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CLINICAL INVESTIGATION NON-VASCULAR INTERVENTIONS

Palliative Percutaneous Cryoablation and Cementoplasty of Acetabular Metastases: Factors Affecting Pain Control and Fracture Risk

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Abstract

Purpose To characterize the response of patients with acetabular metastases following combined cryoablation and cementoplasty (CCC) for pain palliation and fracture risk reduction, based on completeness of ablation and the presence of pre-existing pathologic fracture.

Materials and Methods Thirty-nine consecutive acetabular CCC procedures were performed in 37 patients (24 M:13F, age 66 ± 8 years). Pain was assessed using a 0–10 numeric rating scale. Development of new or progression of pre-existing fractures and local tumor progression (LTP) were determined on follow-up imaging. Pain score reduction and fracture development rates were compared by ablation completeness and the presence of pre-existing fractures.

Results Twenty-three of 27 (85%) patients with evaluable pain scores had reduced pain, decreasing from 7.5 ± 2.1 to 3.6 ± 2.6 ($p < 0.0001$). Of 39 tumors, 28 (72%) were completely ablated with no significant difference in pain reduction after complete versus incomplete ablations ($p = 0.9387$). Six of 30 (20%) patients with follow-up imaging demonstrated new/progressive acetabular fractures. Four of 5 (80%) patients with LTP developed new/progressive fractures compared to 2 of 25 (8%) without tumor progression ($p = 0.0003$). Pre-existing fracture was not associated with subsequent fracture/fracture progression ($p = 0.2986$). However, patients with prior acetabular radiation therapy or surgery had increased fractures following treatment ($p = 0.0380$).

Conclusion Complete acetabular tumor ablation during CCC was not associated with superior pain relief compared to subtotal ablation but did result in improved fracture stabilization. Pre-treatment pathologic fractures were not associated with fracture progression, but new/progressive fractures were more frequent in patients with prior radiation therapy or surgery.

Keywords Acetabulum · Cryoablation · Percutaneous cementoplasty · Palliative treatment · Pathologic fracture

Introduction

The estimated prevalence of bone metastases among adults in the USA was 330,000 in 2012 [1]. Fifty percent of patients with osteolytic metastases develop intractable pain with decreased quality of life, frequently due to pathologic fracture [2]. Treatment of skeletal metastases that cause pain or are at risk for fracture can improve the quality of life in these patients [3].

Minimally invasive, focal ablative techniques applied to painful bone metastases include radiofrequency ablation,

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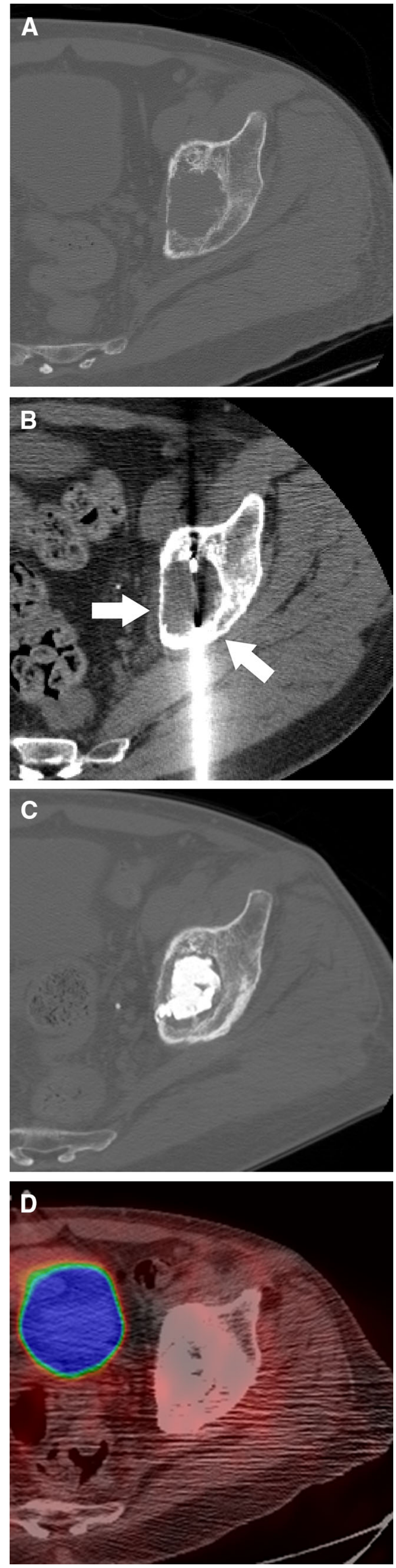
cryoablation, and microwave ablation [4–7]. These therapies may reduce pain and provide local tumor control, but they do not add structural support to areas of bone destruction. Percutaneous instillation of cement into bone, termed osteoplasty or cementoplasty, has been employed to add structural support and treat painful metastatic skeletal lesions [8, 9]. Cementoplasty may be especially valuable after thermal ablation procedures that further weaken the surrounding bone. Safety and efficacy of radiofrequency ablation and cryoablation combined with cementoplasty have been reported in series treating skeletal metastases in various locations, including the pelvis [10, 11]. In the acetabulum specifically, microwave ablation and radiofrequency ablation in combination with cementoplasty have been shown to improve patient pain [12, 13].

