



Percutaneous management of bone metastases: state of the art, interventional strategies and joint position statement of the Italian College of MSK Radiology (ICoMSKR) and the Italian College of Interventional Radiology (ICIR)

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Abstract

Interventional radiology provides local management of bone metastases (BM) with a palliative intent in most cases, or with a curative intent in selected patients. Its role has rapidly expanded in the last decade, offering new treatment solutions often in combination with surgery, radiation therapy and medical treatments. The aim of the present paper is to increase awareness, acceptance and adoption of interventional radiology procedures for the treatment of BM; and to present the joint position of the Italian College of Musculoskeletal Radiology and the Italian College of Interventional Radiology.

Keywords Bone metastasis · Skeletal-related events · Interventional radiology

Epidemiology and clinical manifestations of bone metastases

Bone metastases (BM) are the most common malignant lesions of the bone, commonly involving the axial skeleton, pelvic ring and proximal extremities [1]. In the USA, it is estimated that approximately 100,000 individuals develop BM every year [2]; and the incidence is expected to increase in the future due to the improved survival of cancer patients. The incidence of BM is particularly high in patients suffering from breast, prostate or lung cancer; intermediate in those presenting with melanoma, renal or thyroid cancer; and relatively low in patients presenting with gastrointestinal tumors.

BM significantly impact patients' clinical status due to pain, fractures, compression of nearby structures such as nerves, hypercalcemia, and often require radiation therapy (RT) and/or surgery, especially when spinal cord compression is noted. All these events are commonly known as skeletal-related events (SREs) [3]. Pain is the most common SRE and may have a nociceptive, neuropathic, or mechanical origin [4]. Fractures are the second most common SRE and have a significant impact on patients' quality of life and survival [1, 3]. Usually three types of fractures occur in cancer patients, namely pathologic fractures (PF), impending fractures (ImF), and fractures related to bone insufficiency (BiF). PF are a direct consequence of bone weakness due to the presence of BM, which are generally lytic and located in weight-bearing bones. ImF are painful BM in weight-bearing areas, often requiring preventive consolidation to avoid PF. Lastly, BiF result from bone reabsorption due to

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medical therapies (e.g., hormonal therapies, steroids) and/or cytokines produced by the tumor [5–7].

Current treatment modalities to treat pain and prevent fractures are medical therapy (including analgesics, bisphosphonates and denosumab) and RT; both allow good but far from excellent results. As a matter of fact, it has been demonstrated that pain is not adequately treated in 56–82.3% patients [8]. Although RT is considered the best evidence-based non-interventional treatment for BM-related pain, several limitations have been observed: (a) ineffectiveness in case of radio-resistant tumors such as renal cancer or melanoma; (b) 1–2-week latency between the end of treatment and the onset of pain relief; (c) overall (complete and partial) pain relief observed in less than 60% of patients and recurrent pain in up to 50% of those who respond by 20–24 weeks after the end of treatment; (d) retreatment is not always possible if the maximal radiation dose has already been delivered; (e) no immediate bone consolidation is provided [3–5]. Although the recently introduced tumoricidal stereotactic body RT yields higher rates of local tumor control and pain management compared with standard external beam RT [9, 10], the risk of secondary fracture is significantly increased when the former technique is used [9]. Despite all the aforementioned drawbacks, RT still remains the most common treatment for BM, especially for patients in poor general conditions. On the other hand, bone-targeting agents interfering with tumor-mediated osteolysis, can reduce but not completely remove the risk of SREs [3].

In this setting, interventional radiology procedures may play an important primary or complementary role to manage BM [11–13], especially in the palliative setting where pain and fracture management is necessary.

The aim of the present paper is to increase awareness, acceptance and adoption of interventional radiology procedures for the treatment of BM; and to present the joint position of the Italian College of Musculoskeletal Radiology and the Italian College of Interventional Radiology.

Interventional procedures

Osteoplasty

Indications

Percutaneous osteoplasty refers to polymethylmethacrylate (PMMA) injection into weakened or fractured bone. Osteoplasty is shown to be effective in achieving consolidation and pain relief in patients affected by painful lytic BM at risk for PFs. Osteoplasty is also currently used to treat BiF. The best indication of osteoplasty is bones in which compressive stress is predominant, such as in the vertebral body, the acetabulum and the proximal/distal epiphyses of long bones.

In the vertebral body, despite an increased risk for epidural leakage, posterior wall disruption does not represent an absolute contraindication to vertebroplasty [14] (Fig. 1). On the other hand, in case of tumor compression of the spinal cord or in case of vertebral instability due to tumor involvement of the posterior elements of the vertebra, surgical decompression/stabilization should be considered as early as possible. In long bones, pure diaphyseal consolidation by osteoplasty should be avoided unless the intent is purely palliative in an end-stage bedridden patient. This is due to the fact that PMMA has limited resistance to torsion and bending; therefore, surgical endomedullary nailing is the preferred option to achieve effective biomechanical stabilization. Moreover, prior osteoplasty precludes endomedullary nailing, rendering surgical external fixation the only available option when fixation is required [15].

Absolute contraindications to osteoplasty are local/systemic infection, known allergy to the PMMA and irreversible coagulopathy.

