

Novel hyperthermia for metastatic bone tumors with magnetic materials by generating an alternating electromagnetic field

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Received: 23 May 2006 / Accepted: 9 March 2007 / Published online: 9 May 2007
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Abstract We have developed a novel hyperthermic treatment modality using magnetic materials for metastatic bone tumors. The purpose of this study is to show the results of novel hyperthermia for metastatic bone tumors. This novel hyperthermic treatment modality was used for 15 patients with 16 metastatic bone lesions. In seven lesions, after curettage of the metastatic lesion followed by reinforcement with a metal intramedullary nail or plate, calcium phosphate cement (CPC) containing powdery Fe_3O_4 was implanted into the cavity. In one lesion, prosthetic reconstruction was then performed after an intralesional tumor excision. For the remaining eight lesions, metal intramedullary nails were inserted into the affected bone. Hyperthermic therapy was started at 1 week post-operatively. To comparatively evaluate the radiographic results of patients who underwent hyperthermia (HT group), we also assessed eight patients who received a palliative operation without either radiotherapy or hyperthermia (Op group), and 22 patients who received operation in combination with postoperative radiotherapy (Op + RT group). In HT group, all patients had an acceptable limb function with pain relief without any complications. On radiographs, 87, 38, and 91% were, respectively, considered to demonstrate an effective treatment outcome in HT group, Op group, and Op + RT group. The patients in HT group showed a statistically better radiographic outcome than the patients in Op group ($P = 0.0042$). But when compared between HT group and

Op + RT group, there were no significant difference ($P = 0.412$). This first series of clinical hyperthermia using magnetic materials achieved good local control of metastatic bone lesion.

Keywords Hyperthermia · Treatment · Metastatic bone tumor · Magnetic material · Electromagnetic field

Introduction

Patients with metastatic bone tumors in the extremities sometimes require surgical intervention to prevent reduction of quality of life due to a pathological fracture. The addition of localized radiotherapy after internal fixation reduces the risk of further bone destruction, which leads to increased pain, loss of fixation, and the need for additional orthopedic procedures [1, 2]. However, radiotherapy sometimes induces soft tissue damage, including muscle induration, joint contracture, and skin erosion [2]. Moreover cancer cells are not always radiosensitive.

Hyperthermia has been studied using an experimental animal model to treat various types of advanced cancer from 1940s [3]. Recent progress in cell biology has revealed hyperthermia, variously reported between 40 and 45°C, to trigger tumor cell death by apoptosis although the exact temperature differs in the individual condition [4, 5]. It is now well-known that hyperthermia-induced apoptosis is characterized by the occurrence of intranucleosomal DNA cleavage [6]. Hyperthermia have now reached a stage of clinical application to treat advance cancer, such as recurrent rectal cancer, prostate cancer, uterine cancer, head and neck cancer, lung cancer, and breast cancer, especially in conjunction with radiotherapy or chemotherapy [7–13].

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Heating the tumor in hyperthermic applications is usually achieved by means of external sources such as microwave, ultrasound or water bath [14]. However in using these external sources, peritumoral normal tissue may be injured. In contrast, magnetically induced heating of magnetic materials comprises a minimally invasive method providing an internal source. The concept of hyperthermic cancer therapy that utilizes magnetic materials and an alternating magnetic field, have been developed by many researchers [15–17]. Hilger et al. showed the feasibility of thermal ablation of breast cancer with magnetic nanoparticles using animal model [18]. Yan et al. showed the treatment using Fe_2O_3 nanoparticles combined with magnetic fluid 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 that this hyperthermic strategy has a significant inhibitory effect on the weight and volume of xenograft liver cancer [19]. Johannsen et al. showed the first report on clinical application of hyperthermia of human cancer using magnetic nanoparticles [12]. They injected magnetic nanoparticle suspensions transperineally in to 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 Ikenaga et al. [20, 21]. In an in vitro study Hilger et al. showed the impact of magnetic thermoablation in muscle tissue using iron oxide particles, and also demonstrated the applicability of local magnetic thermoablation as a therapy of muscle lesions in the long-term [18]. We modified these new hyperthermic strategies as an option to treat metastatic bone tumors, and developed bone cement made of glass ceramic that is partly replaced by magnetite [22–24]. When this magnetite cement was inserted into the metastatic lesion followed by exposure to an alternating electromagnetic field, this magnetite cement generated heat according to the principle of physical energy conversion called “hysteresis loss.” As a result, any metastatic cancer cells thereby suffer apoptotic cell death and necrosis [20, 22, 23, 25]. Since our magnetite cement has not yet been approved by Ministry of Health, Labor, and Welfare of Japan, we decided to use titanium alloy or stainless intramedullary nail or powdery Fe_3O_4 as magnetic materials. We have continually performed experimental studies using animal models [22, 24, 26], and finally started clinical applications of this treatment modality from March 2003 after obtaining approval from our Institutional Ethics Investigational Review Board.

