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GENERAL REVIEW • TUMORS - METASTASES

What's new in management of bone metastases?

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Abstract
Metastases are the most common malignancy in bone. In patients with bone metastases, especially if a limited expected survival, the indications for surgical treatment are limited, immediate pain relief and improvement in the functional status are important, and complications of treatments are unwanted. Novel medical treatments can offer an effective palliative option in these patients. Advances in interventional radiology and surgery have led to the development of less invasive techniques with the aim to achieve the same clinical results with less surgical morbidity. These include embolization, electrochemotherapy, magnetic resonance imaging-guided high-intensity focused ultrasound, and thermal ablation. Less invasive techniques combine the advantages of less invasive procedures including decreased blood loss, earlier functional recovery and initiation of adjuvant medical therapies and seem to be both effective in pain relief and local tumor control.

Keywords Bone metastases · Novel therapies · Denosumab · Interventional radiology · Embolization · Thermal ablation · Magnetic resonance imaging-guided high-intensity focused ultrasound · Electrochemotherapy

Introduction

The prevalence of metastatic bone disease is approximately 280,000 new cases per year [1] and is expected to increase as patients with cancer live longer [2]. The bone is the third most common site of metastatic disease after the lungs and the liver; postmortem analyses have shown that approximately 70% of all patients with breast and prostate cancer and 35–42% of patients with lung, thyroid and renal cancer have skeletal metastases [3]. The annual cost of treating patients with metastatic bone disease in the USA is approximately $12.6 billion, which accounts for the 17% of the annual cost of total cancer treatments [4].

Although malignant primary bone tumors are usually managed by orthopedic surgeons with expertise in oncology, patients with metastatic bone disease may also be treated by general orthopedic surgeons at community hospitals [2]. However, district hospital orthopedic surgeons should be aware of the principles of bone tumor surgery and should know the limits and indications to refer their patients to specialized tumor centers. Metastatic bone lesions have more similarities than differences; for the most part, surgical intervention is similar across the spectrum. Predicting the survival of these patients is useful to direct care and guide treatment [5]. Indication for surgery depends on pain or impending or actual pathological fractures and differs between nations [6, 7]; in USA, up to 71% of patients are treated due to an impending fracture compared with only 18% in Nordic countries [6].

Over the last few decades, advances in medicine and surgery have been incorporated into the management of patients with metastatic bone disease. Immediate pain relief and improvement in the functional status are particularly important for these patients [6]. In the decision for surgical and/or medical treatment, life expectancy for the patients with metastatic bone disease is the most important factor; a short life expectancy indicates a less invasive procedure with earlier rehabilitation and fewer possible complications [7]. In this setting, novel medical and less invasive surgical

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treatments aim to reduce the surgical trauma compared to conventional surgical techniques in these patients.

Novel medical treatments

Bone metastases lead to local bone destruction and skeletal impairment. Osteoclast inhibitors such as bisphosphonates have been used as key pharmaceutical treatments and standard treatment for solid cancers with bone metastases or multiple myeloma [8]. Within the class of bisphosphonates, zoledronic acid has been shown to effectively decrease the risk of pathological fractures and other skeletal events including hypercalcemia [9]. Some authors have shown that denosumab may delay and prevent skeletal events in metastatic bone disease more effectively than zoledronic acid [10]. However, other authors found similar results with denosumab and zoledronic acid in the treatment of bone metastases [9]. By binding to RANKL, denosumab inhibits the interaction between receptor activator of nuclear factor-k B (RANK) and RANKL, which in turn decreases osteoclastic activity, decreases bone resorption and increases bone mass [9]. Henry et al. [9] reported a randomized double-blind study of denosumab versus zoledronic acid for the treatment of patients with metastatic bone disease; denosumab was found to be as effective as zoledronic acid in preventing or delaying skeletal events, including pathological fractures.