Technique

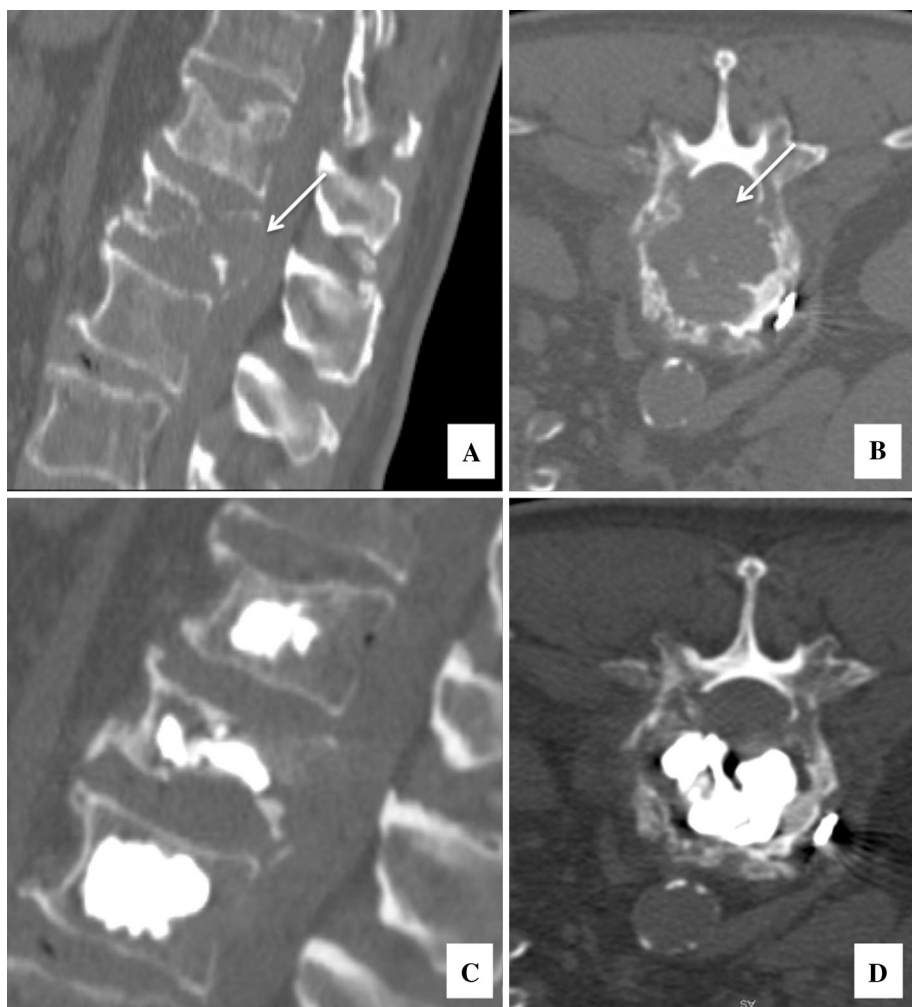
The procedure can be performed under fluoroscopic and/or CT-guidance often under local anesthesia/mild sedation. PMMA is injected under continuous fluoroscopic guidance through a 10–13 G trocar in its toothpaste consistency. PMMA-based cements certified for radiological use are radiopaque, which enables the operator to monitor the PMMA distribution within the bone and allows the prevention of leakages. The consolidation time of PMMA is variable (8–20 min), and its polymerization results in an exothermic reaction with temperature > 70 °C, which is, however, inadequate to achieve effective local tumor control.

Results

Osteoplasty has been proved to be effective for the symptomatic treatment of osteolytic tumors including multiple myeloma. In the spine, effective and long-lasting pain control is achieved in 60–85% cases [16]. Outside the spine, referring mainly to the pelvic ring, similar results have been reported [17]; however, careful injection is warranted, especially for acetabular tumors with cortical disruption, as intra-articular leakage may result in rapidly evolving chondrolysis [18].

For long bones, effective pain management and functional amelioration can be achieved in 89.4% and in 71.8% cases, respectively [15]; nevertheless, the rate of secondary fractures is estimated to be as high as 8–9.1% with the highest rate (40.6% at 1-year) reported in the proximal femur [15, 19, 20].

Fig. 1 **a, b** Painful lytic metastasis of T12 in a 70-year-old patient suffering from hepatocellular carcinoma; the metastasis disrupted the posterior wall of the vertebral body (white arrows). **c, d** Percutaneous vertebroplasty was safely performed with immediate pain relief and no cement leakage (vertebroplasty was also performed in T11 and L1 during the same interventional session due to painful pathological fractures)



Osteosynthesis

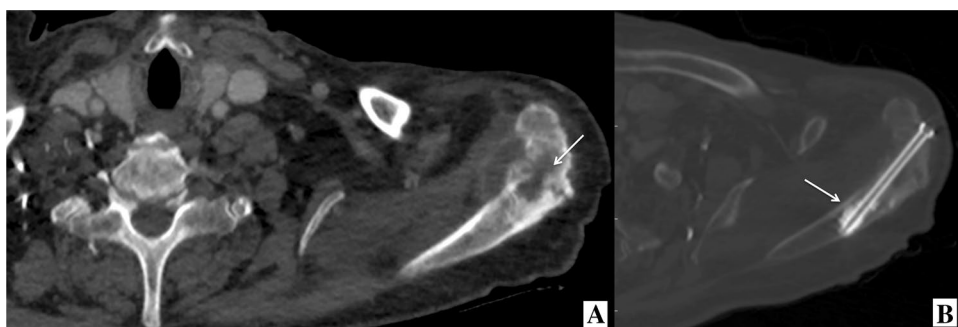
Indications

Percutaneous osteosynthesis is consistent with screw fixation to consolidate minimally/non-displaced fractures of the pelvic ring [21]. The technique can also be performed in the proximal femur to consolidate ImF (i.e., Mirels' score ≥ 8) without significant trochanteric and cortical involvement

[22, 23]. Additionally, fractures of the shoulder girdle have been also reported to be managed by this technique [24] (Fig. 2).

Whenever possible, surgery should be preferred to percutaneous osteosynthesis; since the long-term effectiveness of this technique still requires further supporting evidence. Accordingly, osteosynthesis should be strictly reserved for non-surgical cancer patients with limited life expectancy to provide rapid analgesia and mobilization

Fig. 2 **a**) Painful pathological fracture (white arrow) of the left acromion in a 69-year-old patient suffering from lung cancer. **b**) The fracture was fixed percutaneously by means of a compressive screw; the screw tip was fixed in distal normal bone through the injection of few ml of cement (white arrow)



without the need for suspension of systemic therapies, which is often necessary with surgical treatments. Moreover, compared to surgery, risk of bleeding and infection is also significantly reduced.

