at 5-month follow-up demonstrate the distribution of bone cement in the tumor. There is no evidence of an enlarging lytic lesion or a pathological fracture. She was not taking any pain medications and her pain score was 0 (pain scale: 1 to 10).

Toyota et al also treated 17 patients with 23 painful bone lesions using RFA followed by percutaneous cement injection over a 2-year period.²⁰ The technical success rate was 100%. Although no major complications were reported, the patient who had his femur treated fractured it 2 days later in a fall. The locations of the lesions were as follows: thoracic spine (n = 3), lumbar spine (n = 3), sacrum (n = 2), pelvis (n = 10), humeral head (n = 2), femur (n = 1), maxilla (n = 1), and mandible (n = 1). Immediate pain relief was achieved within 3 days in all 17 patients, defined as a significant decrease in VAS score and, in 41%, a decrease in analgesic dose. The mean duration of pain relief was 7.3 months. Furthermore, 31% of patients experienced an improvement in mobility; three bedridden patients were able to sit up, and two wheelchair-bound patients were able to stand or walk. Three patients experienced pain recurrence 2 weeks to 3 months after treatment. One patient

who had previously received high-dose irradiation developed recurrence 2 weeks following the procedure. It was noted that, during RFA of the sacral metastasis in this patient, temperatures did not rise above 50°C because the generator showed roll-off instantly. Although the authors believe combination therapy is an effective new technique for the treatment of bone pain, they question the utility of the treatment in weightbearing long bones and in tissue with altered impedance properties. The response rates (100%) with respect to pain relief from these two studies on combination therapy suggest it is equally effective to or more effective than vertebroplasty (94 to 97%)^{17,24} or RFA (95 to 100%) alone.^{10,15} Combination therapy is a promising technique that warrants further investigation with respect to long-term efficacy.

Considering the reduced life expectancy in patients with advanced neoplasms, an ideal procedure

for the palliation of bone pain should provide lasting relief in a timely manner, improve a patient's quality of life, decrease hospitalizations, and be well tolerated. Although radiation therapy remains the standard of care, the novel, minimally invasive, image-guided procedures also meet palliation goals. In some aspects they provide distinct advantages over radiation therapy: The onset of pain relief is more rapid, the bone can be stabilized with cement injection, and RFA can often be repeated at the same site should the tumor recur. At the very least, these new techniques offer patients viable alternatives when conventional therapy fails.

Arterial Embolization of Hypervascular Bone Tumors

Arterial embolization for treatment of painful bone metastases was first reported in the 1970s.²⁵⁻²⁷ Since

then, development of digital subtraction angiography and advances in microcatheter technology have greatly simplified embolization procedures. In the setting of painful bone metastases, embolization has been used most commonly in treatment of hypervascular bone tumors from renal cell carcinoma, thyroid carcinoma, and hepatocellular carcinoma.²⁸⁻³¹ Today, preoperative embolization of hypervascular bone metastases is accepted as the standard of care, and the procedure can provide substantial pain relief in selected patients with bone metastases (Fig. 2).²⁸⁻³⁴

Patients undergoing embolotherapy usually require only conscious sedation. Only patients with severe, intolerable pain may require general anesthesia. Conventional angiographic techniques are used to delineate the extent of the disease and the arterial supply to the tumor. In addition to branches from the regional parent arteries, tumors often parasitize arterial feeders from other, less

Figure 2 A 50-year-old man with advanced renal cell carcinoma complained of severe pain in the right hip region. (A) Sequential contrast-enhanced axial computed tomography images of the right hemipelvis demonstrate a large soft tissue mass invading and destroying the right iliac bone, acetabulum, and pubis. (B) Selective digital subtraction angiogram of the right internal iliac artery demonstrates large hypervascular tumor. (C) After superselective catheterization and embolization of several branches of the right internal iliac artery, angiogram demonstrates marked reduction in tumor stain.

