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REVIEW ARTICLE

A novel hyperthermia treatment for bone metastases using magnetic materials

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Abstract Patients with bone metastases in the extremities sometimes require surgical intervention to prevent deterioration of quality of life due to a pathological fracture. The use of localized radiotherapy combined with surgical reinforcement has been a gold standard for the treatment of bone metastases. However, radiotherapy sometimes induces soft tissue damage, including muscle induration and joint contracture. Moreover, cancer cells are not always radiosensitive. Hyperthermia has been studied since the 1940s using an experimental animal model to treat various types of advanced cancer, and studies have now reached the stage of clinical application, especially in conjunction with radiotherapy or chemotherapy. Nevertheless, bone metastases have several special properties which discourage oncologists from developing hyperthermic therapeutic strategies. First, the bone is located deep in the body, and has low thermal conductivity due to the thickness of cortical bone and the highly vascularized medulla. To address these issues, we developed new hyperthermic strategies which generate heat using magnetic materials under an alternating electromagnetic field, and started clinical application of this treatment modality. The purpose of this review is to summarize the latest studies on hyperthermic treatment in the field of musculoskeletal tumors, and to introduce the treatment strategy employing our novel hyperthermia approach.

Keywords Hyperthermia · Bone metastasis · Pathological fracture · Magnetic material · Electromagnetic field

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Introduction

Bone is the most common site of cancer metastasis, and is particularly important in breast and prostate cancers because these diseases have a high prevalence of bone metastases. At postmortem examination, ~70% of patients dying of these cancers have evidence of metastatic bone disease. Cancers of the thyroid, kidneys, and lungs also commonly give rise to bone metastases with an incidence of 30–40% at postmortem examination [1].

Patients with bone metastases in the extremities sometimes require surgical intervention to prevent deterioration of quality of life due to pathological fractures, which commonly occur as a result of lytic lesions in weight-bearing bones. Destruction of both cortical and trabecular bone is structurally important. Fractures are highly unlikely to occur (2.3%) when less than 50% of the cortex is destroyed, and are most likely to occur (80%) when over 75% of the cortex is destroyed [2].

Radiotherapy is generally a safe and effective treatment modality, and is well established for patients with bone metastases. However, radiotherapy without surgical reinforcement cannot prevent pathological fractures in patients presenting with impending fractures of long tubular bones. The addition of internal fixation before localized radiotherapy can reduce the risk of further bone destruction,

which leads to increased pain, loss of fixation, and the need for additional orthopedic procedures [3, 4]. Radiotherapy also sometimes induces soft tissue damage, including muscle induration and joint contracture [4]. Moreover, cancer cells are not always radiosensitive. Better methods are therefore needed to treat patients with bone metastases. We have developed a novel hyperthermic strategy which generates heat using magnetic materials under an alternating electromagnetic field to treat bone metastases, and have started clinical applications of this treatment modality.

The purpose of this review is to summarize the use of hyperthermic treatment in the field of musculoskeletal tumors, and to introduce our new treatment strategy using hyperthermia.

The history of therapeutic hyperthermia and the mechanisms of cancer cell death

Although there have been many references to the use of heat to treat human cancer, dating back to the writings of Hippocrates, the scientific approach to hyperthermia has been studied since the 1940s [5]. Hyperthermia can be applied by several methods: local hyperthermia by external or internal energy sources, regional hyperthermia by perfusion of organs or limbs, or by irrigation of body cavities, and whole body hyperthermia [5].

There is a clear rationale for using hyperthermia in cancer treatment. Recent progress in cell biology has revealed that hyperthermia, variously reported between 40 and 45°C, triggers tumor cell death by apoptosis, although the exact temperature differs depending on the individual conditions [6, 7]. Treatment at temperatures between 40 and 45°C is cytotoxic for cells in an environment with a low pO_2 and low pH conditions, which are usually found within tumor tissue due to the insufficient blood supply [5]. It is now well-known that hyperthermia-induced apoptosis is characterized by the occurrence of intra-nucleosomal DNA cleavage [8]. Furthermore, recent experiments revealed that hyperthermia can increase tumor immunogenicity by stimulating antigen-presenting cells through heat shock proteins secreted from lysed tumor cells [5].