Technique

Percutaneous osteosynthesis is performed under fluoroscopic and/or CT-guidance. Due to the long procedural time (around 2 h due to challenging bone access), general anesthesia is usually preferred over local anesthesia/mild sedation.

Threaded screws are used in case of mildly displaced fractures in order to achieve maximal inter-fragment compression. Totally threaded, non-compressive screws are preferred in cases of non-displaced fractures. Commonly applied screws are self-drilling self-tapping thus allowing for accurate cut and thread and avoidance of cut bone jamming. Finally, PMMA-injectable screws providing distal holes are preferred in cases of advanced osteoporotic bone to enhance screw anchoring.

The most challenging phase of the procedure is often the perpendicular bridging of the fracture line by means of a 1.8–2 mm k-wire; after which, the screw is manually advanced over the wire by means of a screwdriver until its distal tip is safely anchored within distal healthy bone, and its head abuts the cortical bone.

Results

Osteosynthesis has been shown to be effective for the symptomatic treatment of pelvic fractures or those of the proximal femur. In a study of 64 patients undergoing pelvic osteosynthesis alone or in combination with osteoplasty, a median pain reduction of 6/10 points was noted, with only two secondary fractures observed in the proximal femur [25]. Another similar series of 33 patients reported an effective analgesic/functional amelioration in 87.1% cases at 1-month follow-up [21]; nevertheless, three major and one minor complications were reported. Moreover, although no secondary fractures were reported, unfavorable local evolution of the treated site (i.e., poor consolidation and/or screw loosening) was noted in 12.5% cases on imaging follow-up (mean 8.7 month) thus, suggesting the need for strict clinical follow-up. Additionally, in a small series of 11 osteosyntheses of the proximal femur, rapid pain control and consolidation were reported (significant and mild amelioration in pain/walking in 63.6% and 27.3% patients, respectively) at 1-month follow-up, without any secondary fracture [23].

Thermal ablation

Indications

Thermal ablation is used to destroy tumors through the direct application of heat- or cold-based energies [13, 26–29], delivered percutaneously with the exception of High-intensity focused ultrasound (HIFU). Thermal ablation can be performed with a curative or palliative intent (Fig. 3).

All techniques applying heat-based energy achieve tumor destruction through coagulation necrosis. On the other hand, cryo-mediated damage is much more complex [30]. The final necrotic volume depends on the amount of energy delivered and the local tissue characteristics such as vascularization, which may be responsible for energy dissipation (i.e., heat/cold-sink effect) [26, 31].

Compared to RT, the effects of ablation are immediate and there is no limit to the number of ablative treatments that can be performed on the same tumor, which is not the case for RT as it cannot be repeated once the maximum dose of the target organ is reached. In the majority of cases, bone consolidation can be combined with ablation in the same session.

Anesthesia (deep sedation, general anesthesia, nerve block or spinal anesthesia) is usually required [32]. Although all imaging modalities can be potentially used, CT and fluoroscopy play a major role.

Absolute contraindications include coagulation impairment and infection. Antibiotic prophylaxis remains controversial although it is generally applied [32].

Techniques

Laser Lasers deliver electromagnetic energy in the infrared wavelength through small optic fibers deployed coaxially into 18G needles. Lasers do not interfere with metallic implants and are fully MRI compatible. However, only small ablation zones can be obtained since, even when multiple fibers are activated simultaneously, ablations zones rarely exceed 2–3 cm [31–33]; for this reason, lasers can be applied to treat only small benign bone tumors such as osteoid osteoma [34].

Radiofrequency ablation (RFA) RFA is probably the most commonly applied technique in bone ablation [31, 33, 35]. Coagulative necrosis is achieved through ionic agitation (i.e., frictional heating) induced by electric current delivered through electrodes. For this reason, RFA cannot be used if pacemakers or other implantable electric devices are present, or in case of osteoblastic BM impeding effective conduction of the electrical current, which can flow between the electrode and the grounding pads attached on the skin of the patient (unipolar system), or between two electrodes or two dipoles localized at the distal tip of the same electrode

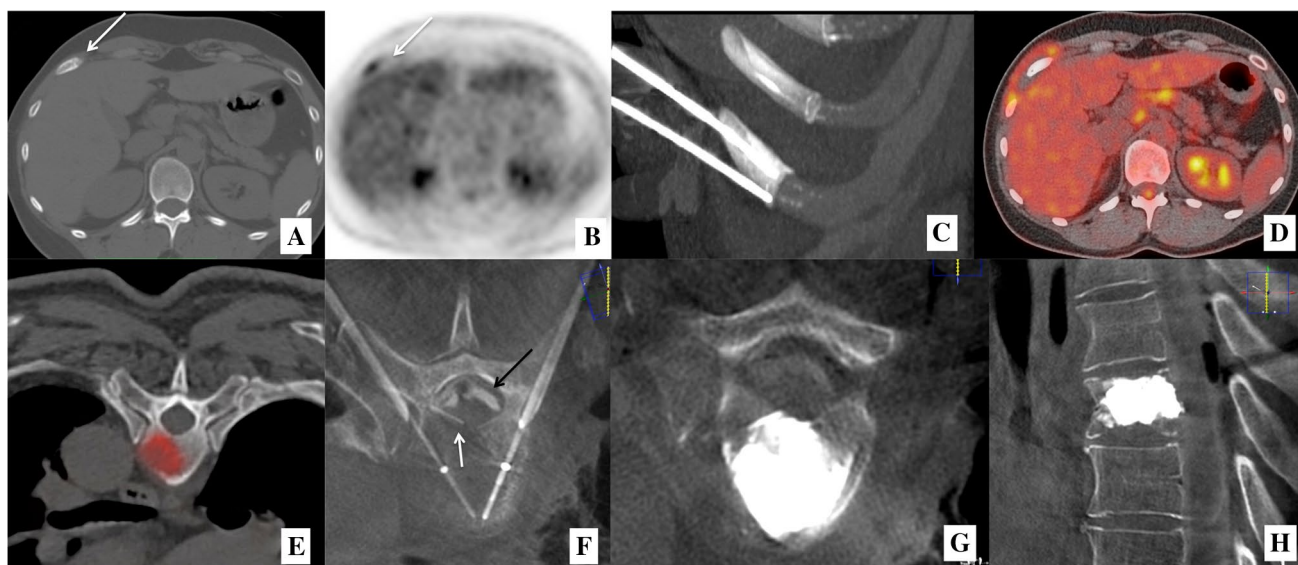


Fig. 3 Curative treatment. **a** Single metastasis (white arrow) of the rib in a 45-year-old patient with a history of breast cancer. **b** The metastasis was FDG-avid on PET-CT (white arrow). **c** After cryoablation, **d** effective local tumor control was noted at 12-month PET-CT follow-up. Palliative treatment. **e** Painful (VAS 9/10) T5 FDG-avid metastasis from gastric cancer in a 68-year-old patient. **f** Bilateral

