35 Ablative Techniques for Painful Metastasis (Radiofrequency ablation, Microwave ablation, Cryoablation, Chemical ablation, and HIFU)

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Introduction

Cancer pain remains a major issue despite the WHO recommendations, and it has been estimated that approximately 30% of cancer patients have poor pain control, particularly in their last year of life [1, 2]. External beam radiation is currently the most accepted first line of treatment for painful metastatic bone lesions. However, radiation is successful in relieving pain in 60% of patients and is often temporary [3]. Radiation therapy is also associated with the risk of injuring the adjacent tissue [3]. Ablative techniques using image guidance have emerged as safe and efficacious palliative treatment for painful lesions in cancer patients [4–10]. These techniques have evolved during the recent years [5, 6]. Additionally, most recent reports indicate that these techniques are cost-effective and may also be able to improve the overall survival rate [11].

The most common palliative interventional radiology (IR) techniques that are implemented for treatment of intractable pain secondary to cancer include radiofrequency ablation (RFA), microwave ablation (MWA), cryoablation, chemical ablation (CA), and high-intensity focused ultrasound (HIFU). These techniques have been used for the treatment of painful osseous metastatic disease, head and neck lesions, ablation of painful soft tissue lesions, neurolysis, and ablation for decreasing mass effect. In this chapter, these techniques will be described, and their applications will be elucidated through multiple cases using pertinent evidence from the literature.

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General Considerations Prior to Percutaneous Image-Guided Ablation

The first step in applying image-guided ablation techniques to cancer patients is patient and lesion selection. Complete and thorough physical examination should be performed to determine the location of pain and its severity. The patient's cross-sectional images should be thoroughly reviewed to determine the safest approach for ablation. Tumors that are less than 1 cm away from the spinal cord, major motor nerves, and arteries supplying the bladder, bowel, or central nervous system are considered relative contraindications to ablation [12]. Osteolytic and mixed osteolytic/osteoblastic osseous metastatic lesions are the most suitable for ablation therapy. Ablation is less effective in pure osteoblastic lesions. Due to the high density of the pure osteoblastic lesions, access to them is difficult and there is poor RFA energy deposition [13].

Most authors recommend pretreatment pain assessment utilizing the Brief Pain Inventory Short Form or Memorial Pain Assessment Card (MPAC) [7]. This scale is used for quantitative posttreatment evaluation. Prior to the ablation treatment, the treatment expectations should be discussed in detail with the patient, patient's family, and other caregivers.

Most ablations can be performed with conscious/moderate sedation, local anesthetics, and as an outpatient procedure. At our institution, general anesthesia is used in patients with elevated baseline pain that are on large doses of opioids.

Computed tomography (CT) scan is the most common modality used for image guidance. Ultrasound can be used as image guidance in more superficial lesions. MRI-guided ablation has been used less frequently due to the need for special MRI compatible probes.

The ultimate objective of ablation is to destroy the sensory afferent nerves in the region of involvement which could be a lytic bone cortex, involved periosteum or a soft tissue mass.

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Radiofrequency Ablation (RFA)

Background

Radiofrequency refers to the frequencies ranging from 350 to 500 kHz in the electromagnetic spectrum. This high frequency is delivered in alternating currents through a shielded electrode, and the electromagnetic energy induces thermal injury to the tissue surrounding the electrode, producing temperatures in excess of 50–100 °C. The heat results in coagulation necrosis and protein denaturation. The amount of cell death is dependent on the distance of the tissue from the electrode (most important factor), the intensity of current generated, and the duration of radiofrequency current application [14–16].

Advantages and Limitations

The Main Advantages of RFA over Other Thermal Ablation Techniques:

1. Immediate cell death
2. Well-controlled focal area of coagulation necrosis around the needle tip or electrodes
3. Ability to accurately monitor the ablation temperature
4. Can be performed with local anesthesia and moderate (conscious) sedation
5. Probe placement is achieved using percutaneous image guidance [16].

The Limitations of RFA

1. *Heat sink* effect. RFA efficacy decreases when the treating lesion is adjacent to a high-flow vessel due to the thermal modulation from the blood flow [17–19].
2. *Charred tissue* effect. If the power is increased too high too fast, the tissue around the probe becomes desiccated producing significant gas. This tissue will act as an insulating sleeve around the probe limiting transmission of the temperature and limiting the effect of RFA.
3. RFA is contraindicated in tumors that come in contact with metallic objects.
4. The ablation margin cannot be visualized with CT scan.

