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Review Article

State-of-the-art of minimally invasive treatments of bone metastases

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HIGHLIGHTS

- Bone metastases are common in patients with malignant tumors and are highly dangerous.
- Options for treatment of bone metastases are diverse, choosing the appropriate treatment is difficult.
- Minimally invasive interventional procedures have less surgical trauma, fewer contraindications, high pain relief rate, and quicker patient recovery.
- Interventional procedures are emerging as a novel and effective option for the treatment of bone metastases.

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ABSTRACT

Bone metastases is a common manifestation of advanced malignant tumors. With the recent advances in medical technology, the survival period of patients with malignant tumors is prolonged, and the probability of bone metastases is significantly increased. Approximately 70% to 80% of patients with breast or prostate cancer will eventually develop bone metastases. In addition, thyroid, lung, and kidney carcinomas are all known to cause bone metastases, with a 30% to 40% incidence upon postmortem assessment. Bone metastases often lead to severe pain, pathological fractures, and nerve damage and have become a critical factor affecting the quality of life and life expectancy of cancer patients. Although treatments for bone metastases are diverse, choosing the appropriate treatment is difficult. Both conservative treatment and open surgery have certain drawbacks and may not be appropriate for all patients. Interventional procedures have the advantages of less trauma with quicker recovery and represent a viable alternative. This review provides updates on the progress of research on the interventional treatment of bone metastases and directions regarding relevant further studies.

Contents

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1. Introduction

Bone is the most common site of metastasis for malignant tumors other than lung and liver, and the incidence of bone metastasis is significantly higher than that of primary malignant bone tumors[1,2](Coleman 2001). Based on biopsy results and typical imaging findings, bone metastases occur in 70% to 80% of breast or prostate cancer patients, and almost 90% of myeloma patients. Besides, thyroid, lung, and kidney carcinomas are all known to cause bone metastases, with a 30% to 40% incidence upon post-mortem assessment. However, only 5% of patients with gastrointestinal cancer will eventually develop bone metastases[3]. Bone metastases most often occur in the spine, followed by the pelvis, ribs, and femur. The destruction of bone and the invasion of surrounding soft tissue caused by tumor growth are the main causes of severe pain in patients. In the absence of aggressive treatment for metastases, large and medially located tumors can easily induce bone-related events, such as pathological fractures, neurological compression symptoms, and even paraplegia, which can have a significant impact on patients, including pain, reduced weight-bearing capacity, and limitations in daily activities [2,4,5]. The methods currently applied to clinical practice for the treatment of bone metastases include radiation or chemotherapy, bisphosphonates, targeted therapy, immunotherapy, open surgery, and minimally invasive interventional treatment methods. Despite the variety of therapeutic approaches, choosing a treatment modality for bone metastases is sometimes difficult, and a significant proportion of patients do not receive appropriate treatment [6]. Fig. 1 shows the various treatment options for bone metastases.

Radiotherapy and chemotherapy are vital to the treatment of bone metastases and can provide some pain relief and control of new metastases throughout the body. Radiotherapy is considered the standard of care for bone metastases and is widely used in clinical practice. However, it is less effective in patients with pathological fractures and spinal instability. Studies have noted that radiotherapy is ineffective in approximately 1/3 of patients with bone metastases [7]. Data from *meta*-analysis studies have revealed that > 40% of patients achieved approximately 50% reduction in pain levels about 1 month after radiotherapy, but less than 30% of patients achieved complete pain relief [8]. Radiotherapy generally takes 4–6 weeks to exert its optimal effect, but a significant proportion of patients with bone metastases have a short survival expectancy [9]. Radiotherapy does not achieve the goal of rapid pain relief and improvement of the patient's emotional state and quality of life as soon as possible. Stereotactic radiotherapy (SRT) is a widely used radiotherapy modality in recent years. SRT uses stereotactic technology to localize the lesion and irradiate the target area. It uses a single high dose of a small field set beam to produce focal necrosis, thus achieving a surgery-like effect. SRT uses 3D image reconstruction technology to obtain the precise spatial location of the lesion in the body with the help of fixation devices and computer calculations. SRT destroys the target tissue with little damage to the surrounding tissues through precise 3D stereotactic positioning and steep gradient changes in the irradiation dose between the target structure and the surrounding tissues. Although SRT for bone metastases has a higher rate of pain relief (approximately 50%–85%), it dramatically increases the risk of pathological fracture of the osseous lesion. Some studies reported a risk probability of as high as 10%–20% [10–14]. Some scholars believe that radiotherapy is not suitable for the treatment of metastatic bone tumors with low sensitivity and for patients who cannot receive high doses of radiation, such as patients with tumors composed of cells that contain a gene for radiation resistance, dormant tumor, and hypoxic tumor [4].

A significant proportion of patients treated with radiotherapy experience a recurrence of pain within a short period of time [4,15]. The American Collaborative Group on Radiation Oncology has studied the response rate of bone metastases to radiotherapy and showed that 54% of patients achieved complete pain relief, and 90% achieved partial pain relief; however, the probability of pain recurrence within 3 months among patients with effective treatment was 30% [16]. A similar conclusion was obtained in a study by Andrade, in which pain recurrence occurred at a rate of 35% approximately 1 month after radiotherapy [17].

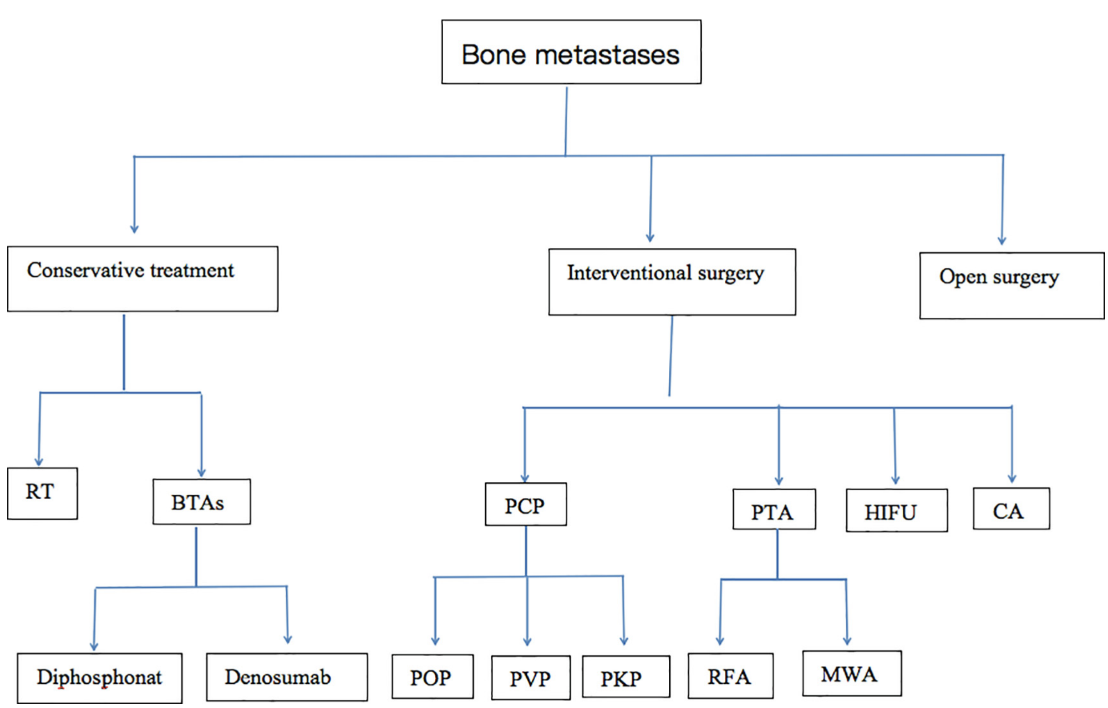

Fig. 1. Treatment of bone metastases. Asbbreviations: RT: Radiation therapy; BTAs: Bone-targeted agents; PCP: Percutaneous cementoplasty; POP: Percutaneous osteoplasty; PVP: Percutaneous vertebraplasty; PKP:Percutaneous balloon kyphoplasty; PTA: Percutaneous thermal ablation; RFA: Radiofrequency ablation; MWA: Microwave ablation; HIFU: High intensity focused ultrasound; CA: Cryoablation.

