Original Article

Effect of palliative microwave ablation on metastatic osseous pain: a single-center retrospective study

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Background: Bone is among the most common metastasis sites in patients with advanced cancer. Approximately two-thirds of bone metastasis results in pain, the majority of which is moderate to unbearable pain, which seriously affects the quality of life of patients. With the development of ablation techniques, microwave ablation (MWA) has great potential to eliminate the pain caused by bone metastasis. This study aimed to evaluate the efficacy and safety of image-guided (computed tomography-guided) percutaneous MWA for metastatic osseous pain.

Methods: This is a retrospective study involving 18 patients with cancer-related pain caused by osseous or soft tissue metastasis in the First Affiliated Hospital of Soochow University from June 2015 to October 2020. All patients (14 men and 4 women; mean age 60.2 years) underwent image-guided percutaneous palliative MWA. A paired-sample t-test was used to compare the changes in Numeric Rating Scale (NRS) score and dosage of morphine preoperatively and postoperatively (at 24 h, 3 days, and 14 days after MWA). In addition, we assessed the level of pain relief according to the patients' subjective feelings.

Results: The paired-samples *t*-test showed that the NRS score (6.83±0.92 *vs.* 1.67±0.97, P<0.05) and dosage of morphine (85.56±17.23 *vs.* 32.78±4.61, P<0.05) were significantly decreased at 3 days after MWA. At 14 days after MWA, the NRS score (6.83±0.92 *vs.* 0.94±0.87, P<0.05) and dosage of morphine (85.56±17.23 *vs.* 10.56±8.73, P<0.05) were also markedly decreased. Moreover, according to the patients' subjective feeling, 88.89% patients had pain relief postoperatively, while the remaining patients had no progress.

Conclusions: Image-guided (Computed Tomography-guided) percutaneous MWA can effectively relieve pain, thus improving the quality of life in patients with osseous metastasis. MWA is a feasible, safe, and effective treatment for pain caused by bone metastasis.

Keywords: Bone metastasis; palliative microwave ablation; interventional cancer pain management; osseous pain

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Introduction

Bone is one of the most common metastatic sites in advanced malignant tumors, with approximately 40% of advanced cancer patients developing bone metastasis (1). Eighty percent of patients with bone metastases experience pain, and of these, 50% is severe pain and 30% is refractory pain (2). The short-term relief or eradication of pain caused by osseous metastasis can improve the quality of life of patients.

Tumor patients with bone metastasis primarily receive palliative treatment, with pain management including radiotherapy, chemotherapy, surgical palliative surgery, and the use of analgesics according to the World Health Organization (WHO) cancer pain treatment ladder. However, it has been reported that this ladder fails to provide sufficient relief in 10–20% of patients (3). Palliative surgery causes large trauma and bleeding, which is harmful to advanced patients. The maximum effect of local radiotherapy to control bone pain is limited by irradiated tissue, dose limits, delayed onset of pain relief, insufficient duration of symptom relief, and radio-resistant tumor subtypes (4,5).

The development of thermal ablation, such as radiofrequency ablation, hypothermia ablation and microwave ablation (MWA) provide a new treatment option for patients with bone metastasis. The tumor thermal ablation procedures are usually guided by imaging, and the application of thermal ablation can be percutaneous, during open surgery, or during laparoscopic surgery, which has the following energy forms: radiofrequency current, microwaves, lasers, focused ultrasound, and cryoablation. Compared to other modalities, MWA has the following advantages: wider heating area, shorter heating time, larger heating tissue volume (6-8). By ablation radiation and the movement of water molecules, MVA heat tissue, making it undergo coagulative necrosis to kill lesions (9). However, the clinical data on MWA for tumors remain scarce. This article provides clinical data on pain relief and local tumor control after bone metastases from different primary tumors, and analyzes and evaluates the efficacy and safety of MWA, and the data are true and reliable. In this study, 18 patients with bone metastasis were selected to retrospectively analyze the efficacy and safety of MWA in controlling pain in patients with bone metastasis. We present the following article in accordance with the STROBE reporting checklist (available at https://dx.doi.org/10.21037/apm-21-2164).

Methods

Ethical approval and consent

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. All participants provided an informed consent agreement.