A meta-analysis of 6 randomized controlled trials involving 13,733 patients confirmed only slightly superior effectiveness of denosumab compared to zoledronic acid in decreasing the rate of skeletal events [10]. However, occurrences of adverse events such as hypocalcemia, renal adverse effects and new primary malignancy (second cancers) were significantly different between denosumab and zoledronic acid. Only the occurrence of osteonecrosis of the jaw showed no significant difference between the denosumab and zoledronic acid groups. A second cancer occurred significantly more frequently in patients treated with denosumab than with zoledronic acid [10]; expression of RANKL plays an important role in B and T cell differentiation; and its inhibition could eventually increase the risk of new malignancies due to immunosuppression [11]. Zheng et al. [8] compared three randomized controlled trials with a total of 5544 patients with advanced solid tumors and bone metastases; there were 2776 patients treated with denosumab and 2768 patients treated with zoledronic acid. They found that denosumab was superior to zoledronic acid in delaying time to skeletal events; however, no significant difference was found in overall survival improvement between denosumab and zoledronic acid [8].

Although a potential novel treatment option, the above data do not support denosumab over traditional agents such as bisphosphonates for the management of metastatic bone disease in patients with solid tumors and conclude that the long-term safety of denosumab has not yet been assessed and long-term treatment surveillance is still ongoing [11, 58].

Less Invasive Treatments

Novel surgical and interventional radiology techniques for the management of patients with metastatic bone disease include embolization, thermal ablation therapy, high-intensity focused ultrasound and electrochemotherapy.

Embolization

Embolization has been applied for the treatment of bone metastases either alone or in combination with other treatments [12, 13]. Trans-arterial embolization of a hypervascular bone metastasis such as from renal or thyroid cancer using particles, liquid glue or other embolic agents can reduce intraoperative blood loss and operative time in those lesions subsequently to be treated with surgery [14–16]. Preoperative embolization showed greater effectiveness in reducing intraoperative blood loss when surgery was performed on the same day of embolization [17]. Kato et al. studied 65 cases of spinal metastases from thyroid and renal cancer to compare intraoperative blood loss according to the completeness of embolization and the time interval between embolization and surgery; the intraoperative blood loss was significantly lower with complete compared to partial occlusion of the pathological vessels with embolization (mean ± standard deviation, 809 ± 835 vs. 1210 ± 904 mL, $p = 0.03$). In the patients with complete vessels occlusion, the intraoperative blood loss as well as the perioperative transfusion requirements was significantly lower in the same-day embolization and surgery group compared to the next-day surgery group [17]. Pazionis et al. compared 27 patients with renal cancer and 12 patients with thyroid cancer who underwent embolization before surgery with 41 patients who did not have embolization before their surgical operations; the patients treated with embolization had a less mean estimated blood loss (0.90 L vs. 1.77 L; $p = 0.002$), fewer requirements for packed red blood cells (2.15 units vs. 3.56 units; $p = 0.020$) and shorter operative time (3.13 h vs. 3.91 h; $p < 0.001$) [16].

Embolization also has an effective palliative role for pain and neurological symptoms in patients with bone metastases [18]. Facchini et al. [18] studied 164 cancer patients treated with embolization for metastases of the spine from variable primary cancers. Pain score and need for analgesics reduced by 50%; mean duration of pain relief was 9.2 months (range, 1–12 months). The addition of chemotherapeutic drugs (trans-arterial chemo-embolization, TACE) seems to give longer pain relief than embolization alone probably due to an additional response of local administration of the chemotherapy drugs [19]. Rossi et al. [20] performed selective and super-selective embolization in 243 patients with bone metastases from variable primary cancers showing a reduction of pain score in 97% of patients (Fig. 1) and a mean duration of pain relief of 8.1 months (range, 1–12 months). Embolization may also reduce tumor vascularization before thermal ablation to limit the heat/cold-sink effect of ablation [21].

