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A Multimodal Clinical Approach for the Treatment of Bone Metastases in Solid Tumors

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Abstract

Context: Bone metastasis (BM) is a frequent complication of cancer, representing the third most common site of secondary spread in solid cancers behind the lung and liver. Bone metastasis is found in up to 90% of prostate and breast cancer patients. They can cause significant complications, such as pathological fractures and paralysis of the spine, which decrease daily functioning and quality of life (QoL) and worsen prognosis. The growing life expectancy of cancer patients due to improvements in systemic therapies may further increase BM's eventuality and clinical burden in cancer patients.
Evidence Acquisition: Four physicians from five different specialties were interviewed and resumed the most relevant literature of the last 20 years focusing on pain treatment in BM patients.
Results: Treatment for BM ideally involves various types of specialists and assessments. The disease status and patient background should be considered, requiring holistic care and expertise from various medical specialties.
Conclusions: Interventional, nuclear medicine, radiotherapy, and mini-invasive techniques can be safe and effective for relieving pain and modifying health-related QoL in BM patients.

Keywords: Cancer Pain, Pain Management, Skeletal Metastasis, Radiation Therapy, Radiometabolic Therapy

1. Context

Bone metastasis (BM) is relatively frequent in cancer, representing the third most common site of secondary spread in solid cancers behind the lung and liver (1). The clinical incidence is somewhat underestimated, as, in some autoptic studies, BM is found in up to 90% of prostate and breast cancer patients (2). Epidemiological data on secondary bone involvement from primary solid cancers are summarized in Table 1. Bone metastases represent a significant cause of morbidity and quality of life (QoL) worsening, as they may determine pain, fractures, neurological symptoms, and hypercalcemia. These problems are usually called skeletal-related events (SREs) (3). Although SREs are usually not fatal per se, an indirect effect on mortality is quite likely. Furthermore, the increasing life expectancy of cancer patients due to the improvement of systemic therapies may increase the clinical burden of BMs in cancer patients in the future.

Many BMs are found incidentally at primary cancer staging or during follow-up. Even if it is initially asymptomatic, pain represents the most common symptom at diagnosis. However, outside of clinical trials and in the absence of symptoms and/or laboratoristic abnormalities (hypercalcemia, bone-specific alkaline phosphatase increases), bone staging is usually not recommended since

Table 1. Cumulative Incidence of Bone Metastasis Among Different Solid Cancers

Cancer Type	Incidence at Diagnosis (%)
Lung cancer	49
Prostate cancer	15
Breast cancer	14
Gastrointestinal cancer	7
Kidney cancer	5

pre-clinical findings play no direct role in survival (4). Subsequent workup generally includes radiographic study, computed tomography (CT), or magnetic resonance imaging (MRI) as clinically indicated, and bone scan or positron emission tomography (PET) for whole-body evaluation. This review summarizes the main approaches to conservative treatment of BMs from a systemic and locoregional perspective.

2. Evidence Acquisition

Several physicians from different specialties were interviewed and asked to summarize the most relevant studies/trials published in the past 20 years focusing on pain treatment in BM patients. The literature search was conducted in the PubMed/MEDLINE database. No interval nor language restriction was used to select articles in this narrative review.

3. Results

3.1. Systemic Treatment

Systemic treatment for BMs consists of administering osteoclasts inhibitors, i.e., bisphosphonates and denosumab. These agents can reduce the frequency of SREs and delay their onset. Their rapid administration following BM diagnosis is recommended (5). Bisphosphonates decrease bone reabsorption and increase mineralization by inhibiting osteoclast activity by inducing their apoptosis, altering differentiation, and maturation (6). The most substantial evidence of bisphosphonates' efficacy is a meta-analysis of 44 randomized studies involving more than 37,000 patients with breast cancer (7). Compared to the placebo, bisphosphonates significantly reduced the absolute risk of SREs (excluding hypercalcemia) by 14% and delayed the median time to SREs, with a modest positive impact on bone pain and QoL (8).

