



Ablation of painful metastatic bone tumors: A systematic review

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ABSTRACT

The pain is the most common problem in patients with bone metastases. It is not related to the characteristics of the tumor (type, location, number or size of metastases). Currently, the bone metastases can be treated with chemotherapy, hormonal therapy, surgery and radiotherapy, but the drugs most used in the treatment of pain are opioids. These drugs give benefit between 8 and 12 weeks and often give non negligible toxic effects. Percutaneous techniques are varied and, when there is indication, can be used to reduce pain and dose of morphine in these patients, being safe and effective techniques already at 4 weeks of treatment.

The choice of a methodical of ablation compared to another depends on the type, size and location of the lesion. Moreover, the combined treatments of ablation and cementoplasty are also useful to stabilize the bone lesion.

This review article analyzes techniques and effectiveness of percutaneous treatments of skeletal metastases.

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1. Introduction

Painful skeletal metastases are a common problem in cancer patients.

The causes of pain in patients with bone metastases are not fully understood, and the presence of pain is not correlated with the type of tumor, location, number or size of metastases.

Possible mechanisms of pain include:

1. stretching of the periosteum secondary to tumor growth;
2. fractures (both micro fractures and macro fractures);
3. cytokine mediated osteoclastic bony destruction, resulting in stimulation of nerve endings in the endosteum and tumor growth into surrounding nerves and tissues.¹

Various therapies, including chemotherapy, hormonal therapy, surgery and radiotherapy are currently used for palliative purpose.

Some patients are unable to benefit from these conventional treatments and the relief from pain, when it occurs, is not achieved before 4–12 weeks.²

While chemotherapy reduces primary the mass and secondary injury in the 20–80% of patients, on the other induces drug resistance and resumption of bone pain and also frequent outbreaks of myelosuppression given the toxicity of many drugs used in the current treatment protocols.³

Hormonal therapy is effective only in metastases from the breast and prostate cancer.

The surgical option is reserved for those patients with pathological risk of fracture or spinal cord compression.

Finally, local radiotherapy is dogged in many cases by toxic effects (nausea, vomiting and diarrhea) and radioisotope therapy shows effectiveness in subjects with multiple bone metastases, but on the other hand it is not regarded as standard treatment for single metastases.^{4,5}

Based on these considerations, analgesic drugs (opioids) are today a first line treatment in metastatic pain and in some cases they remain the only alternative for palliation of symptoms.⁶

The side effects, especially in prolonged treatments are constipation, severe limitation of physical and mental status cirrhosis and liver coma.

Several authors have studied various alternative strategies for treating pain from bone metastases involving the use of percutaneous imaging guided treatments with the aim of disrupt focal bone lesions: ethanol, thermotherapy interstitial laser induced,^{1,7} percutaneous radiofrequency ablation^{1,8–11} and, more recently,

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cryoablation, plasma mediated radiofrequency ablation^{1,7} and microwave ablation.^{12–14}

This review article will examine these ablative techniques, their complications and effectiveness.

2. Ablative therapies for bone metastases

2.1. Pre procedural assessment

2.1.1. Imaging

The discovery of a secondary location of a solid tumor influences diagnosis, treatment and prognosis of cancer patients, so the detection of bone metastases assumes importance not only for the TNM staging but also for the therapeutic address to the primary tumor and the painful symptoms.

Scintigraphy uses the tracer Technetium 99m MDP is captured by the bone in direct proportion to osteoblastic activity. After 3 h we get an image representing total body functional framework of metabolic bone. The exam is very sensitive (80–90%), but little specific.¹⁵

The radiological examination is positive when the 30–50% of tissue is destroyed by metastases.

Further changes including the SPECT technique and the trifasic technique led to an increase in the specificity of skeletal scintigraphy.

Compared to scintigraphy, conventional radiology is later in identifying changes attributable to metastases, but more reliable and accurate especially in terms of topographic localization. Ultimately, the two methods associated have a good specificity (95%).¹⁶

Conventional plain radiography is an inexpensive and convenient method of evaluation, sensitive in cases of destruction of bone tissue in particular when there is cortical involvement, but may be little sensitive in the early stages of some cancers that are located in the spinal cord (as do the majority of metastases).¹⁷

While the CT is the best method for evaluating injuries at the cortical, MRI is more accurate for the diagnosis of bone metastases at sponge that has not yet altered the trabecular architecture.