The clinical value of hyperthermia, in addition to other treatment modalities, has been shown in randomized trials. For example, significant improvements in clinical outcome have been demonstrated for tumors of the head and neck, breast, brain, bladder, cervix, rectum, lung, esophagus, prostate, vulva and vagina, and also for melanoma, especially in conjunction with radiotherapy or chemotherapy [5, 9, 10]. In the field of bone metastases, Fan et al. [11] reported that 57 of 62 patients treated with intra-operative microwave-induced hyperthermic treatment had shown excellent local control. Sakurai et al. [12] reported that hyperthermic treatment combined with external radiation therapy improved local control in thirteen patients with primary non-small cell lung cancer directly invading to bone.

However, the bone has several special properties which discourage oncologists from developing hyperthermic therapeutic strategies for bone metastasis. Heating of the tumor is usually achieved by means of external sources such as microwaves, ultrasound or a water bath [5]. However, even if these external sources are applied for bone metastases, it is difficult to achieve enough heat conduction to the tumor because the bone is located deep in the body and has low thermal conductivity, with a highly vascularized medulla. However, hyperthermia for bone tumors can be achieved using the polymerization heat of polymethylmethacrylate bone cement as a hyperthermic treatment [13, 14]; however, the generated heat tends to be unreliable and insufficient to reduce bone tumor growth [15]. Microwave-induced hyperthermia [11], laser-induced thermotherapy [16], and radiofrequency ablation [17] have been recently used, especially for spinal and pelvic metastasis. However, these therapeutic modalities are unsatisfactory for lesions located in the long tubular bones of the limbs, because pathological fractures cannot be prevented without surgical reinforcement of the bone lesion.

We therefore developed a new hyperthermic therapeutic strategy that uses magnetic materials for metastatic bone tumors based on experimental studies [15, 18–20], and have also started clinical investigations [21].

Novel hyperthermia induced using magnetic materials

The unique feature of magnetic materials is their reaction to a magnetic field. Physical energy conversion occurs in an alternating magnetic field, and hysteresis loss is a very important feature of magnetic materials, because it enables effective hyperthermia.

The concept of hyperthermic cancer therapy that utilizes magnetic materials and an alternating magnetic field has been proposed by many researchers [22–24]. Yan et al. showed that treatment using Fe_2O_3 nanoparticles combined with magnetic field hyperthermia could inhibit not only the proliferation of cultured liver cancer cells, but also induce apoptosis of cultured liver cancer cells. Moreover, they showed that this hyperthermic strategy has a significant inhibitory effect on the weight and volume of xenograft liver cancer [25]. Similarly, Hilger et al. [26] showed the feasibility of thermal ablation of breast cancer with magnetic nanoparticles using an animal model. Johannsen et al. [27] published the first report of the clinical application of hyperthermia for human cancer using magnetic

nanoparticles. They injected magnetic nanoparticle suspensions into the prostate under ultrasound and fluoroscopy guidance, and showed that hyperthermia using magnetic nanoparticles was feasible and well tolerated for a patient with previously irradiated and locally recurrent prostate carcinoma.

Localized hyperthermic treatment for musculoskeletal tumors with ferromagnetic ceramics was first reported by Kokubo [28] using an animal model. He made a bioactive and ferromagnetic glass ceramic by heat treatment of a Fe_2O_3–$CaO.SiO_2$–B_2O_3–P_2O_5 glass, and showed that this glass ceramic was useful as a thermoseed for hyperthermic treatment of cancer [28–31].

We modified these new hyperthermic strategies for use in treating bone metastases. First, we developed an alternating electromagnetic field generator (Yamamoto Vinita Co., Ltd., Osaka, Japan) [15, 18, 20]. The output power of the electromagnetic field was 7 kW, at a fixed frequency of 1.5 MHz. Exposure of the affected limb to the electromagnetic field can be achieved by inserting the limbs into a cylindrical coil of the generator (Fig. 1).