The use of available bone targeted agents (BTAs), such as diphosphonates and denosumab, seems to be gaining more prominence recently in patients with bone metastases, which can reduce the osteolytic effect of tumors and anti-hypercalcemia caused by bone metastases. These drugs have considerably delayed the onset of bone pain and reduced the incidence of SREs in bone metastases patients, which is especially recommended for all breast cancer patients, myeloma patients and castration resistant prostate cancer patients with bone metastases [18,19]. As for patients with advanced lung cancer, renal cancer and other solid tumors, results from randomized controlled trials suggest that it can be used in those patients with survival longer than three months and clinically significant bone metastases [18–20]. Open surgery is widely used, especially for patients who are expected to survive for a long time and those with combined presence of nerve compression and skeletal instability [21].Open surgery, on the other hand, is generally invasive and fraught with complications. It frequently necessitates a lengthy postoperative recovery period; it may postpone treatment of the primary disease and increase mortality rates, which some patients find unacceptable; and it is frequently ineffective in treating multiple bone metastases [22,23]. The average length of stay in hospital after open surgery for femoral metastases was 13.9 days; the postoperative complication rate was 8%, and the mortality rate was 13.9% at 3 months after surgery [22]. Considering the low quality of life and short survival time of patients with bone metastases, minimally invasive interventional procedures have been increasingly used for the treatment of bone metastases in recent years. They have the advantages of less surgical trauma, fewer contraindications, high pain relief rate, and quicker patient recovery. In this article, we intended to present the current research progress of the main minimally invasive interventional techniques for the treatment of bone metastases.

2. Commonly used minimally invasive treatment methods

2.1. Pain relief techniques (cementoplasty)

Percutaneous cementoplasty (PCP) is currently the most widely used method among minimally invasive treatments of bone metastases. These treatments include percutaneous osteoplasty (POP) and percutaneous vertebroplasty (PVP). A working channel is established through the percutaneous penetration of a bone puncture needle into the target site under fluoroscopy or computerized tomography (CT), through which a formulated polymethylmethacrylate (PMMA) is slowly injected into the diseased bone. Although the mechanism of this technique is not completely clear, the main principles of pain palliation are as follows. 1) Temperature-mediated destruction of nociception nervous terminals provides the foundations for pain palliation. 2) Solidification of PMMA between bone trabeculae after exothermic treatment is performed to enhance the strength of bone and restore the original height of bone. 3) The heat production and release of chemically toxic substances during the solidification of PMMA are performed to kill tumor cells [24–26]. However, some studies have concluded that PVP has weak anti-tumor effects, and a study recently suggested that it does not have tumoricidal effects [27]. Therefore, the anti-tumor effect of PMMA needs to be further verified through animal studies or in vitro experiments.

POP is used for both extremity and pelvic metastases, but it is most commonly used for metastases in the acetabular and femoral regions. Studies have demonstrated that POP is an effective treatment for bone metastases in the extremities and pelvic area, with the main risks being pathological fractures and nerve injury. In general, POP can be used alone or in combination with ablation and internal fixation devices. Fig. 2 shows a schematic diagram of POP in combination with ablation. Fig. 3 illustrates the surgical procedure. There is insufficient evidence from clinical studies to verify whether POP combined with ablation is superior to POP alone in the treatment of bone metastases, especially when the lesion is located in the bone and does not invade soft tissue [28,29]. However, it has been suggested that when osteolytic bone metastases are large and invade soft tissues, ablation can reduce the pain associated with the invasion of surrounding soft tissues. Thus, cementoplasty and ablation are frequently combined to treat pelvic metastases, which are often large and invade the soft tissues surrounding the pelvic girdle. Another study concluded that POP has a weak antitumor effect and that PMMA infusion increases the risk of cancer cells entering the circulation within minutes after injection. So, ablation can be performed before cement infusion to obtain better

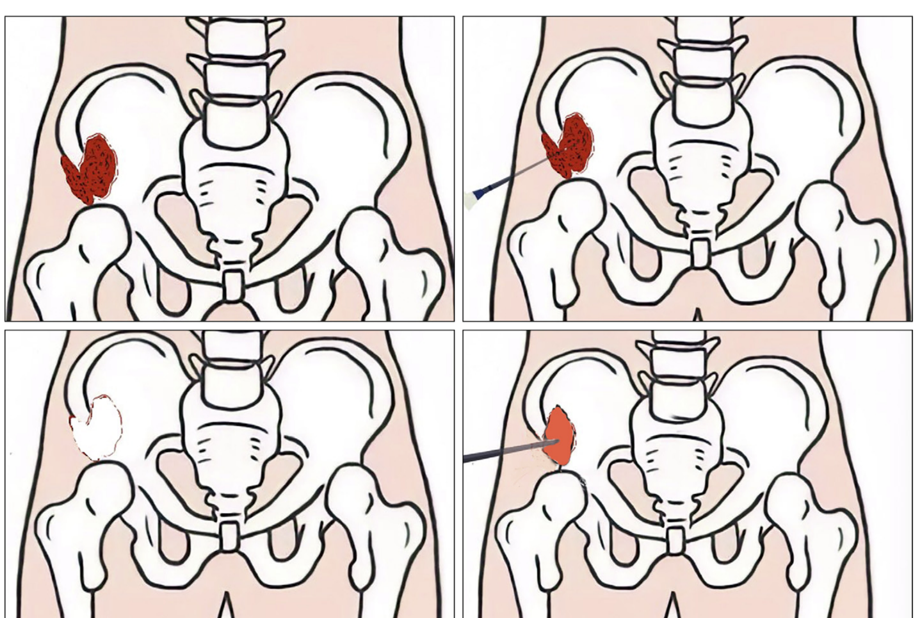

Fig. 2. Schematic diagram of POP combined with MWA. (A) presents a bone metastasis of the ilium that has broken through the cortex. (B) Percutaneous microwave ablation. (C) presents that the tumors apoptosis after ablation. (D) Percutaneous osteoplasty: injection of bone cement into the diseased ilium.