Description of the Technique

Heating the tissue at 50°–55 °C for 4–6 min results in irreversible cellular damage [20]. The ablation zone should cover the entire tumor and extend 5–10 mm into the normal surrounding tissue resulting in an ablation margin of 5–10 mm thickness [16, 20]. For a more effective ablation zone, a methodical increase in energy is recommended than a quick rise in temperature. Rapid rise to temperatures greater than 105 °C will result in carbonization, boiling, and vaporization of the tissue around the probe resulting in decreased energy transmission and consequently limiting larger ablation zone. Ultimately, the goal is to heat the tissue to 50°–100 °C for 4–6 min without causing vaporization or charring of the tissue [21]. Following 5 min of coiling, the probes may be repositioned and subsequent ablation can be performed if deemed necessary. Depending on the size of the tumor, a single probe/antenna (ranging from 14 to 17 gauges) or multiple probes may be used. Figure 35.1 demonstrates a patient with painful metastatic bone lesion from lung cancer that RFA was performed and his pain was relieved.

Application of Technique to Cancer Patients and Literature Review

RFA was initially used for treatment of benign skeletal lesions like osteoid osteoma but has rapidly emerged into the treatment of choice for palliation of painful metastatic skeletal lesions that are not responsive to pain medications and external beam radiation therapy [22]. RFA may relieve cancer pain in patients with soft tissue metastasis from a variety of malignancies including rectal cancer, fallopian tube carcinoma, and bladder carcinoma [8, 23–25]. The effectiveness and safety of RFA in managing painful osseous metastasis has been documented in two multicenter prospective studies. A multicenter trial involved 9 sites in the United States and Europe with 43 patients [26]. The second study was performed by the American College of Radiology Imaging Network in 9 sites in the United States on 55 patients [10]. In this study, Dupuy et al. demonstrated that RFA effectively relieved pain from osseous metastatic disease up to 3 months following ablation with less than 5% complication rate [10]. In a more recent study performed by Guenette et al., RFA

