



Original article

Percutaneous image-guided cryoablation of painful bone metastases: A single institution experience



Nicolas Gallusser¹, Patrick Goetti¹, Fabio Becce, Frédéric Vauclair, Hannes A. Rüdiger, Pierre E. Bize, Stéphane Cherix*

Lausanne University Hospital, 46, rue du Bugnon, CH-1011 Lausanne, Switzerland

ARTICLE INFO

Article history:

Received 19 December 2017

Accepted 7 January 2019

Keywords:

Bone metastases

Cryoablation

Percutaneous therapy

Pain

Local disease control

ABSTRACT

Background: Bone metastases are frequently painful and may lead to various complications that can affect quality of life. While external beam radiation therapy is the standard first-line treatment, 20–30% of patients do not experience sufficient pain relief. Cryoablation is increasingly being used for the treatment of musculoskeletal metastases. The purpose of our retrospective study was to analyze pain relief and local disease control after percutaneous image-guided cryoablation (PCA) therapy of painful bone metastases.

Materials and methods: Sixteen patients treated with PCA for painful bone metastases ($n = 18$) over a 5-year period (from June 2011 to June 2016) were retrospectively reviewed. Five patients also benefited from long bone fixation because of an impending fracture. We analyzed the impact of treatment on pain relief, using a numerical rating scale (NRS), and local disease control.

Results: The mean follow-up period was 12 months (range, 1.5–39 months). At last oncological outpatient consultation, 75% (12/16) of patients had good pain relief, while 63% (10/16) had locally stable disease or no local recurrence of the treated bone metastases. The mean NRS score decreased significantly from 3.3 to 1.2 after PCA ($p = 0.0024$). The five patients with concomitant long bone fixation all had satisfactory pain relief at the last follow-up visit.

Conclusion: PCA is a safe and valid treatment option for pain and local disease control in cases of painful bone metastases after failed standard first-line therapy. This technique can also be effectively associated to prophylactic long bone fixation and may allow for easier rehabilitation protocols when treating weight-bearing bones.

Level of evidence: IV, Retrospective case series.

© 2019 Elsevier Masson SAS. All rights reserved.

1. Introduction

Bone is the third most common site of metastasis with primary malignancies mainly from the prostate, lung, kidney, breast, and thyroid. Up to 85% of patients who died of breast, prostate, or lung cancer have bone metastases at death time [1]. Bone metastases may lead to various complications that can affect quality of life, including pain, fractures, loss of mobility, and thereby reduction of autonomy [1,2]. In addition, chronic pain can cause depression and anxiety [3,4].

Currently, treatment for patients with bone metastases is primarily palliative and includes localized therapies (interventional analgesia, radiation therapy (RT), and surgery), systemic therapies (chemotherapy, hormone therapy, immunotherapy, radiopharmaceuticals, and bisphosphonates), and analgesia (opioids and anti-inflammatory drugs) [5]. External beam RT is the standard first-line treatment for patients with localized painful bone metastases. However, 20% to 30% of patients treated with RT do not experience sufficient pain relief [6–11]. In addition, patients who have recurrent pain in a previously irradiated field may not be eligible for further RT because of the limited dose tolerance of the tissues.

For patients who fail to obtain sufficient pain relief with conventional therapies, minimally invasive techniques have been developed for local pain control in metastatic disease. Radiofrequency ablation (RFA) may significantly diminish pain in some cases, yet this technique does not allow for accurate monitoring

* Corresponding author. Service d'orthopédie et de traumatologie, Département de l'appareil locomoteur, Lausanne University Hospital, 46, rue du Bugnon, CH-1011 Lausanne, Switzerland.

E-mail address: stephane.cherix@chuv.ch (S. Cherix).