predictable sources. Coaxial catheterization with the use of microcatheters and microwires is essential for safe, selective embolization. Appropriately sized permanent solid embolization particles (e.g., polyvinyl alcohol [PVA], tria-acryl microspheres, and others) are often used to occlude the arterial supply at the tumor bed, and larger solid particles (e.g., Gelfoam pledgets [Johnson & Johnson, Somerville, NJ]) may be used to occlude the more proximal feeders. Metallic coils, used in earlier series, are not recommended. There are few contraindications for embolization. These include severe renal insufficiency, severe allergic reaction to iodinated contrast medium, and severe atherosclerotic disease. No maximum tumor size has been determined. Tumors in close proximity to viscera and neurovascular bundles can be treated safely. Furthermore, previous surgery and stabilization with metallic devices do not preclude embolotherapy.

Postembolization syndrome, albeit in its mild form, is often encountered following embolotherapy. In a retrospective review of 61 cases of arterial embolization of hypervascular bone metastases, Barton et al reported that 72% of patients experienced postembolization syndrome.³⁴ All patients are admitted to the hospital for observation and/or symptomatic control of nausea, vomiting, pain, or fever. In our experience, hospitalization is often brief and patients are usually discharged within 24 hours. Other than a mild form of postembolization syndrome, complications are rare. Nontarget embolization, muscle or skin necrosis, and arterial thrombosis are potential complications but are encountered infrequently. Meticulous angiographic technique, selective catheterization, and appropriately sized particles are essential components of embolotherapy and minimize the number of iatrogenic complications. Pain relief is expected to begin a few hours after embolotherapy is completed. Typically, the duration of pain relief ranges from 1 to 8 months,^{27,29,34} although some authors have demonstrated longer periods of response.²⁶ Because tumors are capable of revascularization and growth, symptoms may recur after a variable period of time. Repeat angiography and embolization may provide additional periods of relief from pain.

Whereas the earliest papers on arterial embolization of bone metastases focused on the technical feasibility and applicability of the procedure in different tumor types, later series have served to confirm the initial findings.^{25-27,30} In their 1996 series, Barton et al embolized 11 patients with bone metastases for pain palliation.³⁴ Following the procedure, all 11 patients experienced pain relief within 12 hours to a few days. The duration of response was 2 to 8 months, and five patients were pain free at time of death. Furthermore, all patients were weaned successfully from opiate analgesics. In 2003, Eustatia-Rutten et al reported the outcomes of palliative embolization of bone metastases in patients with differentiated thyroid carcinoma.²⁹

Forty-one embolizations were performed in 16 patients. Treatment was considered successful in 59%, as indicated by improvement of clinical symptoms and absence of tumor progression for at least 1 month after embolotherapy. Median duration of symptom relief was 6.5 months. Twenty-six embolizations were preceded or followed by additional therapies. Subgroup analysis revealed that additional therapies did not influence the success rate, although patients treated with additional radioiodine or external irradiation enjoyed a longer symptom-free survival interval (median, 15 months). Despite the high rate of bone metastases in patients with renal cell carcinoma, to date no large series of embolotherapy has been reported for palliating pain in these patients. Several series have included a few patients whose metastatic renal cell carcinoma was treated with embolization.^{26-28,35,36} The results were promising, but the details were scant.

The most recent series in the literature have examined the role of arterial embolization as an alternative to or in combination with other modalities of therapy for pain palliation. In 1996, Murakami et al compared embolotherapy with radiation therapy for painful osseous metastases from hepatocellular carcinoma.³¹ After embolization therapy, complete, partial, or no pain relief was achieved in 57%, 29%, and 14% of patients, respectively. Radiation therapy resulted in complete, partial, or no pain relief in 47%, 47%, and 6% of patients, respectively. The authors concluded that both embolotherapy and radiation therapy are effective methods of palliation for these patients and the treatment should be chosen on an individual basis. Uemura et al compared the efficacy of three different methods of treating bone metastases from hepatocellular carcinoma.³⁷ In their retrospective review of 39 metastatic bone lesions, 11 lesions were treated with transarterial embolization only, 17 lesions were treated with a combination of transarterial embolization and external radiotherapy, and 11 lesions were treated with external radiotherapy alone. Although each treatment was successful in providing initial pain relief, patients who underwent transarterial embolization experienced relief more rapidly. Rates of pain recurrence were 75% for the group treated with transarterial embolization alone, 20% for the group treated with the combination of transarterial embolization and external radiotherapy, and 88% for the group treated with external radiotherapy alone. Their data show that, although arterial embolization and external radiotherapy alone can provide temporary pain relief for hypervascular bone metastases, the use of the two treatments in combination results in a higher rate of permanent relief. The authors hypothesized that the radiation effect on the arterioles helps prevent tumor revascularization, thus resulting in an additive effect to the occlusion of larger vessels achieved by transarterial embolization.