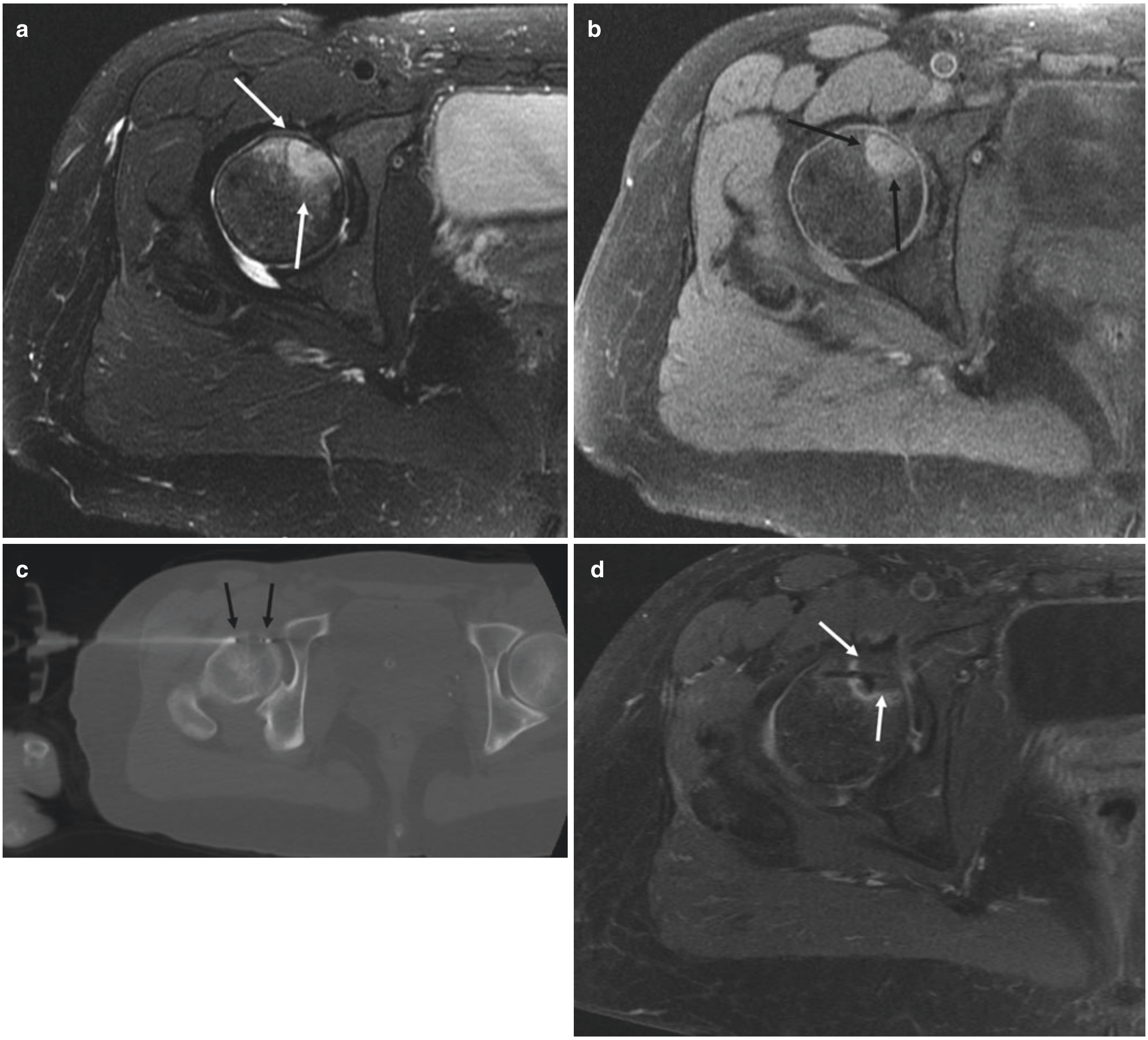

Fig. 35.1 (**a**) T2 axial fat saturation MR image of the right femur demonstrating a hyperintense lesion in the anteromedial aspect of the femoral head (white arrows). (**b**) Same lesion demonstrating enhancement on T1-post-contrast images (black arrows). (**c**) RFA probe inside the lesion (black arrow). (**d**) Three-month follow-up MRI of the right hip demonstrates post-ablation changes with no enhancement (white arrows)

was performed in 49 subjects with painful osseous metastasis. The aim of this study was to identify any correlation between the pre- and post-ablation imaging features and pain relief [27]. Guenette et al. concluded that existing pathologic fracture and smaller tumor size were predictive parameters of success.

Table 35.1 demonstrates the list of the most recent studies on the efficacy of RFA in relieving cancer pain.

Table 35.1 Review of literature of different ablation techniques

Author	Year	Study design	Modality	# of pt.	Efficiency in pain relief	Complication rate
Callstrom et al. [28]	2002	Prospective	RFA	12	Both worst pain score in a 24-hr period and mean pain significantly decreased at 4 weeks posttreatment	None
Goetz et al. [26]	2004	Prospective Multicenter	RFA	43	Average pain decreased from 6.6 of 10 at baseline to 3.7 at week 4, 2.9 at week 12, and 1.3 at week 24	7%
Thanos et al. [29]	2008	Retrospective	RFA	30	Significant decrease in the mean past-24-h Brief Pain Inventory (BPI) score for worst pain, for average pain, and for pain interference during daily life (4.7, 4.8, and 5.3 units, respectively) 4 and 8 weeks after treatment Marked decrease (3 out of 30 patients 4 and 8 weeks after treatment) in the use of analgesics	None
Carrafiello et al. [30]	2009	Prospective	RFA	10	3-month follow-up showed a statistically significant reduction of pain	None
Dupuy et al. [10]	2010	Prospective Multicenter	RFA	55	The average improvement in pain relief was 26.3 at 1 month on a 100-point scale (0, no relief; 100, complete relief) and 16.4 at 3 months	Grade 3 < 5%