To our knowledge, this is the first report on the clinical application of hyperthermia for metastatic bone tumors with magnetic materials by generating an alternating electromagnetic field. The purpose of this study is to show the clinical outcome of hyperthermia using magnetic materials on human subjects.

Patients and methods

Patients

The patients who underwent hyperthermia for metastatic bone tumors with magnetic materials (HT group)

Informed consent was obtained from all patients according to the guidelines of the institutional ethics review board. Patients eligible for the study were suffering from previously untreated and histologically confirmed metastatic bone tumors in the extremities. From March 2003 to November 2005, we treated 42 patients with metastatic bone tumors in the extremities. Of 42 patients, 14 patients received only radiotherapy because they had too poor general condition to undergo the operation and two patients underwent only operation because low-priority of radiotherapy for operated limb due to multiple metastases. Of 26 patients, 11 patients with a metastatic lesion at the proximal end of femur or humerus were precluded to undergo our hyperthermia because it was structurally impossible to perform hyperthermia for proximal lesions of the extremities using our electromagnetic field generator. Therefore, our novel hyperthermia modality was performed on 15 patients, including seven males and eight females, with 16 metastatic lesions, and then they were prospectively followed-up (Table 1). The age of the patients at operation ranged from 41 to 80 years of age (median 63 years), and the follow-up period ranged from 3 to 37 months (median 10 months). The primary lesions included three lung cancer, three hepatocellular carcinomas, two renal cell carcinomas, two sarcomas, and others. Regarding the operation sites, eight were the humerus, five the femur, two the tibia, and one the fibula. Seven patients received systemic therapies including chemotherapy, hormonal therapy, and interferon.

The patients of the control group (“Op group” and “Op + RT group”)

We established two control groups; one was the “Op group” who underwent a palliative operation without postoperative radiotherapy from 1995 to 2003, and another is the “Op + RT group” who underwent an operation in

Table 1 Details of the 15 patients who underwent hyperthermia for metastatic bone tumors with magnetic materials (HT group)

Number	Age (G)	Primary cancer	Location	Surgical procedure	MSTS	Rad. assess	Complication	Follow-up period (mos)	Result	Systemic adjuvant therapy
1	57 (M)	Lung ca. (ad.ca.)	Femur	IMN	83	G	Feeling of heat	3	DOD	No
2	60 (F)	RCC	Femur	Cure + CPC-Fe + Plate	63	P	No	33	AWD	IFN
3	69 (F)	Sarcoma (MFH)	Femur	Cure + CPC-Fe + IMN	63	G	No	28	NED	No
4	61 (F)	Parotid gland ca.	Femur	IMN	57	P	No	37	DOD	No
5	54 (F)	Gastric ca.	Fibula	IMN	73	E	Feeling of heat	8	AWD	Chem.
6	67 (M)	HCC	Humerus	IMN	63	G	No	6	DOD	No
7	63 (F)	HCC	Humerus	IMN	57	E	No	11	DOD	No
8	65 (F)	Lung ca. (ad.ca.)	Humerus	Cure + CPC-Fe + Prosthesis	60	E	No	5	DOD	No
9	65 (F)	Lung ca. (ad.ca.)	Humerus	Cure + CPC-Fe + IMN	70	E	No	34	AWD	Chem.
10	80 (M)	Prostate ca.	Humerus	Cure + CPC-Fe + IMN	100	E	No	13	AWD	Chem.
11	63 (M)	RCC	Humerus	IMN	100	E	No	10	AWD	Hormonal T
12	57 (M)	Myeloma	Tibia	Cure + CPC-Fe + IMN	63	G	No	10	DOD	No
13	41 (F)	Sarcoma (MPNST)	Tibia	Cure + CPC-Fe + IMN	97	G	Feeling of heat	13	AWD	Chem.
14	69 (M)	HCC	Humerus	Cure + CPC-Fe + IMN	70	G	No	9	DOD	No
15	56 (M)	Bladder ca.	Humerus	Cure + CPC-Fe + IMN	97	E	No	4	AWD	No
					90	E	No	3	AWD	Chem.