In 1998, Nagata et al described the use of trans-arterial chemoembolization for the treatment of primary and metastatic bone tumors.³⁸ Patients (n = 10) with primary bone or soft tissue sarcomas underwent chemoembolization as part of combination treatment with radiotherapy, with or without hyperthermia. Patients (n = 31) with metastatic bone tumors, refractory to or recurrent following radiotherapy, were treated only with arterial chemoembolization. A combination of 20 to 40 mg of doxorubicin and 50 to 100 mg of cisplatin was used for primary tumors; 20 to 40 mg of doxorubicin was used for metastatic lesions. An initial response with a decrease in pain level to below pre-embolization level was achieved in 1 to 2 days. At the 2-week follow-up, 89% of patients with primary bone tumors and 76% of patients with metastatic lesions had sustained pain relief. A more recent series by Chiras et al evaluated the effect of arterial chemoembolization on pain control and tumor response in surgically unresectable metastatic bone tumors following failure of radiotherapy and chemotherapy.³⁹ Twenty-five patients with analgesic-resistant bone pain from lytic metastases underwent superselective arterial catheterization and chemoembolization with pirarubicin mixed with PVA foam, followed by chemo-infusion of carboplatin. Eighty-three percent of patients had significant pain relief with an associated decrease in analgesic use. The mean duration of response was 12 months (range, 4 to 36 months). Tumor response was measured radiographically: 40% of patients had stable disease, 16% of patients demonstrated a partial response with < 50% decrease in tumor bulk, and 8% of patients had a response of > 50% reduction in tumor volume. The authors concluded that tumor response to the local delivery of antineoplastic agents enhanced the durability of pain relief when compared with the data reported in the literature on response duration following bland arterial embolization.

Embolotherapy is a safe and effective treatment for the palliation of pain related to hypervascular bone metastases. Clear benefit has been demonstrated with bland arterial embolization alone; however, more recent data suggest that the combination of arterial embolization with other treatment modalities offers the potential for additional benefit with respect to prolonged durability of pain relief and decreased tumor volume.

PALLIATION OF VISCERAL PAIN

Celiac Ganglion Block

Celiac ganglion block is applied most commonly to patients with pancreatic, gastric, or biliary cancer who have severe intractable abdominal pain. First described in 1919 by Kappis, the procedure has undergone technical revision and refinement with respect to methodology and the use of radiologic guidance.⁴⁰ The celiac

plexus consists of three sets of sympathetic ganglia that serve as a relay station for visceral afferent nerve fibers that carry pain sensation from all abdominal and most pelvic viscera. The signal leaves the plexus along the vagus, thoracic, and lumbar splanchnic nerves. The celiac ganglia, the largest of the three, are located anterolateral to the aorta and < 1 cm inferior to the origin of the celiac artery. The other ganglion pairs are the superior mesenteric and aorticorenal ganglia, which are located slightly inferior to the celiac ganglia.

Although the early experience with image-guided celiac block involved the use of angiography and/or fluoroscopy, CT has emerged as the modality of choice for guiding the procedure because it both increases precision in needle placement and decreases risk of inadvertent injection of neurolytic agent into the spinal cord, vascular structures, or abdominal viscera.^{41,42} Either an anterior or a posterior approach may be used. One or two biopsy needles are placed just anterior to the diaphragmatic crus at or slightly inferior to the origin of the celiac artery. A small amount of air or diluted contrast material is injected through each needle to confirm appropriate needle placement. This is followed by the injection of ~20 mL of 98% alcohol in each needle, or 40 mL if a single-needle approach is used. Before the needles are removed, 3 to 5 mL of saline is injected in each needle to clear residual alcohol and to prevent alcohol from tracking back along the needle path. During and soon after the alcohol injection, all patients experience abdominal pain or "burning" pain in the back, which may require the administration of narcotics immediately following the procedure.