Thacker et al. [8]	2011	Retrospective	RFA	22	Decrease in pain score at 24-h post-procedure from 6.0 ± 1.41 to 5.0 ± 2.04	4.5%
Guenette et al. [27]	2013	Prospective multicenter	RFA	49	RFA was more effective in patients with existing pathologic fracture and patients with smaller tumor size	Not reported
Clarencon et al. [31]	2013	Prospective	RFA	24	Pain was significantly reduced at 6 months FU (mean VAS reduction = 4.1; $P < 0.00001$)	12.5%
Pusceddu et al. [32]	2012	Retrospective	MWA	21	On average, the mean BPI score during the 3-month follow-up period was reduced by 92% (41–100%)	None
Kastler et al. [33]	2013	Retrospective	MWA	25	Immediate pain reduction in 93% of patients with a mean duration of 5.5 months	4%
Callstrom et al. [34]	2006		Cryo			
Masala et al. [35]	2011	Prospective	Cryo	20	Quantitative analysis provided by PET correlated with the response to cryoablation as assessed by CT data and clinical VAS evaluation	Not mentioned
Thacker et al. [8]	2011	Retrospective	Cryo	36	Decrease in pain score at 24 h post-procedure from 6.5 to 3.5	None
Callstrom et al. [36]	2013	Prospective multicenter	Cryo	61	Mean score worst pain in 24-h period decreased from 7.1/10 to 5.1/10, 4.0/10, 3.6/10, and 1.4/10 in 1, 4, 8, and 24 weeks after the procedure, respectively	2%
Prologo et al. [37]	2014	Retrospective	Cryo	50	Statistically significant decreases in the median VAS score and narcotic usage at both 24 h and 3 months	11%
Gangi et al. [38]	1994	Retrospective	CA	25	Within 24–48 h 74% of the cases demonstrated reduction in analgesic needs	
Catane et al. [39]	2007	Prospective	HIFU	13	MRI-guided HIFU provided safe and effective noninvasive alternative for palliation of pain	0%
Liberman et al. [40]	2009	Prospective Multicenter	HIFU	31	Significant pain improvement in 72% of the patients	0%
Napoli et al. [41]	2013	Prospective	HIFU	18	Statistically significant decrease in pain between baseline and follow-up findings	0%