bipolar RFA was performed with thermal monitoring at the level of the posterior wall (white arrow) and hydro-dissection of the epidural space (black arrow); **g, h** in the end, vertebroplasty was performed to prevent a secondary vertebral body collapse. Pain relief (5/10) was noted by the 15th postoperative day

(bipolar system). Compared to the unipolar system, the bipolar electrode requires a smaller power and produces smaller but more predictable ablation zones. For these reasons, they are specifically used in the spine [36, 37]. Once heat is generated, it diffuses away from the electrode tip by contiguity. High impedance (i.e., tissue resistance in receiving the electrical current, for example, in sclerotic BM) represents the main limitation in achieving large ablation zones. Electrodes are generally cooled with cold saline to avoid tissue charring and carbonization around the tip with the aim of reducing impedance, thus enlarging the ablation zone. Nevertheless, RFA cannot achieve ablation zones that exceed 3–4 cm.

MicroWave Ablation (MWA) MWA uses electromagnetic energy, which is delivered through an antenna [31, 35, 38]. Electromagnetic waves induce molecular agitation and subsequent tissue heating. Compared to RFA, MWA energy can radiate through all biological tissues and enables faster and larger (up to 5 cm when multiple antennas are activated simultaneously) ablations. The main drawbacks of MWA are: (a) oval-shaped ablations, especially with first generation antennas; (b) limited experience available with BM due to the fact that the technique is relatively new [39, 40].

Cryoablation (CA) CA destroys tumors using cold temperatures (up to -40 °C) dissipated into tissues through dedicated cryoprobes [30–33, 35]. Rapid argon decompression at the distal tip of the probe is responsible for iceball growth, while helium is used to melt the iceball (i.e., active thawing). Repeated cycles of freezing–thawing have been

demonstrated to be more effective in enlarging the iceball size. For this reason, a double 10-min freeze cycle interrupted by a 10-min thaw is the classic ablation protocol. Cellular death occurs through a complex mechanism that is not completely understood, including mechanical damage to cellular membranes induced by ice crystals, osmotic changes into the tissue, endothelial injury, ischemia, and cryo-immunological effects. Compared to the other techniques of ablation, the main advantages of CA are: (a) precise control of the ablation area due to adequate visualization by common imaging modalities (especially CT or MRI), thus allowing for precise intra-operative evaluation of tumor coverage; (b) multiple probes (up to 40 with the most recent systems, each with different sizes and shapes of ablation) can be simultaneously activated with a final synergistic effect; therefore, the iceball can be shaped according to tumor morphology, and large-volume BM can be treated; (c) possibility of treating osteoblastic BM since the iceball can easily go through cortical and blastic bone; (d) since the iceball has intrinsic anesthetic properties, the procedure is less painful compared to heat-based techniques; accordingly, CA is preferred for the treatment of BM with soft tissue extension. In terms of drawbacks, CA is expensive and time-consuming; moreover, it requires enough space in the operating theatre to lodge gas bottles, unless mural systems delivering the gas are available.

HIFU HIFU is a heat-based technique that does not require any skin incision or needle insertion to destroy the

tumor as it works with a focalized ultrasound beam (i.e., mechanical energy) that is generated by a transducer placed on the skin of the patient [31, 41–44]. The beam passes through tissues without damaging them, and is focused on the target lesion where the mechanical energy is converted into thermal energy. The most advanced technique of guidance is MRI, and the combined system is called MRgFUS (i.e., Magnetic Resonance-guided Focused Ultrasound Surgery). Apart from its totally “non-invasive” profile, MRgFUS has the benefit of allowing optimal MRI resolution to target BM, and allows monitoring of the temperature reached within the tumor, surrounding it as well as in interposed tissues (except bone). Nevertheless, the technique is still not considered safe for spinal ablation and accordingly only superficial or lytic BM showing cortical disruption are treated by this technique. On the other hand, since bone can absorb the ultrasound beam, it is possible to induce high periosteal temperatures to achieve effective pain management in case of painful BM. Drawbacks include limited availability of the technique, long procedural time (2–3 h), and contraindication in patients contraindicated to MRI.

Protective measures to adopt during bone ablation

Thermal ablation is generally considered safe; nevertheless, the most common complications include the unintentional ablation of nearby non-target organs, particularly

nerves. Therefore, careful mapping of the regional anatomy is mandatory to identify structures at risk. Protective measures should be adopted when there is less than 10 mm safety margin between the presumed ablation area and nearby non-target structure.