Denosumab is a monoclonal antibody against the Receptor Activator of Nuclear factor Kappa B Ligand (RANKL), which is a critical component in osteoclast differentiation and activation (9). A patient-level meta-analysis of three trials comparing denosumab with zoledronic acid - the most common bisphosphonate used in clinical practice - in patients with multiple myeloma, prostate and breast malignancy, and other solid cancers concluded that denosumab was superior to zoledronic acid in reducing the risk and delaying the onset of SRE, similar to a more recent meta-analysis (10, 11). However, no significant differences were observed between the two treatments in survival (7).

Regarding side effects, both treatments are associated with a risk of electrolyte disorders and hypocalcemia. Therefore, all patients on treatment with osteoclast inhibitors should receive vitamin D and calcium supplementation. Also, both agents need to monitor the renal function, and zoledronic acid dosing is impacted by potential iatrogenesis. Paradoxical osteonecrosis of the jaw may onset at a similar rate with both agents, and all patients should undergo a dental examination and periodical follow-up to receive counseling regarding good oral health. Further, oral bisphosphonates may determine upper gastrointestinal disorders (oesophagitis, gastric reflux, or ulcers) (3). The main regimens used in current clinical practice are summarized in Table 2. It is generally accepted that treatment with osteoclasts inhibitors should be continued indefinitely, even beyond an SRE, as these drugs may delay subsequent SREs (3).

Table 2. Osteoclast Inhibitors and Main Regimens Used in Current Clinical Practice

Agent	Regimen
Zoledronate	4 mg IV q3-4ww or 4 mg IV q12ww
Pamidronate	90 mg IV q3-4ww
Clodronate	1600 mg OS daily
Ibandronate	50 mg OS daily or 6 mg IV q3-4ww
Denosumab	120 mg SC q4ww

3.2. Radiotherapy (RT)

The goals of ionizing radiation utilized in radiotherapy to treat BMs are to diminish osteoclasts activation and kill tumor cells by damaging the DNA (12). Specifically, there is a significant onset of tumor necrosis and a considerable decrease in vessel density following a single fraction of high-dose radiotherapy delivered as stereotactic body radiotherapy (SBRT) (13). Stereotactic body radiotherapy is a highly focused radiotherapy technique that provides an intense radiation dose to the target volume with submillimeter accuracy, thereby limiting the dose to the surrounding healthy tissues. The optimal fractionation regimen is still an unresolved issue. Generally, the preferred schedules are as follows:

- 8 Gy in a single fraction as the standard of care for symptomatic and uncomplicated BMs and end-of-life patients (14);

- Conventional radiotherapy, with three-dimensional conformal radiation therapy (3DCRT) or intensity-modulated radiotherapy (IMRT) techniques, delivered a range of radiation doses between 20 Gy in five fractions and 30 Gy in 10 fractions or 45 Gy in 15 fractions. These schedules are considered the mainstay for the treatment of BMs, particularly for patients at risk of pathological fractures (14).

The development of new technologies, including image-guided radiotherapy (IGRT), micro-multileaf collimation, and highly reproducible immobilization devices, has resulted in the propagation of SBRT techniques. The SBRT techniques allow rapid dose drop during short treatment courses with ablative intent. Stereotactic body radiotherapy is indicated in solitary lesions or up to three lesions measuring less than 5 cm in diameter in selected cases of re-irradiation and the radiation of tumors with specific radiobiological tissues (such as sarcoma, thyroid cancer, renal cell carcinoma, and melanoma). Several fractions schedules are used: 16 – 24 Gy/1 fraction, 24 Gy/2 fractions, 24 – 30 Gy/3 fractions, 30 Gy/4 fractions, and 30 – 40 Gy/5 fractions (the latter is dedicated to larger tumors) (15). The results of an exploratory IRON-1 trial suggested the superiority of 24 Gy single-fraction SBRT in terms of pain relief over 30 Gy in 10 fractions with 3DCRT (16). A study conducted following a cycle of SBRT demonstrated that the incidence of myelopathy was less than 0.5%, and the local control of the tumor was observed in more than 80% of patients; this information was obtained from histopathology reports demonstrating the absence of viable residual tumors following surgery (17). Also, the SABR COMET study, a phase 2 randomized trial, demonstrated improved results in targeting oligometastatic disease with SBRT (18). The response can last for months, with a mean remission time of 19 weeks (19). Sprave et al. found that QoL following SBRT for spine metastases was not inferior to that of conventional palliative radiotherapy (20).