Thermal ablation

Percutaneous thermal ablation was introduced in clinical practice as a palliative treatment of painful bone metastases in early 2000 [22, 23]. Several techniques are currently available for tumor tissue thermal ablation, causing an irreversible architectural deconstruction by thermal effects. The mostly used techniques include radiofrequency, cryo, laser and microwaves thermal ablation [24]. Radiofrequency thermal ablation (RFA) is the most widely adopted thermal ablation method with a proved high success rate, not only in the treatment of liver, lung and kidney tumors, but more recently for the treatment of bone (Fig. 2) and soft tissue tumors for skeletal events and local tumor control [25]; computed tomography (CT) guidance provides for rapid and precise placement and control of the ablation electrodes [25]. CT-guided RFA of bone metastases can effectively palliate pain at 1 and 3 months after treatment [26]. Adverse events related to CT-guided RFA have been observed in approximately 5% of the patients and are mainly attributable to neurological damage and/or neuropathic pain related to the toxic effect of the heat procedure on adjacent nerves [26]. RFA can also be safely combined with cement injection (cementoplasty), with excellent results in pain palliation and bone stabilization at various skeletal sites including the vertebral bodies and the long bones [26–36]. Compared to RFA, cryoablation may present several advantages, particularly a greater reduction in analgesic doses and shorter hospitalization time after the procedure [30]. Moreover, the tissue treated with cryoablation can be monitored in real time on CT images, recognized as a low-density region ('ice ball') adding safety to the procedure [31]. The major contraindication of RFA is the presence of a pacemaker. Moreover, the larger the lesion, the greater the treatment time, with a possibility of incomplete treatment with partial ablation and/or need for repeat treatment [26]. Cryoablation is preferable for larger and irregularly shaped lesions compared to RFA [35].

Currently, the role of RFA and cryoablation has not only limited to pain palliation, but also for local tumor control with encouraging results [29, 32, 33]. A recent retrospective analysis of patients with oligometastatic bone disease treated with RFA or cryoablation showed local tumor control at a 2-year follow-up in 72% of patients; a size of bone

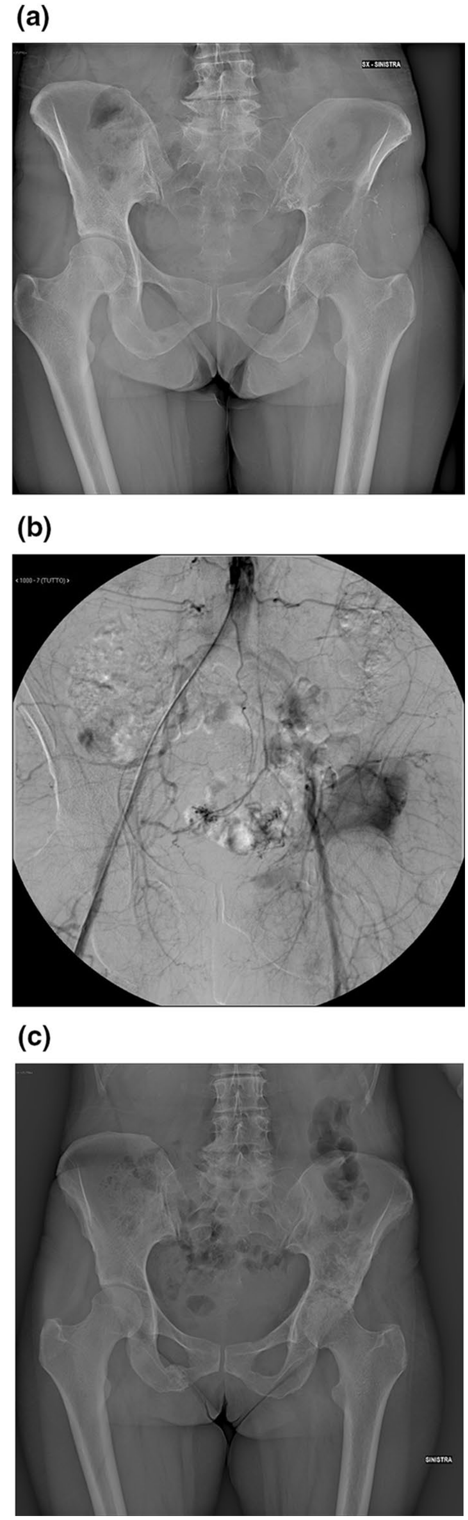

Fig. 1 **a** Anteroposterior radiograph of the pelvis of a 60-year-old woman with a painful supra-acetabular bone metastasis from breast cancer. **b** Arteriography shows pathological vascularization originating from branches of the obturator and deep femoral artery. **c** Anteroposterior radiograph of the pelvis 24 months after embolization shows stable metastatic lesion with ossification