G gender, M male, F female, MSTS the functional results according to the scoring system of Musculoskeletal Tumor Society, ca cancer, ad. ca. adenocarcinoma, RCC renal cell carcinoma, MFH malignant fibrous histiocytoma, HCC hepatocellular carcinoma, MPNST malignant peripheral nerve sheath tumor, IMN intramedullary nail, Cure curettage, CPC-Fe, calcium phosphate cement containing powdery Fe₃O₄, MSTS the functional results according to the scoring system of Musculoskeletal Tumor Society, Rad. assess radiographic assessment, E excellent, G good, P poor, DOD dead of disease, NED no evidence of disease, AWD alive with disease, IFN interferon, Chem. Chemotherapy, Hormonal T hormonal therapy

Table 2 Details of the eight patients who underwent palliative operation for metastatic bone tumors (Op group)

Number	Age (G)	Primary cancer	Location	Surgical procedure	Radiographic assessment	Follow-up period (mos)	Result	Systemic adjuvant therapy
1	34 (F)	Myeloma	Femur	IMN	G	17	DOD	Chem.
2	87 (M)	RCC	Femur	CHS	P	8	DOD	No
3	54 (M)	Prostate ca.	Femur	CHS	P	18	DOD	No
4	63 (M)	Colon ca.	Humerus	Cure + CHS + PMMA	P	35	DOD	No
5	78 (F)	Lung ca. (ad.ca.)	Femur	IMN	G	8	DOD	No
6	75 (M)	Lung ca. (ad.ca.)	Tibia	IMN	P	7	DOD	Chem.
7	79 (F)	Cervical ca.	Tibia	Cure + IMN + CPC	G	11	DOD	No
8	58 (M)	Esophageal ca.	Femur	IMN	P	5	DOD	No

G gender, M male, F female, RCC renal cell carcinoma, ca cancer, ad. ca. adenocarcinoma, IMN intramedullary nail, CHS compression hip screw, Cure curettage, PMMA polymethylmethacrylate bone cement, CPC calcium phosphate cement, G good, P poor, DOD dead of disease, Chem. chemotherapy

combination with postoperative radiotherapy from 2001 to 2003.

“Op group”: from 1995 to 2003, 132 patients with the metastatic bone tumor in their extremities were treated at our institute. Until hyperthermic therapies were started in 2003, we have undergone surgical reinforcement in combination with postoperative radiotherapy for the patients with metastatic bone tumor of the extremities. Therefore there were the limited patients in Op group (Table 2). The selection criteria of the eight patients in the Op group are as follows: (1) a low-priority of radiation therapy for operated limb because of multiple bone metastases in 3, brain metastases in 2, and metastases to other visceral organ in 2, (2) the patient’s rejection of irradiation in one patient.

“Op + RT group”: from 2001 to 2003, 51 patients were treated due to metastatic bone tumors of the extremities. Of 51 patients, 18 patients received only radiotherapy because their general condition was too poor for them to undergo the operation and three patients underwent only an operation because of a low-priority of radiotherapy for the operated limb due to multiple metastases. Of 30 patients, eight patients with a metastatic lesion at the proximal end of femur or humerus underwent a wide tumor resection and a prosthetic reconstruction. Therefore, the remaining 22 patients were selected as the “Op + RT group” (Table 3).

Surgical procedure

All surgical procedures were performed under general anesthesia. The surgical procedures for the patients who underwent hyperthermic treatment can be categorized into two groups. For eight patients not expected to have a long survival, only reinforcement with an intramedullary nail was performed without any excision of the metastatic lesion. In contrast, for eight patients who were expected to have a long survival, after curettage of the lesion followed

by either a prosthetic replacement ($n = 1$) or reinforcement with a metal intramedullary nail or plate ($n = 7$), calcium phosphate cement (CPC) containing a powdery Fe_3O_4 was implanted into the cavity. As a CPC, we used BIOPEX[®]-R (PENTAX Corp., Tokyo, Japan [27, 28]). A powdery Fe_3O_4 , which consists of 13-(μm -diameter particle was made by Nippon Electric Glass Corp. Ltd., Ohtsu, Japan. The tumor was exposed via an appropriately sized bone window, and careful curettage was then performed using a curette. After curettage of the tumor, internal reinforcement was performed using intramedullary nail or plate fixation. Next, the powdery Fe_3O_4 was prepared to become a 40% weight ratio of total CPC weight. Thereafter, the liquid components, the powder of the CPC and Fe_3O_4 were mixed manually together until a smooth consistency was obtained (Fig. 1a, b). The bone defect was filled with the CPC containing powdery Fe_3O_4 either by hand or by injection through a blunt needle, depending on the shape and size of the bone defect (Fig. 1c). After sufficiently washing the wound using physiological saline, the muscle, subcutaneous tissue, and skin were then carefully closed in layers.