Surgical decompression and/or stabilization, followed by radiotherapy, is the standard of care in patients with good performance status and oligometastatic disease in whom vertebral metastases determine instability and neurological deficits. Assessment of functionality in such patients is most validly and reliably measured using the Karnofsky Performance Status (KPS) scale (20). Radiotherapy after the surgery has commonly been performed using conventional methods, although recently, SBRT has been explored, identified, and tolerated (21). Conventional schedules delivered with 3DCRT or IMRT are indicated in residual postoperative tumors, severe spinal cord compression, and complete spinal cord injury and when more than three contiguous vertebral levels are involved (22).

In recent years, there has been an increase in patients requiring re-irradiation, whereas up to 40% do not receive pain control following primary RT, and pain recurrence occurs in about half of the initial respondents within one year from RT (23). The International Bone Metastases Consensus Working Party has promoted RT appropriate re-irradiation criteria, recommending an interval of at least four weeks for re-irradiation in patients who did not respond to primary RT (24). The most common RT techniques for the treatment of BMs are summarized in Table 3.

3.3. Nuclear Medicine

In recent decades, nuclear medicine has gained relevance in treating patients with osteoblastic bony metastases (25). The European Association of Nuclear Medicine (EANM) recommends bone-seeking therapeutic radiopharmaceuticals in painful osseous metastases manifesting osteoblastic responses demonstrated by intense uptake in bone scans; prostate cancer BMs are the most validated employment due to the high incidence of osteoblastic metastases (26, 27). However, there is also scientific evidence for the effectiveness of bone-seeking radiopharmaceuticals in tumors producing bone lesions with a mixed pattern (osteoblastic/osteolytic) (28). Radiopharmaceuticals for the treatment of BMs include beta- and alpha-emitting radiotracers (25, 26). Beta-emitting radionuclides encompass Phosphorus-32 (^{32}P), Strontium-89 (^{89}Sr), Renium-186 and -188 (^{186}Re, ^{188}Re), Samarium-153 (^{153}Sm), Selenium-117m (^{117m}Sn), and Lutetium-177 (^{177}Lu) (29). Apart from these, a special mention is needed for ^{131}I, whose use against BMs has been limited in patients with thyroid cancer (30). Conversely, alpha-emitting therapy currently relies primarily on the clinical use of Radium-223 (^{223}Ra). Other promising novel alpha- and beta-emitting radiopharmaceuticals for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC) include ^{225}Ac-PSMA-617 and ^{177}Lu-PSMA-617, although reported data on these treatments are still preliminary (Table 4) (31).

For several reasons, beta-emitting radiopharmaceuticals are being replaced in everyday practice by alpha-emitter radiopharmaceutical Radium-223 Dichloride ($^{223}RaCl_2$), commercially available as Xofigo® (Bayer). Xofigo® has been explicitly registered for treating symptomatic BMs (at least three) from castration-resistant prostate cancer (CRPC) in the absence of visceral metastatic disease (27). Whereas beta-emitters provide only palliative benefits, Xofigo® has been demonstrated to improve overall survival (OS) and prolong the length of

Table 3. Most Common Radiotherapy Techniques for Treatment of Bone Metastasis

	Uncomplicated Bone Metastases	Complicated Bone Metastases	End of Life Patients	Symptomati Patients	Oligometastatic Patients (1 - 3 Lesions to Max 5 Lesions and < 5 cm Diameter Lesions)	RE-Irradiation	Post-surgery RT
8Gy (3DCRT) in a single fraction	x		x	x		x	
30 Gy in 10 fractions (3DCRT or IMRT)	x	x		+/-			x
45 Gy in 15 fractions (3DCRT or IMRT)	x	x		+/-			
20 Gy in 5 fractions (3DCRT or IMRT)	x	x		+/-		+/-	+/-
16-24 Gy in a single fraction (SBRT)	x			+/-	x		
24 Gy in 2 fractions (SBRT)	x			+/-	x		
24-30 Gy in 3 fractions (SBRT)	x			+/-	x		
30 - 40 Gy in 5 fractions (SBRT)	x			+/-	x	+/-	

Abbreviations: 3DCR, 3D conformal radiotherapy; IMRT, intensity modulated radiotherapy; SBRT, stereotactic body radiation therapy; (+), recommended; (+/), physician's choice.