Participants

Eighteen patients (14 males and four females; mean age 60.2 years, range: 36–77 years) with osseous metastases from the First Affiliated Hospital of Soochow University between June 2015 and October 2020 received image-guided percutaneous MWA. As shown in *Figure 1*, we screened the subjects rigorously. The inclusion criteria were as follows: (I) patients with bone metastasis confirmed by computed tomography (CT), positron emission tomography - computed tomography (PET-CT), magnetic resonance imaging (MRI), bone scan, or bone biopsy; and (II) patients with a NRS score >4 prior to MWA. The exclusion criteria were as follows: (I) patients with spinal cord paralysis; (II) patients with partial or systemic infection; (III) cases where the image could determine the position of bone rotation and adjacent important nerve and vascular bundles; and (IV) patients with serious cardiopulmonary disease.

The numbers of patients with primary cancer were as follows: lung cancer, seven; renal cancer, two; colon cancer, two; breast cancer, one; esophageal cancer, one; cholangiocarcinoma, one; bladder cancer, one; thoracic adenocarcinoma, one; soft tissue sarcoma, one; and primary unknown, one. In total, there were 16 single bone metastases and two multiple bone metastases. Additionally, the numbers of surgical sites were as follows: rib, 13; iliac bone, three; paraspinal, one; and fibula, one.

Study design and variables

A single-center retrospective study was conducted. Changes in the NRS pain score and dosage of morphine (before *vs.* after MWA) were set as the main outcome variables. The NRS pain score and dosage of morphine of all patients was assessed before and after MWA (at 24 h, 3 days, 14 days postoperatively). In addition, the degree of pain relief on the 14th day postoperatively was divided into complete remission, partial remission, stability, and

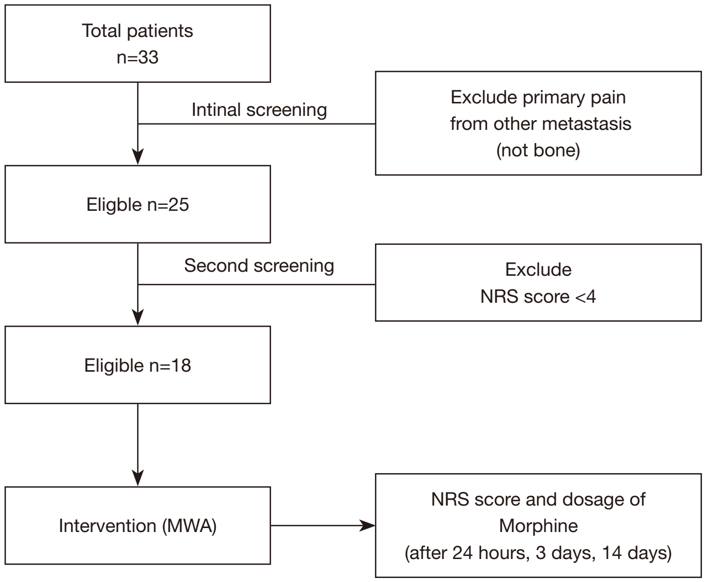

Figure 1 Flow chat of study subject screening and intervention. MWA, microwave ablation.

disease progression, according to the patients' subjective perception. We use self-control experiments to control bias, in other words, we compared the data of patients before and after MWA. And all data on patients enrolled have no missing.

Statistical analysis

Statistical analysis was performed using GraphPad Prism 8.0 software (GraphPad Software Inc., San Diego, CA, USA). Normally-distributed numerical data were expressed as the mean ± standard deviation. The NRS score and dosage of morphine at 24 hours, 3 days, and 14 days postoperatively were respectively evaluated by two-tailed paired t-tests. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characteristics of the enrolled patients

As shown in *Table 1*, a total of 18 patients with metastatic osseous pain were analyzed (14 males and 4 females; mean age 60.2 years, range, 36–77 years). The numbers of patients with primary cancer were as follows: lung cancer, seven; renal cancer, two; colon cancer, two; breast cancer, one; esophageal cancer, one; cholangiocarcinoma, one; bladder cancer, one; thoracic adenocarcinoma, one; soft tissue sarcoma, one; and primary unknown, one. In total, there were 16 single bone metastases and two multiple bone metastases. Additionally, the numbers of surgical sites were as follows: rib, 13; iliac bone, three; paraspinal, one; and fibula, one.