Exposure to alternating electromagnetic field

Alternating electromagnetic field generator was developed by Yamamoto Vinita Co. Ltd., Osaka, Japan [22, 23, 26]. The affected limb was inserted into a cylinder-form coil of the generator (Fig. 2). The power of the electromagnetic field was 4 kW in output, and 1.5 MHz in fixed frequency. The intensity was adjusted to obtain a temperature of around 43°C on the surface of cortical bone. 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. The treatment method including the treatment schedule and exposure time were decided according to the experimental studies using rabbit and

Table 3 Details of the 22 patients who underwent operation in combination with radiotherapy for metastatic bone tumors (Op + RT group)

Number	Age (G)	Primary cancer	Location	Surgical procedure	Total dose (Gy)	Radiographic assessment	Follow-up period (mos)	Result	Systemic adjuvant therapy
1	66 (M)	Lymphoma	Humerus	IMN	50	E	9	AWD	Chem.
2	65 (F)	Thyroid ca.	Femur	Prosthesis	50	G	71	AWD	No
3	56 (M)	Myeloma	Femur	IMN	40	E	31	NED	Chem.
4	53 (F)	Myeloma	Femur	Prosthesis	40	E	24	NED	Chem.
5	57 (M)	Esophageal ca.	Femur	IMN	50	G	6	DOD	Chem.
6	57 (M)	Esophageal ca.	Tibia	Cure + PMMA	50	G	31	DOD	Chem.
7	68 (M)	RCC	Femur	Prosthesis	40	G	28	AWD	No
8	74 (F)	Colon ca.	Femur	IMN	50	G	5	DOD	No
9	49 (F)	Breast ca.	Humerus	IMN	40	E	36	DOD	Chem.
10	54 (F)	Breast ca.	Femur	IMN	30	G	5	AWD	Chem.
11	63 (M)	Lung ca. (ad.ca.)	Tibia	IMN	30	G	14	DOD	No
12	50 (M)	Lung ca. (ad.ca.)	Femur	IMN	40	P	15	DOD	No
13	40 (M)	Lung ca. (ad.ca.)	Femur	IMN	40	G	7	DOD	Chem.
14	44 (F)	Lung ca. (ad.ca.)	Femur	IMN	40	G	37	DOD	Chem.
15	67 (F)	Lung ca. (ad.ca.)	Femur	Prosthesis	40	G	18	AWD	No
16	66 (M)	Lung ca. (ad.ca.)	Femur	IMN	40	E	9	DOD	No
17	70 (M)	Lung ca. (s.c.c.)	Femur	IMN	30	G	5	DOD	No
18	62 (M)	Bladder ca.	Femur	IMN	30	E	5	DOD	Chem.
19	70 (M)	Lung ca. (ad.ca.)	Humerus	IMN	32	E	13	DOD	No
20	66 (M)	Prostate ca.	Femur	IMN	30	G	46	AWD	Hormonal T
21	70 (F)	HCC	Femur	IMN	40	G	23	DOD	No
22	72 (F)	HCC	Humerus	Prosthesis	40	P	12	AWD	No

G gender, *M* male, *F* female, *ca* cancer, *ad. ca.* adenocarcinoma, *RCC* renal cell carcinoma, *HCC* hepatocellular carcinoma, *MPNST* malignant peripheral nerve sheath tumor, *IMN* intramedullary nail, *Cure* curettage, *PMMA* polymethylmethacrylate bone cement, *E* excellent, *G* good, *P* poor, *DOD* dead of disease, *NED* no evidence of disease, *AWD* alive with disease, *IFN* interferon, *Chem.* Chemotherapy, *Hormonal T* hormonal therapy

human cadavers [23, 26]. The temperature of the bone surface was monitored with a fluoroptic thermometer (model 3000; Laxtron, Mountain View, CA, USA) under local anesthesia.