The diagnostic evaluation is important to identify the correspondence between the area of pain indicated by the patient and lesion highlighted by CT or MRI.¹⁸

In addition, these methods are useful as a guide during the percutaneous procedure.

2.1.2. Assessment of quality of life

The assessment of quality of life is established after the procedure.

There are different systems: (1) the Edmonton Symptom Assessment System (ESAS); (2) the Townsend Functional Assessment Scale (TFAS); (3) morphine equivalent; and (4) a site specific pain score (SSPS). The latter is similar to Brief Pain Inventory (BPI) visual analog scale (VAS) score, which is mostly used in the studies in literature.

The evaluation of pain is performed with a VAS characterized by a score ranging from 0 to 10, is considered moderate or severe pain with a score equal to or greater than 4.

Usually, patients are evaluated post procedure by telephone calls on days 1, 2 and 4 and at weeks 1, 2, 4, 8, and 12.

- The ESAS is a nine item, patient rated, symptom vertebral rating scale with domains in global pain, nausea, tiredness, depression, anxiety, drowsiness, appetite, sense of well being, and shortness of breath. Each domain is scored from 0 to 10, with higher scores representing increased disability.
- The TFAS is a functional scale. Patients are classified into four categories: A normal pain free function, B normal function

with pain, C significantly limited function requiring some type of prothesis and D non functional.

- The dose of opioid transformed into the equivalent of morphine before and after the procedure is important to identify variations in dosage.

Finally, the SSPS, similar to BPI, with 0 currency free from pain and 10 worst possible pain from detention that is in motion.¹⁹

2.1.3. Inclusion criteria

The concern of selecting patients to undergo non conventional therapies lies in an attempt to study in subjects such percutaneous treatments could show greater effectiveness in getting the desired result: the palliation of pain. In the literature the most accurate criteria is provided by Callstrom et al.,¹¹ who established that patients with moderate or severe pain must be treated.

Pain should be limited to one or two locations corresponding to the lesions seen on CT or MRI images. Patients with multiple injuries may benefit from a systemic therapy.

2.1.4. Exclusion criteria

Exclusion criteria are: the presence of more than two symptomatic lesions, the blastic nature of metastases (except for the plasma mediated radiofrequency and cryoablation); safety margins of less than 1 cm from the spinal cord, the motor nerve majeure, the brain, the artery of Adamkiewicz and the bladder.²⁰

3. Therapies

3.1. Percutaneous ethanol therapy

3.1.1. Technique

To provide local anesthesia a mixture of iodinated contrast material (25%) and lidocaine 1% (75%) is injected into the area of diffusion then a fine needle is placed into the tumor. In the absence of vascular intravasation or contact with vital structures, absolute alcohol is then injected.²¹

3.1.2. Effectiveness

Gangi and colleagues described the use of CT guided percutaneous administration of 95% ethanol for pain palliation from 27 metastatic bone lesions in 25 patients previously treated with radiotherapy and/or chemotherapy. Sixteen lesions received a single dose of ethanol, while 10 lesions received two doses and one lesion received three doses. The evaluation of treatment efficacy was assessed by the reduction in the use of analgesic medicines 48 h and 2 weeks following therapy. Complete relief pain was achieved in four patients, a 75% analgesic medicine reduction was observed in 11 patients. Seven patients received little or no relief with the treatment.²²

Alcohol diffusion into the tissues next to the tumor area could cause necrosis by dehydration.²¹

3.2. Percutaneous laser induced interstitial thermotherapy

3.2.1. Technique

Gröenemeyer and colleagues reported the treatment of three patients, with spinal metastases, using a Nd:YAG laser with a wavelength of 1064 and the use of 400 µm optic fiber to deliver energy into the lesion area.²³

With local anesthesia and CT guidance, a coaxial system was used via a transpedicular approach. Laser energy was applied at a power of 4–10 W with a pulse length of 0.1–1.0 s at 1 s intervals. In order to achieve coverage greater than 7 mm, the fiber was

repositioned and the thermal treatment repeated, completing the procedure in 60–90 min.

