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Feasibility of a Novel *In-situ* Local Tumor Ablation and Recycling Machine Based on Radiofrequency Dielectric Heating: In-depth Review on Research Background and Preliminary Report of an Experimental Study

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Background: In bone sarcomas, chemotherapy has improved the prognosis with advances in diagnostic and surgical technologies, which has led to attempts to save limbs. As early detection and multidisciplinary treatment have improved the survival rate, curative surgery is considered for selected patients with metastatic bone carcinomas. Limb salvage procedures may vary in relation to the reconstruction method, which is accompanied by different complications. To overcome them, we devised a novel concept, *in-situ* local tumor ablation and recycling machine based on radiofrequency (RF)-induced heating and intended experiments to demonstrate its feasibility.

Methods: The fresh femurs of 6-month-old pigs were used after removing the epiphyses; the distal parts were placed in a heating chamber. Fiber-optic temperature sensors were inserted in the metaphysis, meta-diaphysis, and diaphysis. Temperatures were measured six times each during heating at 27.12 MHz at various powers. Additionally, the compressive and bending stiffnesses were measured six times each for the unprocessed, RF-treated, and pasteurized bones, and the results were compared.

Results: Under 200 W power output, the temperatures at all measurement sites reached 70 °C or higher in 6 minutes, and the temperatures were maintained. The median compressive stiffness of RF-heated bones was 79.2% higher than that of pasteurized bones, but the difference was statistically insignificant. The median bending stiffness of RF-heated bones was approximately 66.3% of that of unprocessed bones, which was 20% higher than that of pasteurized bones.

Conclusions: The feasibility to rapidly attain and maintain temperatures for tumor ablation is shown, which favorably preserves bone stiffness through the *in-situ* local tumor ablation and recycling based on RF heating. The problem of nonuniform temperature distribution might be solved by an optimal design determined from simulation research and additional experiments.

Keywords: *Bone neoplasms, Ablation technique, Radiofrequency ablation, Heating, Autograft*

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Primary bone tumors are relatively common among the various neoplasms occurring in humans, but clinically significant bone tumors, such as locally aggressive and malignant ones, are rare.1) Malignant bone tumors develop as either *de novo* neoplasms in the bone or as secondary tumors in relation to benign precursor lesions or bone diseases; all such malignant tumors are classified as bone sarcoma.1) Paget's disease of bone, irradiated bone, bone necrosis, and certain benign bone tumors are considered as precancerous lesions.1) In addition, metastatic bone cancers are included under malignant bone tumors.1)

Bone sarcomas such as osteosarcoma and chondrosarcoma are very rare, accounting for 0.2% of all malignant neoplasms. Compared to soft-tissue sarcomas, these have about one-tenth the incidence. According to the Annual Report of National Cancer Registration in Korea,2) the number of malignant neoplasms of bone and articular cartilage of other and unspecified sites, which is classified under codes C40–C41 in the International Classification of Disease, the 10th Revision (ICD-10), was 493 (276 in men and 217 in women) and accounted for 0.2% of the total 61 malignant neoplasms. The prevalence was mainly in children and young adults, with the highest incidence rates of 1.4% and 1.1%, respectively, per 100,000 men and women in the age range of 10–14 years.2) The number of incidents was 2,953 in men and 2,623 in women, accounting for 0.3% of the total 61 malignancies.2) While the relative survival rate of patients aged 0–17 years was 45.9% in 1993–1995, it improved to 74.2% between 2014 and 2018 owing to the introduction of systemic chemotherapy, advances in diagnostic technologies such as imaging modalities, and the development of surgical techniques.2) The Survey, Epidemiology, and End Results Program of the National Cancer Institute of the United States reported similar trends in terms of the incidence and survival rates for bone and joint cancers.3)

Several decades ago, osteosarcoma, which is one of the most common bone sarcomas, would have meant limb amputation, and most patients at the time were afraid of death.4) Before the mid-1970s, amputation was the sole and standard treatment for high-grade osteosarcomas, and even after the procedure, only about 10% of patients were cured.4,5) The tumors showed a rapid and aggressive nature, so surgeons of the day believed that amputation of the affected extremity could stop disease progression,4) according to Hippocrates: "Extreme remedies are very appropriate for extreme diseases."5) However, Hippocrates also noted that "Walking is man's best medicine."5) The loss of an extremity can itself be detrimental to comprehensive health.6) A systematic review7) demonstrated that physical function and cosmetic satisfaction were poor in amputees, which was correlated with their dismal quality of life, low self-esteem, and lower confidence in romantic relationships. Another meta-analysis6) determined high long-term mortality even after nontraumatic major lower extremity amputation and explained the strong link between post-amputation function and overall survival.