Several different protective measures are available and include: (a) mechanical displacement of the ablation area (i.e., gentle retraction of the cryoprobe during CA); (b) physical displacement of the non-target structure; (c) clear visualization of the ablation zone with common imaging (i.e., iceball monitoring); (d) temperature monitoring/adjustment in close proximity to the non-target structure; (e) monitoring of the functional status of the non-target structure (i.e., nerve root). In bone ablation, all these measures can be applied (Table 1) alone or in combination to avoid iatrogenic injuries, in particular for nerves and skin. CO₂ or fluids are often injected to achieve physical displacement. CO₂ is preferred over room air since it is much more soluble thus limiting the risk of air embolism. Simple saline (or 5% electrically inert dextrose solution in case of RFA) can be also used (at adjusted dilutions with iodine contrast medium to optimize the visualization under CT-guidance [45]) to displace the non-target organs (i.e., “salinoma”). The great advantage of fluid dissection over

Table 1 Protective measures that can be adopted during ablation

	Advantages	Disadvantages
CO ₂	Low thermal conductivity Highly soluble No renal or hepatic toxicity Non-allergic Low cost Sterile	No cooling or warming properties Distribution in anti-declivous areas Unsuitable for US-guidance
Fluid dissection	Suitable with all imaging modalities (US, CT, and MRI): spontaneous visualization under MRI-guidance; increased visualization under CT-guidance with 5–10% contrast medium dilution Low cost Sterile <i>Allow for temperature adjustment</i>	Distribution to dependent area Potential fluid overload
Angioplasty balloon	Non gravity-dependent distribution No need for volume readjustment	Relatively expensive Technically challenging Unsuitable for the protection of neurological structures
Temperature monitoring	Precise knowledge of the temperature in critical areas	Needs precise thermocouple deployment
Somatosensory-evoked potentials	Precise monitoring of electrical conduction of the tested nerve	Difficult to be performed Requires dedicated trained physicians No neuromuscular blocking neither muscle relaxant agents should be administered during the procedure
Electrostimulation	Simple to be performed No specific training required	Cannot be used continuously in order to prevent muscle fatigue No neuromuscular blocking neither muscle relaxant agents should be administered

CO² is that fluid temperature may allow for warming-up or cooling-down of the non-target structure during ablation.

Angioplasty balloon (5–10 mm×20–40 mm) interposition is rarely used due to the high risk of nerve damage during balloon manipulation.

Temperature monitoring is usually achieved directly through percutaneous deployment of thermocouples or fiber-optic sensors that can be easily combined with fluid dissection, especially when the latter alone is not deemed sufficient. In case of MRgFUS ablation, non-invasive MRI-mediated temperature monitoring can be obtained.

Electrostimulation and somatosensory-evoked potentials allow for the functional monitoring of nerves during the ablation and are particularly useful since nerve roots are very sensitive outside the physiologic range (10–45 °C) [46–50]. Finally, when BM originating from superficial bones are treated, skin protection should be provided. Usually, fluids (including local anesthetic agents) are injected within the sub-cutaneous tissue to increase its width; additionally, sterile gloves filled with hot or cold saline can be transiently applied on the target area to mitigate skin temperature change during the ablation.

Results

Despite the relative few patients that can benefit from curative treatments, growing evidence is demonstrating the effectiveness of such therapeutic treatments in selected patients (Table 2). Interestingly, encouraging data have also been

reported in patients affected by tumors that are commonly considered aggressive, such as lung cancer [51]. Accordingly, it is important to take into account each patients' tumor biology when selecting candidates for curative ablation.

A considerable number of papers provide evidence of ablation in achieving fast and effective pain relief in patients presenting with painful BM (Table 3). The largest experience has been obtained with RFA and CA. Nevertheless, MWA and HIFU have also recently been shown to be effective. Given the “non-invasive” profile of HIFU, it is likely that it will obtain a prominent position in the future for the palliative management of BM.

Embolization

Indications

The aim of trans-arterial embolization (TAE) is to devascularize hyper-vascular BM and to preserve all non-target vessels. Accordingly, TAE should be as selective as possible.

TAE can be applied in case of hyper-vascular BM in order to:

- minimize the blood loss during subsequent surgery; in this scenario, TAE should be performed within 3 days from surgery to reduce the risk of tumor revascularization [52–55];

Table 2 Results of curative ablation

Study	Histology	Site ^a	Ablation modality	Mean tumor size (cm)	No. of patients (no. of tumors)	% Local control	Survival rate	Follow-up (months)	% Complications
Bang et al. [79]	NSCLC	Other	CA	3.1	8 (18)	94	NR	11	11
Bang et al. [80]	Renal	Other	CA	3.7	27 (48)	97	NR	16	2
McMenomy et al. [81]	Mixed	MSK	CA	2.0	40 (52)	87	91% 1 years, 84% 2 years	21	5
Deschamps et al. [59]	Mixed	Bone	CA, RFA	NR	89 (122)	67% 1 year	91% 1 year	22.8	9
Welch et al. [82]	Renal	Other	CA, RFA	NR	NR (46)	93	NR	22.5	0
Tomasian et al. [83]	Mixed	Spine	CA	NR	14 (31)	97	NR	10	0
Erie et al. [84]	Prostate	MSK	CA, RFA	1.6	16 (18)	83	100% 2 years	27	0
Wallace et al. [85]	Mixed	MSK	CA	13.0 cm ³	56 (92)	79% 1 years	NR	NR	4.3
Ma Y et al. [51]	NSCLC	Bone	CA, RFA, MWA	3.6	45 (76)	68% 1 years	NR	NR	2.6%
Mean						88.5%		16	

NR not reported, CA cryoablation, RFA radiofrequency ablation, MWA Microwave ablation, MSK musculoskeletal, NSCLC Non-small-cell lung carcinoma

^aStudy includes metastatic sites beyond bone and soft tissue; only data related to bone and soft tissue metastases are reported

Table 3 Results of palliative ablation

Study	Ablation modality	No. of patients (no. of tumors)	Mean tumor size (cm)	Mean pain score change	No. (%) of patients with reduced pain	Follow-up (months)	No. (%) of major complications
Goetz et al. [86]	RFA	43 (43)	6.3	7.9–1.4 (6.5/10)	41 (95)	6	3 (7)
Dupuy et al. [65]	RFA	55 (55)	5.2	NR (14.2/100)	NR	3	3 (5)
Wallace et al. [87]	RFA	72 (110)	NR	8.0–2.9 (5.1/10)	45 (78)	1	4 (6)
Baagla [88]	Bipolar RFA	50 (69)	NR	5.9–2.1 (3.8/10)	35 (70%)	3	0
Cazzato et al. [36]	Bipolar RFA	11 (11)	NR	7.8–1.1 (6.7/10)	11 (100)	1.9	2 (18.2)
Callstrom et al. [89]	CA	61 (69)	4.8	7.1–1.4 (5.7/10)	42 (69)	6	1 (2)
Prologo et al. [90]	CA	50 (54)	NR	8–3 (5/10)	47 (94)	3	4 (8)
Pusceddu et al. [40]	MWA	18 (21)	5.3	5.6–0.5 (5.1/10)	17 (94)	3	0
Liberman et al. [91]	HIFU	31 (32)		5.9–1.8 (4.1/10)	18 (72)	3	0
Napoli et al. [92]	HIFU	18 (18)	3.2	7.1–1.1 (6/10)	16 (88.8)	3	0