Given the complex surrounding anatomy, acetabular tumors pose a particular challenge for percutaneous ablation. Specifically, important motor nerves surround the region and must not be ablated to avoid morbidity. Furthermore, extension of the ablation zone into the hip joint or weight-bearing femoral head must be minimized to avoid complications of hemarthrosis, avascular necrosis with femoral head collapse, or subsequent degenerative arthritis [14–16]. As pain from bone tumors is generally considered to arise from the bone–tumor interface [17], most palliative treatment is focused on this region of the tumor. In some cases, the metastasis may be incompletely ablated to minimize the risk of periprocedural complications. However, it is unclear whether complete ablation leads to better outcomes in terms of palliation of pain and fracture risk reduction (Fig. 1).

The purpose of this study was to characterize the response of patients with osteolytic acetabular metastases treated with combined cryoablation and cementoplasty (CCC) for pain palliation and fracture risk reduction based upon the completeness of tumor ablation and the presence of a pre-existing pathologic fracture (Fig. 2).

Materials and Methods

Institutional Review Board approval was obtained, and informed consent was waived for this single-center, retrospective review. A prospectively maintained departmental tumor ablation registry was searched for CCC performed to treat metastases in the acetabulum between January 2004 and September 2012, yielding 39 combined procedures performed in 37 patients, including 2 patients treated for bilateral tumors (Table 1). Procedures performed after this period were not included due to different techniques, including vertebral augmentation balloon assistance as well as intermittent bipolar radiofrequency ablation instead of or in combination with cryoablation, used in the treatment of



◀**Fig. 1** Successful complete cryoablation and cementoplasty for pain and fracture risk reduction. **A** A 75-year-old man with a 4.0 cm osteolytic Hurthle cell carcinoma metastasis to the left acetabulum presented for treatment of pain, scored as 8/10. **B** Ablation zone (arrows) covered the entire tumor during cryoablation. **C** Cement filled the tumor cavity after cementoplasty with no fracture on 3-month follow-up CT. Patient's pain was rated as 3/10. **D** No residual tumor seen on 19-month follow-up PET/CT

acetabular tumors since that date [18]. Patients with plasmacytomas or multiple myeloma were included due to the similar behavior of these tumors to metastases, but primary bone tumors were not included. Mean patient age was 66 ± 8 years. Mean tumor size was 4.5 ± 1.3 cm, and 12 different primary tumor histologies were included in the cohort, most commonly renal cell carcinoma (36%), plasmacytoma or multiple myeloma (18%), and lung carcinoma (15%).

Patient Selection and Pre-procedural Assessment

Inclusion criteria were the presence of an osteolytic acetabular metastasis causing moderate-to-severe pain or at risk of pathologic fracture. Patients with painless acetabular tumors were evaluated pre-procedurally by an orthopedic surgeon and subjectively deemed at sufficient risk for fracture to warrant intervention. All patients had cross-sectional imaging of the pelvis performed using computed tomography (CT) or magnetic resonance imaging (MRI) within 10 weeks of treatment (mean 19 ± 9 days). Pre-existing pathologic fractures were identified within the index tumors as linear areas of decreased attenuation on CT or signal intensity on MRI or areas of cortical discontinuity on either imaging modality. Patients with purely osteoblastic metastases were excluded from CCC based on uncertainty regarding the benefit of cement stabilization in these tumors. The referring clinician and/or interventional radiologist assessed each patient's acetabular pain level within one week prior to cryoablation, and pain was graded using the Numeric Rating (10-point) Scale (NRS). Informed consent was obtained from all patients for the CCC procedures.