Advances in chemotherapy over the past few decades have dramatically changed the prognosis for patients with localized osteosarcomas.4,5) Modern multiagent-dose-intensive chemotherapeutic regimens have decreased the incidence of distant metastasis and mortality rates.4,5) In particular, preoperative chemotherapy has improved the success of limb salvage procedures by sterilizing the peritumoral reactive zone via ablation of the microscopic lesions at the periphery and facilitating the achievement of a safe surgical margin.4) In addition, current imaging technologies, such as magnetic resonance imaging, computed tomography (CT), and positron emission tomography/CT, as well as new reconstruction biomaterials, have supported surgeons with more precise preoperative plans and a wider range of surgical options.4,5) Such advances have inspired the innovation of operative techniques with less radical and more conservative interventions.5) In terms of local recurrence, limb salvage surgery (LSS) is comparable to amputation.4) In addition, an update to the National Cancer Database reported that limb salvage was significantly associated with better survival benefits over amputation even when controlling for important confounders.8)

Meanwhile, the number of patients with carcinomas has increased.2,9) The Scandinavian Skeletal Metastasis Registry reported that the number of cancer patients has increased by 18% over the past decade,9) and the Annual Report of National Cancer Registration in Korea2) showed that the number of cancer cases was 101,847 in 1999, 192,561 in 2009, and 254,718 in 2019. Nevertheless, the 10-year relative survival rates of patients diagnosed with cancer in 1993–2014 increased steadily even excluding thyroid cancer, which has a relatively good prognosis.2) Compared to patients diagnosed in 2001, the 5-year relative survival rates of those diagnosed in 2006–2010 and 2015–2019 increased by 5.2% and 16.6%, respectively.2) This was possible owing to the early detection of diseases, along with the development of surgical techniques, radiation treatment, and systemic therapies such as chemotherapy, target therapy, hormone therapy, and immunotherapy. Bone is the third most frequently metastasized region, following the lung and liver, and the risk of bone metastasis also increases as cancer patients survive longer.10) Conventionally, management of bone metastasis was simply aimed at pain reduction and functional preservation to maintain the quality of life until patient death. However, recently, curative surgery similar to LSS has been attempted in cases with solitary or oligo-metastasis as in localized sarcomas along with the development of multimodal interdisciplinary management, and the number of subjects with indications for such treatment is increasing.10)

LSS involves a surgical process with wide excision of a malignant tumor, including an appropriate surgical margin, and reconstruction of the resultant bone and soft-tissue defects.11,12) Various materials have been used for reconstruction, and the resection strategy may vary depending on the reconstruction method. Each technique of the LSS is accompanied by different complications in the long term; therefore, revisional surgeries are frequent.11-13) Ever since Austin Moore created a tumor prosthesis using a cobalt-chrome alloy in 1943, diverse metallic endoprostheses have been manufactured from vitallium, stainless steel, and polythene over the next few decades.13) As the conservative treatments of musculoskeletal tumors have expanded since the 1970s, implantable options of mega prostheses have increased with the development of modular systems instead of custom-made prostheses and expandable prostheses for the pediatric pupulation.13) Currently, the tumor prosthesis is the most commonly used skeletal substitute.11) However, patients who underwent LSS with the endoprosthesis have metal implants that are as long as the resected bone in the body, which can lead to early postoperative complications such as bacterial infections and long-term problems such as delayed infection, aseptic loosening, and polyethylene wear.11) These complications are expected to further increase as the number of long-term survivors increases with advances in systemic treatments.