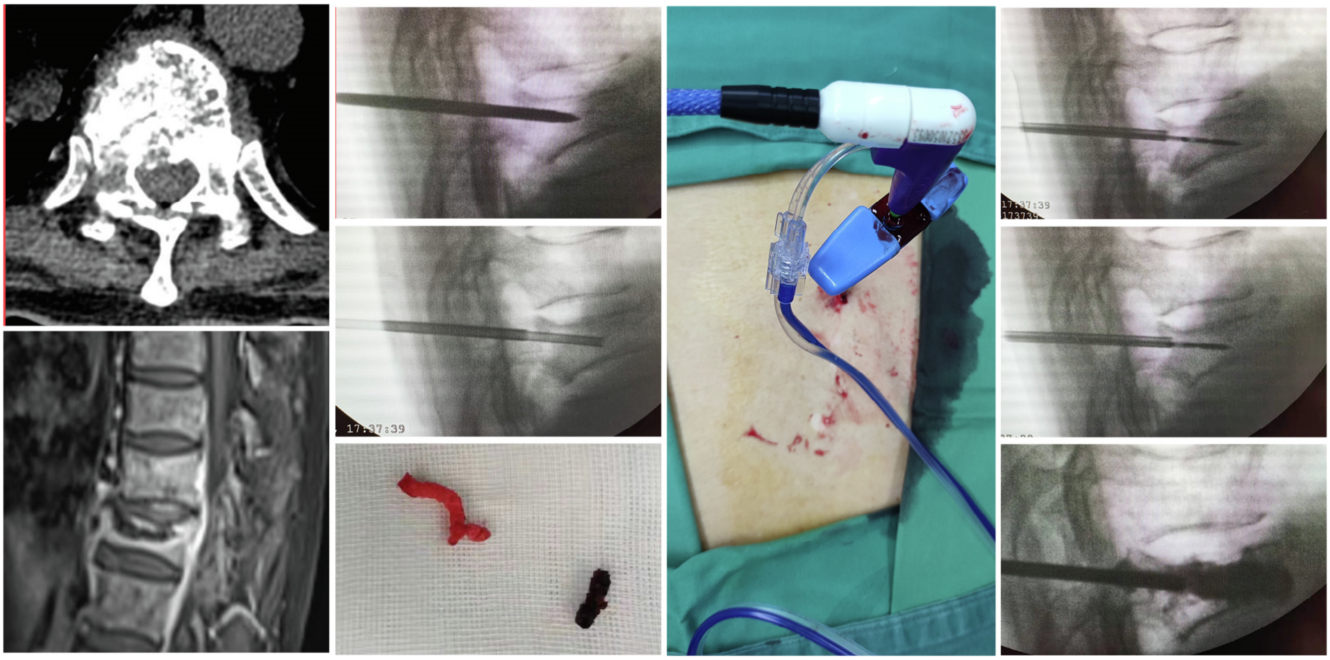

Fig. 3. A 82-year-old man with spine metastases due to lung cancer: (A) Preoperative computed tomography (CT) on the coronal plane showed spine metastases with "insect erosion" changes. (B) Preoperative magnetic resonance imaging (MRI) on the sagittal plane showed spine metastases complicated with vertebral compression fracture at T12. (C) The bone puncture needle entered the vertebral body through the pedicle to establish a working channel. (D) The hollow biopsy needle was used to biopsy the focal tissue through the working channel. (F)-(H). Microwave ablation. (G) and (H) showed the multiple short-time intermittent ablation method for which the ablation needle retreated as ablation progressed. (I) Percutaneous vertebroplasty. E. The focal tissues were compared before and after ablation. The black is the tumor tissue after ablation, indicating carbonization.

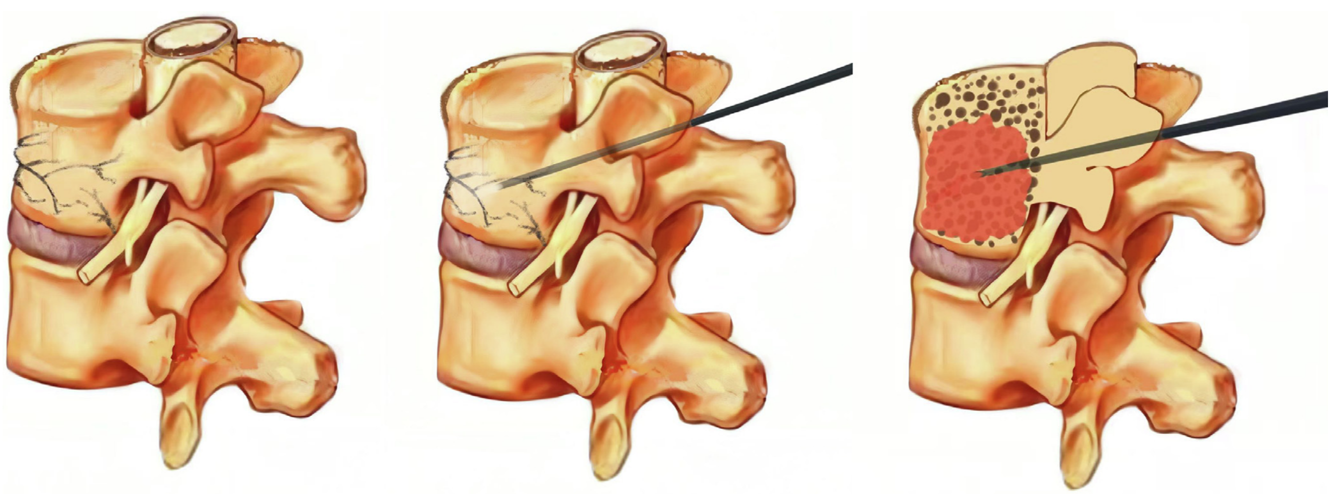

Fig. 4. Schematic diagram of PVP (a pedicle approach). (A) presents a centrum with pathological fracture due to bone metastases. (B) Penetration into the vertebral body via the pedicle approach. (C) Injection of bone cement into the diseased vertebral body.

local tumor control [27,30,31]. Levy [31] conducted a multicenter study that included 100 cases, 97 of which were treated with cementoplasty combined with radiofrequency ablation therapy. Of these patients, 59% achieved pain relief within 3 days postoperatively, and 83% of the follow-up patients still had significant pain relief at 3 months postoperatively. The authors concluded that ablative therapy relieves tumor-induced pain and decreases tumor load, whereas cementoplasty enhances the mechanical stabilization of the bone. Such stabilization acts synergistically to increase the therapeutic effect, but this view is not yet supported by high-level evidence in the literature.

PVP has the same mechanism of action as POP and is now widely used in vertebral metastases. Fig. 4 shows a schematic diagram of PVP. The reliable safety and efficacy of PVP in the treatment of spinal metastases has been established beyond doubt; it has an overall efficiency of 60%–97% [25,32–38]. The most common complication of this technique is cement leakage, but the vast majority of these leaks are asymptomatic [36,39]. An observational study from Peking University investigated the epidemiology of cement leaks and further developed an algorithm to detect the high risk of cement leaks [36]. This study reported that the overall bone cement leakage rate was 61.17% (189/309) after exclusion of discal cement leakage and paravertebral cement leakage. And, these characteristics identified as having significant predictive value, including increased number of treated vertebrae levels, cortical osteolytic destruction in the posterior wall, extravertebral bone metastases, and younger age, could be used to develop a predictive algorithm to detect the high risk of cement leaks among advanced cancer patients with metastatic spinal disease treated with PVP. Hector et al [39] systematically studied the occurrence of complications in patients with bone metastases treated with PVP. A total of 117 patients with 304 diseased vertebrae treated with PVP had 423 postoperative cement leaks, of which 332 were vascular cement leaks and 91 were non-vascular cement leaks. The non-vascular leaks were all asymptomatic, and only two patients (1.7%) with vascular leaks developed symptomatic pulmonary embolism; one of these two patients died due to pulmonary embolism. There were six additional local complications, namely, two cases of puncture site hematoma and four cases of radicular pain due to nerve injury.

Although the incidence of serious complications due to bone cement leakage is low, it is still essential to make every effort to avoid leakage intraoperatively. The following measures can be taken to prevent cement leakage [40]. First, the injected cement should not be too runny, and the cement can be filled in advance by using a cement injector and then injecting the cement into the vertebral body when the cement is in the shape of toothpaste; second, the speed must be slow when injecting the first shot of cement and fluoroscopy while injecting, because the first injected cement is the thinnest and is most likely to leak outside the vertebral body; then, after injecting the bone cement, insert the pusher of the bone cement injector and wait for about 2–3 min for the bone cement to harden before pulling out the bone cement injector, so as to avoid bringing the bone cement into the puncture channel when pulling out the bone cement injector.