¹ N. Gallusser and P. Goetti contributed equally to this work.

of ablation margins and may be complicated by thermal injuries of surrounding structures [12–14]. On the contrary, the ablation zone of percutaneous cryoablation (PCA) can be controlled using computed tomography (CT), magnetic resonance imaging (MRI), or ultrasound, the latter modality being more limited for monitoring the ablation area because the superficial margin of the ice ball produces an impenetrable acoustic shadow. PCA is currently widely used to treat prostate, kidney, liver, lung, breast, and uterus tumors. It is also increasingly being used to relieve pain in musculoskeletal metastases and seems to provide sustainable pain control [5,15–21]. Moreover, it is associated with a greater reduction in analgesic doses and shorter hospital stays than RFA to treat painful metastases involving bone [22]. The purpose of our retrospective study was to analyze pain relief and local disease control after percutaneous image-guided cryoablation therapy of painful bone metastases.

2. Materials and methods

After obtaining consent from our regional ethics committee (CER-VD, protocol 114/15), we reviewed our institutional database and identified 21 patients with painful bone metastases treated

with PCA between June 2011 and June 2016. Five patients were not followed-up in our institution and were thus excluded due to missing data. The remaining 16 patients were included in this retrospective study. The characteristics of the case series are summarized in Table 1. The medical records of all patients were reviewed. We analyzed the impact of treatment on pain relief and local disease control. Pain was assessed preoperatively and during the periodic oncological controls. A visual analogue scale (VAS) was not used for all patients, but pain was assessed using a numerical rating scale (NRS) and registered in medical records [23]. Self-reported pain > 2 points was defined as unbearable and used in part as an indication for PCA. Postoperative pain was assessed at each follow-up using the same scale. Patients with NRS ≤ 2 points were considered as successfully treated by PCA, whereas those reporting NRS > 2 points were considered failures of pain control treatment. Tumor progression was evaluated using MRI and/or positron emission tomography/CT. Lesions were defined as locally controlled if there was no focal enlargement or abnormal radiotracer uptake. The occurrence of any complication related to the procedure was noted. The mean follow-up was 12 months (range, 1.5–39 months).

PCA was proposed for pain management in the palliative support of oncological disease. We further proposed this procedure in

Table 1
Patients with painful bone metastases treated with PCA.

Case	Age	Initial diagnosis	Prior treatments	Treated lesion	Additional interventions
#1	56	Tonsillar spinal cell carcinoma, pT2 N3 M1 (skull)	Surgery; Chemotherapy; Radiation therapy	Local recurrence brachial plexus and vertebral (C7-T2) involvement	–
#2	67	Breast carcinoma, grade 2, pT2 pN3 cM0	Surgery; Chemotherapy; Hormonotherapy	L5 vertebral body metastasis	–
#3	80	Pulmonary adenocarcinoma “Pancoast”, grade 3, ypT3 ypN0 cM0	Multiple surgeries; Chemotherapy; Radiation therapy	Vertebral and paravertebral D11-12	Kyphoplasty, corpectomy and posterior fixation after 1 month; Radiation therapy
#4	43	Clear cell sarcoma foot, cTx N0 M1 (bone, lymph nodes)	Multiple surgical resections of the primary tumor and locoregional recurrences	Diaphyseal femur metastasis	Plating
#5	71	Renal clear cell carcinoma, grade 3, cTx Nx M1 (lung, bone, liver, adrenal glands)	Radiation therapy; Chemotherapy	Diaphyseal femur metastasis	IM nailing
#6	65	Cutaneous spinal cell carcinoma, grade 2, pT3 cN0 M0	Multiple surgical resections of the primary tumor and locoregional recurrences; Chemotherapy; Radiation therapy	Bone and soft tissue pelvic metastases	–
#7	60	Renal clear cell carcinoma, Tx, Nx, M1 (brain, ribs, femur)	Partial nephrectomy; Chemotherapy; Radiation therapy	Diaphyseal femur metastasis	IM nailing; Radiation therapy; Two surgical revisions for pathological fracture and secondary loss of reduction
#8	52	Nodular melanoma, Breslow 1.52 mm, Clark 4, pT2, N1a, M0	Multiple surgical resections of the primary tumor and pulmonary metastasis	Ilium metastasis	–
#9	51	Endometrial stromal sarcoma	Multiple surgical resections of the primary tumor and pulmonary metastasis	Diaphyseal femur metastasis	IM nailing
#10	58	Renal cell carcinoma, pT3a pN1 M1	Surgery; Chemotherapy; Radiation therapy	Ischio-pubic ramus	–
#11	67	Pulmonary carcinoid tumor, pT2a N1 M0	Surgical resection of the primary tumor	12th rib	–
#12	74	Hepatocellular carcinoma, pT2 pN0 M0	Multiple surgical resections of the primary tumor and locoregional recurrences; Radiofrequency ablation; Chemotherapy	6th rib	–
#13	71	Rectal adenocarcinoma, pT3 N1a M0	Multiple surgical resections of the primary tumor and locoregional recurrences; Chemotherapy; Radiation therapy	sacrum	–
#14	62	Pulmonary adenocarcinoma, Stage IV	Chemotherapy	Diaphyseal femur metastasis	IM nailing
#15	53	Breast carcinoma, St IIB, T2 N1 M0	Surgery; Chemotherapy; Hormonotherapy	8th rib	Radiation therapy
#16	64	Hepatocellular carcinoma, pT2 pN0 M0	Chemotherapy, Radiation therapy of osseous metastasis	7th and 8th ribs	–