Assessment

The assessments were based on clinical examinations and radiographic findings. The functional assessments were performed according to the scoring system of Musculoskeletal Tumor Society [29]. The radiographic outcome was evaluated by radiographs at 3 months after surgery. The radiographic outcome was assessed according to following criteria. ‘‘Excellent’’ means a reduction of the lesion with visible bone formation. ‘‘Good’’ means no progression of the lesion for more than 3 months. ‘‘Poor’’ means a progression of the lesion. To evaluate the effectiveness of hyperthermia on radiographic findings, a univariate analysis was performed using the Mann–Whitney *U*-test for non-parametric data and StatView statistical software (Version 5.0; SAS Institute Inc., Cary, NC, USA).

Results

There were no adverse effects after the operation (e.g., excessive postoperative drainage, erythema) in the early postoperative period. No patients developed a postoperative infection. Regarding the adverse effects related to hyperthermia, three patients felt a heat sensation during exposure to electromagnetic field. However, these feelings of heat disappeared immediately when the generator switch was turned off, and hyperthermia was carried out for 15 min of total exposure time. All patients underwent ten sessions of hyperthermic treatment as planned. None of patients suffered any burns. In addition, no soft tissue injury was observed due to elevated temperatures, including muscle necrosis, vascular damage, and nerve injury. No allergic reaction was observed during the follow-up period. None of the patients had any pain at the operation site. In addition, no toxicity was detected in routine blood examinations.

In all patients who underwent hyperthermic treatment, pain relief was obtained after operation.

Fig. 1 The surgical method to fill calcium phosphate cement (CPC) containing Fe_3O_4 after reinforcement using an intramedullary nail. (a) CPC and the powdery Fe_3O_4 were prepared. (b) The liquid components, the powder of the CPC and Fe_3O_4 were mixed manually together to become a smooth consistency. (c) The bone defect was filled with the CPC containing powdery Fe_3O_4 by injection through a blunt needle and by hand

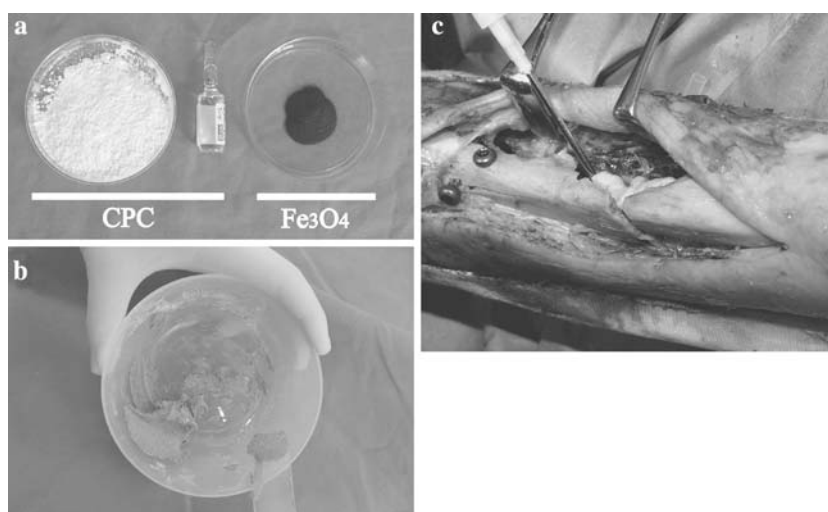


Fig. 2 Hyperthermia was performed by inserting the affected limb into a cylinder-form coil of the electromagnetic field generator. The power of the electromagnetic field was 4 kW in output, and 1.5 MHz in fixed frequency. Hyperthermic treatment was performed postoperatively on days 8, 10, 12, 15, 17, 19, 22, 24, 26, and 29. The exposure time was 15 min per day

The functional assessment after hyperthermia ranged from 57 to 100% (average 80%) in the upper extremities, and from 57 to 97% (average 72%) in the lower extremities.

On radiographs, in HT group, eight lesions (50%) showed an excellent outcome (Figs. 3, 4, 5), while six lesions (37%) showed a good outcome. Two lesions (13%) showed a poor outcome and thus required additional surgery because of local recurrence. When compared the radiographic results between the patients who underwent hyperthermia with CPC containing a powdery Fe_3O_4 and the patients without that, there were no significant difference ($P > 0.999$). In contrast, in Op group, three lesions (38%) showed a “good,” while five lesions (62%) showed

a “poor.” In Op + RT group, seven lesions (32%) showed a “excellent,” and 13 lesions (59%) showed a “good,” while two lesions (9%) showed a “poor.” When the lesions with an “excellent” or “good” outcome were classified to the “effective” treatment, 87, 38, and 91% were, respectively, considered to demonstrate an effective treatment outcome in HT group, Op group and Op + RT group. The patients in HT group showed a statistically better radiographic outcome than the patients in Op group ($P = 0.0042$). But when compared between HT group and Op + RT group, there were no significant difference ($P = 0.412$).