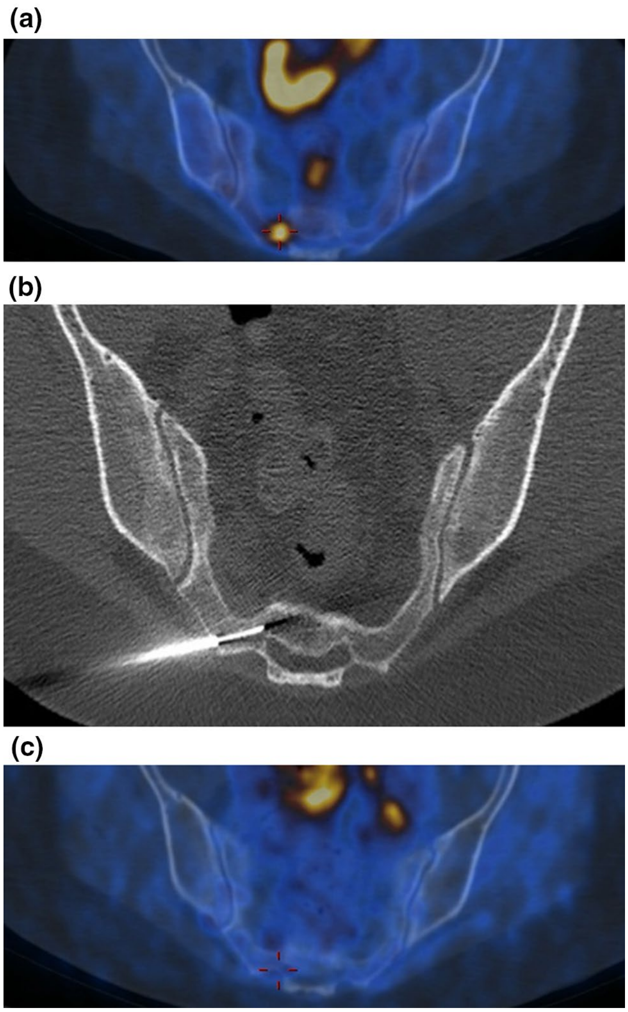

Fig. 2 **a** PET–CT scan shows a sacral bone metastasis in a 52-year-old woman with thyroid cancer. **b** CT-guided radiofrequency thermal ablation was done. **c** Complete normalization of the PET–CT 6 months after treatment

metastasis > 2 cm was the most important predictor for local disease progression [34].

Magnetic resonance imaging-guided high-intensity focused ultrasound

An exciting new technique for the treatment of bone metastases is magnetic resonance (MR) imaging-guided high-intensity focused ultrasound (HIFU), also known as MR imaging-guided focused ultrasound surgery (MRgFUS). MRgFUS combines the use of HIFU—focusing high-intensity ultrasounds (mechanical waves–radiations) on a target to be destroyed or altered with the guidance of MR imaging (Fig. 3). The technique includes a powerful and noninvasive treatment tool (HIFU) aided with MR imaging guidance [37]. It provides for precise delivery of energy to a target, without ionizing radiation exposure and a lack of cumulative doses. Several lesions may be treated per session and treatment may be repeated as many times as needed. The main limitation for the treatment of bone metastases is their anatomical location; any site can be treated with MRgFUS except for the vertebral bodies [37].

Liberman et al. [38] reported a decrease in the average visual analogue scale (VAS) score from 5.9 points to 1.8 points at a 3-month follow-up in 25 patients (9 patients reported a 0 point VAS); 52% of patients reported substantial pain relief within 3 days; no major complications were reported. Napoli et al. [39] presented the potential role of MRgFUS for local tumor control; they reported increased bone density with a restoration of cortical borders in 5 of the 18 patients treated with MRgFUS (27.7%) and complete and partial responses to treatment in two (11.1%) and four (22.2%) patients, respectively, with a non-perfused volume between 20% and 93%.