Microwave Ablation (MWA)

Background

Microwave applies electromagnetic waves and produces alternating electric fields. This causes rotational movements in the water molecules within the tissue surrounding the microwave probes resulting in frictional heat [42]. This heat ultimately causes coagulation necrosis in the ablated tissue, similar to RFA. Bone tissue has low conductivity and high impedance. Therefore, theoretically, since microwave is relatively insensitive to impedance, it may be advantageous in bone tissue [43].

Advantages and Limitations

Main Advantages of Microwave

1. Since microwave uses frictional heat and is not dependent on convection of electrical current, the microwave generators do not require ground pads.
2. Microwave produces larger tumor ablation volumes compared to RFA due to higher intratumoral temperatures [44, 45].
3. MWA is faster than RFA [44].
4. Ability to use multiple applicators [46].

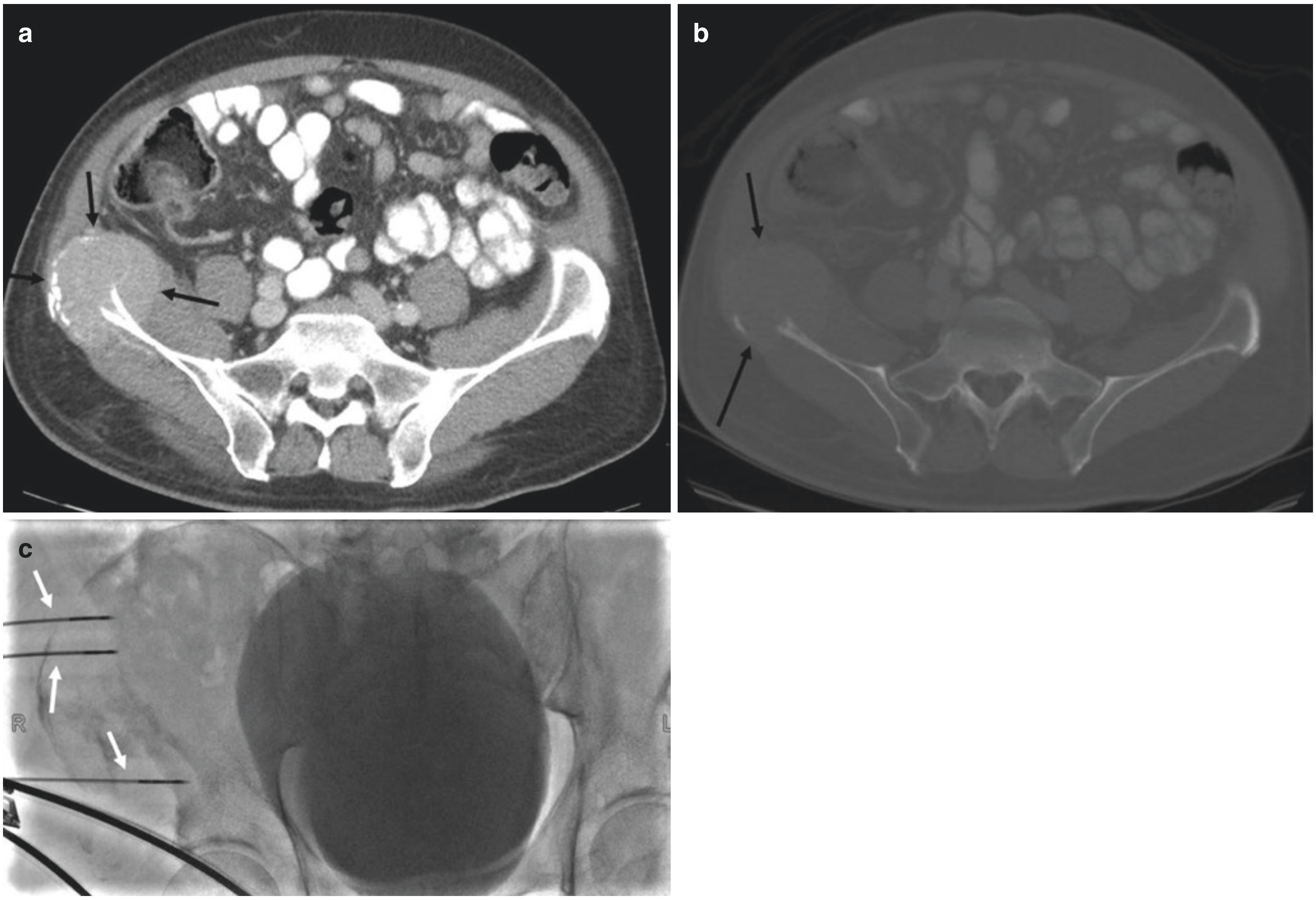

Fig. 35.2 CT scan of a patient with hepatocellular carcinoma and painful metastasis to the right iliac bone. (**a**) Mixed lytic/sclerotic lesion in the right iliac bone in soft tissue window (black arrows). (**b**) The metastatic lesion in bone window (black arrows). (**c**) Fluoroscopic lesion with multiple microwave probes in the lesion (17 G probe, NeuWave Medical, Madison, WI; white arrows)

5. Due to electromagnetic nature of microwaves, there is no *heat sink* effect or *charred tissue* effect. Therefore, optimal heating of cystic masses and tumor close to large vessels (>3 mm in diameter) can be achieved [43, 46, 47].
6. Less procedural pain probably because there is not flow of current within the patients' body.

Main Limitations of MWA

1. The ablation margin cannot be visualized with CT scan.

Description of the Technique

Microwave uses frequencies of at least 915 MHz–2.45 GHz [48]. A single 14.5-gauge antenna is usually used when the tumor is less than 3.5 cm in maximal diameter, and more than two antennas are used when the tumor is larger than 3.5 cm. In order to pierce the cortex, a 13-G bone biopsy needle can be used and can serve as a coaxial introducer for the antenna. The introducer is then retracted prior to delivery of energy. Percutaneous approach can be achieved using ultrasound or CT guidance. If the lesion is too close to the skin (<3 cm), skin precaution should be performed to avoid skin burn.

Figure 35.2 demonstrates a patient with painful metastatic bone lesion from lung cancer that MWA was performed, and her pain completely improved.

Application of Technique to Cancer Patients and Literature Review

MWA is independent on tissue conduction, produces high tissue temperatures, and is less sensitive to "heat sink" effect. Therefore, theoretically MWA should be effective in bone lesions. Early reports have demonstrated that MWA can efficiently decrease pain in cancer patients [32, 33]. In a retrospective study performed by Pusceddu et al., 21 patients with metastatic bone lesions were treated with MWA. Patients reported a significant reduction in their pain with improved quality of life as early as 1 week after the procedure, as measured by BPI score [32]. In another retrospective study, performed on 15 patients, Kastler et al. concluded that MWA is a safe and effective method of treating painful refractory bone and soft tissue tumors [33]. MWA is a powerful tool, and precaution should be used when the lesion is located near vital structures or close to the skin. Kastler et al. recommended multiple, short, relatively low-powered heating cycles, especially in cases of small lesions. Table 35.1 demonstrates the list of the most recent studies on the efficacy of MWA in relieving cancer pain.

Cryoablation

Background

Cryoablation causes cytotoxic effect through formation of intracellular ice crystals. These ice crystals cause protein denaturation, cell membrane rupture, and shearing of the intracellular structures. A liquid gas, commonly argon or nitrous oxide, runs through the cryoablation probes. This gas rapidly cools the tip of the cryoablation probe and forms an ice ball around the probe. Ice formation is followed by a thawing phase, commonly by using helium. The freezing and thawing phases cause water to rush into the tumor cells resulting in swelling and bursting of the cells [49]. The temperature necessary to cause cellular necrosis depends on the cell type and tissue type. Tissue destruction is complete at −20 °C to −40 °C. This temperature is achieved approximately 3–5 mm deep to the visible edge of the ice ball, which corresponds to 0 °C [50, 51]. The mechanism by which cryoablation reduces pain has not been studied. However, it most likely reduces pain by reducing tumor burden and osteolysis. The size of the ablation zone is dependent on the size of the cryoprobe, the length of the uninsulated tip, and the freezing time.