NRS score and dosage of morphine before and after MWA

All patients successfully underwent palliative MWA. As shown in *Table 2*, the NRS of patients enrolled before MWA is 6.83±0.92, the morphine dosage per day 85.56±17.23 mg, the NRS and morphine dosage per day at 24 hours after MWA is 7.00±1.14 and 88.33±22.03 mg, the NRS and morphine dosage per day at 3 days after MWA is 1.67±0.97 and 32.78±4.61 mg, the NRS and morphine dosage per day at 14 days after MWA is 0.94±0.87 and 10.56±8.73 mg. As shown in *Figures 2,3*, compared to the preoperative values, the NRS scores were lower at 3 and 14 days after MWA ($P<0.05$) and the dosage of morphine was also decreased ($P<0.05$), especially at 14 days after MWA.

The level of pain relief at 14 days postoperatively

As shown in *Figure 4*, 14 days after MWA, 5 patients had complete relief, 11 patients were partially relieved, and the remaining patients did not progress. Overall, 88.89% patients enrolled had different degrees of pain relief.

Complications

All patients experienced a few postoperative complications associated with MWA, such as skin burns, nausea and vomiting, and infection. However, one patient developed fever symptoms for 24 hours after MWA, and eight patients suffered from pain at the surgical site.

Discussion

Bone is one of the most common metastatic site of advanced tumors, especially in prostate and breast cancers, in which an autopsy is conducted for 70% of patients. Bone metastasis also occurs in 30–40% of bronchial, thyroid, and renal cancer patients (discovered at autopsy) (10), and is often prevalent in the axial skeleton, especially the rib. Furthermore, approximately two-thirds of bone metastases result in pain, with majority of these cases being moderate to severe pain. This significantly reduces the quality of life of patients and affects their sleep, mood, and general daily life (11), which may lead to reduced compliance.

Notably, tumor cells themselves do not destroy bone tissue, they do by expressing an inflammation molecule, such as nuclear factor kappa-B (NF-κB), which binds to its receptor activator of nuclear factor-κB/receptor activator of nuclear factor-κB ligan (RANK/RANKL), thereby activating the downstream pathway (12). Pain caused by bone metastases involves nociceptive pain and neuropathic pain. Nociceptive pain is primarily an inflammatory process and constant remodeling activity at the bony site. Inflammatory factors, such as cytokines, histamines, serotonin, prostaglandins, and endothelins, combine with primary neurons to transmit the pain signal to the brain center. These continuous inflammatory factors could further activate the pain signal, thereby reducing the pain threshold (known as peripheral sensitization), which will lead to an increased pathological pain response (12). In addition, with the growth of osseous metastasis, additional pain may occur due to the compression of the nerve root and spinal cord (13). Moreover, tumor cells could stimulate the activation and appreciation of osteocytes, which produce acidic microenvironments at the absorption socket. This in turn facilitates the opening of ion channels, such as the transient potential receptor vanilloid receptor 1 (TRPV1) and acid-sensitive channels (ASICI), resulting in the passage of pain signals to the brain center (14). Also, tumor cells reshape the bone sensory nerve and the sympathetic nerve under the action of the nerve growth factor, thus increasing the bone nerve fiber density and sensitizing the neurons (15).

Table 1 Clinical characteristics of the enrolled patients

Patient characteristics	Data
Total number	18
Mean age (year)	60.2 [36–77]
Gender	
Male	14 (78%)
Female	4 (22%)
Primary cancer	
Lung cancer	7 (39%)
Renal cancer	2 (11%)
Colon cancer	2 (11%)
Breast cancer	1 (6%)
Esophageal cancer	1 (6%)
Cholangiocarcinoma	1 (6%)
Bladder cancer	1 (6%)
Thoracic adenocarcinoma	1 (6%)
Soft tissue sarcoma	1 (6%)
Primary unknown	1 (6%)
Bone metastases	
Single	16 (89%)
Multiple	2 (11%)
Surgical site	
Rib	13 (72%)
Iliac bone	3 (17%)
Paraspinal	1 (6%)
Fibula	1 (6%)
Ablation parameter	
Average ablation power (W)	46.90 [40–60]
Average ablation time (minute)	6.79 [1–15]