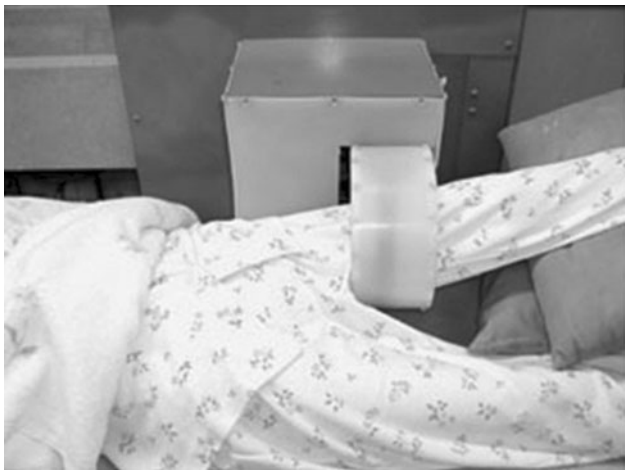

Fig. 1 Hyperthermia was postoperatively applied by inserting the affected limb into a cylindrical coil of the electromagnetic field generator

Next, we created a new bone cement made of glass ceramic that was partly replaced by magnetite (Fe_3O_4) powder [15, 18, 19], and examined the heat induction generated by hysteresis loss [18]. The composition of this material resembles the bioactive bone cement described by Kawanabe et al. [32], with a portion of the bioactive glass ceramic component replaced by magnetite. The temperature of this thermoseed rose in proportion to the weight ratio of magnetite powder, the volume of the thermoseed, and the intensity of the magnetic field. Furthermore, the heat induction in this thermoseed implanted into rabbit and human cadaver tibias was investigated by applying a magnetic field with a maximum of 300 Oe and 100 kHz. This system could easily produce heat in the thermoseed in bone beyond 50°C. When the temperature of the thermoseed in rabbit tibias was maintained at 50–60°C, the temperature at the bone surface rose to 43–45°C; but at a 10-mm distance from the thermoseed in the medullary canal, the temperature did not exceed 40°C (Fig. 2). These results demonstrate that ferromagnetic bone cement may be applicable for the hyperthermic treatment of bone tumors.

We next examined the antineoplastic effects of this treatment using an animal model. VX-2 tumors were transplanted into the tibia of rabbits. One week later, bone cement containing magnetite at a 60% weight ratio was implanted into the same site, followed by exposure to an alternating magnetic field for 50 min. We observed that the temperature of the tibia could rise to over 43°C, and that tumor growth was inhibited without any systemic adverse effects [20] (Fig. 3).

Since our first magnetite cement has not yet been approved by the Ministry of Health, Labour and Welfare of Japan, we decided to use a calcium phosphate cement

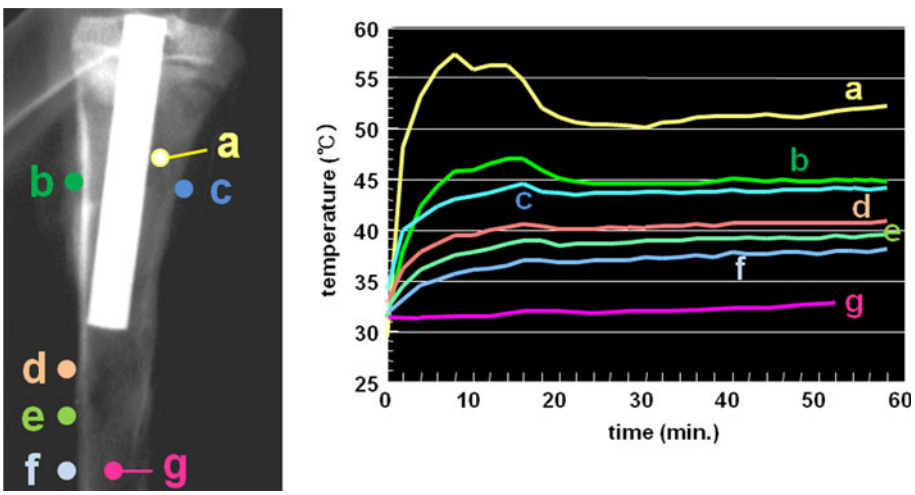

Fig. 2 Monitoring of the temperature at the various portions of a rabbit tibia. These data show the following: heat is easily generated on the surface of the magnetic material, the cortical bone has good heat conductivity, and the cancerous bone has poor heat conductivity