3.2.2. Effectiveness

Three months after treatment, the patients had 45, 30, and 35% pain reduction.²³

This procedure is not adequate for treatment of very large lesion.²¹

3.3. Percutaneous cryoablation

3.3.1. Technique

Cryoablation has a long history of successful treatment of neoplasms in several organs, including prostate, kidney, liver and the uterus. Newly developed percutaneous cryoprobes are based on delivery of argon gas through a segmentally insulated probe, with rapid expansion of the gas that results in rapid cooling, reaching 100 °C within a few seconds.

A single cryoprobe provides an ice ball of approximately 3.5 cm diameter. A great advantage of the cryoablation systems is that the use of multiple cryoprobes allows the generation of large lesions by avoiding the need to perform the time consuming overlapping ablations needed with other ablation at the single ablation interfaces.²⁴

Cell death from cryoablation is due to two causes. First rapid freezing immediately adjacent to the probe results in intracellular ice formation and subsequent cell destruction. At a further distance from the probe, relative gradual cooling causes osmotic differences across the cell membrane, with secondary cellular dehydration and death.²⁵

This method has the advantage of being able to be used in blastic metastases, but has the disadvantage of using a large applicator diameter and the procedure being a long time.

3.3.2. Effectiveness

Preliminary data suggest that cryoablation is effective in treating painful primary and secondary bone neoplasms [25]: 16 tumors in 14 patients were treated with percutaneous cryoablation using MR guidance. These investigators reported a significant reduction of pain in the immediate postoperative period that continued over the long term, with associated significant improvement of quality of life.

The main pitfalls are the length of the procedure (about 30 min) and the cost of the equipment. Complications depend by needle's access as radiofrequency procedure.

3.4. Percutaneous radiofrequency ablation (RFA)

3.4.1. Technique

The RFA is based on creation of a thermal cellular damage converting radio waves into heat.²⁶

The electricity generated goes from active electrode (positive) to dispersive electrode (negative), which can be placed below the thigh of the patient (technical monopolar) or be placed within the active electrode (technical bipolar). The liquid contained in the cell tissues (0.9% saline content) without any difficulty allows the passage of electric current, however, by gradually increased impedance of the tissue. The current passing in the tissues is responsible for the phenomenon of ionic agitation and then the production of heat from friction²⁷ (Fig. 1).

It is obvious that the decrease of temperature tissue is directly proportional to the distance from the $(1/r^2)$ and that, in the light of this, necrosis mostly those areas tissue near the electrode where there are values of intensity current highest, moreover RFA mediated thermal necrosis is hampered by vascular flow.²⁸

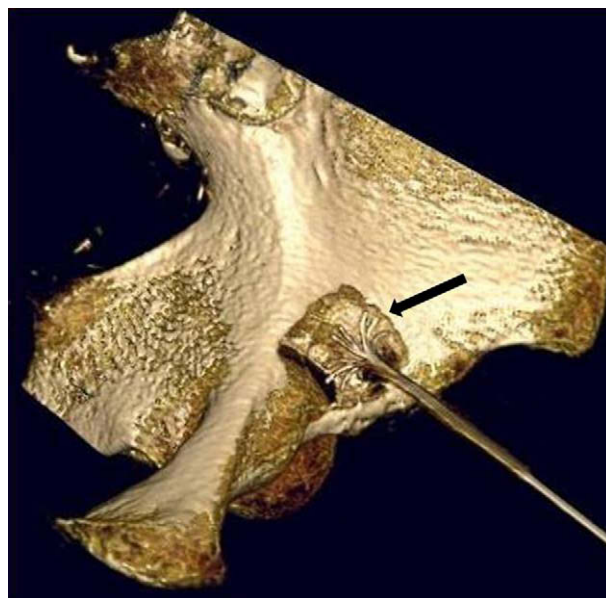


Fig. 1. Transverse three-dimensional volume CT image obtained at the level of acetabulum shows RF electrode deployed in a soft tissue of a metastatic lesion (arrow).

The advantage of RFA consisting of needles with relatively smaller size compared to the other ablation devices, the disadvantages are data from long procedures (about 30 min) and more needle placement required for a wide area to treat.

The procedure can be performed under general anesthesia or deep sedation with cyclical administration of alfentanil and midazolam and continuous infusion of propofol is done often with local anesthesia in the skin area of introduction of the needle.

Different types of generators and needle can be used and also imaging guidance can be employed differently.