IM; intramedullary.

combination with long bone fixation in cases with an impending fracture. The need for prophylactic osteosynthesis of long bones was defined according to Mirels' scoring system [24]. One patient benefited from a posterior cervical spine fixation, and five had long bone fixation. All patients had pain self-reported as high or disabling (NRS > 2 points) prior to the intervention. During the study period, 16 patients underwent 18 PCA procedures. The mean patient age at the time of PCA was 62 years (range, 43–80 years). All had undergone multiple treatment modalities prior to PCA such as surgery, RT, or chemotherapy. The indication for PCA was painful bone metastasis and/or locoregional recurrence of sarcoma in two cases, lung cancer in three, renal carcinoma in three, breast cancer in two, skin cancer in two, hepatic carcinoma in two, rectal carcinoma in one, and oropharyngeal cancer in one case. Two patients benefited from a second session of PCA because of local tumor progression.

We proposed PCA in association with prophylactic long bone fixation for five patients with an impending femoral fracture. Four received a femoral nail, while one a 4.5 mm plate. In all cases, we did staged procedures in a single anaesthesia. PCA was performed first. Three to six cryoprobes were positioned percutaneously under image guidance and used for two repeated sessions of cooling (12 minutes followed by 6 minutes). The ice-ball progression was monitored using CT and/or ultrasound. Prophylactic osteosynthesis was then performed immediately after PCA in the operating room. A second-generation cephalosporin was used for antibioprophyllaxis. We reamed using a reamer-irrigator-aspirator (RIA; DePuy Synthes, Oberdorf, Switzerland) system before introducing a long cephalomedullary nail with static locking screws for the four nailing interventions. The last case underwent a lateral approach to the femoral shaft with prophylactic fixation using a 4.5 mm plate and locking screws. We opted for femoral fixation with plating rather than nailing because the primary tumor was a sarcoma, we did not want to enter several compartments during surgery. All patients were allowed to walk with full-weight bearing the day after the intervention.

3. Results

At last oncological outpatient consultation, 12 of the 16 patients (75%) had sufficient pain relief. The remaining four patients had disabling pain, which was due to tumor progression in three cases; while the fourth patient was never relieved of pain by either therapy. None of these four patients had concomitant long bone fixation. On the contrary, all patients with concomitant femoral fixation had satisfactory pain control at last follow-up. The mean NRS score before intervention was 3.3 (range, 3–4). After PCA, the mean NRS score decreased significantly to 1.2 (range, 0–4) ($p = 0.0024$, Wilcoxon signed-rank test). At last follow-up visit, 10 of the 16 patients (63%) had persistent local disease control (no progression or no evidence of disease). The remaining six had local metastasis progression. The mean time to progression was 5.9 months (range, 1–25 months). Three patients died of the disease during the study period. The remaining 13 (81%) were alive with disease at the last follow-up. No patient reported immediate complication related to PCA. One patient needed two surgical revisions for secondary pathological fractures due to bone necrosis 7 months after PCA of a bulky metastasis of the femoral diaphysis. He healed after two open internal fixations with cement augmentation (Fig. 1).