The technique was further improved by Dr. Pflugmacher in 1997 with the invention of percutaneous balloon kyphoplasty (BKP) [41]. BKP has essentially the same effect as PVP, but BKP is performed by first creating a gap in the vertebral body with a balloon to restore the height of the vertebral body and then injecting PMMA; this is the main difference between BKP and PVP [38]. Berenson et al [35] showed in a randomized controlled trial that BKP is effective and safe in the treatment of vertebral metastases combined with compression fractures. However, due to spinal metastases, compression fractures are often accompanied by cortical destruction at the posterior margin of the vertebral body, which may be exacerbated during balloon spreading by BKP implantation, thereby resulting in increased cement penetration [42]. At the same time, the process of balloon implantation and spreading may also push the tumor into the vertebral canal, resulting in implantation and metastasis [43].Nevertheless another study revealed that BKP could restorate the original somatic morphology and diminish the spinal kyphosis. PMMA leakages not observed in the BKP, instead have been found in the PVP localized in the intersomatic or perispinal areas[38]. In conclusion, for vertebral metastases without compression fractures, PVP is sufficiently effective and cheaper than BKP. However, for patients with compression fractures, no studies proved that BKP is more effective and safer than PVP [37].

2.2. Minimally invasive bone strenthening procedures

Bone destruction caused by metastases frequently results in mechanical instability and even pathological fracture of the bone, in which case the main goal of treatment is to stabilize bone metastatic structural defects at risk of fracture as soon as possible and to avoid delaying oncological care. The exothermic solidification of bone cement, as mentioned earlier, increases the strength of the bone. However, it is distinguished by greater compressive stress resistance and less resistance to shear, bending, and torsional stresses [44,45] . Sutter et al. conducted a controlled study to investigate the ability of femoroplasty (POP for the proximal femur) as a prophylaxis to attenuate the potential for fracture under simulated fall conditions with cadaver femur specimens [44]. This study showed that when the osteoporotic femora were loaded in simulated fall conditions, femoroplasty significantly increased fracture load and energy to fracture, and cement filling in the femoral neck may play a more important role in the extent to which femoroplasty affects the mechanical strength of the proximal femur. Nevertheless, it should be noted that this study was based on cadaver specimens and osteoporotic proximal femurs, and that the amount of cement injected and the shape of the disseminated cement formation were relatively easy to control, unlike proximal femoral bone metastases, because metastatic lesions are solid composition, to a certain extent, on the blocking effect of bone cement injection and dispersion.

Generally, POP alone can be applied to bones with concentrated compressive stresses, such as acetabular metastases, whereas POP alone without internal fixation is associated with a risk of secondary pathological fracture in bones with concentrated shear and torsional stresses, such as the diaphysis and metaphysis of long limbs. Several studies have suggested that it is associated with a risk of fracture in cases of impending pathologic fracture of the proximal femur because it provides insufficient mechanical stability [46–49]. Interestingly, a current systematic review compared the efficacy of POP alone and POP in combination with internal fixation devices for impending pathologic proximal femoral fractures from metastatic malignancy [50]. The results showed no significant differences between them in terms of pain relief, operative time, and fracture-related complication rates. It is worthy of note that since all studies in this review were short follow-ups and there is a paucity of large clinical trials, the decision of a combined procedure should be individualized by taking into account the nature, location, and size of metastatic lesions as well as the overall medical condition of patients. Besides, the Mirels' score system has been commonly used to assess the risk of fracture in long bone metastases and can help determine whether a combination of internal fixation devices is requisite. Generally, patients with a Mirels' score of > 9 are more likely to have a pathological fracture and require an internal fixation device [51]. However, Van der Linden believed in his review that the Mirels' score system is unreliable because of its low specificity and positive predictive values (13% and 14%) [52]. Similarly, several other studies found the Mirels' score system to be insufficiently specific for predicting fracture [53,54]. They also pointed out that most conventional risk factors may overestimate the actual occurrence of a pathological fracture with the consequence of surgical overtreatment if they were to be used in deciding which treatment to apply for patients with a limited life expectancy [52–54]. Van der Linden proposed another method to assess the risk of pathological fracture in femoral metastases. Patients with>30 mm of axial cortical involvement are at a higher risk of pathological fracture, and the intraoperative application of an internal fixation device is justified [52,55]. Deschamps supported this view and advocated the use of cortical involvement exceeding 3 cm or complicated with previous small rotor fractures as an indication for prophylactic osteosynthesis [49]. In general, to avoid excessive surgery, caution should be exercised when these risk factors are to be applied directly to patients, as the risks of surgery may outweigh the proposed benefits of improved pain and function. On top of that, the clinician has to balance the cortical involvement of tumor bone with the performance status and life expectancy of each individual patient.

The predominant goals of minimally invasive internal fixation procedures are to prevent impending fractures or stabilize a pathological fracture. Concerning the minimally invasive surgical tools, several kinds of internal fixator devices have been reported, the most common being intramedullary nails, screws or hollows, and stainless steel spinders. Intramedullary nails are the most commonly used and can nearly always be implied in actual or impending shaft fractures, which occur most often in the femur or the humerus [56,57]. For actual or impending fractures of the proximal femur, which are most common in the femoral neck, followed by the subtrochanteric and intertrochanteric regions, an intramedullary reconstruction nail including femoral neck and head fixation is also recommended as a viable option [58]. Intramedullary nails have several advantages: they protect a long segment of bone, the required dissection is small, the periosteum's blood supply is preserved, and rigid fixation can be achieved by locking the nail with proximal and distal interlocking screws and/or using bone cement around the nail[59].

However, there are still some remarks to be made about the intramedullary nailing procedure. Tumor spread along the nail track needs to be considered, and nailing should be avoided in patients with a good prognosis. As for lesions located at the femoral or humeral neck and head, particularly when a fracture has occurred, treated with intramedullary nails showed higher mechanical failure and reccurence rates compared with arthroplasty. As a result, hemiarthroplasty or total arthroplasty is generally preferred to internal fixation for this condition, especially for patients with a longer life expectancy. [60,61] Additionally, as load-sharing devices rather than load-bearing devices, intramedullary nails are at risk of failure without cement augmentation. Other disadvantages include the need for adequate bone stock at the site of the locking screw and the inapplicability of lesions near the joint. However, if the lesion is located at the head or condyle of the femur or humerus, intramedullary nailing may not be appropriate in this case. POP alone, or in combination with screws or thermal ablation, can be efficient enough in cases with short-term survival. [62]. Kim et al. carried out a retrospective observational study that included 89 patients in which percutaneous hollow perforated screw (HPS) fixation combined with POP was performed as a minimally invasive technique that provides effective pain relief and early stabilization for the treatment of patients with femoral neck metastasis [63].

2.3. Local ablative techniques

2.3.1. Radiofrequency ablation or microwave ablation

Radiofrequency ablation (RFA) is an imaging-guided percutaneous puncture method used to reach the lesion. In RFA, small electrodes with dual regulation of temperature and heat production power are used to generate high-frequency current (>10 kHz) to make the tissue ions in the living body vibrate in the direction of the current change, accordingly, causing the tissue ions around the electrodes with the current action to rub against each other and subsequently generate heat. Coagulative necrosis of the tissue is the result of RFA. Considering the advantages of minimal invasiveness, effective thermal coagulation, and targeted destruction of diseased tissues, RFA is gradually gaining the attention of scholars [64]. RFA treatment lies in the fact that malignant tumors are more sensitive to heat than healthy tissues. Basic and clinical studies have delineated that bone tumor tissues are sensitive to thermal damage, and any tumor cell can be killed at 50 °C [65–67]. The main mechanisms of RFA for pain palliation in bone metastases are believed to be as follows. On the one hand, the intraoperative heat production of RFA can directly and effectively destroy the sensory nerve endings of the focal bone cortical surface, periosteum and surrounding soft tissues, thereby cutting off local pain transmission pathways [68]. On the other hand, tumor cells can produce various cytokines and tumor growth factors, such as tumor necrosis factor-a, interleukin and endothelin, and so on, which can increase the sensitivity of sensory nerves to stimuli, consequently decreasing pain thresholds [69,70]. Certain tumor-derived factors promote osteoclast activity and thus aggravate pain [71]. RFA reduces pain by killing tumor cells, decreasing the concentration of pain-inducing cytokines and tumor growth factors, and inhibiting osteoclast activity. In addition, the tumor blood supply is blocked after ablative inactivation of the lesion. The apoptosis of tumor cells in conjunction with the gradual atrophy and collapse of tumor tissue at a later stage inhibit the further destruction of periosteum and surrounding soft tissues by tumor cells, contribute to reduce postoperative recurrence, and indirectly prevent the development of microscopic and macroscopic fractures to release pain [69]. Callstrom [72] conducted a study on the RFA treatment of a single-arm clinical trial of osteolytic bone metastases. Twelve patients with single focal osteolytic bone metastases who failed to respond to radiotherapy were selected and treated with RFA only, and the study demonstrated that the patients' mean pain score (VAS) decreased from 8 preoperatively to 3.2 at 4 weeks postoperatively without serious complications. Goetz et al [73] enrolled 43 patients with bone metastases in a multicenter clinical study of RFA. Most of the patients were treated with radiotherapy preoperatively. The results showed that 95% of the patients experienced postoperative pain relief.