The results of a phase III trial on MRgFUS substantially contributed to the evidence of safety and efficacy for the palliation of painful bone metastases [40]. This study enrolled 147 patients with painful bone metastases that were randomly assigned to MRgFUS or placebo treatment. The primary end point was an improvement in self-reported pain score without any increase in pain medication during the 3 months after treatment. Response rate was 64.3% in the MRgFUS group and 20.0% in the placebo group ($p < 0.001$). The most frequent adverse event encountered in this study was pain that occurred in 32.1% of MRgFUS patients; pathological fractures occurred in two patients, and third-degree skin burns and neuropathy in one patient each. Overall, 60.3% of the adverse effects were resolved within the same day of treatment. This study supported the role of MRgFUS as noninvasive and safe for painful bone metastases when standard treatments have failed [40].

Lee et al. [41] performed a matched-pair study on MRgFUS versus conventional radiation therapy for patients with painful bone metastases. MRgFUS provided a similar overall treatment response but faster pain relief compared with conventional radiation therapy. The authors supported the role of MRgFUS as the first-line treatment for painful bone metastasis in selected patients. Preliminary clinical studies also report that MRgFUS may be a potentially safe and effective noninvasive treatment option for radiation therapy refractory pain to metastatic bone lesions, with > 70% of patients experiencing variable pain reduction after MRgFUS treatment [42, 43].

Electrochemotherapy

Electrochemotherapy (ECT) was first described by Mir in 1991 for the treatment of cutaneous nodules of head and neck malignant tumors [44]. ECT is based on a combination