Three patients had post-procedure external beam RT. In one case (#7), this treatment was decided at the beginning of the management of the metastatic lesion as an adjuvant therapy. The other two cases had RT 5 and 8 weeks after PCA because of persistent disabling pain.

Detailed results are reported in Table 2.

4. Discussion

We retrospectively studied a consecutive series of 18 PCA procedures to treat painful bone metastases in 16 patients over a 5-year period. Our aim was to determine the efficacy of the treatment on pain relief and local disease control. At the last follow-up, 75% of patients had satisfactory pain relief and 63% had no local progression of the disease. Control of painful bone metastases requires a specific approach and RT is generally proposed as the standard first-line treatment. In addition, survival from metastatic breast or prostate cancer has improved with chemotherapy and hormonal agents [25,26], while immunotherapy is still under evaluation [27,28]. Minimally invasive techniques, such as RFA, provide significant and long-lasting pain relief for patients who did not respond to conventional first-line therapies [12,13]. For treating painful metastases involving bone, PCA can be performed close to critical structures because of the ice-ball formation monitoring with CT imaging and thermal isolation of the neurovascular bundles with gas.

In a single-center prospective clinical trial using PCA to treat painful skeletal metastases, Callstrom et al. showed a significant reduction in pain and narcotics use 4 weeks after the procedure, with 79% (11/14) of patients showing no recurrence of disabling pain at 6 months [17]. In a further prospective multicenter study, the same authors reported highly significant pain reductions in 75% (46/61) of studied patients. At 6 months follow-up, 67% (41/61) reported satisfactory pain control [18]. We found similar results, with 75% (12/16) of patients reporting satisfactory pain control at the last follow-up. Of the patients with more than 4 months follow-up, 73% (8/11) did not report a recurrence of pain.

Recently, Susa et al. reported PCA results for locally recurrent or metastatic bone and soft tissue tumors in nine patients. Local control was obtained in all cases; however, two patients (22%) required a second procedure because of local recurrence [19]. A single-institution retrospective study by McMenomy et al. evaluating PCA to treat limited metastases to the musculoskeletal system had a goal of complete disease remission, and reported local control was achieved in 87% (45/52) at a median follow-up of 21 months. Thirteen of 19 treated bone metastases (68%) and 32 of 33 soft-tissue metastases (97%) showed locally controlled disease [29]. Similarly, we found 10 of the 16 patients (63%) had locally stable disease or no local recurrence of the treated metastases at the last follow-up. The remaining six patients had local progression. The mean time to progression was 5.9 months (range, 1–25 months).

Surgical treatment of bone metastases aims at providing stability of the involved bone segment and rapid function recovery. Moreover, patients who undergo prophylactic fixation have shorter hospital stays, easier rehabilitation, improved quality of life, and better functional results than those undergoing surgery for an actual pathological fracture [30,31].

Cementoplasty, i.e. percutaneous delivery of polymethylmethacrylate cement, associated with image-guided therapy (RFA or PCA) has been proposed to treat patients with osteolytic metastasis at risk of fracture [32–36]. Studies focusing on cementoplasty without concomitant tumor ablation localized in the proximal femur report fracture rates ranging between 24 and 41% at 1 year [37,38]. On the other hand, Prologo et al. have identified adverse events after PCA of painful bone metastases in a retrospective series of 61 patients [39]. Two patients received a PCA associated with cementoplasty of the proximal femur, which was complicated by a fracture in the weeks following the procedure. In our study, we performed long bone fixation for impending fractures associated with PCA. These patients had satisfactory pain control at the last follow-up. PCA induces bone necrosis and additional treatments, such as RT or systemic treatments, may prevent the bone from remodeling