Microwave ablation is a novel clinically applied technique, and its underlying principle is similar to that of radiofrequency ablation, i.e., thermal ablation. Fig. 5 shows a schematic diagram of MWA. Fig. 6 illustrates the surgical procedure. Microwave ablation utilizes the microwave magnetic field released by the microwave ablation needle to cause the surrounding polar molecules and charged particles to rotate at high speed and heat up by friction, thereby resulting in tissue coagulation, dehydration, and necrosis, and then achieving the treatment purpose [74].In comparison to radiofrequency ablation, microwave ablation is an open system that does not require the placement of electrode plates outside the body, has a high ablation frequency (915 or 2450 MHz) and strong penetration, has a synergistic effect of combined ablation with multiple needles, and has little influence from carbonization, blood, and cerebrospinal fluid flow. Accordingly, microwave ablation has the characteristics of rapid heat production, high intratumor temperature, short ablation time, and large ablation range [74]. Zhang et al[75] studied the efficacy of microwave ablation combined with cementoplasty in the treatment of bone metastases. One hundred and forty-seven cases were selected for inclusion in the study. Results indicated that patients' postoperative VAS pain scores improved at 24 h, 1 week, 4 weeks, 12 weeks, and 24 weeks postoperatively. Patients took less pain medication than before, and their ability to perform daily activities improved. Only four cases had complications, as follows: one pathological fracture, one nerve injury, and two skin soft tissue infections. Bone cement leakage occurred in 69 cases without adverse effects. Qiu et al [76] came to a similar conclusion that microwave ablation is safe and effective in the treatment of bone metastases. Pusceddu et al[77] reported that microwave ablation significantly reduced pain in patients with bone metastases and could reduce the tumor recurrence rate from 26% – 67% to 6%.

Thermal ablation therapy alone has its limitations [4,75,76,78,79]. Although thermal ablation alone for spinal metastases can shrink the tumor tissue, the cavity left behind is prone to vertebral compression fractures and spinal stenosis under body load [78]. For weight-bearing areas of the extremities and acetabulum, radiofrequency ablation therapy alone can reduce the mechanical stability of the bone and raise the risk of secondary pathological fractures. Accordingly, when the lesion is located in a critical weight-bearing area or when the risk of pathological fracture is assessed to be high, a combination of cementoplasty or minimally invasive internal fixation surgery ought to be applied [79]. Studies revealed that the utilization of vertebroplasty or internal fixation after radiofrequency ablation of tumors is effective in relieving patients' pain and avoiding vertebral collapse [4,77–79]. Otherwise, Dupuy et al [80] concluded that osteogenic lesions are usually inappropriate for RFA, because electrode pins are tricky to open in osteogenic lesions.

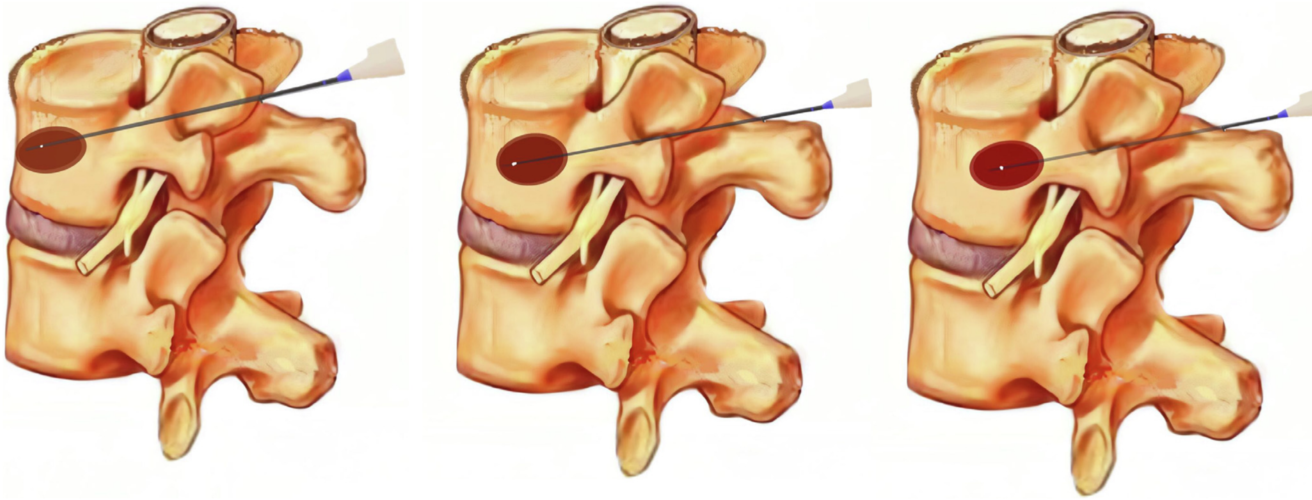

Fig. 5. Schematic diagram of microwave ablation. Multiple short-time intermittent ablation method has the following details: ablation power is set at 60 W, ablation time is set at 1~2 min for each site, and ablation needle is gradually retreated after ablation. The white dot is the microwave emission point, and the red area represents the ablation range. Ablation power and time can be changed on a case-by-case basis. (A) ~ (C) show the multiple short-time intermittent ablation method for which the ablation needle retreated as ablation progressed. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

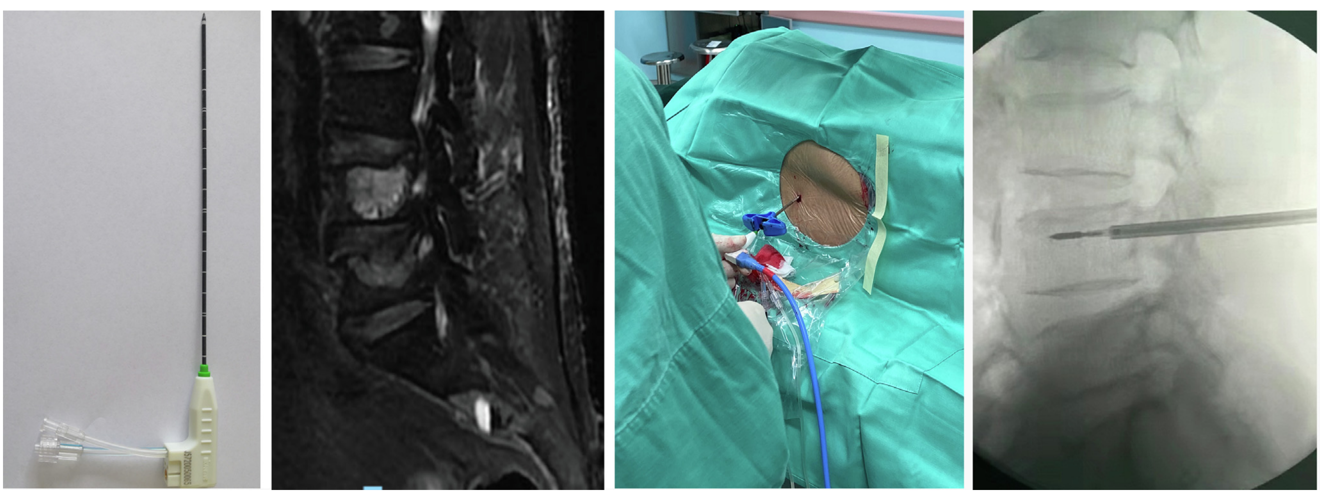

Fig. 6. A 72-year-old woman with spine metastases due to lung cancer: A. Microwave ablation needle B. Preoperative magnetic resonance imaging (MRI) on the sagittal plane showed spine metastases at L4, and L5. C. Microwave ablation was performed in lateral decubitus position. D. Intraoperative lateral X-ray showed microwave ablation was performed on the lesions of L4.