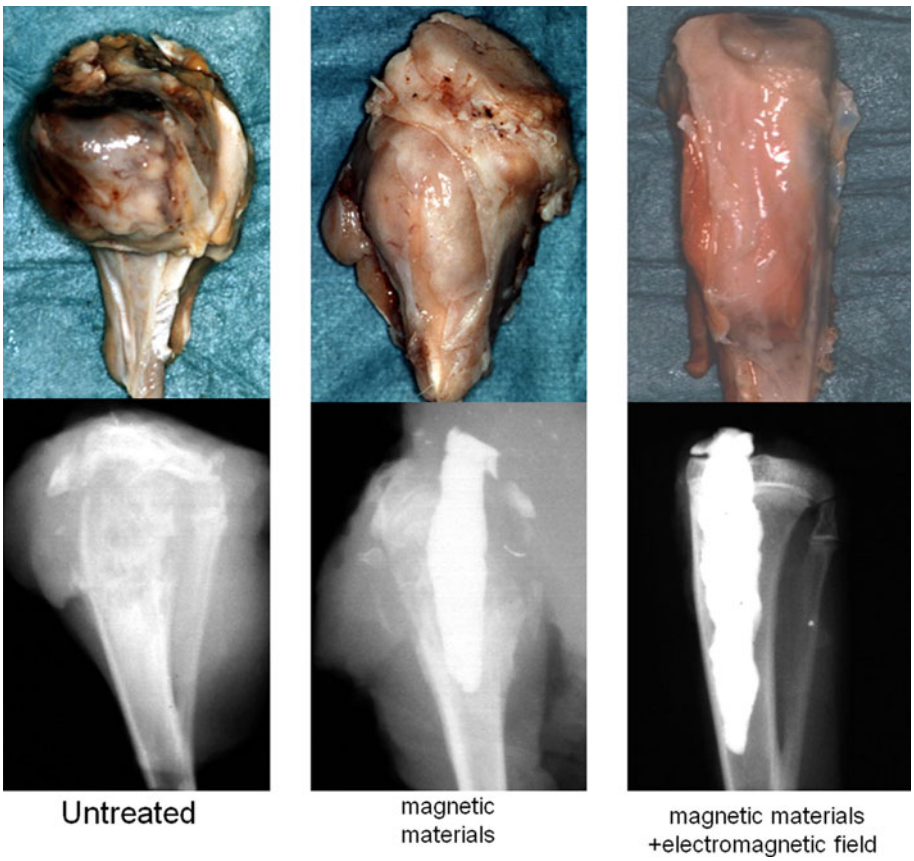

Fig. 3 The effects of hyperthermia with magnetic materials under an electromagnetic field. VX2 sarcoma cells were implanted into the tibias of rabbits. In radiographs, massive bone destruction was observed in rabbits treated with neither magnetic materials or the electromagnetic field. However, when the magnetic materials were implanted and the electromagnetic field was applied, the bone destruction was strikingly inhibited. This suggests that our new hyperthermic therapy has a prominent anti-tumor effect on metastatic bone tumors