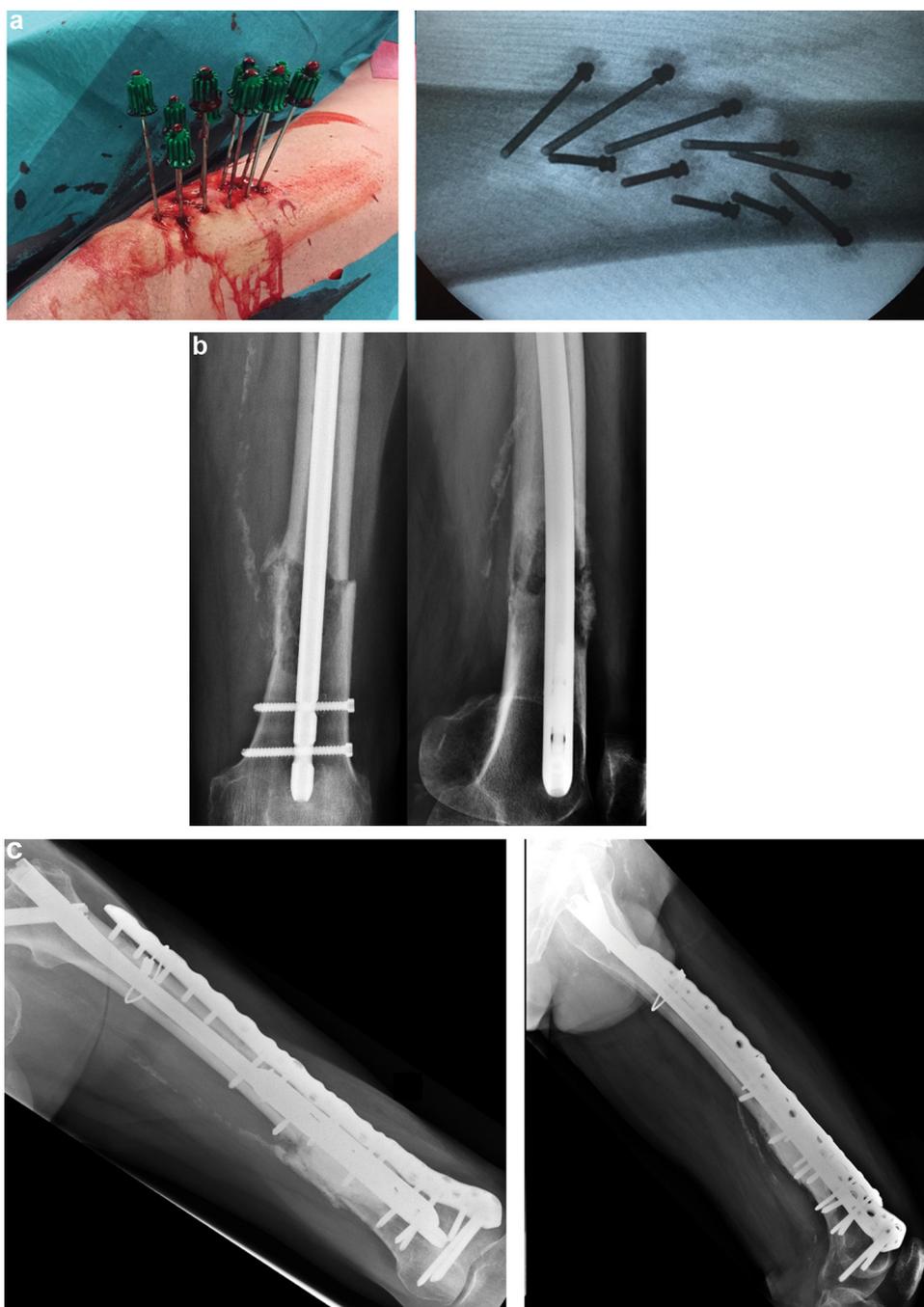


Fig. 1. (A) Left: perioperative photograph of the cryoprobes positioned in the distal femur. Right: fluoroscopic image of the cryoprobes treating the bone metastasis. (B) Radiographs obtained 6 months after PCA combined with prophylactic intramedullary nailing displaying a non-traumatic pathological fracture. (C) Radiographs obtained 17 months after initial treatment and 7 months after the last procedure (internal fixation with cement augmentation); bone consolidation was acquired.

and healing. One of our patient presented with a late pathological fracture due to bone necrosis after treatment of a bulky metastasis. He needed two surgical revisions to stabilize his distal femoral diaphysis. More cases are needed to determine when additional (open) surgical stabilization should be considered, as this mostly depends on the metastasis size and location. To our knowledge, this is the first study to describe the results of PCA associated with prophylactic long bone fixation.