Bipolar technique was first reported in 2003 in explanted and in vivo livers. It uses one electrode thermally shielded by the opposing second electrode, which also actively heats nearby tissue. Thus, the heat is trapped between the two electrodes, obviating diversion of the current from the ablation site in any direction.²⁰

3.4.2. Effectiveness

Callstrom and colleagues,⁹ have demonstrated the safety and efficacy of RF for reducing pain in 12 patients, improving the quality of life and reducing the use of analgesics in patients with metastases that involved the bone. Their benefit was obtained in a week.

In a recent multicenter study of Goetz¹⁰ found that 43 patients, reported an increase in the dose of opioids on the first day after treatment and a subsequent decrease of over 50%.

In the latter study, there were more complications in three patients: the first had second degree burn in the skin of the earthing, another had intestinal and bladder incontinence and finally in a patient an acetabular fracture occurred in the area treated at 6 weeks of treatment with RFA.

Kojima⁸ and Carrafiello,³ analyzing in total 26 patients with 31 lesions, have obtained technical success in 100% of cases, reduction of pain respectively in 96 and 100% of cases and a reduction of opioids in 87 and 100% of cases.

In order to increase the accuracy of ablation in case of bone lesions in the vicinity of organs like the spinal cord, Buy and colleagues²⁰ have studied the effectiveness of saline infused bipolar radiofrequency ablation in paraspinal neoplasms.

Normal saline (0.9%) infusion has been shown to be effective in enlarging the area of necrosis during radiofrequency ablation, acting as

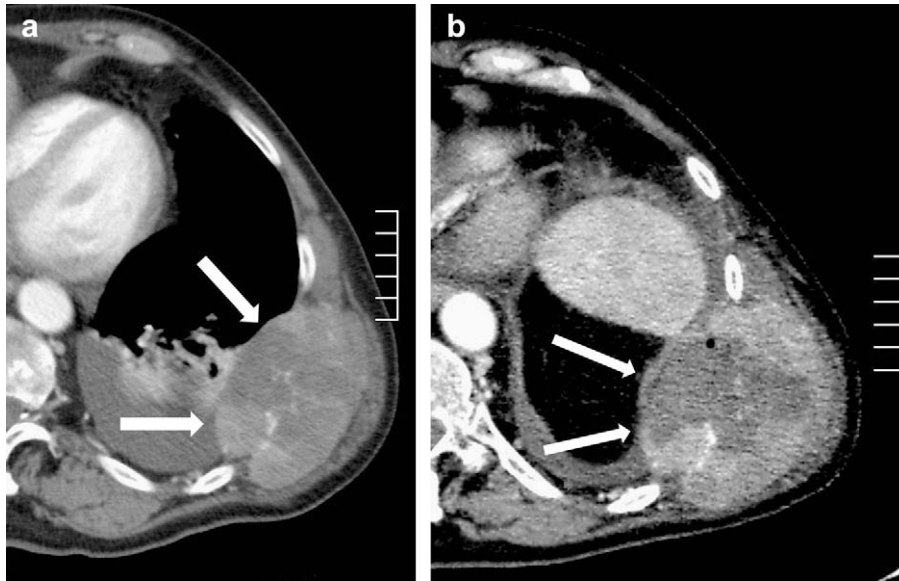


Fig. 2. (a) Transverse CT contrast enhanced image shows a metastatic lesion involving the left rib (arrows). (b) Transverse CT contrast enhanced image obtained at the same level after ablation shows a large low of attenuating area consistent with necrosis (arrows).

a liquid electrode with conductivity three to five times greater than that of blood and 12–15 times greater than that of soft tissue.²⁰

In this connection, literature showed 80–95% of patients undergoing radiofrequency ablation of bone metastases experienced a clinically significant decrease in pain.⁹

In this connection, literature showed 80–95% of patients undergoing radiofrequency ablation of bone metastases experienced a clinically significant decrease in pain, with the complication rate ranging from 0 to 6.9%⁹ (Figs. 2a,b).

3.5. Plasma mediated radiofrequency ablation

3.5.1. Techniques

The term coblation means “controlled ablation” and represents a new generation technique for the ablation of bone lesions. It consists of electricity liable to create a field of ionized particles that break the bonds within organic soft tissue (ablation). The result is a dissolution of tissue and the formation of a cavity.

In the treatment of bone metastases, its use is justified by the ability of method to control precisely the territory and limits of ablation, importantly in lesions adjacent to the spinal cord or organs abdominal or pelvic cables.