Table 4. Characteristics of Main Radionuclides Used for Treatment of Bone Metastases

Radionuclide	Half-life (Days)	Decay Used for Treatment of Bone Metastases	Maximum Range (mm)
^{223}**Ra**	11.4	α	0.08
^{25}**Ac**	10	α	< 0.1
^{186}**Rn**	3.8	β^-	3.7
^{188}**Rn**	0.7	β^-	2.4
^{32}**P**	14.3	β^-	8.5
^{89}**Sr**	50.5	β^-	7
^{153}**Sm**	1.9	β^-	3
^{117}**mSn**	13.9	β^-, conversion electrons	0. 2 - 0.3
^{177}**Lu**	6.2	β^-	1.8

time to the first SRE compared to a placebo (32). Furthermore, ^{223}Ra presents a shorter tissue range (< 0.1 mm) and causes less damage to the surrounding tissue compared to beta-emitting radionuclides (i.e., 3.3 mm for ^{153}Sm and 7 mm for ^{89}Sr) (33).

Furthermore, pain response to nuclear medicine therapy achieves favorable rates, with comparable or higher efficacy than radiotherapy, and reduces analgesic use in patients with mCRPC (34, 35). These findings may also be valid for $^{223}RaCl_2$ based on post hoc analyses of the ALSYMPCA phase-III trial, a placebo-controlled, double-blind study of 921 patients with mCRPC and BMs who had either received, were not favorable to receive or declined docetaxel (31, 36). In this study, improvements in QoL measured by the validated EuroQoL 5D (EQ-5D) and the disease-specific functional assessment of cancer therapy-prostate (FACT-P) scores were more significant in patients treated with $^{223}RaCl_2$ (31). Also, nuclear medicine therapeutic approaches for BMs are mostly characterized by only absent to mild hematological toxicity. No significant difference in grade 3 or 4 anemia, thrombocytopenia, and neutropenia has been reported between patients treated with alpha-emitting therapy and a placebo (34, 36).

Regarding survival, increases have been demonstrated in the ALSYMPCA study 3 trial, with significantly longer survival in patients treated with Radium-223 than in those on a placebo (36). Subsequently, in the interim analysis of the long-term observational REASSURE study, the authors investigated an eligible population of 564 patients with mCRPC treated with $^{223}RaCl_2$, divided into two groups: 190 who had taken complete chemotherapy (docetaxel and/or cabazitaxel) and 374 who had not received prior

chemotherapy (37). Previously, chemotherapy-treated patients had an Eastern Cooperative Oncology Group performance status of equal or more than 2, more than 20 metastatic lesions, and higher median prostate-specific antigen and alkaline phosphatase levels. In addition, a lower proportion of patients who had received chemotherapy completed six Radium-223 injections, and a higher frequency of drug-related treatment-emergent adverse events (TEAEs) was documented. This finding suggests that chemotherapy reduces bone marrow function (indicating more advanced disease and previous exposure to cytotoxic treatment) and proposes a potential advantage of using $^{223}RaCl_2$ earlier in the course of the disease. Furthermore, a safety profile was confirmed in a later multicenter, early access, single-arm phase 3b-trial involving patients with mCRPC, treated with $^{223}RaCl_2$ combined with enzalutamide or abiraterone (38). However, unresolved issues still exist regarding eventual combination therapies to potentially increase survival in patients with BMs (33).

3.4. Pain Management

Bone metastasis pain generally starts as a periodic vague pain, but as the disease progresses, the pain becomes severe and permanent. Usually, pain severity does not depend on the type or size of the tumor, the number of metastases, or bone involvement (39). Considering the multifactorial nature of cancer-related bone pain, which involves several mechanisms, BM treatment is optimally multimodal (pharmacological and interventional) and requires an adequate pain assessment (40-42). Furthermore, BMs are characterized by breakthrough incident pain, generally triggered by movement, in 40% of cases (43). The definition of breakthrough cancer pain (BTcP) is a peak of pain severity of short duration in patients with an acceptable response to daily analgesics. Besides, BTcP is capable of limiting patients' functional activities and independence (44). Due to its unpredictability, severity, and undesirable effect on daily performance affecting QoL, patients consider BTcP an essential treatment. Pain physicians should focus on optimizing opioid therapy to reduce pain, both at rest and during movementr. Opioid optimization therapy effectively reduces incident BTcP episodes, although it may also be linked to the high risks of opioids' adverse effects (45).