We acknowledge the following study limitations. The retrospective design, combined with the plurality of systemic and locoregional treatments received before the procedure in a small series of patients makes it difficult to interpret the results. Indeed, all patients included in this study had a multimetastatic oncologic

disease at the time of diagnosis. PCA was part of the palliative care of an incurable disease aimed at alleviating disabling pain from bone metastases. The various types of pain were not systematically reported in medical records. We were thus not able to assess this aspect in greater detail than with the NRS. Evaluation of pain medication was also limited by the retrospective study design. However, when reviewing the medical records, patients who reported a pain decrease after PCA, did not show an increase in analgesics use. All these limitations certainly prevents from clearly determining the effectiveness of PCA in the treatment of painful bone metastases. However, we believe that the combination of interventional radiology with minimal-invasive orthopedic surgery as described in our single-center case series shows promising results and should

Table 2
Results of percutaneous cryoablation.

Case	Follow-up (months)	Preoperative pain (NRS)	Postoperative pain (NRS)	Local disease control	Time to progression	Status at last follow-up
#1	3	4	1	Progression	1 month (vertebral)	AWD
#2	39	3	0	Stable	No progression	AWD
#3	3	4	4	Progression	6 weeks	DOD
#4	3	3	0	Progression	3 months	AWD
#5	4	4	1	Stable	No progression	AWD
#6	4	3	3	Progression	4 weeks	DOD
#7	17	3	0	Stable	No progression	AWD
#8	12	3	0	Stable	No progression	AWD
#9	1.5	3	1	Stable	No progression	AWD
#10	6	3	1	Stable	No progression	AWD
#11	33	3	0	Stable	No progression	AWD
#12	4	3	0	Stable	No progression	AWD
#13	14	3	3	Progression	4 months	DOD
#14	3	4	2	Stable	No progression	AWD
#15	22	3	3	Stable	No progression	AWD
#16	26	4	0	Progression	25 months	AWD

NRS: numerical rating scale; DOD: dead of the disease; AWD: alive with the disease.

be considered in the management of patients with painful bone metastases.

5. Conclusion

Our study confirms that PCA is a safe and valid treatment option to achieve long-lasting pain control in cases of painful bone metastases after failed standard first-line therapy. It can also be associated with prophylactic long bone fixation while preserving its efficacy and allowing for easier rehabilitation protocols when treating weight-bearing bones. Further prospective studies are warranted to confirm these encouraging results.

Ethical approval

Ethics committee approval: protocol 114/15, approved on 08.02.2016 by CER-VD.

Disclosure of interest

The authors declare that they have no competing interest.

Funding

None.

Contribution

F. Becce (radiology) managed the radiologic images and participated in the article writing.

P. Bize (interventional radiology) effected the percutaneous cryoablations and the follow-up.

H.A. Ruediger and S. Cherix (orthopaedic oncology surgery) managed the surgeries and the follow-up.