Cryoablation Technique

The cryoablation procedure was performed with patients under general anesthesia and using CT guidance and a commercially available controller (Endocare Cryocare system, HealthTronics, Inc, Austin, TX, USA) with a variety of cryoprobe sizes (1.7 or 2.4 mm outer diameters) as previously described [19]. Generally, 2 or more cryoprobes were used for treatment of each tumor (mean 2.8 ± 1.2, range 1–6), based on radiologist discretion, and were placed with 1–2 cm spacing and within 1 cm of the tumor margin. Two freeze cycles were performed, each of approximately 10-min duration, depending on the adequacy of tumor coverage and proximity of adjacent critical structures. An attempt was made to cover each tumor completely, while avoiding encroachment of the ice ball upon the femoral head and the periacetabular neural structures. In general, this balance was achieved by biasing the cryoprobes away from the joint space, attempting to place them about 1.5 cm away, and closely monitoring with attention to the femoral head. Limited noncontrast CT images were obtained every 2–4 min during each freeze cycle to monitor growth of the ice ball. Intraprocedural neurophysiologic monitoring was performed in 5 (13%) of 39 procedures, as previously described [20]. Patients were admitted for overnight inpatient observation.

Cementoplasty Technique

Cementoplasty was performed on the day of cryoablation (n = 1), or 1 day (n = 32), 2 days (n = 2), 3–5 days (n = 3), or 18 days (n = 1) following cryoablation. Deviations from routine next-day cementoplasty were related to scheduling logistics or, less commonly, patient conditions unrelated to the procedure. Eleven- or 13-gauge bone biopsy needles (Osteo-Site M2, Cook Medical, Bloomington, IN) or 11-gauge curved injection needles (AVAflex, Cardinal Health, McGaw Park, IL) were used to access the same tracts used in the cryoablation procedure for cement injection. Two 30 mL of polymethylmethacrylate cements (Ava-Tex Radiopaque Bone Cement, Cardinal Health, McGaw Park, IL) were prepared and administered within 15 min using an injector set (Duro-Ject, Cook Medical, Bloomington, IN) while monitoring with intermittent CT fluoroscopy based on radiologist preference and equipment availability. When possible, cement was anchored into intact medullary bone either deep to the tumor or during needle withdrawal.

Post-procedural Assessment

Apparent completeness of tumor ablation was assessed by the interventional radiologist at the time of the cryoablation procedure and recorded in the radiology report. Complete ablations were defined as the ice ball encompassing the entirety of the osteolytic acetabular tumor, including any extraosseous soft tissue component, on the final intraprocedural monitoring CT scan. Tumors were also evaluated on any available subsequent pelvic cross-sectional imaging (n = 30) for local tumor progression, defined as new osteolytic bone adjacent to the ablation zone, enlargement of the osteolytic mass, or new or residual enhancing soft tissue component [21]. Fracture progression was