NR not reported, CA cryoablation, RFA radiofrequency ablation, MWA Microwave ablation, HIFU High-intensity focused ultrasound

- b. reduce pain and spontaneous bleeding of tumors that cannot benefit from surgical or percutaneous treatment;
- c. reduce tumor vascularization before percutaneous ablation to limit the heat/cold-sink effect (Fig. 4).

Technique

Many techniques and embolic agents can be used depending on indication, vessels (i.e., size, presence of arterio-venous shunts) and regional anatomy.

In the spine, special consideration to the anterior spinal artery must be made to avoid unintentional embolization resulting in spinal cord ischemia.

Embolic agents can be classified as temporary or permanent and as liquid or solid. Permanent agents are most commonly used for preoperative TAE and for palliative cases; however, temporary agents such as gelatin sponge have also shown their efficacy before surgery [56]. Liquid agents, such as N-butyl cyanoacrylate and Onyx, are more useful (sometimes in combination with coils or plugs) in the presence of



Fig. 4 **a** Large (13 cm) painful right iliac metastasis from hepatocellular carcinoma in a 55-year-old patient undergoing combined single-session embolization and cryoablation; due to the metastasis, the patient was bedridden. **b**, **c** Percutaneous embolization (with glue) was performed just before cryoablation to reduce the cold-sink effect.

d, **e** Cryoablation was accomplished by means of 10 cryoprobes producing a large iceball (*), and with concomitant hydro-dissection to protect the femoral nerve (white arrow). **f** 1-month MRI follow-up showed complete devascularization of the tumor (*); at the same time interval the patient was able to walk again

arterio-venous shunts. Lastly, particles are most commonly used for bone devascularization and the choice of particles diameter (40–1200 micron) is dependent on vessel size and desired distal embolization.

Results

In a large series of 93 patients undergoing pre-surgical embolization of spinal tumors, the benefits of embolization have been demonstrated in terms of reduction of intra-operative blood loss, especially when hyper-vascular BM from renal cell carcinomas were treated, and extensive surgery (corpectomy/vertebrectomy) was performed [57].

Another series of 243 patients undergoing BM embolization reported > 50% and 97% reduction in pain and analgesic consumption, respectively. Nevertheless, post-embolization syndrome, ischemic pain at the embolization site, paresthesia, skin breakdown, and sub-cutaneous necrosis were observed in 35% patients [58].

Pre-procedure work-up, clinical and technical requirements

Normal coagulation parameters, renal function and the absence of infection should be checked. The patients' allergy history should also be recorded. Patients' current medical therapy with particular consideration to anticoagulants and/or antiplatelets should be carefully reviewed and adjusted before the procedure.

Anesthesiology assistance is mandatory during interventional procedure on BM: the choice of the best type of anesthesia should be performed in accordance with the anesthesiology team. Strict sterile environment is required.

After careful review of the diagnostic radiological examinations available, the interventional radiologist should accurately plan the procedure and note the following on a dedicated form: the goal of the procedure (palliative vs. curative); all the non-target structures at risk and protective measures necessary to prevent iatrogenic damage; the need for biopsy (i.e., the primary cancer is unknown; more than one primary tumors are suspected; a molecular target for directed medical therapy can be identified); and the risk of fracture directly related to the BM or secondary to the interventional procedure such as in case of ablation or embolization.

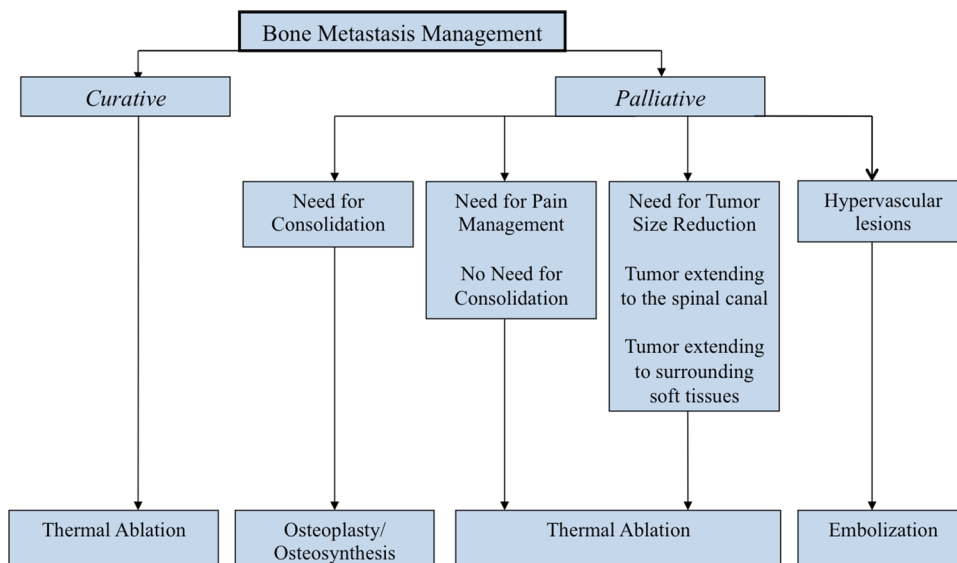
All these details should be documented and discussed with the patient during a dedicated outpatient consultation [39]; in this occasion, a written informed consent should also be obtained.