Bone grafting from one human to another has fascinated mankind for thousands of years. The Old Testament first describes allogeneic transplantation, where one of Adam's ribs was used to create Eve. The first reported allograft was performed in 1880, where an infected humerus of a 4-year-old male was reconstructed with bone harvested from the tibia of another child with rickets.14) Nowadays, established bone banks provide ready and available access to structural allografts from cadaver sources.14) A similar form of structural allograft from the same location can be used for skeletal defects after tumor resection.12) However, allograft reconstructions are also associated with several complications.12) There is a considerable possibility of nonunion between the patient's host bone and the allograft.12) In addition, the transmission of infectious and tumorous diseases is a concern;12) it may also be difficult to find the appropriate size or shape of allograft if there are not many available bones even in large tissue banks.12)

Skeletal reconstruction using recycled autograft is a method of removing and recycling the tumor-bearing bone by various eradication techniques.15) It has the advantages of low cost, no risk of immune rejection, identical anatomical shape, and easy acquisition.15) The tumor ablation methods used include alcohol baths, autoclaving, extracorporeal irradiation, pasteurization, and freezing and thawing.15) Inokuchi et al. first reported the results of reconstruction using a resected and pasteurized autogenous mandible with a malignant bone tumor in 1991.16) Manabe et al.16) first introduced pasteurization in the orthopedic field in 1993. In this method, a resected tumor-bearing bone is immersed in preheated saline, pasteurized for tens of minutes, and then reimplanted.15) The osteoinductivity is completely lost when the bone is treated with irradiation,17) but pasteurization can eradicate the tumor cells while preserving osteoinductivity.18) In our institution, pasteurization by thermal treatment at 65 °C for 30 minutes has been used historically. Manabe et al.16) reported that callus formation was observed at 4–6 months after implantation of the pasteurized bone; in addition, 80% union rate, no local recurrence, 20% severe infection rate, 12% graft fracture, and 4% graft resorption rate were observed.16) With the use of recycled autografts, several complications related to the tumor prosthesis or allograft can be avoided, but surgical infection by bacterial contamination is also possible as the extracorporeal procedure is performed outside the operation field. Nonunion in the diaphysis of a long bone still remains as a challenge that needs to be solved.15)

To overcome the disadvantages of conventional recycled autografts such as nonunion, a technique of pedicle frozen autograft has been developed.19) Marcove et al. first introduced a treatment method for malignant bone tumors using liquid nitrogen in 1969, but the procedure involved repeated freezing and thawing of the resultant cavity after curettage.19) Tsuchiya et al.20) reported cryotherapy for tumor-bearing bones after wide excision in 2005; originally, this procedure was performed outside the surgical field using liquid nitrogen after excising the tumor-bearing bone, as in the other recycling techniques. A union rate of 92.9%, an infection rate of 10.7%, and a graft fracture rate of 7.1% were reported, with a mean duration of 6.7 months required for the union.20) On the other hand, in the procedure of the pedicle frozen autograft, the tumor-bearing region of the bone is soaked into a basket filled with liquid nitrogen for 20 minutes followed by thawing in room air first for 15 minutes and then distilled water for the next 10 minutes without osteotomizing the diaphysis where union is relatively difficult to be achieved.[19)] However, the operators need to hold the limb with the bone tumor and retain a fixed position of the tumor-bearing region in the freezing basket during the processing time. In addition, it is questionable whether the entire bone is frozen evenly, and fractures may occur often during freezing. It may also be impossible to determine the tumor necrosis rate by neoadjuvant chemotherapy in osteosarcomas because it is difficult to collect tumor specimens during the procedure.

A different method of tumor ablation in the original location of the bone was proposed by inserting microwave antennas into the lesion after dissecting it with a surgical margin without an osteotomy.[21)] With such a simple and inexpensive procedure, the best functional outcomes can be expected, but there is still a lack of evidence for the appropriate number of antennas that must be inserted for the best clinical results. There is also the possibility of tumor cells falling onto the surgical field during the procedure with antenna insertion. There are also difficulties with collecting viable tumor tissues, as in the case of pedicle frozen autograft. Therefore, it is the need of the hour to develop new techniques of recycled autografts that minimize osteotomy to prevent diaphyseal complications, minimize the possibility of bacterial contamination by application within the surgical area, guarantee safe procurement of tumor tissues for pathological examinations without tumor contamination in the operation field, transmit the target temperature to enable complete tumor ablation, and maintain long-term durability of the skeletal structure.