The latter, using the coblation, are less vulnerable to damage from cellular and necrosis thermoablation.

Identifying characteristic is the ability to assign, in a very precise way, a minimum amount of heat (unlike conventional electrocauterization), which is important for example in the treatment of spinal lesions. The low energy radiofrequency (100 KHz) is then used to excite electrolytes in half conductive (plasma), as a saline aqueous intracellular or the environment, to form highly ionized particles in the area immediately adjacent to the tip of the device (Fig. 3).

The particles energized have a charge sufficient to break the molecular bonds at a relatively low temperature (from 40 to 70 °C). This process of molecular dissociation converts the tissue ablated in gas and in this way is to create a cavity in the area of treatment. The radiofrequency waves at a frequency exceeding 10 MHz molecular high energy cause friction and therefore heat, which ultimately cause necrosis damaging cells.

Ultimately the coblation uses radio frequency to ionize the tissue and determine extensive cavitation obtaining a consequent mass reduction on surrounding tissue with special signs for injuries

that result in compression on the nerve and vascular structures, the production of that cavitation possibly allow easier injection of bone cement for a subsequent consolidation.

For the coblation procedure is used a kit Cavity SpineWand (ArthroCare Corp.™).

3.5.2. Effectiveness

Benefits are: increased accuracy and control of the proceedings; reduction of operating time; recovery faster and less painful; promoting healing tissue.²⁹

The radiofrequency plasma mediated also solves the problem of injuries osteoblastics, as is indicated in these injuries since “making powder” creating the tissue, clearly demarcated, a real cavity.

Georgy and colleagues²⁹ and Gerszten and colleagues³⁰ have treated a total of 18 vertebral lesions in 18 patients and have obtained respectively 87 and 100% in terms of a reduction of pain. Georgy in 26% of cases (four/15 patients) had complications, leakage of cement, without clinical consequences.

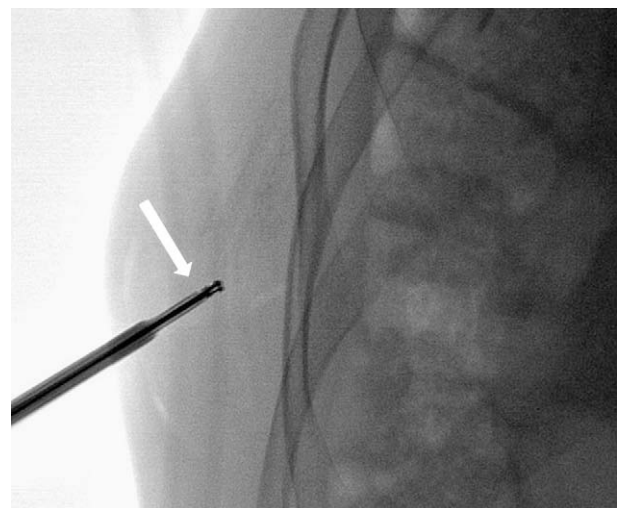


Fig. 3. X-ray radiograph shows a plasma-mediated radiofrequency device (arrow) inserted in a metastatic lesion involving the right rib.

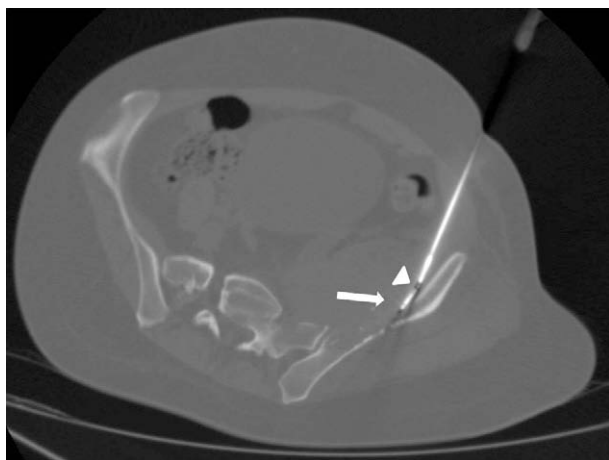


Fig. 4. Transverse CT contrast enhanced image shows the antenna (arrow) located into the lesion of the left iliac bone. Head arrow indicates the point where microwave energy is delivered.