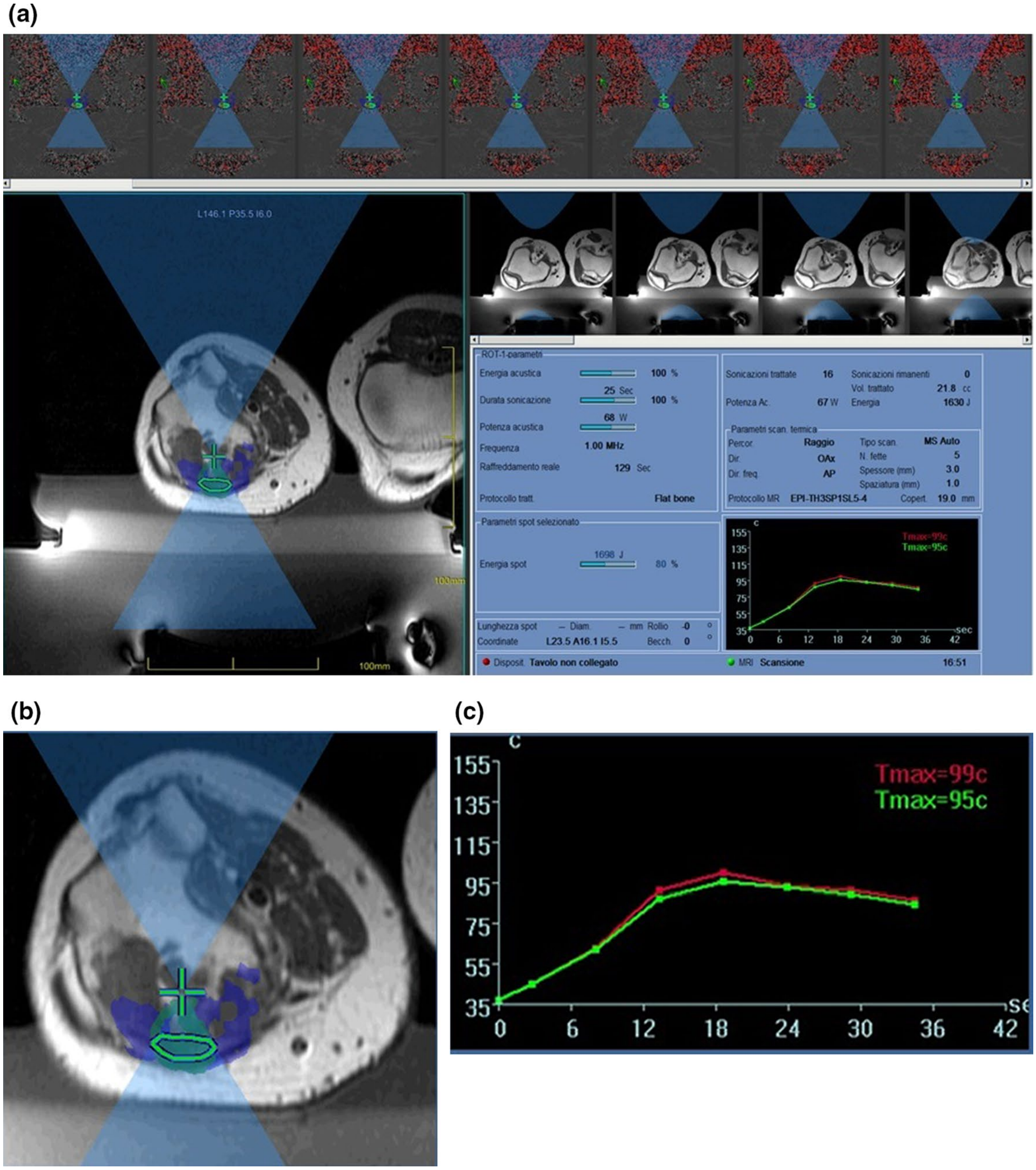

Fig. 3 **a** Screenshot of the MRgFUS device during treatment of a painful bone metastasis of the tibia (axial view) of a 50-year-old woman with breast cancer. The beam path (light blue area) and current MRgFUS treatment (green area) are shown. Areas (bone tissue volumes) previously ablated are highlighted (blue). The higher line shows thermal images during MRgFUS treatment (temperature mapping). **b** Zoom on the treated area. **c** The graph shows the evolution of temperature during MRgFUS treatment (colour figure online)

of electroporation associated with intravenous infusion of a chemotherapeutic drug to which the cellular membranes are usually poor or non-permeant [44]. Electroporation includes local application of electric current pulses to the tumor tissue, inducing the opening of the transmembrane channels, therefore allowing the passage inside the cell of chemotherapeutic drugs, increasing a localized cytotoxic effect. Membrane permeabilization can be temporary (reversible electroporation) or permanent (irreversible electroporation) as a function of the electrical field magnitude and duration, and the number of pulses. The appropriate electric pulses (short and intense square-wave electric pulses) have no apparent cytotoxic or systemic effects [45–50].

Among several clinically approved drugs that have been tested in preclinical studies, bleomycin and cisplatin have shown to be the most effective and suitable drugs for ECT