3.4.1. Pharmacological Treatments

The World Health Organization developed a model for the gradual introduction and upward titration of analgesics based on pain intensity. Furthermore, the results of a 2017 Cochrane Review indicated no valid evidence to favor nor deny the use of non-steroid anti-inflammatory drugs (NSAIDs) alone or in combination with opioids. Accordingly, NSAIDs are not recommended for chronic use, as their long-term intake increases the risk of gastrointestinal bleeding, decreases kidney function, and may determine cardiovascular issues (46). Among them, acetaminophen, up to 4 g daily for mild acute and chronic pain, is safer and better tolerated, although its use is questionable in hepatically-impaired patients (Table 5).

Table 5. Main Available Pharmacological Treatments to Treat Mixed Pain (Characterized by Both Nociceptive and Neuropathic Components)

Mixed	
Nociceptive	**Neuropathic**
Bone-targeting drugs: Bisphosphonates and denosumab	Analgesics: Antidepressants, anticonvulsants, opioids
Radiotherapy	
Vertebroplasty/Kyphoplasty	
Analgesics: Paracetamol, opioids, corticosteroids	

3.4.2. Opioids

Opioids are the basis of pain management in severe cancer pain. It is well-accepted that using opioids requires caution due to the potential iatrogenic complications associated with their side effects, such as somnolence, constipation, opioid-induced endocrinopathy, and their potential for abuse and misuse (47). Moreover, opioids' immunosuppressive action may determine cancer progression. In this scenario, several studies have shown that morphine is most potent in suppressing the immune system, but fentanyl has moderate effects, and tramadol and buprenorphine show the least immune suppression (48, 49). In terms of administration, the first option is the oral route. Individual titration with short- or long-acting opioids (LAO) is strongly recommended to achieve analgesia and minimize side effects. Transdermal formulations should be reserved for patients on a stable dosage, and should be avoided in cachectic patients (40). Opioids exert their clinical effects by influencing opioid receptors μ, δ, and κ. The analgesic effects of opioids are pronounced for the nociceptive component of pain, while adjuvants may be necessary for neuropathic pain management. Specifically, cancer pain is often characterized by a mixed nociceptive-neuropathic pain syndrome (50). In the United States, the dual mu agonism and noradrenaline uptake processes of tapentadol have resulted in multimodal analgesia, being titled the only opioid product approved for neuropathic pain by the Food and Drug Administration (FDA) (51). Several incident pain episodes can be linked with poor basal pain relief. However, an increase in the dosage of an opioid used for background pain may result

in adverse effects, which may be limited in some cases through opioid rotation. Also, BTcP should be treated with rapid onset opioids (ROO) to achieve rapid analgesia (45, 52). Ideally, ROO should be administered when treating BTcP in patients with well-controlled chronic background pain using a long-acting opioid with a daily dose of $\geq$ 60 mg equivalent of morphine, with no more than four events of BTcP per day with a numerical pain score $\geq$ 7 as a target outcome. Also, the ROO dose should be titrated for patients using low-dosage baseline opioids or a proportional dose (1:6 of the baseline opioid treatment) for high-dosage patients (52).

3.4.3. Anticonvulsants and Antidepressants

As above-mentioned, cancer pain is generally characterized by both nociceptive and neuropathic components, identified as "mixed pain." (50) Adjuvants such as antidepressants and gabapentin are used to manage the neuropathic component of BM, with anticonvulsants widely used and recommended for several neuropathic pain syndromes (53). Neuropathic pain treatment should start with various adjuvants as first-line monotherapies, including gabapentin, pregabalin, duloxetine, venlafaxine, and tricyclic antidepressants (TCAs) (53). Further, the role of noradrenergic tapentadol should not be ignored in cancer pain, as it is becoming more readily available worldwide.