S. Cherix and F. Vauclair participated in the revision of the article.

References

- Nielsen OS, Munro AJ, Tannock IF. Bone metastases: pathophysiology and management policy. *J Clin Oncol* 1991;9:509–24.
- Mercadante S. Malignant bone pain: pathophysiology and treatment. *Pain* 1997;69:1–18.
- Massie MJ, Holland JC. The cancer patient with pain: psychiatric complications and their management. *J Pain Symptom Manage* 1992;7:99–109.
- Spiegel D, Sands S, Koopman C. Pain and depression in patients with cancer. *Cancer* 1994;74:2570–8.
- Callstrom MR, Charboneau JW, Goetz MP, Rubin J, Atwell TD, Farrell MA, et al. Image-guided ablation of painful metastatic bone tumors: a new and effective approach to a difficult problem. *Skeletal Radiol* 2006;35:1–15.
- Jeremic B, Shibamoto Y, Acimovic L, Milicic B, Milisavljevic S, Nikolic N, et al. A randomized trial of three single-dose radiation therapy regimens in the treatment of metastatic bone pain. *Int J Radiat Oncol Biol Phys* 1998;42:161–7.
- Price P, Hoskin PJ, Easton D, Austin D, Palmer SG, Yarnold JR. Prospective randomised trial of single and multifraction radiotherapy schedules in the treatment of painful bony metastases. *Radiother Oncol* 1986;6:247–55.
- Cole DJ. A randomized trial of a single treatment versus conventional fractionation in the palliative radiotherapy of painful bone metastases. *Clin Oncol (R Coll Radiol)* 1989;1:59–62.
- Gaze MN, Kelly CG, Kerr GR, Cull A, Cowie VJ, Gregor A, et al. Pain relief and quality of life following radiotherapy for bone metastases: a randomised trial of two fractionation schedules. *Radiother Oncol* 1997;45:109–16.
- Nielsen OS, Bentzen SM, Sandberg E, Gadeberg CC, Timothy AR. Randomized trial of single dose versus fractionated palliative radiotherapy of bone metastases. *Radiother Oncol* 1998;47:233–40.
- Steenland E, Leer JW, van Houwelingen H, Post WJ, van den Hout WB, Kievit J, et al. The effect of a single fraction compared to multiple fractions on painful bone metastases: a global analysis of the Dutch Bone Metastasis Study. *Radiother Oncol* 1999;52:101–9.
- Goetz MP, Callstrom MR, Charboneau JW, Farrell MA, Maus TP, Welch TJ, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. *J Clin Oncol* 2004;22:300–6.
- Dupuy DE, Liu D, Hartfeil D, Hanna L, Blume JD, Ahrar K, et al. Percutaneous radiofrequency ablation of painful osseous metastases: a multicenter American College of Radiology Imaging Network trial. *Cancer* 2010;116:989–97.
- Saliken JC, McKinnon JG, Gray R. CT for monitoring cryotherapy. *AJR Am J Roentgenol* 1996;166:853–5.
- Tomasian A, Wallace A, Northrup B, Hillen TJ, Jennings JW. Spine cryoablation: pain palliation and local tumor control for vertebral metastases. *AJNR Am J Neuroradiol* 2016;37:189–95.
- Ullrick SR, Hebert JJ, Davis KW. Cryoablation in the musculoskeletal system. *Curr Probl Diagn Radiol* 2008;37:39–48.
- Callstrom MR, Atwell TD, Charboneau JW, Farrell MA, Goetz MP, Rubin J, et al. Painful metastases involving bone: percutaneous image-guided cryoablation—prospective trial interim analysis. *Radiology* 2006;241:572–80.
- Callstrom MR, Dupuy DE, Solomon SB, Beres RA, Littrup PJ, Davis KW, et al. Percutaneous image-guided cryoablation of painful metastases involving bone: multicenter trial. *Cancer* 2013;119:1033–41.
- Susa M, Kikuta K, Nakayama R, Nishimoto K, Horiuchi K, Oguro S, et al. CT guided cryoablation for locally recurrent or metastatic bone and soft tissue tumor: initial experience. *BMC Cancer* 2016;16:798.
- Rose PS, Morris JM. Cryosurgery/cryoablation in musculoskeletal neoplasms: history and state of the art. *Curr Rev Musculoskelet Med* 2015;8:353–60.
- Kurup AN, Morris JM, Callstrom MR. Ablation of Musculoskeletal Metastases. *AJR Am J Roentgenol* 2017;209:713–21.
- Thacker PG, Callstrom MR, Curry TB, Mandrekar JN, Atwell TD, Goetz MP, et al. Palliation of painful metastatic disease involving bone with imaging-guided treatment: comparison of patients' immediate response to radiofrequency ablation and cryoablation. *AJR Am J Roentgenol* 2011;197:510–5.
- Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs* 2005;14:798–804.
- Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin Orthop Relat Res* 1989;249:256–64.
- Chia SK, Speers CH, D'yachkova Y, Kang A, Malfair-Taylor S, Barnett J, et al. The impact of new chemotherapeutic and hormone agents on survival in