The occurrence of thermal injury when performing thermal ablation treatment demands to be a focus of research, because serious consequences may arise when the ablation area exceeds the target area. This is particularly true when the tumor is close to critical neurovascular bundles or when the tumor invades the posterior border of the vertebral body and the vertebral arch. Experimental animal studies have demonstrated that irreversible damage to neural tissue may occur when the temperature exceeds 45 °C [81–83]. Nakatsuka et al [84] applied microwave ablation combined with cementoplasty to treat 23 cases of bone metastases, 17 of which were located in the spine. All patients with neurological damage were those with cortical or pedicle disruption at the posterior border of the vertebral body. Thus, care should be taken to prevent damage due to inaccurate control of ablation extent when the tumor is in close proximity to important structures. On the one hand, during thermal ablation treatment, thermocouples for temperature monitoring can be placed next to important tissue structures. Then, when the temperature of the couples exceeds 43 °C–45 °C, saline can be instilled in time to lower the temperature and prevent damage to important tissue structures. However, of particular note is that care should be taken to avoid provoking and damaging important structures when placing the couples [82,85,86]. On the other hand, the use of local anesthesia facilitates intraoperative real-time monitoring of neurological function, which is of great relevance to the reduction of neurological impairment. The American College of Radiology Imaging Network performed RFA under local anesthesia for 55 cases of bone metastases, and only three cases had procedure-related complications. Two of these three cases were due to nerve injury, with an overall complication rate of 5% (3/55) [72]. Pain in patients during and immediately after thermal ablation is a concern of clinicians. Considering the transient pain exacerbation after ablation, Cazzato et al [28] displayed through a systematic review that the post-operative complication rate of MWA was about 4%, which was much lower than the 30% for RFA. In that study, a significant proportion of complications in RFA-treated cases was considered to be intra- or postoperative pain sensation, whereas the low incidence of intra- and postoperative pain sensation in MWA may be due to the lack of attention and reporting in current clinical studies.

2.3.2. Cryoablation

Cryoablation has been applied to bone metastases for more than 10 years. The basic principle of cryoablation is the throttling expansion effect of gas, i.e., the rapid expansion of a high-

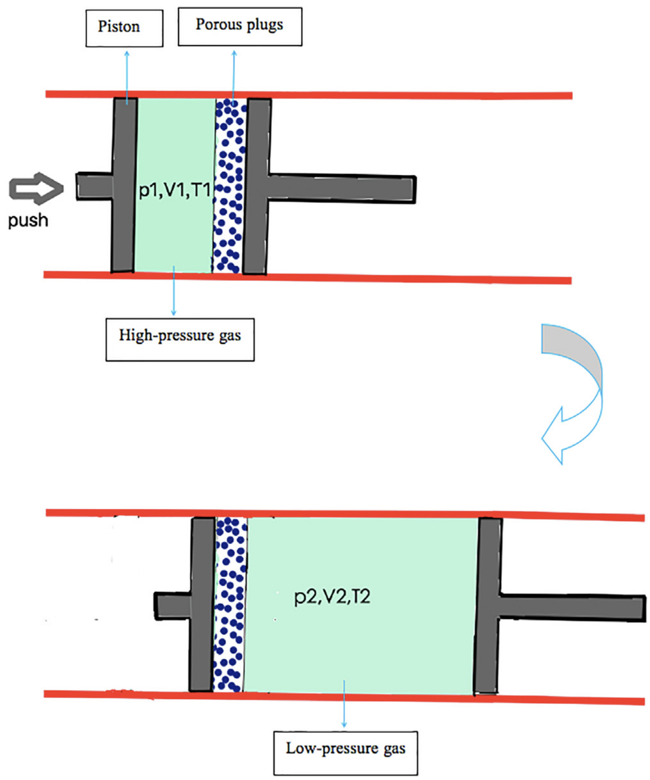

Fig. 7. The throttling expansion process (Joule-Thomson test). After the high-pressure gas passes through the porous valve, its pressure drops significantly. This phenomenon is called throttling. The temperature of gases, such as helium and neon, drops significantly after passing through the throttling, and this phenomenon is the result of the Joule-Thomson effect.

pressure gas flow through a porous plug into a larger space will absorb the surrounding heat, resulting in a significant decrease in the surrounding temperature to produce a freezing effect. Fig. 7 shows a schematic diagram of the throttling expansion process (Joule-Thomson test). Fig. 8 illustrates the imaging comparison of lesions before and after surgery. The critical low temperature that causes cell death is −40 °C [87]. Cryoablation can rapidly freeze cancer tissues below −40 °C and then rewarm them. The process of freezing and rewarming can directly cause dehydration and rupture of cancer cells. Meanwhile, low temperature can cause vasospasm and thrombosis of tumor, thus destroying tumor blood supply and causing hypoxia and apoptosis. Apoptotic tumor tissues left in situ after procedure can be used as antigens to promote anti-tumor immune response. Freezing may increase the sensitivity of cancer cells to chemotherapy or radiotherapy [87–89]. Cryoablation can make the frozen area of sufficient size through the combination of multiple needles, which is convenient to adjust and control the ablation range of tumor, thereby achieving the purpose of conformation ablation. The damage to the surrounding normal tissue is less; consequently, the procedure is safe to treat tumors closed to large blood vessels and other dangerous parts. In contrast to thermal ablation, such as radiofrequency ablation, cryoablation has been found to be characterized by a uniform temperature distribution and higher cell death rate. Moreover, there is no pain caused by high temperature, as a result of no need for general anesthesia, thus the risk of anesthesia is minimized. Multiple tumor lesions can be treated simultaneously, and the formation of ice balls during cryoablation makes the treatment process and treatment effect easy to monitor [90–92]. Studies have shown that cryoablation is a safe, effective, and durable treatment for bone metastases [90–99]. Callstrom et al [90] enrolled 61 patients with bone metastases to analyze the therapeutic effects of cryoablation. All patients were either unwilling to undergo radiotherapy or underwent radiotherapy and found it to be ineffective. This study indicated that 75% of the patients (46/61) experienced 90% or higher degree of pain relief during follow-up; 14% experienced a recurrence of pain approximately 2 months after the procedure; and only one case had a postoperative complication, namely, osteomyelitis. In comparison with previous studies, the authors concluded that cryoablation provides faster pain relief than radiotherapy for bone metastases. It also has a lower probability of pain recurrence; however, there is no sufficient evidence from randomized controlled clinical studies to validate this opinion. Compared with microwave and radiofrequency ablation, cryoablation provides comparable pain relief. Cryoablation is safer when the lesion is close to vital tissues and organs, because the ice spheres produced during procedure are visible on imaging technologies, such as X-ray and CT. In addition, the probability of intraoperative and postoperative pain is lower with cryoablation due to the absence of heat-induced pain [92]. Motta et al [91] applied cryoablation techniques to patients with bone metastases with anesthesia risk assessment ASA III and demonstrated that all patients obtained significant pain relief and none had serious complications. According to research findings of Tomasian et al [93], cryoablation was more advantageous than radiofrequency ablation for osteogenic vertebral metastases. Regarding the need for combination therapy, it has been suggested that the combination of cryoablation with radiotherapy or cementoplasty or bisphosphonates results in a better clinical prognosis than these regimens alone [98–100]. This result is due to the fact that cryoablation provides immediate pain