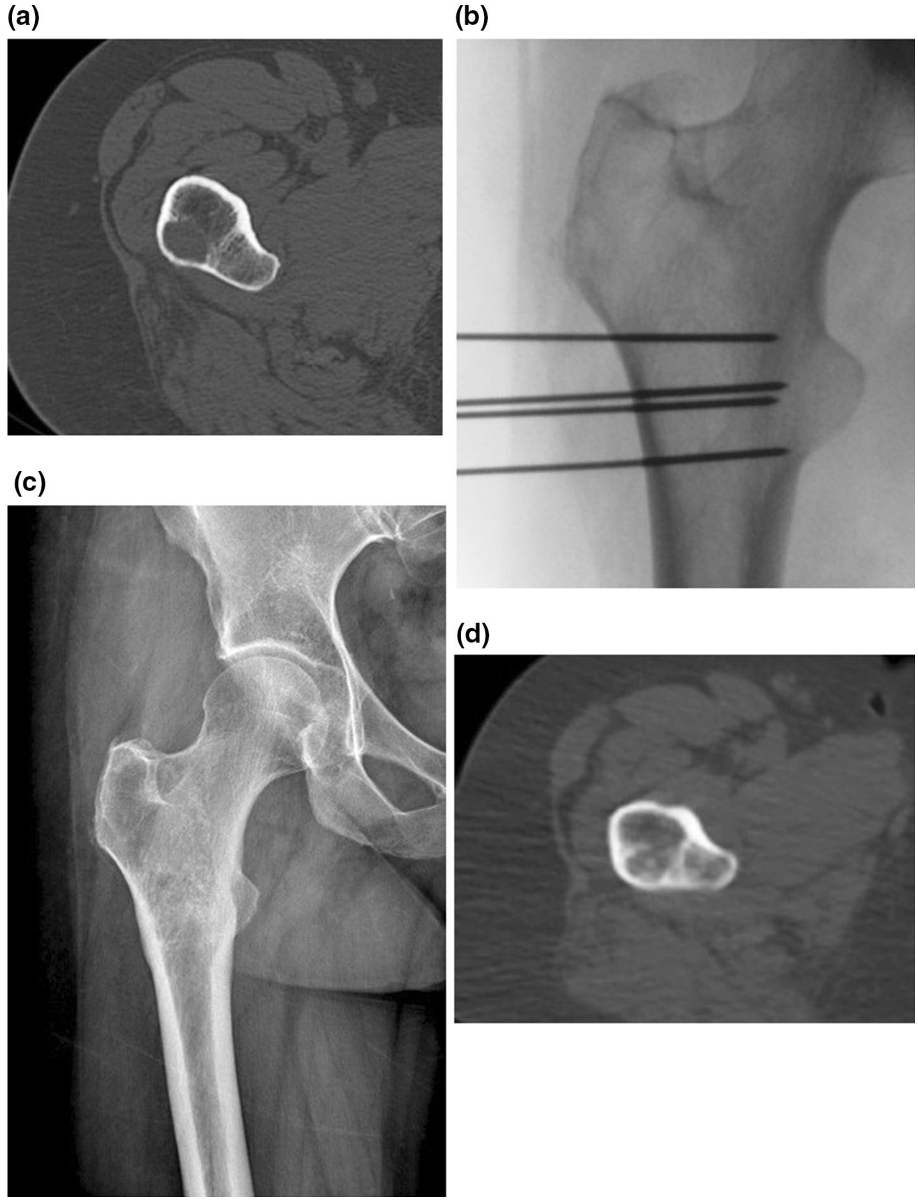

Fig. 4 **a** Axial CT scan of the right femur of a 35-year-old woman with a painful bone metastasis from breast cancer. **b** Radiograph of the right femur during ECT shows insertion of the electrodes at the tumor area. **c** Radiograph and **d** axial CT scan of the right femur 17 months after ECT shows stable lesion with partial ossification

clinical use. After the exposure of tumor cells to electroporation, the cytotoxicity of bleomycin and cisplatin increases almost 8000 times and 80 times, respectively, compared to the drugs normal activity [51].

Fini et al. [52] first performed electroporation on healthy bone tissue with the aim to develop a reproducible technique to introduce electrodes into the target bone tissue and to identify the protocols for electroporation (voltage applied and numbers of pulses) that are sufficient to ablate all bone cells in the target area. They showed that electroporation does not alter bone mineral structure, neither the regenerative activity nor the mechanical competence of the bone. They also investigated the safety of electroporation in proximity to neurovascular structures and the spinal cord; histological examination of the neural structures after electroporation showed transient edema without structural alterations [52].

Based on these encouraging results, the technology of electroporation was further developed to permit the use of ECT for bone malignant tumors. Feasibility was assessed by evaluating the possibility of reliably inserting electrodes percutaneously in bone, according to a predefined geometry to ensure proper electroporation of cell membranes in the bone metastasis [53, 54]. ECT can be performed percutaneously, with CT or fluoroscopy guidance, minimizing the surgical risks and morbidity for the patient [54].

In an in vivo clinical trial, ECT achieved pain relief in 84% of patients; use of pain killers, quality of night sleep and daily activities improved in 55–73% of patients. Importantly, local tumor control (stable disease) was achieved in

90% patients, with only 10% of the lesions showed progression at follow-up [55]. Gasbarrini et al. performed minimally invasive ECT for an L5 vertebral body metastasis from melanoma; 48 months after the procedure, the patient was free of pain without any progression of the disease [56]. Results of these preliminary studies support the role of ECT for the management of patients with painful bone metastases (Fig. 4).

Conclusion

Skeletal metastases influence the quality of life of the patients with a metastatic disease. In these patients, especially if a limited expected survival, the indications for surgical treatment are limited, immediate pain relief and improvement in the functional status are important, and complications of treatments are unwanted. Decisions regarding potential surgery for a metastatic disease require reliable data about the patient's survival and quality of life [57, 58]. Currently, novel less invasive surgical treatments including embolization, thermal ablation, MRgFUS and ECT are available for the management of the patients with painful bone metastases. They combine the advantages of less invasive surgery and interventional radiology procedures for early functional recovery and initiation of adjuvant medical therapies and seem to be effective in both pain relief and local tumor control.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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