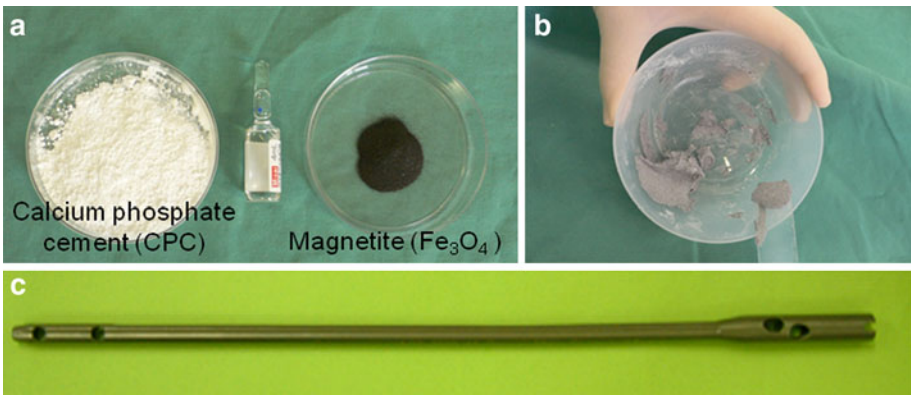

Fig. 4 The magnetic materials used for clinical appreciation of the novel therapeutic hyperthermia. **a**, **b** When the lesion was located at the metaphysis, curettage of the lesion was performed, followed by implantation of calcium phosphate cement containing magnetite into the cavity. **c** In contrast, when the lesion was located at the diaphysis, only reinforcement with an intramedullary nail was performed

containing powdered Fe_3O_4 (Fig. 4a, b) or an intramedullary nail made of a titanium alloy (Fig. 4c) as the magnetic material [21]. Because intramedullary nails made of titanium alloys have been frequently used to fix fractures all over the world, we had no legal constraints against using these nails for the patients with pathological fractures or impending fractures in Japan [33]. Calcium phosphate cement (CPC) is an injectable biocompatible bone substitute, and has been used to fill the bone defect following resection of bone tumors [34]. We have continually performed experimental studies, and found that our novel hyperthermia strategy promised good local control for bone metastasis without any adverse effects which could be detected by hematological examination and histological examination of the liver, kidneys, lungs and brain [35].

Clinical application of novel hyperthermia for bone metastases

We started clinical applications of this treatment modality from March 2003 after obtaining approval from our Institutional Ethics Investigational Review Board [21]. Our treatment strategy requires two types of treatment modalities:

an electromagnetic field generator (Fig. 1), and the magnetic materials (Fig. 4).

The surgical procedures can be categorized into two types. For the lesions located at the metaphysis, we first perform curettage of the lesion. Calcium phosphate cement containing magnetite is then implanted into the cavity. In contrast, for the lesions located at the diaphysis, only reinforcement with an intramedullary nail was performed. In both cases, hyperthermia was performed after the operation. Hyperthermic treatment was performed postoperatively on days 8, 10, 12, 15, 17, 19, 22, 24, 26 and 29. The exposure time was 15 min per day.

To date, this novel hyperthermic treatment has been performed for 23 patients with 25 metastatic bone lesions. The radiographic outcome was assessed according to the following criteria: "Excellent" indicating "reduced with visible bone formation," "Good" meaning "not progressive for more than 3 months," and "Poor" meaning "progressive". As a result, 8 lesions (32%) showed an "Excellent" outcome, while 16 lesions (64%) showed a "Good" outcome. One lesion (4%) showed a "Poor" outcome. When compared to the historical controls at our institute, the radiographic outcomes were statistically superior to those of the patients who received palliative surgery without either radiotherapy or hyperthermia, and similar to outcomes of the patients who received surgery in combination with postoperative radiotherapy. These results suggest that our novel hyperthermic therapy was as effective as surgery combined with radiotherapy (Figs. 5, 6).

With regard to complications, a sensation of heat during hyperthermia was noted by 3 patients, and tumor recurrence was observed in one patient. To our knowledge, this is the first clinical application of hyperthermia for metastatic bone tumors generated using magnetic materials and an alternating electromagnetic field.