Technical success rate for the procedure approaches 100% regardless of the technique used.⁴³⁻⁴⁵ Minor complications such as local pain and diarrhea are common, occurring at rates of 38 to 96%, but are usually self-limiting.⁴⁴ Transient orthostatic hypotension is also frequent after celiac block, and an 8-hour period of recovery in a supine position is recommended. Major complications such as pneumothorax, pleuritic chest pain, hiccoughing, hematuria, and neurological complications (lower-extremity weakness and paresthesia, epidural anesthesia, and lumbar puncture) are rare, with a reported rate of 2%.⁴⁴ With appropriate patient selection and meticulous technique, response rates for palliation of cancer pain as high as 90% may be expected.⁴⁴ Potential causes for failure to achieve pain relief include suboptimal needle placement, insufficient volume of neurolytic agent, poor infiltration of the celiac plexus secondary to tumor involvement or fibrosis, alternative pain pathways, and anatomical variations.^{41,46,47}

In patients with intractable pain related to malignant abdominal disease, image-guided celiac block provides sustained pain relief. In a meta-analysis of the literature examining 1145 patients, Eisenberg et al concluded that celiac ganglion block was effective in

controlling 90% of pain in the first 3 months and that long-term benefit, consisting of partial or complete pain relief at the time of death, was achieved in 70 to 90% of patients.⁴⁴ Several studies have shown that, in addition to pain relief, celiac ganglion block can significantly reduce narcotics requirement,^{45,48-51} although other authors have not found a significant decrease in narcotic consumption following celiac block.^{52,53} Wong et al performed a double-blinded, randomized, controlled prospective study comparing the outcomes of pancreatic cancer patients undergoing celiac ganglion block (n=50) with those of patients treated with systemic pharmacotherapy alone (n=50).⁵³ The outcomes measured were pain intensity, quality of life, opioid consumption, opioid adverse effects, and survival. The authors reported that celiac ganglion block conferred long-term pain relief but did not significantly affect the other measured parameters.

The World Health Organization (WHO) analgesic ladder is the current recommended standard for managing cancer pain.⁵⁴ It proposes a stepwise optimization of systemic pharmacotherapy that uses nonsteroidal anti-inflammatory agents first, followed by opioid agents. Neurolytic block is recommended only when opioids fail to control the pain or when the side effects of systemic pharmacotherapy become too debilitating.⁵⁵ Several authors have challenged the WHO concept of reserving celiac ganglion block as a last resort management tool.^{43,45,51} Akhan et al examined the long-term effects of celiac ganglion block as related to the degree of tumor invasion of the celiac region.⁴⁵ Forty-one patients with inoperable intra-abdominal cancer underwent celiac ganglion block and were followed until death (1 to 24 weeks). The degree of tumor invasion of the celiac axis in each patient was graded on a 4-point scale as determined by the CT appearance of the para-aortic and paracaval fat planes (grade I, no invasion; grade II, < 50% invasion; grade III, > 50% invasion; grade IV, complete invasion). Ninety-five percent of patients experienced significant pain relief associated with decreases in overall pain intensity and mean daily analgesic consumption; however, the degree of pain relief was inversely correlated to the degree of tumor invasion of the celiac axis. Therefore, the authors concluded that performing celiac ganglion block early in the disease process, prior to extensive tumor invasion, can increase its effectiveness.

Splanchnic Nerve Block

For patients in whom celiac ganglion block has failed, splanchnic nerve block may provide a viable alternative. The splanchnic nerves arise from the thoracic sympathetic trunk (ganglia 5 to 12) and carry preganglionic sympathetic fibers as well as visceral afferent fibers from the abdominal organs. The greater, lesser, and least

splanchnic nerves pierce the crura of the diaphragm at the levels of T11 and T12 to join with the celiac ganglion. Interruption of these nerve fibers can provide relief from pain associated with intra-abdominal malignancies.