- a population-based cohort of women with metastatic breast cancer. *Cancer* 2007;110:973–9.
- [26] Ryan CJ, Elkin EP, Cowan J, Carroll PR. Initial treatment patterns and outcome of contemporary prostate cancer patients with bone metastases at initial presentation: data from CaPSURE. *Cancer* 2007;110:81–6.
- [27] Ghisoli M, Barve M, Mennel R, Lenarsky C, Horvath S, Wallraven G, et al. Three-year Follow up of GMCSF/bi-shRNA(furin) DNA-transfected Autologous Tumor Immunotherapy (Vigil) in Metastatic Advanced Ewing's Sarcoma. *Mol Ther* 2016;24:1478–83.
- [28] Nemunaitis J, Barve M, Orr D, Kuhn J, Magee M, Lamont J, et al. Summary of bi-shRNA/GM-CSF augmented autologous tumor cell immunotherapy (FANG™) in advanced cancer of the liver. *Oncology* 2014;87:21–9.
- [29] McMenemy BP, Kurup AN, Johnson GB, Carter RE, McWilliams RR, Markovic SN, et al. Percutaneous cryoablation of musculoskeletal oligometastatic disease for complete remission. *J Vasc Interv Radiol* 2013;24:207–13.
- [30] Ward WG, Holsenbeck S, Dorey FJ, Spang J, Howe D. Metastatic disease of the femur: surgical treatment. *Clin Orthop Relat Res* 2003;415Suppl:S230–44.
- [31] Arvinus C, Parra JL, Mateo LS, Maroto RG, Borrego AF, Stern LL. Benefits of early intramedullary nailing in femoral metastases. *Int Orthop* 2014;38:129–32.
- [32] Castañeda Rodríguez WR, Callstrom MR. Effective pain palliation and prevention of fracture for axial-loading skeletal metastases using combined cryoablation and cementoplasty. *Tech Vasc Interv Radiol* 2011;14:160–9.
- [33] Masala S, Manenti G, Roselli M, Mammucari M, Bartolucci DA, Formica V, et al. Percutaneous combined therapy for painful sternal metastases: A radiofrequency thermal ablation (RFTA) and cementoplasty protocol. *Anticancer Res* 2007;27:4259–62.
- [34] Munk PL, Rashid F, Heran MK, Papirny M, Liu DM, Malfair D, et al. Combined cementoplasty and radiofrequency ablation in the treatment of painful neoplastic lesions of bone. *J Vasc Interv Radiol* 2009;20:903–11.
- [35] Schaefer O, Lohrmann C, Herling M, Uhrmeister P, Langer M. Combined radiofrequency thermal ablation and percutaneous cementoplasty treatment of a pathologic fracture. *J Vasc Interv Radiol* 2002;13:1047–50.
- [36] Toyota N, Naito A, Kakizawa H, Hieda M, Hirai N, Tachikake T, et al. Radiofrequency ablation therapy combined with cementoplasty for painful bone metastases: initial experience. *Cardiovasc Interv Radiol* 2005;28:578–83.
- [37] Deschamps F, Farouil G, Hakime A, Barah A, Guiu B, Teriitehau C, et al. Cementoplasty of metastases of the proximal femur: is it a safe palliative option? *J Vasc Interv Radiol* 2012;23:1311–6.
- [38] Tian QH, He CJ, Wu CG, Li YD, Gu YF, Wang T, et al. Comparison of Percutaneous Cementoplasty with and Without Interventional Internal Fixation for Impending Malignant Pathological Fracture of the Proximal Femur. *Cardiovasc Intervent Radiol* 2016;39:81–9.
- [39] Prologo JD, Patel I, Buethel J, Bohnert N. Ablation zones and weight-bearing bones: points of caution for the palliative interventionalist. *J Vasc Interv Radiol* 2014;25:769–75.