Perspectives

Our hyperthermic strategy has several advantages for the treatment of metastatic tumors of long tubular bones compared to radiotherapy. First, our hyperthermic treatment is minimally invasive to the surrounding soft tissue, because the cooling effect of the intramuscular vascular flow minimizes soft tissue damage to the neurovascular sheath [20]. Second, our hyperthermic strategy can prevent pathological fractures because of the surgical reinforcement of the bone lesion. Moreover, this surgical reinforcement does not require any special techniques other than those routinely used by orthopedic surgeons. Finally, our hyperthermic treatment can be repeatedly applied for recurrent metastatic lesions, in contrast to radiotherapy, which cannot exceed the normal dose limitations.

This hyperthermic strategy may be applicable to other fields. Hyperthermia is already applied for the treatment of soft tissue sarcoma. The combination therapy using both cytotoxic drugs and regional hyperthermia in the treatment of soft tissue sarcoma is based upon experimental and

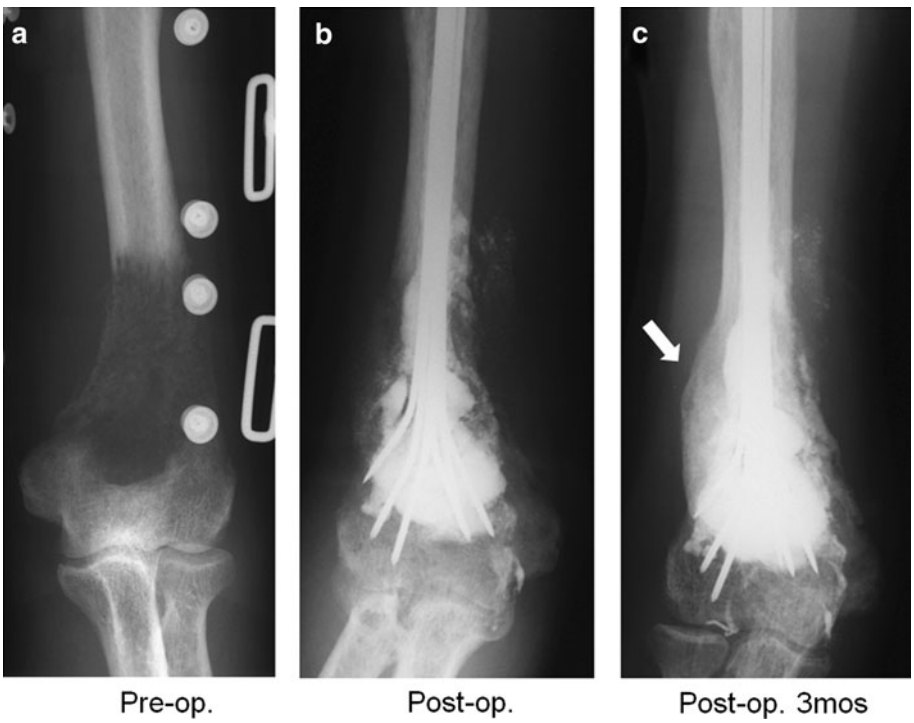

Fig. 5 A radiograph of a bladder cancer that had metastasized to the humerus (**a**). **b** After curettage of the lesion and reinforcement with wire, CPC containing magnetite was implanted into the cavity. **c** At 3 months after undergoing hyperthermia, massive new bone formation had become visible (*arrow*)