3.4.4. Corticosteroids

Corticosteroids have anti-inflammatory and anti-swelling effects, which promote a reduction of peritumoral edema. Also, they may influence the nociceptor threshold by lowering the level of pro-inflammatory cytokines and prostanoids and reducing peripheral neuronal firing, thus decreasing pain intensity (54). Corticosteroid treatment is usually tapered over two weeks using the ones with minimal mineralocorticoid effects. One of the most prescribed corticosteroids is dexamethasone due to its long half-life and the absence of mineralocorticoid properties, with minor fluid retention (55).

3.5. Surgical and Interventional Treatments

Based on the European Society for Medical Oncology guidelines, spine surgery is indicated only in the case of malignant spinal cord compression (SCC) (56). In patients with vertebral metastases without evidence of malignant SCC, spinal instability, refractory mechanical pain to analgesics, and vertebral body collapse, non-invasive percutaneous treatments, such as vertebroplasty or Kyphoplasty, are frequently indicated (42, 57). Vertebroplasty is a minimally invasive technique in which bone cement (polymethylmethacrylate) is injected into the vertebral body. On the other hand, Kyphoplasty involves the placement of a balloon in the vertebral body, containing the spread of cement. Both procedures are considered safe with few side effects (57). However, if the cement leaks, depending on the location of the cement leakage, an adverse event may occur that potentially causes compression of the nerve root or disc irritation. The analgesic effect of these techniques is a consequence of the cement's cytotoxic effect, which results in the necrosis of tumor tissue and stabilization of microfractures. Moreover, another analgesic role is due to the heat produced by the polymerization of polymethylmethacrylate during injection, which helps destroy the nerve terminals in the vertebral body. A recent study demonstrated positive outcomes in treating vertebral body compression fractures due to multiple myeloma using both vertebral body augmentation techniques, indicating rapid and sustained pain relief, improved QoL, and reduced use of analgesics at one year (58).

3.6. Interventional Procedures

Minimally invasive techniques such as radiofrequency ablation, cryoablation, and focused ultrasound may also be suited for treating skeletal metastases as an alternative or adjuvant to conventional therapies (41, 59). These approaches are performed to control pain, preserve and restore physical function, and provide local tumor control (Table 6).

3.6.1. Indications to the Procedure

Ablation is primarily used to manage painful skeletal metastases in patients with disease progression, persistent pain following radiotherapy, or those who refuse radiotherapy. To qualify for ablation, patients should experience at least moderate pain (VAS $\geq$ 4) since mild pain rarely responds to ablation and is better managed with analgesics (60). Furthermore, as these are local therapies requiring an appropriate selection of lesions to be treated, it is advisable to have a limited number (i.e., one to three) of metastases on cross-sectional imaging that correspond to the site of pain during patient physical examination. Otherwise, systemic therapy should be used. Concerning the types of lesions, osteolytic and mixed osteolytic/osteoblastic metastases or those with a prominent soft-tissue component are best suited to ablation. Further, target lesions should be at least 1 cm away from normal critical structures to prevent any damage. Ablation of skeletal metastases may also be performed in non-painful lesions that cause symptoms of hormone excess or as an alternative to surgery to prevent pathologic fracture in a weight-bearing bone. In such cases, ablation is optimally combined with cement installation (i.e., cementoplasty) (61). Absolute contraindications to the procedure include

Table 6. Interventional Treatment of Metastatic Bone Cancer Pain

	Uncomplicated (Without Evidence of Metastatic Spinal Cord Compression)	Complicated (with Evidence of Metastatic Spinal Cord Compression)
Bone surgery	Vertebroplasty/Kyphoplasty should be considered in patients with vertebral metastases.	In selected pts (spinal instability, recurrence after RT or single level site of compression)
Thermal ablation (radiofrequency, cryoablation)	Should be considered	

bleeding disorders, percutaneous inaccessibility of the target lesion, active infection, and contraindication of anesthesia provision.

3.6.2. Preprocedural Imaging and Anesthesia

All ablative techniques should be preceded by cross-sectional imaging using CT scan, PET/CT, or MRI to assess metastases' number, type, location, and extent. Interventional radiological procedures are commonly performed under general anesthesia. Nonetheless, moderate sedation can be chosen in cases of small, easily accessible lesions distant from vital structures.