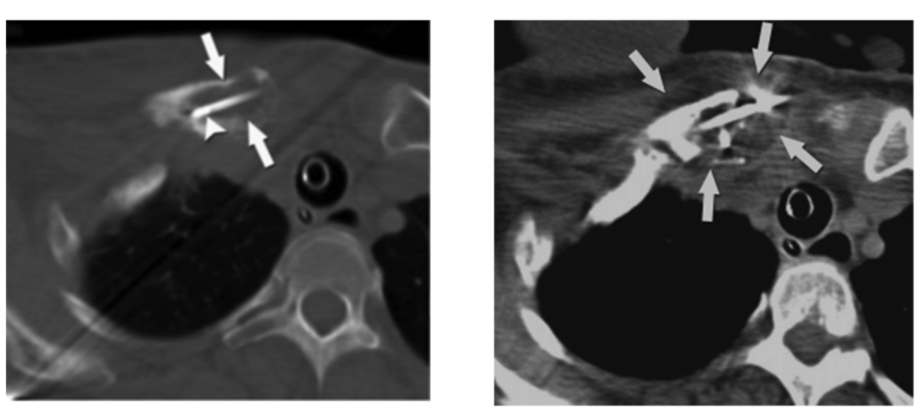

Fig. 8. (A) Noncontrast computed tomography (CT) image of the upper chest with bone windows demonstrates an osteolytic metastasis in the medial head of the right clavicle (arrows). A cryoprobe (arrow head) is placed in the metastasis. (B) Noncontrast CT image of the upper chest with body windows demonstrates an ice ball, visible as a low attenuation area about the cryoprobe with 0 at the ice-ball tissue boundary, extending beyond the margin of the clavicle and the osteolytic metastasis (arrows) [90].

relief, whereas treatment measures such as bisphosphonates or cementoplasty may provide more durable results.

Although cryoablation has a high safety profile, a systematic review of the literature reported that its main complications were fever, nerve injury, and pathological fracture; the overall complication rate was approximately 8% with a fracture rate of 2.6% [101,102].

2.3.3. High intensity focused ultrasound

High intensity focused ultrasound (HIFU) or magnetic resonance–guided focused ultrasound (MRgFUS) is a non-invasive technique that produces biological effects, such as high temperature (above 55 °C), cavitation, and mechanical effects within the tumor area by focusing low energy ultrasound waves outside the body on the target area [103]. Fig. 9 shows a schematic diagram of HIFU. The principle of HIFU for the treatment of bone metastases lies the fact that the bone cortex absorbs more ultrasound energy and has less ability to conduct energy, thereby generating high temperature in the bone cortex and the periosteum on the surface and causing denervation of the periosteum and necrosis of the tumor tissue behind the bone cortex [104,105]. Reduced compression of the surrounding soft tissues by bone metastases after HIFU treatment and lower amounts of immunosuppressive cytokines in the circulating blood may be involved in the pain relief mechanism [104,106,107]. There are three general approaches to reach the target area via the pathways of extracorporeal ultrasound, namely, the near-target area pathway, direct therapeutic target pathway, and the *trans*-soft tissue pathway [108]. Fig. 10 shows a schematic diagram of three different ablation models of HIFU. The first two pathways are suitable for patients with intact or partially present bone cortex adjacent to the tumor, and the third is suitable for patients with complete destruction of the bone cortex adjacent to the tumor. The near-target area pathway involves focusing the ultrasound beam at approximately 10 mm away from the target bone cortex. The cortical surface intersects the beam path to produce a temperature increase. The direct target zone pathway involves the following: the ultrasound beam focuses directly on the cortical surface of the target zone. The *trans*-soft tissue pathway can destroy the remaining periosteal nerves inside the tumor and kill the tumor cells directly by focusing the ultrasound beam inside the osteolytic bone tumor. Giving that the bone cortex next to the tumor is completely destroyed, there is no bone and tumor junction zone in the *trans*-soft tissue pathway. Considering the high absorption of ultrasound energy by the bone cortex, bone metastases with more residual bone mass only require a lower level of ultrasound energy to achieve effective thermal ablation than those with less residual bone mass [109]. Therefore, the effectiveness of HIFU treatment and the level of energy required for treatment can be predicted based on the invasion of the bone cortex by bone metastases.

HIFU is normally performed under MRI guidance, which allows the use of the proton resonance frequency shift that occurs during ablation and real-time temperature monitoring using relevant software; thus, the regulation of ablation is facilitated, and the safety of ablation is increased [110]. Compared with other ablation methods, MRgFUS has a high resolution of both the tumor lesion and the parietal tissues during the procedure, and the intraoperative real-time temperature monitoring is accurate up to 2 °C, which ensures the ablation of the tumor area with sufficiently high temperature while allowing precise temperature control of the surrounding normal tissues to avoid damage. Furthermore, MRI can be used immediately after the procedure to assess the degree of ablation of the target area. Huisman et al [111] applied MRI-guided high-frequency focused ultrasound knife to treat 11 patients with bone metastases whose pain could not be relieved by standard treatment methods (i.e., radiotherapy). Joo et al. [112] showed that patients suffering from pain due to metastases were effectively relieved within 2 weeks, and the pain relief duration could reach>1 year when they were treated with MRI-guided focused ultrasound knife for bone metastases. Another study found that patients who underwent HIFU directly without radiotherapy preoperation had a higher rate of pain relief than those who underwent HIFU after radiotherapy; moreover, for patients with recurrent pain after radiotherapy, HIFU therapy resulted in a higher rate of pain relief than undergoing radiotherapy again [113]. Hurwitz et al. [114] conducted a randomized controlled study, in which 112 cases of bone metastases were included in the MRgFUS group, and 35 cases were included in the control group. Lee et al. [115] compared the efficacy of MRgFUS and conventional radiotherapy in the treatment of bone metastases in a controlled study. The results showed that both were effective and had comparably long-term efficacy (both had > 70% pain relief at 3-month post-treatment follow-up). Nevertheless, the pain relief rate was significantly higher in patients treated with MRgFUS than radiotherapy at 1 week (71% vs 26%, p = 0.0009), suggesting that MRgFUS can provide faster pain relief in patients with bone metastases.

It is relatively safe to perform HIFU. On the basis of an up-to-date published meta–analysis study, which collected 26 studies with a total sample size of 799 patients to evaluate the incidence of adverse events, the overall rate of severe (defined as CTCAE grade ≥ 3) MRgFUS-related adverse events were 0.9% and mild (defined as CTCAE grade ≤ 2) MRgFUS-related adverse events were 5.9%, respectively. Among these studies, only seven (0.9%) severe toxicity cases were noted. In detail, severe adverse events com-

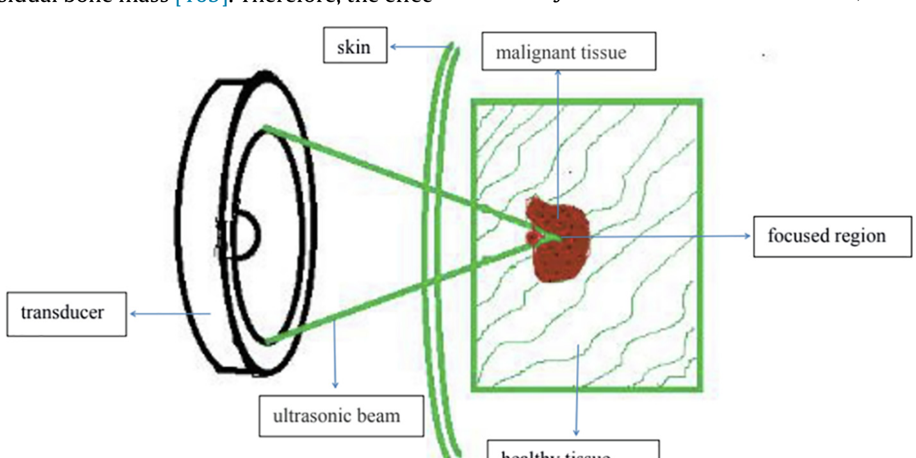

Fig. 9. Schematic diagram of HIFU.