Ever since it was proven in 1891 that radiofrequency (RF) waves could pass through hepatic tissues and lead to an increase in the tissue temperature,[22)] medical equipment utilizing RF heating has been introduced from the early- and mid-1900s.[22,23)] Since the treatment of bone tumors by RF ablation was reported first in 1992, the technique has been used to manage several skeletal lesions, such as osteoid osteoma and metastatic cancers.[23)] Hence, we devised a novel concept, the *in-situ* local tumor ablation and recycling machine, based on RF dielectric heating (Fig. 1), and conducted experiments to demonstrate its feasibility.

METHODS

Since this research was an experimental study on animal carcasses, institutinal review board approval was not required.

Experimental Bone Model

As it is important to preserve the joints in LSS as much as possible, an experimental bone model was produced assuming transepiphyseal resection from among the various clinical and surgical situations. Fresh femurs of 6-month-old three-way hybrid pigs were used after procurement by slaughtering. After the epiphyses were cut off, intramedullary cancellous bone was copiously curetted.

Experimental Machine and Apparatus for RF Dielectric Heating

An experimental machine was produced, reflecting the abovementioned concept of *in-situ* local tumor ablation and recycling (Fig. 2A); it consisted of a container for applying heat by accommodating a part of the bone model and a unit for supplying RF to the accommodating space. The container had an electrode to transfer the RF to a subject in the accommodation space. The supply unit includes an RF generator, a matching box, and a cable connecting the supply unit and electrode. The electromechanically controlled matching box maintains the input impedance and zero phase angle. The operating frequency is 27.12 MHz, which is one of the industrial, scientific, and medical frequencies. As the molecules of an object in the container vibrate according to the applied RF, heat is generated within the object.

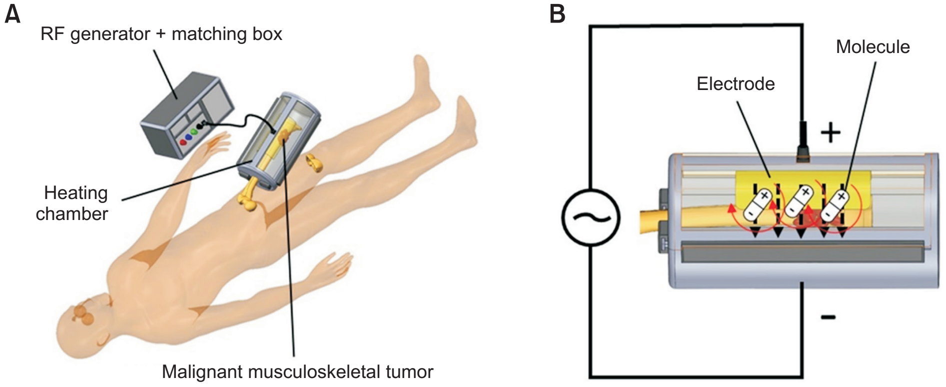

Fig. 1. Schematic diagram of an *in-situ* local tumor ablation machine using radiofrequency (RF) dielectric heating. (A) Concept. (B) Principle of operation.