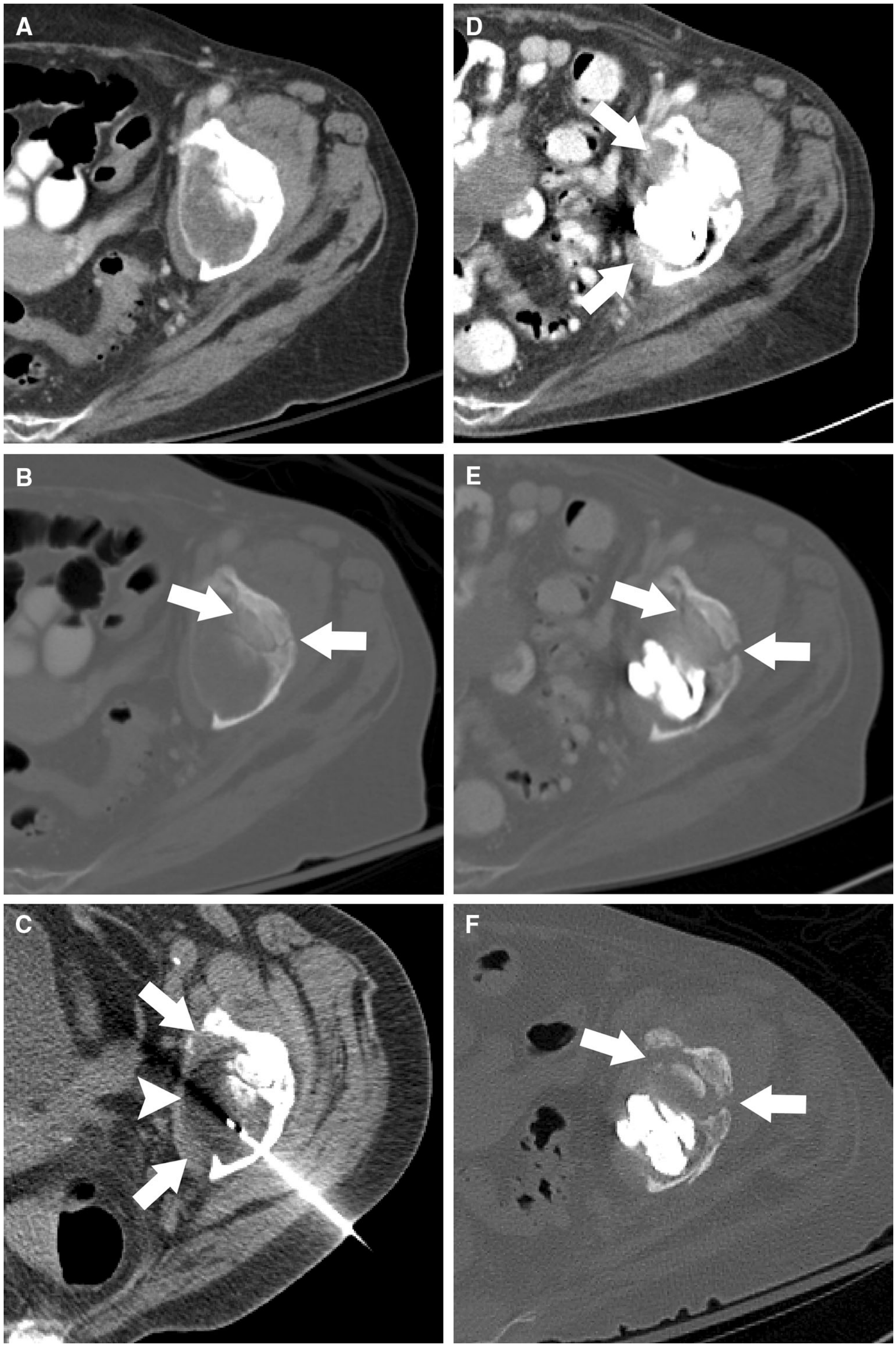


Fig. 2 Incomplete cryoablation and cementoplasty for pain and fracture risk reduction. **A** A 71-year-old woman with a 5.6 cm osteolytic renal cell carcinoma metastasis to the left acetabulum presented for treatment of pain, scored as 10/10. **B** Pre-procedural CT showed a nondisplaced pathologic fracture (arrows). **C** Ablation zone (arrowhead) covered most of the tumor during cryoablation, with a small amount of tumor left untreated anteriorly and posteriorly (arrows). **D** Local tumor progression (arrows) was evident about the cement filling the tumor cavity after cementoplasty on 1-month follow-up CT. Patient's pain was rated as 5/10. **E** Fracture progression (arrows) was seen by this time. **F** The fracture (arrows) progressed even further with increased displacement by 2 months after the combined procedure

Table 1 Patient and tumor characteristics

Patient/tumor characteristic	*N* (%) or median (range)
Patients	37
Male:female	24 (65):13 (35)
Age	65 (48–87)
Moderate–severe pain	34 (92)
Complete pain scores available	27 (73)
Follow-up imaging available	30 (81)
Tumors	39
Right:left	18 (46):21 (54)
Column involvement	
Anterior	21 (54)
Posterior	6 (15)
Anterior and posterior	12 (31)
Primary tumor histology	
Renal cell carcinoma	14 (36)
Plasmacytoma/multiple myeloma	7 (18)
Lung carcinoma	6 (15)
Unknown primary	4 (10)
Other	8 (21)
Pre-existing fracture	30 (77)
Previous treatment	17 (44)
Radiation therapy	15 (38)
Hip arthroplasty	1 (3)
Radiation and hip arthroplasty	1 (3)

characterized as a new pathologic fracture in tumors with no pre-ablation fracture or increase in the length or extent of fracture in those with fracture present at the time of ablation. Patient pain at the ablation site was assessed within one week following the cementoplasty procedure using the NRS via telephone interview. Subsequent NRS pain assessments and post-procedural imaging were driven by routine clinical care. As most patients were evaluated near one-month post-procedure, NRS assessments nearest to that time point were collected and used for comparisons. The latest imaging examinations were used for comparisons to best assess duration of local control. Complications occurring within 30 days of the combined procedure were assessed using the Clavien–Dindo classification system [22]. Per convention, grade I–II complications were considered minor, and grade III–V complications were considered major.