Advantages and Limitations

Main Advantages of Cryoablation

1. The main advantage of cryoablation over other ablation techniques is that cryoablation forms a distinct ice ball that can be seen with CT scan, MRI, or ultrasound and can be used to precisely monitor tumor coverage [52, 53]. The ice ball boarder also confirms proper exclusion of critical structures adjacent to the ablation margin [54]. Any structure/tissue beyond the low-attenuation ice ball is safe from the thermal injury.
2. Decreased intra-procedural and post-procedural pain [8]. Compared to RFA, patients treated with cryoablation do not experience increased pain during the procedure or immediately after the ablation [8].
3. Multiple probes can be used because each probe acts independent to others.

Main Limitations of Cryoablation

1. More time-consuming than RFA and MWA, typically takes 25–30 min. This is because unlike radiofrequency and microwave ablation, cryoablation provides no zone of direct or active cooling, and so the surface area of the cryoablation probe limits cooling efficiency.
2. Risk of cryoshock: This systemic complication that includes hypotension, multi-organ failure, respiratory compromise, and disseminated intravascular coagulopathy happens when the ablation zone is reperfused after the ice ball is melted. The rapid release of the cellular debris into the systemic circulation causes cryoshock. This is rarely seen with heat-based ablation techniques [50].
3. May be more expensive than RFA. More probes are needed during cryoablation, therefore increasing the cost.
4. Since cryoablation does not use heat, there is no cautery effect which may result in bleeding complications.
5. Organ fracture may happen due to the fact that frozen tissue is more brittle.

Description of the Technique

Cryoablation of the bone or soft tissue is performed under moderate conscious sedation or general anesthesia. The probes are larger than those used for RFA ranging from 11 to 17 gauges. Multiple probes can be used to provide synergistic effect and increase the size of the ice ball. Like other ablation methods, CT scan is the most common modality used for guidance in placement of the cryoprobes. The probe(s) should be placed approximately 1 cm from the margins in order to provide complete coverage of the tumor. When using multiple probes, the probes should be placed 2 cm from each other. The probes should be placed in parallel along the long axis of the tumor. If the mass is larger than 8 cm in diameter, it should be treated in two sessions on sequential days. If the area of ablation is in close proximity to the bowel, bladder, or skin, hydrodissection can be performed to displace them [55]. Non-contrast CT scan should be performed every 2–5 min throughout the freezing phase of the ablation to monitor the size, location, and extent of the ice ball coverage. The ablation zone is identified as a well-marginated low-attenuation area seen on non-contrast CT scan and best visualized on body window and level settings of (W400, L40). As mentioned earlier the visible edge of the ice ball corresponds to 0 °C, and therefore cell death occurs approximately 3 mm deep to this edge. After the freezing process, the probes should be actively thawed for 10–15 min. The probes should only be removed once the temperature reaches approximately +25 °C.

There are numerous reported variations on freeze–thaw–freeze cycles that depend on tumor type and size; however the most common method for cryoablation involves a 10-min freeze, 5-min thaw, and then a second 10-min freeze (10-5-10 min). Figure 35.3 demonstrates a patient with breast cancer with painful osseous lesion in her hip. Cryoablation was performed and was able to relieve her pain.

Application of Technique to Cancer Patients and Literature Review

Cryoablation has been reported to be an effective and safe method in the treating painful osseous metastases [8, 34, 36]. In a retrospective study, Thacker et al. reviewed 58 patients with painful osseous metastasis [8]. These patients were divided into 2 groups of 36 (cryoablation) and 22 (RFA). Patients who had undergone cryoablation had significantly less short-term analgesic requirement and shorter hospital stay compared to the group that received RFA [8]. In a multicenter clinical trial, 61 patients with 1 or 2 painful osseous metastasis were evaluated [36]. This study reported highly significant reduction in pain scores (75% of the patients achieved 90% or higher pain relief) and