Kappis first described neurolysis of the splanchnic nerves in 1914.⁵⁶ Recently, interest in the procedure has been renewed by the development of minimally invasive, image-guided techniques. Percutaneous splanchnic nerve blocks can be performed under fluoroscopic or CT guidance, using an anterior or posterior transcrural or transthoracic approach, with disruption of the nerve fibers either from chemical neurolysis or RFA.⁵⁷ The biopsy needles or radiofrequency probes are placed at the anterolateral aspects of T11 or T12. The needle is aspirated and if no fluid is obtained, a small amount of nonionic contrast is injected to confirm needle position. Imaging should confirm that the contrast solution hugs the spine. To ensure the procedure will relieve pain and not exacerbate symptoms, it is recommended that patients first undergo a trial block with local anesthesia to predict their response to splanchnic nerve blockade.^{57,58} Prior to RFA, sensory and motor test stimulation is performed to confirm a reproducible sensation in the epigastrium and to exclude intercostal muscle contraction. Two to three radiofrequency lesions are created on each side, with settings at 80°C for 60 to 90 seconds.^{57,58} Alternatively, traditional chemical neurolysis with ~10 mL of alcohol or 6 to 10% phenol can be performed. Complications include pneumothorax, transient diarrhea, diaphragmatic paralysis, and cardiac arrhythmias.⁵⁷

Proponents of the splanchnic nerve block have advocated its inherent anatomical and technical advantages over the more commonly performed celiac ganglion block. First, the splanchnic nerves have a more predictable anatomical location and are not as closely associated with vital vascular and neurological structures, thus allowing for the use of novel techniques such as RFA. Second, the use of RFA increases the accuracy of nerve destruction, obviating the uncertainty related to the uncontrolled diffusion of chemical neurolytic agents. Third, the data show that RFA provides immediate pain relief, whereas the effect of chemical neurolysis is frequently delayed.⁵⁷

Data on the efficacy of the procedure are not as prevalent as that on celiac ganglion neurolysis; however, splanchnic nerve ablation with alcohol has been associated with pain relief in ~70% of patients.⁵⁹ Furthermore, Marra et al reported that pain relief in patients undergoing splanchnic nerve block was superior to that in patients undergoing celiac axis block.⁵⁹ The data on RFA of the splanchnic nerves for pain palliation are even more limited. Garcea et al reported on 10 patients with chronic pancreatitis who underwent RFA of the splanchnic nerves for pain control. Statistically

significant changes observed included decreases in pain scores, opioid consumption, and acute hospital admissions for pain control as well as improvements in anxiety levels, overall mood, daily activity, and general perception of overall health.⁵⁷ Prithvi Raj et al⁵⁸ reported the largest series in the literature, consisting of 107 patients who underwent unilateral or bilateral splanchnic nerve ablation for chronic benign or malignancy-related abdominal pain that was unresponsive to systemic analgesia. All patients reported a > 50% reduction in pain intensity immediately following the procedure. Long-term results show that ~40% had an excellent result, defined as sustained pain relief correlating to reduction in pain on VAS by 50 to 75%. Only 15% of patients had a poor result, which was defined as a pain reduction < 10%.⁵⁸ Clearly, the initial data on RFA of the splanchnic nerves for pain palliation appear promising; however, prospective, randomized, controlled trials are needed to study its efficacy and safety in comparison to systemic analgesic therapy and neurolytic celiac ganglion block.

CONCLUSIONS

A neglected public health problem in the recent past, cancer pain today is recognized internationally as a significant health issue. Pain management is vital to reduce patients' suffering and improve their overall comfort. To date, this enormous need remains largely unmet. Given the high prevalence and complex nature of cancer pain, it is unrealistic to expect one profession or group of specialists to undertake the enormous task of pain management in cancer patients. Nevertheless, the availability of minimally invasive, image-guided interventions offers interventional radiologists a major role in the multidisciplinary management of cancer pain.

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