Recently, the treatment of metastatic bone-related pain mainly involved the following: (I) analgesics (including non-opioid and opioid analgesics); (II) radiotherapy (especially single-dose, low-fractionated); (III) interventional methods (such as posterolateral fusion with autologous bone grafting and minimally invasive procedures); and (IV) bone-targeting therapies (including nerve growth factor inhibitors and osteoclast inhibitors) (16). With the development of

Table 2 NRS and dosage of morphine before and after microwave ablation (MWA)

	Prior to MWA	24 h postoperatively	3 days postoperatively	14 days postoperatively
NRS score	6.83±0.92	7.00±1.14	1.67±0.97	0.94±0.87
Dosage of morphine (mg/day)	85.56±17.23	88.33±22.03	32.78±4.61	10.56±8.73

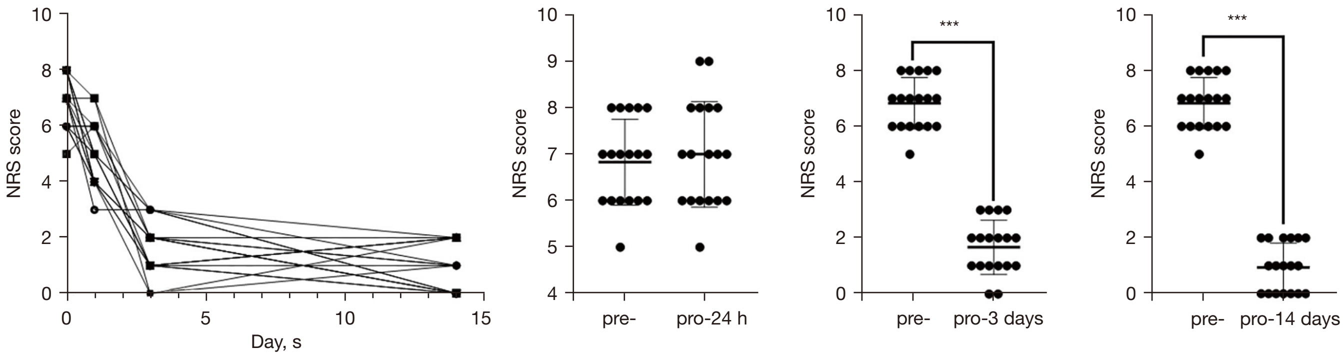

Figure 2 Changes in NRS from baseline to 14 days before and after MWA. pre-: before MWA; pro-3 days: 3 days after MWA; pro-14 days: 14 days after MWA. The NRS score at 24 hours, 3 days, and 14 days postoperatively were respectively compared and evaluated to that preoperatively by two-tailed paired *t*-tests. Compared to the preoperative values, the NRS scores were lower at 3 and 14 days after MWA, ***, P<0.05 was considered to indicate a statistically significant difference.