Statistical Analysis

Standard descriptive methods were used to summarize the sample data. Categorical variables are reported with frequency counts and percentages, and continuous variables are reported with means and standard deviations. Categorical variables (proportions) were compared using Chi-squared tests, and pain score comparisons were performed with Student's t tests [23, 24]. Statistical analyses were performed by using the R software package (R Foundation, Vienna, Austria).

Results

Response: Pain

Ten patients had incomplete pain scores, including 4 treated to reduce fracture risk rather than for palliation of pain. Twenty-seven patients had complete pre- and post-procedural pain scores recorded, including 7 (26%) scores less than 3 weeks post-treatment, 14 (52%) between 3 and 6 weeks, and 6 (22%) between 6 and 15 weeks. Overall, 23 (85%) patients had decreased pain, 2 (7%) showed no change in their pain scores, and 2 (7%) reported worsening pain. Mean pain scores decreased from 7.5 ± 2.1 pre-procedure to 3.6 ± 2.6 post-procedure ($p < 0.0001$).

As determined at the time of cryoablation, 28 (72%) tumors were completely ablated, and 11 (28%) were incompletely ablated. Among these two groups, 17 patients and 10 patients had sufficient pain scores for evaluation, respectively. Both sets of patients had significantly decreased pain post-procedure as summarized in Table 2. Mean pain scores decreased from 7.1 ± 2.2 to 3.1 ± 2.2 ($p < 0.0001$) among patients with complete ablations compared to a decrease from 8.3 ± 1.9 to 4.4 ± 3.1 ($p = 0.0032$) among patients with incomplete ablations. There was no significant difference in the degree of pain reduction between groups ($p = 0.9387$).

Response: Tumor and Fracture Progression

Thirty (81%) patients had follow-up pelvic CT or MRI scans performed with mean follow-up duration of 4.8 ± 6.7 months. Five (17%) patients showed LTP, including 2 of 23 (9%) patients with ablations considered complete at the time of treatment. Three of 7 (43%) patients with known incomplete ablations showed LTP on follow-up imaging. A total of 6 (20%) patients showed new fractures or progression of pre-existing fractures. Analysis of fracture progression is summarized in Table 3. Four of 5 (80%) patients with LTP developed new or progressive fractures, while only 2 of 25 (8%) patients without local tumor progression developed new or progressive fractures ($p = 0.0003$).

The presence of a pre-existing fracture was not associated with a significantly increased likelihood of fracture progression in patients with follow-up imaging. Seven of 22 (32%) patients with pre-existing fractures developed fracture progression, while one of 8 (13%) patients without

Table 2 Pain palliation by ablation completeness

	Complete ablation, *N* (%) or mean ± SD	Incomplete ablation, *N* (%) or mean ± SD	*p* value
Tumors	28 (72)	11 (28)	
Pain scores available	17 (63)	10 (37)	
Mean pain pre-procedure	7.1 ± 2.2	8.3 ± 1.9	0.1634
Mean pain post-procedure	3.1 ± 2.2	4.4 ± 3.1	0.2144
Change in mean pain score	4.0 ± 3.2	3.9 ± 3.3	0.9387

Table 3 Fracture progression by patient or tumor characteristic

Patient/tumor characteristic	Increased or new fracture, *N* (%)	No increase or new fracture, *N* (%)	*p* value
Pre-existing fracture ($N = 22$)	7 (32)	15 (68)	0.2986
No pre-existing fracture ($N = 8$)	1 (12)	7 (88)	
Prior treatment ($N = 13$)	6 (46)	7 (54)	0.0380*
No prior treatment ($N = 17$)	2 (12)	15 (88)	
Local tumor progression ($N = 5$)	4 (80)	1 (20)	0.0003*
No local tumor progression ($N = 25$)	2 (8)	23 (92)	

* Significant ($p < 0.05$)

a pre-existing fracture developed a new fracture ($p = 0.2986$). Thirteen patients with follow-up imaging had prior acetabular radiation therapy, surgery, or both. Six of these 13 (46%) patients developed new or progressive fractures. In contrast, only 2 of 17 (12%) patients without prior radiation or surgical treatment developed new or progressive fractures ($p = 0.0380$).