In three patients (patients 1, 6, and 7 in Table 1), we monitored the temperature of the bone surface using thermometer. The heat was monitored at the surface of the cortical bone set up at the center of the coil of the electromagnetic generator. We showed the temperature change of the surface of the cortical bone during exposure to the electromagnetic field in the patient who was treated using intramedullary nail as magnetic material (patient no. 7 in Table 1) (Fig. 5f). In this patient, the temperature of the bone surface reached more than 40°C within 2 min, and then it reached a plateau within 4 min, thus showing a temperature of higher than 42°C.

Discussion

The bone has several special properties, which discourage the oncologist from developing hyperthermic therapeutic strategy. The bone is deeply located in the body, too hard to approach penetrating the cortex, and low-thermal conductive with highly vascularized medulla. Hyperthermia for bone tumors using the polymerization heat of polymethylmethacrylate bone cement is now widely performed [30, 31]. However, the generated heat tends to be unreliable and

Fig. 3 (a) A 63-year-old patient with metastatic lung cancer to the humerus (*open arrow*). (b) After curettage of the lesion followed by reinforcement with intramedullary Kurschner wire, CPC containing Fe_3O_4 was implanted into the cavity. (c) At 6 months after undergoing hyperthermia, massive new bone formation has become visible (*open triangle*)

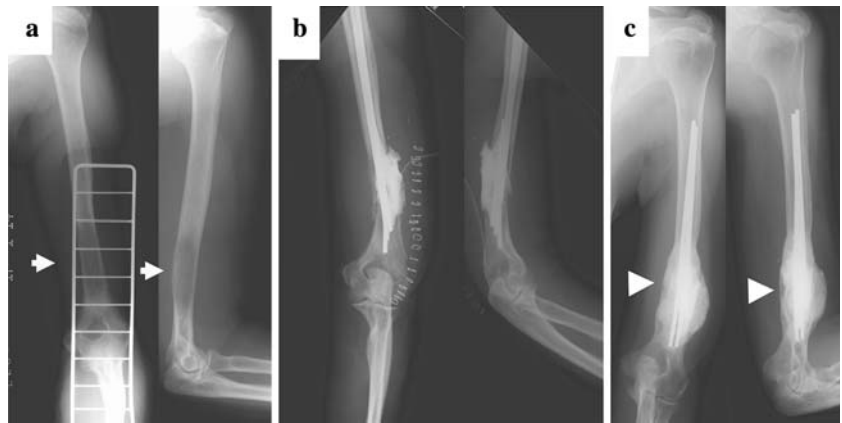
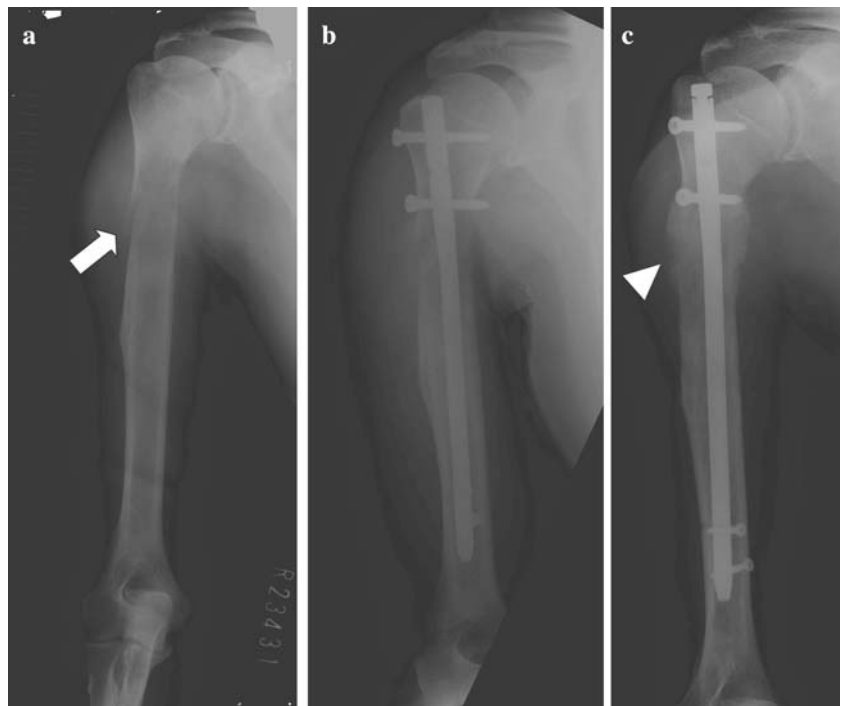