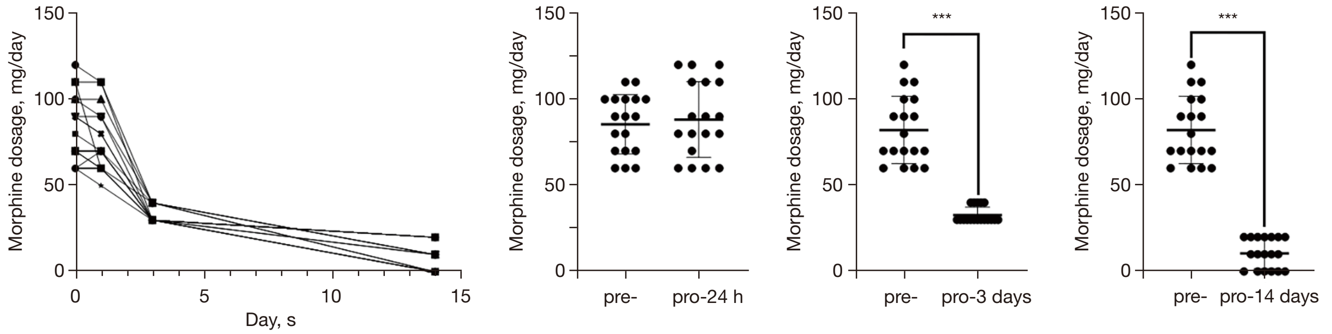

Figure 3 Changes in morphine dosage per day from baseline to 14 days before and after MWA. pre-: before MWA; pro-3 days: 3 days after MWA; pro-14 days: 14 days after MWA. The morphine dosage per day at 24 hours, 3 days, and 14 days postoperatively were respectively compared and evaluated to that preoperatively by two-tailed paired *t*-tests. Compared to the preoperative values, the morphine dosage was lower at 3 and 14 days after MWA, ***, P<0.05 was considered to indicate a statistically significant difference.

thermal ablation, patients with advanced osseous metastasis can benefit from image-guided MWA. Compared to other antineoplastic therapies, MWA is simpler to operate, with shorter treatment time, higher safety and smaller side effects. However, MWA still faces challenge that how to control heating patterns to accurately kill lesions and protect surrounding normal tissue (17). To date, MWA has been widely used in the treatment of solid tumors, such as hepatocellular carcinomas and other solid tumors in the lung, breast, thyroid, kidney, adrenal gland, abdominal wall, and uterus (18-21).

The main principle of MWA is dipole rotation theory: when the electric field is applied, the water molecules rotate and constantly arrange and oscillate, generating heat. During MWA, the microwave electromagnetic field causes water molecules to stir in the tissue, creating friction and heat, as well as cell death through coagulative necrosis. Also, because the tumor tissue is rich in water, is relatively

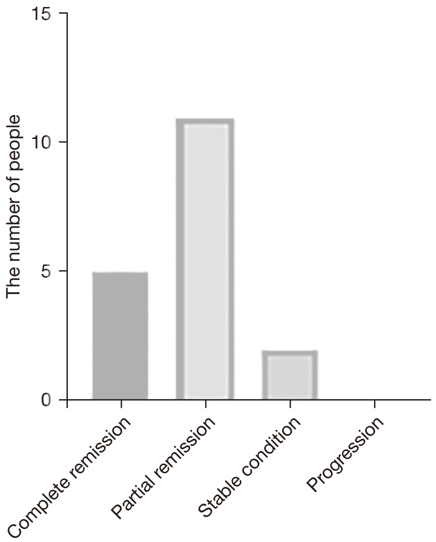

Figure 4 The level of pain relief at 14 days postoperatively. 14 days after MWA, 5 patients had complete relief, 11 patients were partially relieved, and the remaining patients did not progress.

anaerobic, and has a low pH value, it is more sensitive to heat than normal tissue. Utilizing these characteristics, MWA transforms microwave into heat energy in tumor tissue by ablation needle under the guidance of imaging technology, resulting in complete coagulative necrosis of the tumor tissue due to the high temperature produced locally in a short time, thus killing the tumor and causing minimal damage to the normal surrounding tissue (22). As MWA shrinks or eliminates bone metastases, the tumor cell-induced inflammatory factors, cytokines, and neurotransmitters decrease or disappear, thereby reducing the conduction of pain signals. Moreover, the pressure of bone metastases on the peripheral nerves and the spinal cord is also reduced. MWA offers the following advantages: reproducibility, low complication rates, and availability. Additionally, the time of MWA treatment is shorter, the target to be treated can be larger, and the propagating of MWA is less influenced by neighboring tissues (17). A clinical study found that MVA can effectively reduce pain caused by rib metastases (23). While a few articles were reported that MWA is applied in treating osseous pain.

In our study, 18 patients undergoing MWA were retrospectively analyzed. The results showed that image-guided MWA could effectively and safely relieve pain caused by osseous metastasis in a short time, and the efficacy of pain relief can maintain a longer time. All patients had various degrees of pain relief. Overall, MWA is a safe, effective, and feasible therapeutic option that is worthy of promotion for the treatment of metastatic osseous pain. However, more investigations with larger samples are needed to further assess the safety and efficacy of MWA.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-2164

Data Sharing Statement: Available at https://dx.doi.org/10.21037/apm-21-2164

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-2164). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University. All participants provided an informed consent agreement.

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