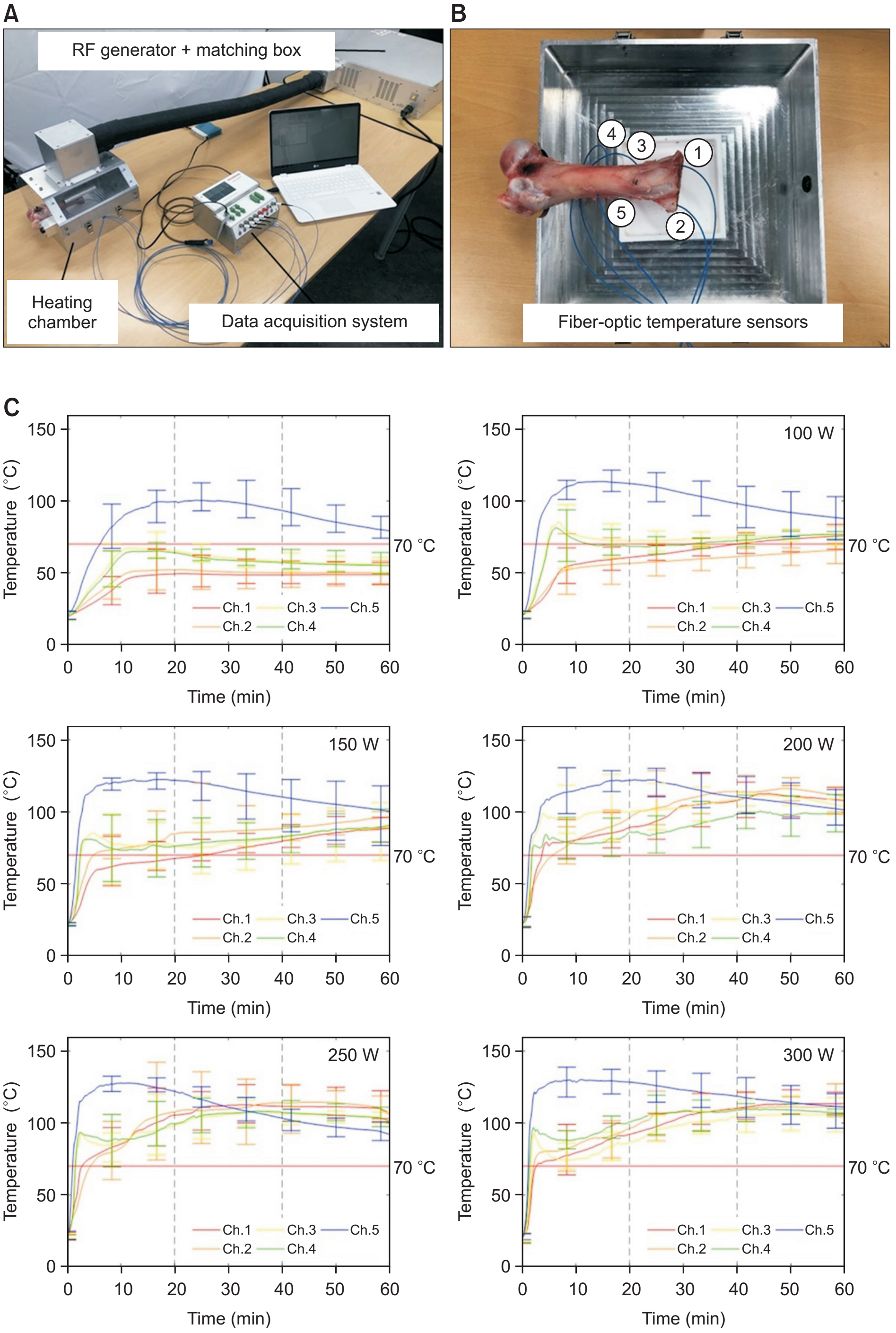

Fig. 2. Temperature measurement was performed during radiofrequency (RF) dielectric heating. (A) Experimental machine and apparatus. (B) Temperature sensors inserted in a bone model positioned in the heating chamber. (C) Temperature change at each measurement site according to the power output.

Experiments

Bone temperature measurement during heating

The distal part of the experimental bone model was accommodated in the machine for RF dielectric heating. The distal end, which is the cut surface, is placed in the middle of the electrode plate. The length of the accommodated portion of the bone was 10.75 cm. Two fiber-optic temperature sensors were inserted in the metaphysis, two in the meta-diaphysis, and one in the diaphysis. For the heating experiments, the RF generator power varied from 50 W to 300 W in steps of 50 W. The temperature changes at each measurement site were recorded six times during heating at each power for 60 minutes (Fig. 2B).

Processed bone stiffness measurement

Experiments were conducted to compare the stiffnesses of the bone models recycled by different methods. Unprocessed bones were used as controls, along with the pasteurized and proposed RF-heated bones. The median weights and lengths of the bone models for compressive stiffness measurements were 200 g (range, 198.6–216.7 g) and 152.5 mm (range, 141–166 mm) for the unprocessed bones; 216.65 g (range, 183–227.3 g) and 162.5 mm (range, 137–176 mm) for the RF-heated bones; and 204.25 g (range, 192.1–227.6 g) and 143.5 mm (range, 140–155 mm) for the pasteurized bones. There were no statistically significant differences in the weights and lengths between the unprocessed, RF-heated, and pasteurized bone models ($p = 0.612$ and $p = 0.093$, respectively). In addition, the median weights and lengths of the bone models for bending stiffness measurements were 198 g (range, 170.2–219.4 g) and 139.5 mm (range, 129–153 mm) for the unprocessed bones; 200.65 g (range, 170.2–232 g) and 143 mm (range, 131–146 mm) for the RF-heated bones; and 201.65 g (range, 184.1–212.2 g) and 139.5 mm (range, 130–145 mm) for the pasteurized bones. The unprocessed, RF-heated, and pasteurized bone models did not show statistically significant differences in their weights and lengths ($p = 0.86$ and $p = 0.596$, respectively).