Fig. 4 (a) The patient with metastatic prostate cancer to the humerus with a pathological fracture (*open arrow*). (b) Reinforcement with intramedullary nailing was performed. (c) The fracture was united without any disease progression at 3 months after hyperthermia (*open triangle*)

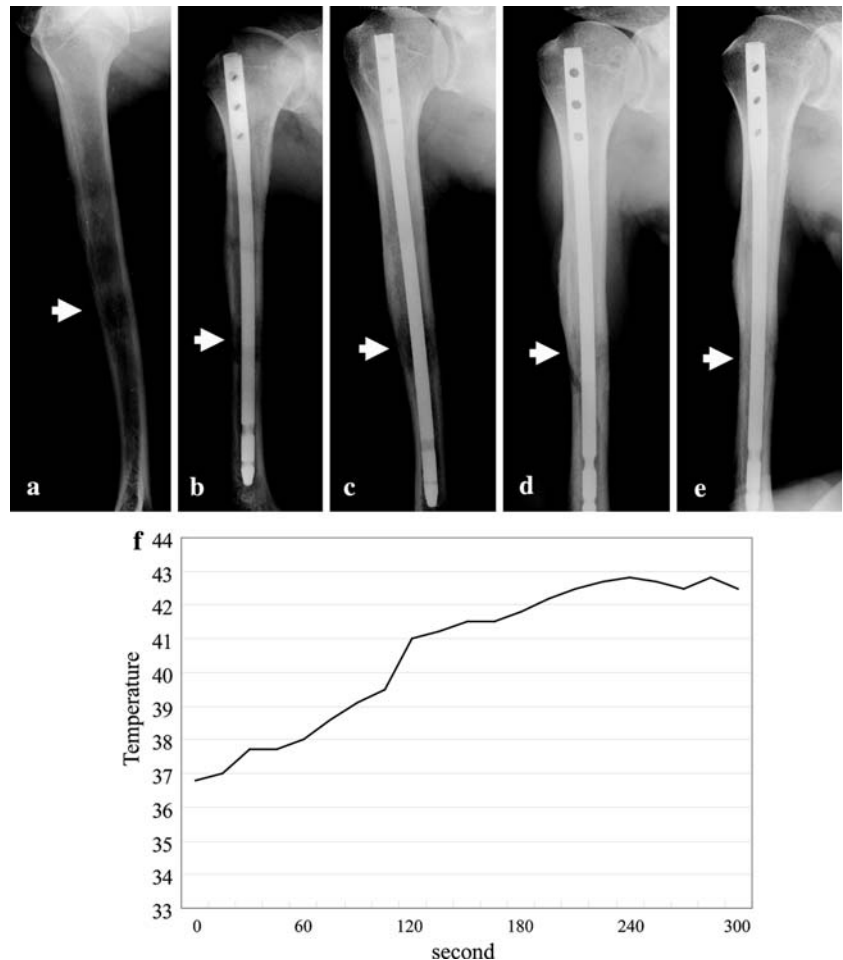


insufficient to reduce bone tumor growth [22]. Microwave-induced hyperthermia [8], laser-induced thermotherapy [32, 33], and radiofrequency ablation [33] are recently used especially for spinal and pelvic metastasis. But these therapeutic modalities are unsatisfactory for the lesions located in the long tubular bone of the limb, because pathological fractures cannot be prevented without a surgical reinforcement of the bone lesion. Therefore, we developed a new hyperthermic therapeutic strategy with magnetic materials for metastatic bone tumors based on experimental studies [22–24, 26], and have also started clinical investigations. This first series of a new clinical hyperthermia treatment modality showed a good clinical outcome.