3.6. Microwave ablation

3.6.1. Technique

Microwave is a new technique using a frequency range from 900 to 2450 MHz and in the frequency spectrum, then fits between radio waves and infrared. The water molecules are polar and electric charges on molecules are not symmetrical: hydrogen positive, oxygen negative.

The electromagnetic radiation has an electric charge and interaction with the molecules of water produces a series of oscillations of the molecules themselves depending on the provision of an office. For a wave that has a frequency of 9.2×10^8 Hz, the positions sign change 2 billion times per second. The increase in temperature is a measure of how fast moving molecules in a substance upon a passage of radiation¹³ (Fig. 4).

For the procedure microwave generator (Valleylab™) is used and two antennas percutaneously (VT1237, Valleylab™ MWA).

3.6.2. Effectiveness

The benefits of treatment compared with RF ablation are: achieving high temperatures in the tumoral area (120–140 °C); a large volume of ablation for penetration of energy deeper; time ablation faster; no dispersion of heat in the vicinity vessel.¹⁴

The methods of thermoablation with radiofrequency and microwave have the disadvantage that it can not be used in osteoblastic metastases.

They can also cause thermal injury to adjacent organs.

To avoid this complication, there are several options:

create an interface or air (in microwave) or with water (in RFA) to limit the territory of ablation.

It is possible also to place thermocouples behind the structures at risk of thermal damage, which measured the temperature during the procedure, the operator is useful in deciding whether or not to interrupt the ablation:

use bipolar radiofrequency;²⁰
use plasma mediated radiofrequency.^{29,30}

Dupuy and colleagues have produced the first experimental studies and clinical about thermoablation with microwave in bone metastases,^{13–15} quoting an excellent technical result both in terms of volume of necrosis, and process speed, and no complications.

3.7. Combined therapies

All ablative techniques may be followed by cementoplasty provided that it integrates the cortical bone.

The aim of this method lies in micro fractures stabilization and reductions of mechanical forces, especially in larger lesions destructive, lose their physiological structure.

A system is used to inject cement. The choice on the quantity of cement to be used is made considering the measures of metastatic lesion.

Toyota and colleagues³¹ stress as the procedure is easy running, low cost, low invasive, even if they are still unknown the effects of this combination of therapy with radiotherapy.

Twelve percent of cases had complications (hematoma) (two/17 patients).

Schaefer and colleagues³² remember that the coagulation necrosis induced by RFA facilitates the uniform distribution of cement within the lesion whether the methodical cementoplasty is indispensable to obtain a decrease in bone pain and stabilization.

The results obtained in the radio frequency combined with cementoplasty were excellent, in both case reports^{32–34} that in series^{9,31,35,36} where the pain reduction occurred in 100% of cases similar to As personal experience has shown, however, numerically small.

It should be noted that, while in studies carried out only with radio or only cementoplasty has obtained a technical success of 100% compared with a result in terms of pain reduction between 80 and 100%, from other techniques combined radio and cementoplasty assured the reduction of pain in all cases handled, but a technical success as a percentage slightly lower.

4. Pain relief

Regarding the ablation of bone metastases, the true goal is not so much the complete ablation of metastases, but the reduction of pain. Pain relief depends, directly, from needle positioning.¹

Whatever the technique of ablation is used, the mechanism of pain reduction is not yet clear, but some cases goes to the following directions:

- destruction of sensory fibers of periosteum and cortical;
- decompression mechanical volume tumor;
- destruction of tumor cells that produce cytokines such as TNF α (tumor necrosis factor alpha) and interleukins that promote the transmission of pain;
- inhibition of osteoclast.^{37,38}

It is also possible that these results are obtained for synergistic effect with conventional palliative therapies which patients were previously screened.

In any case, many authors^{1,3,8–10,20} highlight the fact that the ablative therapies and, above all, the combination therapies^{31–36} with cementoplasty bring a decrease in pain in 4 weeks after treatment and a half dose opioids after a month.

5. Conclusions

Currently there are not yet common opinions on what is the best method for treating bone metastases. Surely the choice of a methodical of ablation compared to another depends on the type, size and location of the lesion. All procedures aforementioned can be performed in out setting patient too.

It seems clear that what justifies the use of these therapies is the fact that where there is an indication, they guarantee a reduction of pain significantly faster than conventional

therapies, making, in a short time, a significant improvement in the quality of life.

Conflict of interest

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Ethical approval

None declared.

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