3.6.3. Techniques

Radiofrequency ablation (RFA) is the most widely adopted thermal ablation technique for tumors and BMs. The RFA relies on a needle electrode to deliver an alternating current (450 to 600 kHz) that heats the tissue around the tip of the electrode; when a temperature above 60°C is reached, the affected cells die due to coagulative necrosis. Differently, cryoablation is based on the insertion of one or more cryoprobes into the tumor.

Focused ultrasound (FUS) is a completely non-invasive technique that typically uses MRI guidance to deliver non-ionizing ultrasonic waves, causing thermal tumor ablation. The sonication duration is approximately 30 seconds, with a cool-down interval of 90 seconds (62). During the procedure, thermal monitoring imaging sequences allow for the visualization of the ablation while avoiding adjacent structures. This technique is limited to treating more superficial tumors rather than those that can be reached with other traditional percutaneous ablative interventions. Microwave ablation is a heat-based technique similar to RFA that uses 17 G antennae to convey microwaves (915 MHz) to a target lesion, causing ionic agitation and localized heating (63). Microwaves are less influenced by tissue impedance, allowing for better bone penetration than RFA, with no need for grounding pads. Laser ablation employs optical fibers to deliver infrared light energy. These fibers are placed coaxially through a thin access needle into the tumor. This modality is primarily used to treat small osseous lesions (i.e., osteoid osteomas) rather than skeletal metastases (64).

3.7. Outcomes

3.7.1. Bone Pain and Local Tumor Control

Local thermal ablation is considered a good option for patients who have persistent or recurrent bone pain following radiotherapy. Equally, RFA and cryoablation have been reported to be safe and highly effective for treating symptomatic skeletal metastases. Moreover, cryoablation can achieve a high degree of local tumor control for BMs, as described in several case series. Lastly, a randomized controlled, multicenter phase III trial demonstrated FUS's potential in improving self-reported pain scores three months following the procedure without increasing analgesic medications (62).

3.8. Complications

Percutaneous ablation therapies for skeletal metastases carry a risk of complications, such as injury to healthy structures during needle insertion or adverse effects due to specific ablation modalities, especially thermal injuries. The latter includes bowel perforation, temporary or (rarely) permanent damage to neural structures, fistula formation, and muscular injury close to the ablation site. Further, RFA may result in skin burns at the grounding pad sites, while cryoablation carries the risk of frostbite. Pathologic fractures are a significant complication following ablation. For this reason, cementoplasty may be performed as an adjunctive measure to stabilize weight-bearing bones and minimize the risk of fractures (65).

4. Discussion

Bone metastases are a common complication of cancer. They can cause significant complications, such as pathological fractures and paralysis of the spine, adversely affecting daily functioning and QoL and worsening prognosis. Treatment for BMs ideally involves various types of specialists and assessments. The disease status and patient background should be considered. For this purpose, a multidisciplinary team is likely to be most effective. To collaborate with other specialists, a guideline describing each specialty field is necessary. The clinical benefits associated with the treatment of BMs by multidisciplinary teams and multimodal approaches have been described

in several papers (66). The treatment targets pain control and severity reduction. For this reason, the therapeutic measures of bone pain in these patients should be multimodal, including causal anticancer and symptomatic pain management. All interventions should be individualized to relieve pain, improve quality of life and function, and increase survival. Various issues should be addressed in clinical decision-making, such as the primary lesion's location, the patient's general condition, spinal instability, the nature of the lesion, radiotherapy and drug resistance, and the patient's mental and psychological burden.

In summary, interventional and mini-invasive techniques can be safe and effective treatments to reduce pain and improve health-related QoL in patients with BMs.

Footnotes

Authors' Contribution: Study concept and design: GLB, EL, SP, MF, AP, RL, and NQ; Analysis and interpretation of data: MF, AP, RL, and NQ; Drafting of the manuscript: GLB, EL, SP, MF, AP, FI, GS, RL, and NQ; Critical revision: GLB, AP, FI, GS, RL, and NQ; Final approval: GLB, EL, SP, MF, FI, and GS.

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