The RF-heated bone was processed with a minimum temperature point of 70 °C for 30 minutes under an RF power of 200 W. To prepare the pasteurized bones,[15] the bone models were enclosed in a plastic container filled with aseptic distilled water preboiled at 70 °C, and the container was placed into a water-bath pasteurization machine. Pasteurization was then performed at 70 °C for 30 minutes. The force and displacement were measured using a compressor, and the compressive and bending stiffnesses were estimated (Fig. 3A and B). In the compressive stiffness test, the proximal part of the bone model was fixed to a jig using a resin so that the bone cutting surface was parallel to the press surface of the tester. Pressure was then applied to the jig to compress the bone, and displacement of the bone based on pressure was evaluated. The compressive stiffnesses of the unprocessed, pasteurized, and RF-heated bones were measured and compared for six samples each. In addition, the bending stiffness test was conducted using 4-point jigs. Since the bone models

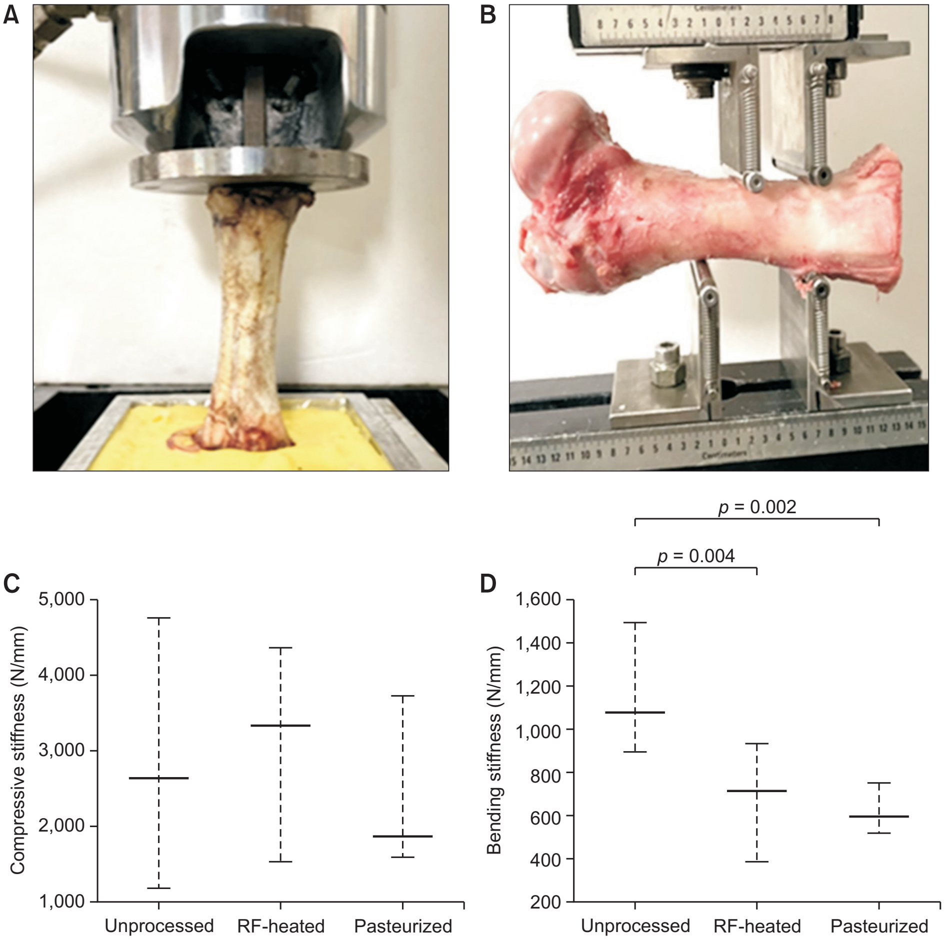

Fig. 3. Stiffnesses of the processed and unprocessed bones were measured. (A) Experiment to measure compressive stiffness. (B) Experiment to measure bending stiffness. Comparison of the compressive (C) and bending (D) stiffnesses among the unprocessed, radiofrequency (RF)-heated, and pasteurized bones.