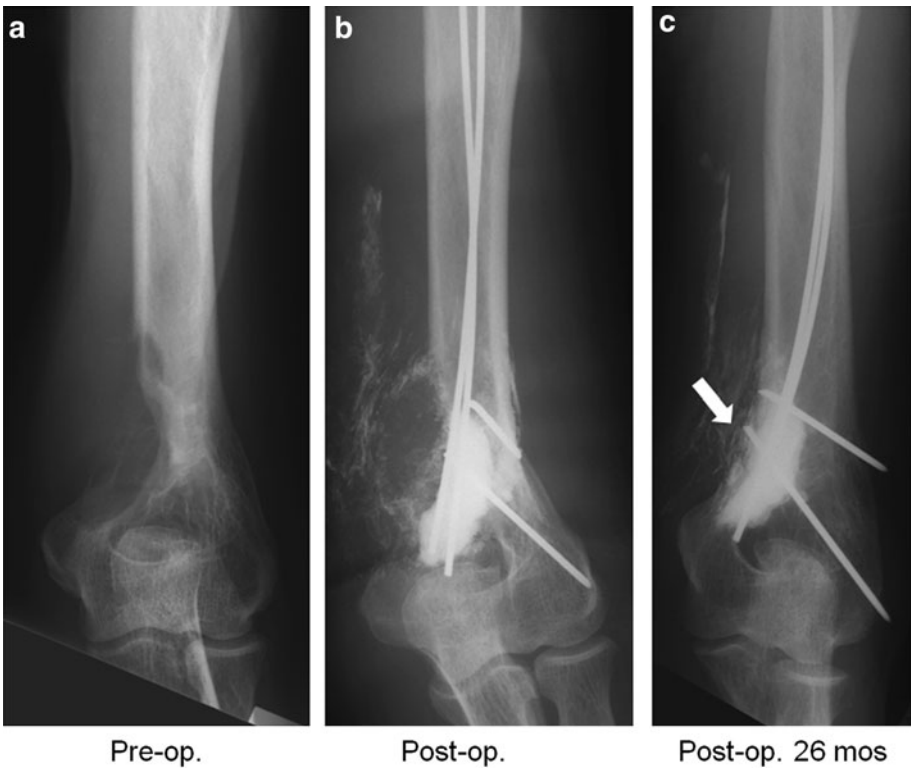

Fig. 6 A radiograph of a hepatocellular carcinoma that had metastasized to the humerus. After curettage of the lesion followed by reinforcement with wire, CPC containing magnetite was implanted into the cavity. At 26 months after undergoing hyperthermia, no recurrence was visible (*arrow*)

clinical evidence showing that heat induces tumor cell death by direct thermal toxicity and enhances the efficacy of some drugs, such as alkylating agents and platinum analogs [36, 37]. Recently micro- or nano-particles have attracted attention as a new heat source. Another new method for inducing interstitial hyperthermia is to inject a fluid containing magnetic nanoparticles intratumorally, and to apply alternating magnetic fields [23]. Kobayashi et al. [23] reported the use of magnetic cationic liposomes, where a group of cationic magnetic particles can be used as carriers to introduce magnetic nanoparticles into target cells, since their positively charged surface interacts with the negatively charged cell surface. Hyperthermia using cationic magnetic particles combined with chemotherapy or radiotherapy might also improve the therapeutic outcome of soft tissue sarcoma patients.

Despite the potential of therapeutic hyperthermia for bone metastases, there are some problems that still need to be solved. First, one of the most common sites of the metastatic bone tumors is the axial bones, including the pelvis and the spine. However, the size of the cylindrical coil of the current generator is too small to apply this hyperthermic therapy to these sites. To address this problem, we tried to make a magnetic field generator with a large coil. However, in our experiments, the increased size of the coil diminished the power of the magnetic field, and decreased the efficacy of heat induction. The design of a new and modified magnetic field generator is warranted. Second, thermal monitoring has recently evolved from the recording of the temperature at 1–8 fixed locations to real-time control based on high-density thermal profile mapping and/or non-invasive real-time characterization of temperature and distribution of physiological changes [38]. To assure its clinical effectiveness and to certify the safety of our hyperthermic treatment, effective real-time and non-invasive monitoring of the temperature is needed.

Conclusion

About two decades ago, the median survival of patients with bone metastasis from advanced lung cancer was typically measured in months, while the median survival of the patients with bone metastases from prostate cancer or breast cancer was measurable in years [39, 40]. However, recent development of new chemotherapies, including targeted therapies, has dramatically improved these patients' prognoses. Paradoxically, the improvement of prognosis of these cancer patients will lead to an increase in the number of patients with pathological fracture or impending fractures due to bone metastases, even if systemic therapy for bone metastases makes great progress. The results of our first series of clinical hyperthermia using magnetic materials achieved good local control of metastatic bone lesions. However, further investigations are

needed before this technique can be employed as a standard therapy for bone metastases.

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Conflict of interest No author has any conflict of interest.

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