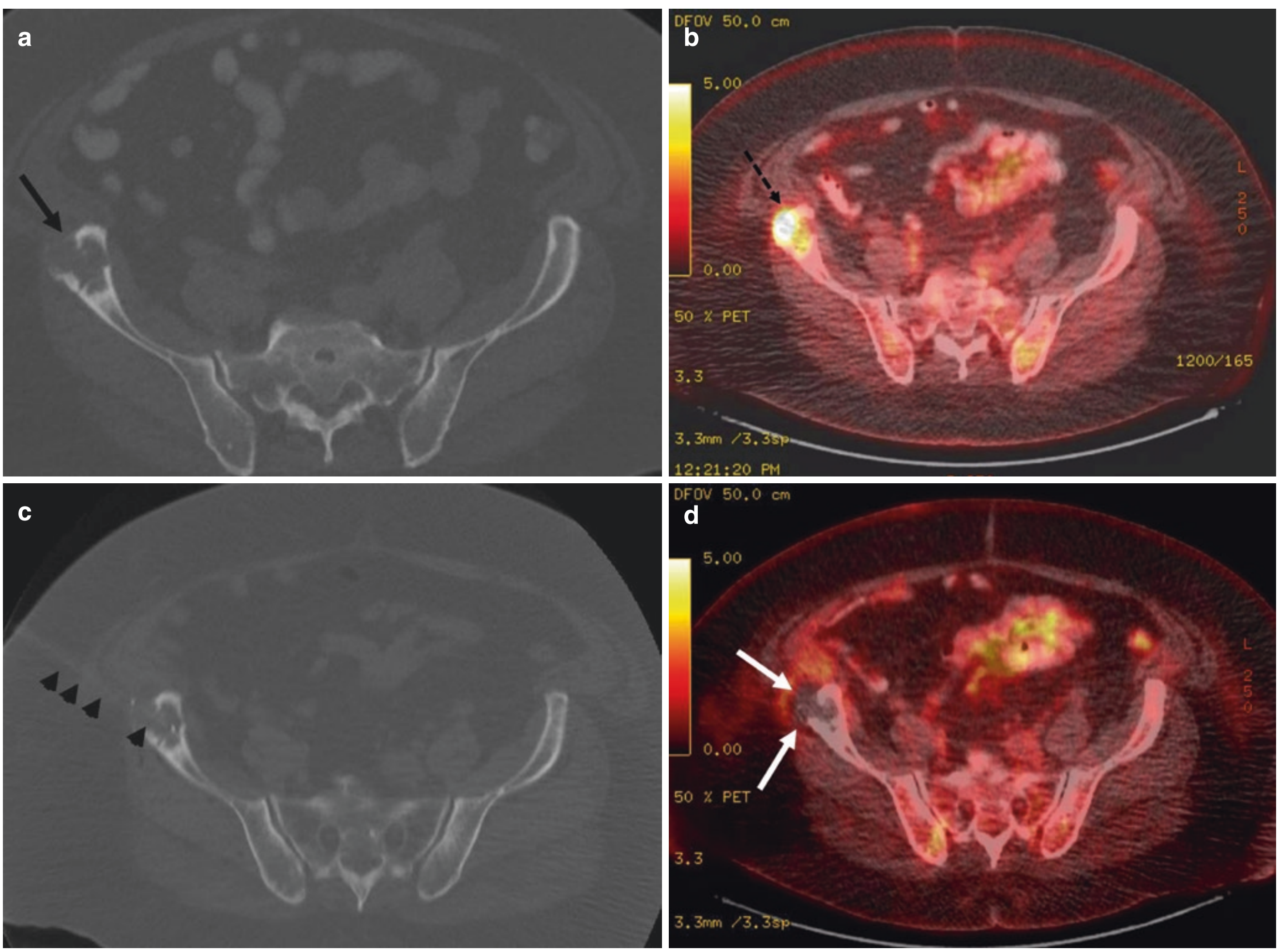

Fig. 35.3 (**a**) CT scan demonstrates a lytic lesion with cortical destruction in the right iliac bone (black arrow). (**b**) Same lesion is shown on a PET/CT scan which demonstrates FDG uptake in the lesion and the adjacent soft tissue component (dashed black arrow). (**c**) Cryoablation probe (Ice Force 2.1 CX probe, Galil Medical Inc., Arden Hills, MN; black arrow heads) inside the lesion. (**d**) PET/CT scan performed 3 months post-ablation demonstrating the lesion that is no longer FDG avid (white arrows)

improvement in the quality of life at 1, 4, 8, and 24 weeks after treatment with cryoablation [36]. The pain relief was durable in 86% of the patients. In a similar study, Masala et al. demonstrated significant pain relief after cryoablation for painful osseous metastases in 20 patients [35]. In another recent study on cryoablation in 50 patients with osseous metastasis, pain was significantly decreased at 24 h and 3-month follow-up [37]. Finally, Rosenthal and Callstrom published a comprehensive review of case studies and small series on efficiency and safety of cryoablation for painful osseous metastases [56]. Cryoablation has also been effective in relieving pain from celiac plexus involvement by pancreas cancer and intractable pudendal nerve involvement [57, 58].

Chemical Ablation (CA)

Background

Chemical ablation (CA) is achieved by percutaneous injection of chemical agents that induce cell death. Cell death happens due to vascular and cellular effects. There are two main chemical agents that are used in clinical practice including ethanol and acetic acid. Acetic acid diffuses better than ethanol and produces a bigger area of necrosis compared to ethanol, and therefore it may be preferred to treat large tumors [59]. Ethanol and acetic acid cause denaturation of the cell protein and dehydration of the cytoplasm. Additionally, they result in endothelial cell necrosis and platelet aggregation which leads to vascular thrombosis and ischemia.