Outcomes: Complications and Retreatment

Four patients (11%) experienced major complications. One patient treated for multiple myeloma showed progression of an ipsilateral femoral head and neck fracture requiring hip arthroplasty. The fracture was at least partially related to underlying myelomatous involvement and pre-existing femoral head injury from the deformed acetabulum that was treated with ablation. In addition, one patient required reconstruction of a total hip arthroplasty secondary to a peri-prosthetic fracture. One patient was treated with an intraarticular hip injection for continued pain and avascular necrosis of the femoral head following the procedure. A single patient had a nonfracture major complication (grade III), namely leakage of cement into the periacetabular soft tissues, requiring neurolysis of the sciatic nerve to relieve pain.

Minor complications (grade I) included asymptomatic cement extravasation in the soft tissues in 2 patients and into the hip joint in one patient as well as a small thermal injury at the skin entry site in one patient that was managed conservatively. Four patients (11%) received subsequent radiation therapy due to continued pain.

Discussion

The current study shows that CCC effectively decreases patient pain, and relatively few patients develop new or progressive fractures. Pain palliation was similar between patients with complete and incomplete tumor cryoablation. New or progressive fractures were more common in patients with LTP compared to those without. For patients with acetabular tumors, achieving local tumor control appears to be important to avoid the morbidity associated with a new or progressive fracture.

The improvement in post-procedural pain scores for patients regardless of completeness of tumor ablation may be related to the mechanism of pain generated by these tumors. Pain from skeletal tumors is generally believed to arise from the bone–tumor interface, and this portion of the tumor was targeted in all cases and usually treated [25]. However, for safety purposes, margins of tumors near vital structures, especially the femoral head and major pelvic motor nerves, were sometimes incompletely treated. The deeper intramedullary tumor components may be a less significant source of pain, and incomplete tumor necrosis here may not impair pain relief when the cortical boundary of the tumor is treated. This matches the results of others that have reported effective pain palliation with CCC, even when the entire bony tumor could not be treated [26]. Additionally, it has been suggested that microfractures and bone instability may be responsible for pain generation in skeletal tumors in axial load-bearing locations [17]. The cementoplasty procedure should stabilize these microfractures even when an incomplete ablation is performed.

Although there was no difference in pain reduction with incomplete tumor cryoablation, patients with complete tumor ablation showed improved fracture risk reduction. In fact, 92% of patients with local tumor control on imaging follow-up showed stability in fracture status compared to 20% of patients with LTP. These distinctions may be difficult to make prospectively as there were patients (8%) thought to have complete cryoablation procedures, as determined by the radiologist at the time of ablation, who developed LTP on follow-up imaging.

Moreover, pathologic fractures within acetabular tumors prior to CCC did not predispose patients to develop subsequent fracture progression. Interestingly, 6 of 8 patients with new or progressive fractures following acetabular CCC had pre-ablation radiation therapy or surgery. These findings raise the possibility that CCC may be more useful as a first-line palliative treatment for painful acetabular tumors, rather than reserving this procedure as salvage therapy for those who fail other interventions.

The current study has several important limitations, including its retrospective design, and heterogeneous cohort of primary tumor histologies. Completeness of ablation was based on coverage of each tumor's soft tissue and osteolytic components on CT; not all patients had pre-procedural MRI scans, and infiltrative bone marrow disease could have been left untreated in some "complete" ablations. There was no comparison arm of patients undergoing no treatment, cryoablation alone, or cementoplasty alone. Thus, assessment of the true benefit of CCC, or separation of the benefits of the ablative and consolidative components of the procedure is impossible. Analgesic consumption and patient mobility data were not recorded reliably for comparison. Assessment of pain scores and post-ablation follow-up imaging was driven by clinical status and not uniform in timing, and some of the post-procedural assessments were performed via telephone rather than in person. Finally, complete pain scores and follow-up imaging were unavailable for a small subset of the patients.

Future studies could compare CCC with cementoplasty alone or other instrumentation procedures for pain palliation and fracture risk reduction or evaluate the triage of patients between percutaneous procedures and radiation therapy or surgery. Moreover, prospective evaluation with multimodal post-procedural imaging could clarify the role of residual disease in pain recurrence and fracture development.

Conclusion

Overall, CCC appears effective in the palliative management of painful acetabular tumors even when complete tumor ablation cannot be achieved. The combined procedure is safe and provides stabilization for acetabular tumors at risk for fracture. However, patients with local tumor progression or prior treatment with radiation therapy or surgery show increased frequency of subsequent fracture progression following treatment.

Compliance with Ethical Standards

Conflict of interest ANK and MRC receive royalties from UpToDate, Inc. and have received research support from Galil Medical. MRC also has received research grants from General Electric Medical Systems, Thermedical, and Siemens Medical. MRC is a paid consultant for Covidien.

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