were unstandardized samples, it was difficult to measure the absolute stiffness. When a person is standing upright, the femur receives a bending force from the posteromedial to the anterolateral direction. Accordingly, the jig points were positioned so that a similar force direction could be simulated with the 4-point jig. One point on the upper loading jig was placed at the point of diaphysis, and another point was installed 5 cm distal to the former. One point on the lower support jig was placed 3 cm proximal to the first point of the upper jig, and the other point was installed 8 cm distal to this preceding point. The bone was fixed to the jig so that the anterolateral aspect faced downward. Force was then applied to the two points of the upper loading jig, and bone displacement was measured while applying pressure to the jig. Therefore, the unit of the bending stiffness was N/mm, as in the case of the compressive stiffness. The bending stiffnesses were also measured and compared for six samples of each type of bone.

Statistics

Continuous variables were presented as medians and ranges. Statistical differences in the weights and lengths of the RF-heated, pasteurized, and control bones were analyzed using the Kruskal-Wallis test. Differences in bone stiffness between two groups were evaluated using the Mann-Whitney *U*-test.

RESULTS

Bone Temperature Changes During Heating

The experimental results are shown in Fig. 2C. Observations of the changes in the temperature inside the bone over time showed that an initial rapid temperature rise occurred and converged to a certain value. When 200 W of power was supplied, it was confirmed that the temperatures at all measurement sites reached 70 °C or higher in 6 minutes and that the temperature was maintained. At a power below 200 W, the temperature increase rate was lower or the minimum temperature did not exceed 70 °C. A power value of more than 200 W also helped achieve the target temperature in a short latency, but the maximum temperature was higher than necessary.

Processed Bone Stiffness Comparison

Compressive stiffness

The median compressive stiffnesses of the unprocessed, RF-heated, and pasteurized bones were 2,636.1 N/mm (range, 1,166.1–4,751.7 N/mm), 3,326.6 N/mm (range, 1,529.1–4,363.5 N/mm), and 1,856 N/mm (range, 1,586.8–3,717.7 N/mm), respectively. The median compressive stiffness of the pasteurized bones was approximately 70.4% of that of the unprocessed bones, and the median value of the RF-heated bone was 79.2% higher than that of the pasteurized bone. Nevertheless, these differences were not statistically significant between any two groups and between the three groups (Fig. 3C).

Bending stiffness

The median bending stiffnesses of the unprocessed, RF-heated, and pasteurized bones were 1,074.65 N/mm (range, 891.48–1,491.9 N/mm), 711.98 N/mm (range, 381.91–931.27 N/mm), and 593.295 N/mm (range, 514.1–748.42 N/mm), respectively. The median bending stiffness of the RF-heated and pasteurized bones was approximately 66.3% and 55.2% of that of the unprocessed bones, respectively. The median value of the RF-heated bone was 20% higher than that of the pasteurized bone. Statistical analyses demonstrated that the bending stiffness in the group with the unprocessed bones was significantly higher than that in the groups with the RF-heated and pasteurized bones ($p = 0.004$ and $p = 0.002$, respectively) (Fig. 3D).

DISCUSSION

In this study, we proposed the novel concept of *in-situ* local tumor ablation and recycling machine based on RF dielectric heating. The study was conducted using an experimental machine and bone models of porcine carcasses, which showed that the temperatures at all sites of measurements in the bone models reached temperatures that can achieve tumor cell eradication in a short latency along with temperature maintenance. Biomechanical experiments were performed to demonstrate that the differences in compressive stiffness were not statistically significant among unprocessed, RF-heated, and pasteurized bones; the median bending stiffness of the RF-heated bone was also higher than that of the pasteurized bones.

The principle behind surgical removal of malignant musculoskeletal tumors is to resect the tumors, including the surrounding normal tissue cuff to not leave microsatellite lesions or tumor cells that may exist in the reactive zone around a tumor. When tumor cells or tissues are directly exposed to the surgical field during surgery, the field may be contaminated by the malignant tissues or cells, thereby increasing the possibility of local recurrence. Therefore, the no-touch technique is preferred over invasive methods, such as catheter or antenna insertion for local tumor ablation. Eventually, we decided to construct a device including a container that could completely encapsulate a tumor-bearing bone. Initially, we attempted to design a machine with a container having a water bath that could be used within the surgical field by applying the conventional pasteurization procedure. However, we expected that it would not be straightforward to seal the space between the bone insertion hole of the container and the bone to prevent water leakage or to use the actual device owing to the weight of the container with water. Next, a microwave machine was devised that could be mounted around a tumor-bearing bone, but there was the risk that the microwave application may not ensure complete tumor eradication owing to uneven heating of the target area.