Advantages and Limitations

Main Advantages of CA

1. Cheapest method of ablation.
2. Rapid relief of pain: pain relief occurs in 24–48 h.

Main Limitations of CA

1. CA is a painful procedure, particularly in the bone.
2. Diffusion of the chemical agent is not predictable and uncontrollable; therefore it may result in injury to the adjacent nervous structures and intravascular injection.
3. Degree of necrosis is highly variable.
4. Potential complication is massive tumor necrosis specifically after injection of more than 30 ml of alcohol.

Description of the Technique

Procedure is performed under CT guidance. Ethanol 95% is mixed with contrast and injected. A 22-gauge spinal needle is used to inject the ethanol into the lesion. The non-necrotic part of the tumor is targeted. Therefore, a contrast-enhanced CT is usually performed prior to the procedure to identify areas of necrosis in the lesion. Initially, lidocaine diluted with 25% contrast medium is injected into the lesion. This reduces the pain provoked by alcohol injection. CT scan is performed to evaluate the distribution of the contrast media. The distribution of the contrast within the tumor is used to predict the dispersal of the injected alcohol. If contrast diffuses beyond the tumor margins and approaches a critical structure like nerves, injection of ethanol or acetic acid cannot be performed. Depending on the size of the tumor and the type of chemical agent used, 5–25 ml is instilled into the tumor [38].

Application of Technique to Cancer Patients and Literature Review

Although CA is the cheapest and the easiest ablation method, the use of other ablation techniques has reduced the utilization of this technique. This ablation technique is utilized mainly when other ablation techniques are not feasible. Gangi et al. reported 74% reduction in pain in 25 patients with 27 bone metastases after 24–48 h of 95% ethanol injection [38].

High-Intensity Focused Ultrasound (HIFU)

Background

High-intensity focused ultrasound (HIFU) is a noninvasive ablative technique using ultrasound waves within an area of human tissue, generating local heat, leading to cellular death. HIFU was first used in human in the 1950s in treatment of patients with Parkinson’s disease [60]. Real-time US or MRI is used for guidance. MRI can provide additional information that can be used for precise treatment mapping. Focused ultrasound waves are generated and focused for 15–25 s. These focused waves result in tissue heating in an elliptical-shaped spot measuring up to 7 cm. Bone absorbs ultrasound waves approximately 50 times more than soft tissues, and thermal conductivity of the bone is minimal. Therefore, when HIFU is used to treat osseous metastatic disease, the focus point is placed behind the targeted bone to allow a larger field of heating. Bone procedures are typically 2 h long. The procedure is painful and should be performed under deep sedation or locoregional anesthesia.

Advantages and Limitations

Main Advantages of HIFU

1. The main advantage of this modality is that the treatment is performed under real-time MRI guidance. The tumor can be precisely localized using real-time MRI, and thermal dose can be accurately deposited.
2. Noninvasive thermal ablation modality.

Main Limitations of HIFU

1. Time-consuming. Bone procedures typically take 2 h.

Description of The Technique

Patients are placed on the MRI table and positioned in a way that the target lesion is aligned with ultrasound transducer. The transducer is located in the MRI table within an oil bath. The transducer is coupled to the patient's skin using a gel pad to eliminate air across the path of the ultrasound beam. Since MRI is used for guidance, the treatment planning is performed in three dimensions, coronal, sagittal, and axial planes.

Application of Technique to Cancer Patients and Literature Review

MRI-guided focused ultrasound ablation was effective in treating soft tissue tumors such as uterine fibroids [61]. Additionally, this modality has been used as a noninvasive treatment for benign and malignant breast tumors [62]. HIFU with or without MRI guidance has been reported among different studies to significantly reduce pain from osseous metastasis disease [39–41, 63]. Catane et al. used MRI-guided HIFU in 13 patients with symptomatic bone metastases and were successful in improving pain score and reducing analgesic dose in these patients [39]. In a multicenter study, Liberman et al. used MRI-guided HIFU in 31 patients and reported significant improvement in pain in 72% of their patients [40]. In a recent study performed by Napoli et al., 18 consecutive patients with painful bone metastases were treated with MRI-guided focused ultrasound [41]. Pain was significantly decreased when compared to baseline, and no treatment-related adverse event was reported.

Conclusion

Palliative treatment of painful metastatic disease can be efficiently and safely achieved by percutaneous ablation techniques. The therapeutic armamentarium includes radiofrequency ablation, microwave ablation, cryoablation, chemical ablation, and HIFU. Multiple studies have demonstrated the efficiency and safety of these techniques. Thorough knowledge of indications, limitations, and protective techniques of each ablation technique is mandatory for a successful treatment.

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