No serious adverse effects were observed during the follow-up period. Only three patients experienced a heat

sensation during exposure to an electromagnetic field. These feelings of heat disappeared immediately when the generator switch was turned off, and hyperthermia could thus be carried out as planned in all patients. In an experimental study using human cadavers, the temperature at the cortical surface increase to 43–45°C when the implanted materials were heated above 60°C [26]. In the experimental study using VX-2 tumor-transplanted rabbit model, there were no histological changes in the surrounding soft tissue after hyperthermia [26]. We speculate that the absence of any heat-related soft tissue injury may be due to a “radiator effect” which is produced by the microvessels, which absorb the heat of microenvironment. We concluded that our hyperthermia with magnetic materials is therefore a safe therapeutic procedure.

Fig. 5 (a) A 63-year-old patient with metastatic hepatocellular carcinoma to the humerus (*open arrow*). (b) Reinforcement with intramedullary nailing was performed. The lytic area of the humerus was found to have gradually disappeared at (c) 3, (d) 5, and (e) 7 weeks postoperatively (*open triangle*). (f) In this patient, the temperature of the surface of cortical bone reached more than 40°C within 2 min, and then it reached a plateau within 4 min, thus showing a temperature of higher than 42°C



The functional assessment after hyperthermia ranged from 57 to 100% (average 80%) in the upper extremities, and from 57 to 97% (average 72%) in the lower extremities. The limb function of the patients who underwent an operation for metastatic bone tumors is sometimes worse than that for primary bone tumors, because the former often have other lesions, which affect the patient's motility and activity of daily life. For example, no. 11 patient (Table 1) who was operated for metastatic renal cell cancer got a poor functional result, because a metastatic spinal lesion in sixth and seventh cervical spine caused paresis and intractable pain of the affected limb. We believe that the patients treated by our hyperthermia modality thus had an acceptable limb function.

On radiographs, when the lesions with an "excellent" or "good" outcome were classified to the "effective" treatment, 87, 38, and 91% were, respectively, considered to demonstrate an effective treatment outcome in HT group, Op group and Op + RT group. The patients in HT group showed a statistically better radiographic outcome than the patients in Op group ($P = 0.0042$). But when compared between HT group and Op + RT group, there were no significant difference ($P = 0.412$). These results

suggest that the hyperthermia using magnetic material may be so effective as an operation being combined with postoperative radiotherapy in term of radiographic outcome (Table 4).

Our hyperthermic strategy has the following advantages for the treatment of metastatic tumor of long tubular bone, compared to radiotherapy. First of all, our hyperthermic treatment is minimal invasive for surrounding soft tissue although irradiation sometimes induces soft tissue damage, including muscle induration, and joint contracture and skin erosion [2]. Second, our hyperthermic strategy can prevent pathological fractures because of the surgical reinforcement of the bone lesion. Moreover, this surgical reinforcement never requires any special techniques, which may further burden the orthopedic surgeon. Finally, our hyperthermic treatment can be repeatedly applied for recurrent metastatic lesions, even though radiotherapy cannot surpass the normal dose limitations.

We did not always monitor the thermometric parameters of hyperthermic treatment, because the heat monitoring system is invasive for the patients. In three patients (patient no. 1, 6, and 7 in Table 1), we monitored the temperature of the surface of the cortical bone using thermometer. The

Table 4 The radiographic outcomes

	HT (%)	Op (%)	Op + RT (%)
Excellent	8/16 (50)	0	7/22 (32)
Good	6/16 (37)	3/8 (38)	13/22 (59)
Poor	2/16 (13)	5/8 (62)	2/22 (9)

HT a group treated with hyperthermia, *Op* a group treated with palliative operation, *Op + RT* a group treated with operation in combination with postoperative radiotherapy

heat was monitored at bone surface set up at the center of the coil of the electromagnetic generator. In these patient, temperature of the surface of cortical bone reached more than 40°C within 2 min, and reach plateau within 4 min thus showing a temperature of more than 42°C. Because the radiographic assessment showed good response in these three patients, we could not demonstrate any relationship between tumor temperature and tumor response in this study. Further clinical study is needed.

In conclusion, our novel clinical hyperthermia modality using magnetic materials was thus found to achieve a good local control of metastatic bone lesions. We have recently started a randomized study to compare the clinical results between “HT group” and “Op + RT group.” Further investigations are needed before this technique can be employed as a standard therapy for metastatic bone tumors.

Acknowledgments We thank the secretarial staff of the Department of Orthopedic Surgery, Mie University School of Medicine, for their generous cooperation. This work is supported in part by the grant from the Ministry of Health, Labor, and Welfare (Grants-in Aid for Clinical Cancer Research).

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