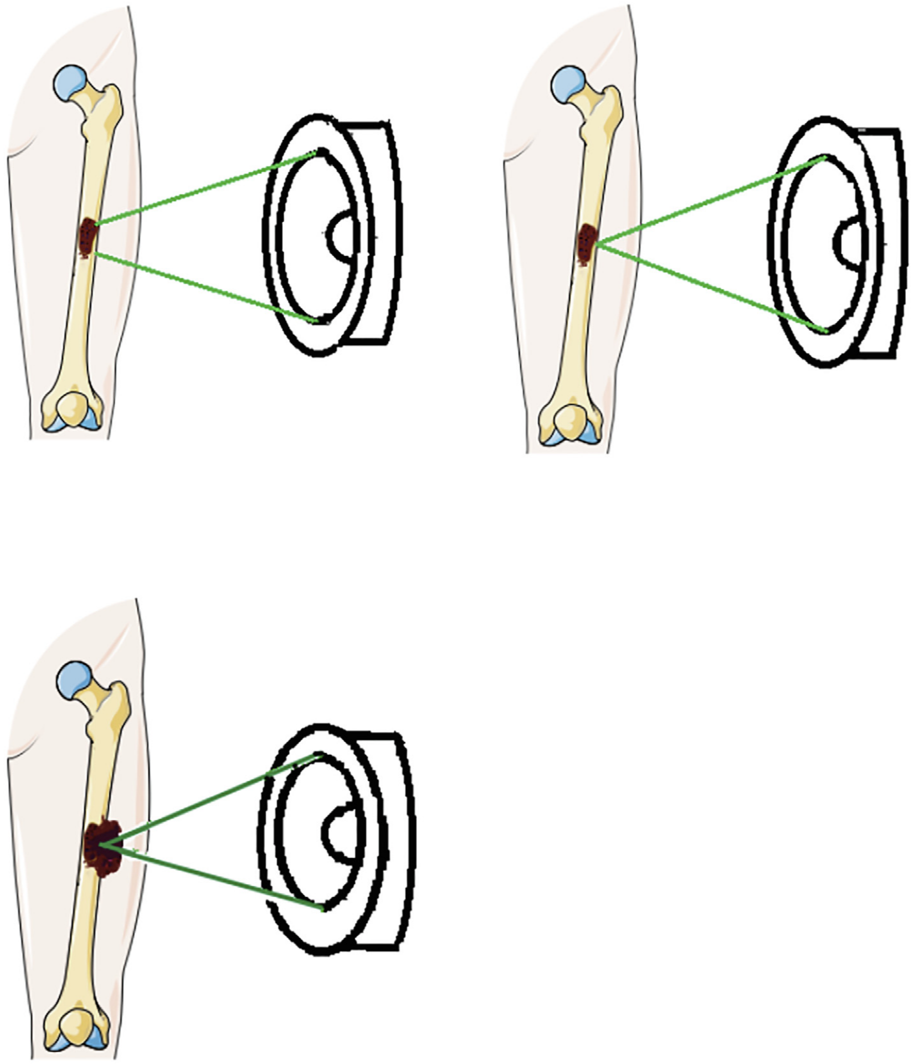

Fig. 10. The ablation models of HIFU. Three different ablation models: the near-target pathway, direct therapeutic target pathway and the *trans*-soft tissue pathway. (A) The bone cortex next to the tumor is intact or partially destroyed, and the planed focus of the ultrasonic beam is distal to (behind) the bone. (B) The bone cortex next to the tumor is intact or partially destroyed, and the planed focus of the ultrasonic beam is directly positioned on the cortical surface of the targeted region. (C) The bone cortex next to the tumor is completely destroyed, and the planed focus of the ultrasonic beam is inside the osteolytic bone tumor.

prised four fractures, one DVT, and two cases of grade III skin burn. Conversely, 47 (5.9%) mild toxicity cases (CTCAE grade less than 3) were recorded, encompassing post-treatment pain (24 cases), low-grade skin burns (5 cases), focal edema (7 cases), focal numbness (8 cases), and post-treatment fever (3 cases) [116].Specifically, post-radiotherapy acute pain fare had an incidence ranging from 40% to 68% compared with only 3% observed with MRgFUS in these studies [116,117].

Same as thermal therapy, pain sensation during procedure is another main complications of performing MRgFUS, which had been reported incidence of up to 11.8% in the study [117]. Considering the short time of application of this technique and the limitations of ultrasound's own characteristics, few clinical reports have investigated its application in the treatment of bone metastases. Further studies are needed to determine the mechanism and principles underlying its treatment of bone metastases, as well as the standardized procedure of its operation.

3. Discussion and proposals

In summary, there are several kinds of interventional therapies or minimally invasive surgeries for patients with bone metastases. The above methods are relatively frequently used clinically at present. With the development of novel medical concepts and minimally invasive techniques, some patients with bone metastases are no longer merely treated with conservative palliative treatment or highly invasive open surgery. Minimally invasive or interventional therapies are gradually being used to reduce trauma and to hasten recovery. Many factors affect the choice of treatment measures and prognosis because of the different conditions of patients with bone metastases. Clinicians should evaluate in detail the patient's pathological type of lesion, age, physical condition, and economic situation to develop an individualized therapeutic schedule.

At present, most of the current studies are single-center clinical experiences with short follow-up, and a standardized system of minimally invasive treatment has not been developed. In particular, the comparison of efficacy and safety between radiotherapy and various interventional techniques has not been adequately studied. In response to the above research gaps, we present the potential trends in this field, as follows. 1) More high-quality randomized controlled studies may need to be conducted to compare the therapeutic effects of interventional therapies or minimally invasive surgeries for patients with bone metastases with those of conventional RT, which is often used as a first-line treatment. 2) The development of a treatment guideline to guide the selection of appropriate populations, the standardization of the treatment process and operational procedures may be helpful and instructive to clinicians who plan to perform minimally invasive treatment for patients with bone metastases in the future. 3) Optimizing the treatment strategy for patients with bone metastasis by integrating multimodal treatments with minimal toxicities to reduce pain, restore function, and maintain quality of life is also imperative. 4) With regard to the choice of image guidance modality, X-rays and CT guidance are still dominant due to their good validity. With the popularization of MRI technology and equipment, MRI is playing an increasingly important role in the diagnosis and treatment of diseases. Compared with X-ray and CT, MRI have ascendancy over them with the virtues of no radioactivity, clear images, and high tissue resolution. Furthermore, MRI can guide and monitor ablation temperature in real time, simultaneously the ablation range is more distinguishable than that of CT. All of these characteristics give MRI the advantage of being more effective and safer. However, MRI may not be easily accessible in some hospitals. On the one hand, MRI is expensive and time consuming, also the technique seems to be complex to operate. And on the other, there are few studies on MRI-guided interventional therapy for bone metastases, and its operation process and feasibility study results are not fully clear. Therefore, MRI-guided interventional treatment of bone metastases is likely to develop into a new research direction in the future. 5) Additionally, it is worthy of note that pain perception is needed to be fully assessed and valued intra- and postoperative, most notably thermal ablation operation. Lidocaine injection into the lesion trans puncture channel has been proposed as a valid option, which promises to uncover a novel response to intraoperative pain perception.

Author contributions

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication. CL wrote the manuscript. QW, DC and HL assisted in searching and screening the literature. ZH, CDL and XD provided guidance for the literature search, the writing of the paper and guaranteed the integrity of this work.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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