Interventional strategies

According to the Cardiovascular and Interventional Radiological Society of Europe (CIRSE) Quality Improvement guidelines for bone tumor management, the strategy of the interventional treatment can be curative or palliative (Fig. 5) [32].

Curative treatment can be proposed to selected oligometastatic patients presenting with limited bone disease (<3 potentially treatable BM, each ≤ 3 cm in size). A series of prognostic factors favouring curative treatments have been identified: oligometastatic/metachronous status; the absence or limited cortical bone disruption; limited BM size (<2 cm); long life expectancy; and good patient performance status [59]. Moreover, curative treatments may be indicated in patients with a slow-evolving disease [60], or

Fig. 5 Curative or palliative treatment for the management of BM. (Adapted from reference [32])



in those presenting with a long-lasting stability of the systemic metastatic burden with one or few BM not responding to conventional systemic therapies (i.e., oligoprogression). Nevertheless, all the aforementioned conditions are generally uncommon and for this reason, only a few patients may benefit from curative treatments.

Only ablative techniques allowing tumor destruction may be used for curative treatment, which requires at least 5–10 mm safety margins to achieve effective local tumor control.

Palliative treatments may be proposed to the vast majority of patients with BM and are intended to manage one or more SREs:

- If fractures should be prevented or treated, percutaneous osteoplasty or osteosynthesis is applied based on the predominant biomechanics of the affected bone and the features of the target BM (Fig. 6).
- If pain management is needed and there is no risk of fracture, thermal ablation should be performed. Patients should be offered such treatment in case of focal pain ($\geq 4/10$ on a 0–10 visual analogic scale over the 24 h) corresponding to a focal BM on cross-sectional imaging. Ideally, ablation should target the interface between the normal bone and the BM; nevertheless, whenever possible, complete BM destruction should be achieved.
- Tumor debulking can be achieved with ablation such as in the case of BM extending to surrounding soft tissues or spinal tumors growing quickly into the spinal canal. Nevertheless, it should be noted that local tumor control cannot be achieved if the BM has already invaded the anterior epidural space.

Despite the curative or palliative intent, when ablation and/or embolization are performed (or following RT), bone strength is impaired; and a substantial risk of secondary BiF exists. Accordingly, based on simple biomechanical consideration, interventional or surgical consolidation is mandatory to avoid a secondary BiF, which usually occurs within the first few weeks even though cases of delayed BiF have been reported [61]. Consolidation should ideally be performed during the same interventional session, or at the latest during the same hospital stay.

Follow-up after interventional treatments

In the majority of cases, the main goal of percutaneous treatment is pain management [8, 62]. For this reason, many authors evaluate procedural success on the basis of clinical data by applying pain scales (e.g., VAS scale, Brief Pain Inventory) or quality of life scores (e.g., McGill Quality of Life Questionnaire) [39, 40, 63–65]. Moreover, scores

assessing the performance status of the patient such as the Karnofsky Performance Score are also used [66]. Additionally, some authors also evaluate the consumption of analgesics including opioids [40, 66] that are nevertheless limited by side effects such as constipation, sedation, and nausea. Clinical data are collected at least 1 week after treatment (to reduce the placebo effects or other confounding factors, such as the effects of analgesics administered during the procedure or pain related to the procedure itself), and thereafter, follow-up is scheduled at 1, 3 and 6 months according to the patients' status and disease evolution.

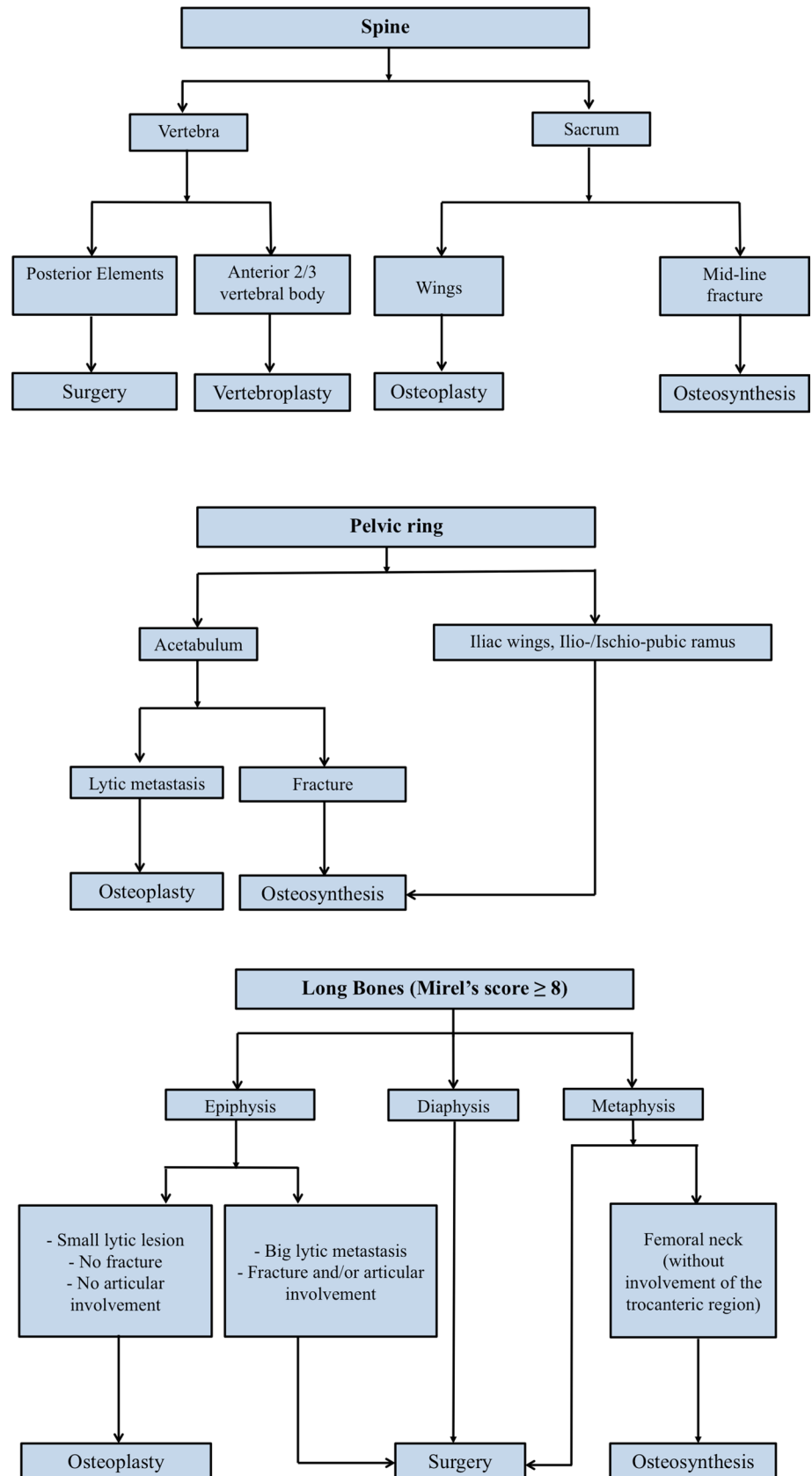
Unless new symptoms occur, imaging follow-up is unnecessary in patients with diffuse metastatic disease who underwent palliative treatments [39, 67]. On other hand, oligometastatic patients treated with a curative intent should undergo periodic imaging follow-up to assess local tumor control (i.e., identification of residual viable or recurring tumor in the treated area). The choice of the most appropriate imaging technique is of paramount importance, and contrast-enhanced techniques (in particular MRI or PET-CT) represent the best choice. MRI is able to depict even the smallest focus of active disease [68, 69]. To avoid confounding variables, such as inflammation, the first follow-up study should be carried out 4 or even 8–12 weeks after the treatment [40, 59, 70]. Finally, it is important to notice that RECIST criteria cannot be used in the setting of BM as RECIST has only been used for soft tissue metastases; moreover, BM is often considered “non-measurable” [68].

Possible interactions with other treatments

The application of interventional radiology for the management of BM is relatively recent. This may explain why no comparative studies are available between interventional treatments and RT, which still remains the widely accepted gold standard for the treatment of SREs, particularly pain [71]. In the few studies describing the combined use of RT and percutaneous treatments [63, 66, 72], authors emphasized the achievement of better results in terms of pain relief when the combined approach was applied as compared to a single treatment modality, without significant increase in morbidity. The exact mechanisms through which the combined treatment relieves pain remain largely unknown, although it has been advocated that tumor microenvironment perturbation resulting from ablation may enhance the effect of RT [73].

The development of immunotherapy has resulted in new and revolutionary advances. Researchers started from the observation of rare cases of abscopal effects after RT [74]. This refers to the remission of tumors outside the radiation field. It has been postulated that this phenomenon is immune mediated and is mainly observed in patients undergoing RT

Fig. 6 Consolidative algorithm based on the biomechanics of the involved bone and the features of the target bone metastasis. (Adapted from Cazzato RL et al. “Percutaneous bone and spine consolidation in cancer patients: who and how?” Magna cum Laude Education Exhibit; Radiological Society of North America; 2017)



and immunotherapy. Indeed, focal treatments such as RT may trigger and potentiate the effects of immunotherapeutic agents; and it has been postulated that similar to RT, thermal ablation can also stimulate a systemic immune-mediated antitumor response [75–78].

Medical therapy for BM disease relies on agents (bisphosphonates or denosumab) avoiding bone loss [3, 7]. To our knowledge, no side effects have been described in patients receiving such agents and interventional treatments.

Surgery can be the definitive solution in oligometastatic patients with slowly evolving disease and long life expectancy. However, there are different limitations to its use since surgical interventions carry a significant risk of infection and bleeding coupled to a long recovery time [67, 71]; as a result of which, a long delay to systemic therapies is expected. All these aspects can negatively affect patients' quality of life and may significantly impact their survival.

Joint position of the Italian College of Musculoskeletal Radiology and the Italian College of Interventional Radiology

1. Due to the complex clinical scenario regarding BM, we suggest that the most adapted therapeutic strategy should be chosen in consensus by a dedicated multidisciplinary tumor board including medical oncologists, radiation oncologists, surgeons and interventional radiologists. The final therapeutic decision should take into consideration the oncologic and clinical status of patients as well as their expectations in order to offer an individualized treatment strategy.
2. In the multidisciplinary tumor board, interventional techniques may be considered as the sole therapeutic option or as part of a more complex therapeutic strategy integrating different interventional and non-interventional treatments.
3. Interventional treatments have several different advantages including the synergic effect with all the other non-interventional treatments, no need for significant interruption of systemic therapies, reduced morbidity and in-hospital stay, and patients' fast recovery. All these aspects may play a crucial role for the selection of the interventional treatment by the tumor board.
4. The interventional treatment should be selected with a clear intent, which can be curative in few selected patients needing local tumor control; or palliative in order to prevent or treat SREs (i.e., pain and fractures).
5. Once the tumor board has selected an interventional treatment, the interventional radiologist should see the patient during a dedicated consultation to explain the risks and the benefits of the procedure.
6. Due to technical and anatomic specifications, interventional treatments should be performed by trained interventional radiologists (or by young interventional radiologists under the supervision of a senior). The physician performing the procedure is responsible for the selection of the best imaging modality and the most suitable device/technique.
7. Interventional procedures on BM are usually painful, and the interventional radiologist performing the procedure may not be able to provide alone the best intraoperative anesthesia and postoperative analgesia; as a consequence, dedicated anesthesiology teams should be involved. Effective analgesic treatment should also be provided in the postoperative phase, which is generally within the first 24 h where more pain is expected.
8. Based on the aim of the procedure, dedicated clinical and/or radiologic follow-up should be scheduled and directly performed by the interventional team.
9. Given the paucity of clinical studies comparing all the different therapeutic options available for the treatment of BM, interventional radiologists themselves and the tumor board should promote clinical trials comparing all the different interventional and non-interventional techniques.

Compliance with ethical standards

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

Human and animal rights 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 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed consent Not applicable.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

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