RFs have large wavelengths that provide a more uniform heating pattern, and a greater penetration depth than microwave frequencies. RF heating is based on the concept of dielectric loss that leads to the dissipation of power into the target material. The major component of dielectric loss in RF results from orientational polarization that occurs in materials composed of molecules with permanent dipole moments. The direction of the dipole at the operating frequency varies according to the direction of the applied electric field. Rotation encounters resistance owing to the thermal agitation and inertial resistances of the surrounding molecules, resulting in mechanical friction. This friction generates heat from the energy stored in the electric field, which forms the basis of RF heating. The main advantage of RF heating is that volumetric energy deposition results in rapid heat generation and eliminates delays associated with heat transfer.24)

RF heating equipment is widely used in various industries, such as wood, paper, plastic, and food industries. Frozen meat on a conveyor belt, which moves between flat electrodes at 3 m/hr, can be thawed by RF heating,25) and *Escherichia coli* in eggs can be decontaminated via RF heating.26) We derived the inspiration for the proposed concept of local tumor ablation and recycling from another study27) that reported that curved electrodes were effective in improving temperature uniformity during RF thawing of cylindrically shaped pork sirloin.

The present study has several limitations. First, no *in vivo* experiments were conducted to evaluate malignant cell eradication by the proposed RF dielectric heating method. Animal studies using sarcoma patient-derived orthotopic xenograft models could be implemented in this regard. Nevertheless, the effect of tumor ablation by hyperthermia is already so well known that no further studies may be required to prove the concept. Second, the present experiments were performed by heat application with open-loop control and no temperature feedback. The temperatures in some parts of the bone models exceeded 100 °C; as mentioned earlier, overheating may clinically affect bone stiffness in the short term and regeneration in the long term. Future research is therefore required to devise a modality for temperature control following contactless measurements applicable in actual surgical procedures to maintain an appropriate temperature range. Third, preliminary results of biomechanical experiments were not clearly relevant. Tissue analysis should be conducted to understand what happens at the tissue level, and yield and post-yield behavior should be assessed, too.

Temperature and duration controls in the heat treatment during recycling are essential for two reasons, namely eradication of malignant cells and preservation of bone inductive activity, while the more important of the two controls should be to achieve complete tumor ablation. The lethal effects of hyperthermia have been proven in previous literature. An experimental study28) investigating the effects of hyperthermia on the viability of swarm rat chondrosarcoma reported that tumor blocks heated to 60 °C or higher for 10 minutes did not show tumor growth 35 weeks after transplantation of the blocks into rats. The first clinical study in orthopedic oncology16) demonstrated that there were no local recurrences at a mean follow-up period of 52 months after implantation of tumor-bearing bones treated by pasteurization at 60 °C for 30 minutes in 25 patients who had sarcoma. Meanwhile, osteoinduction originates from the response of mesenchymal cells in the recipient bed to bone morphogenetic protein (BMP) moved from the bone graft. An experimental study18) on bone inductive activity after heat treatment showed that femoral cortical bones from rats heated in a water bath at 70 °C for 1 hour presented induction of mRNAs for alkaline phosphatase as well as types I and II collagens 11 days after transplantation of the bones into the muscles of rats, indicating preservation of osteoinductivity, while the deleterious effects of hyperthermia were obvious when the bones were treated to 90 °C or higher. Another study17) reported that the BMP of the bone matrix degraded at heat exposures over 70 °C. In the abovementioned clinical study,16) primary bone union was achieved in 20 patients (80%), suggesting that the bone inductive property may not be stunted. Therefore, several existing studies12,15,16) have proposed heat treatment at 60 °C to 65 °C for 30 to 40 minutes to recycle the tumor-bearing autografts. The present study proves that the temperatures at all measurement sites on the bone samples could reach around 70 °C in a short latency and that the temperature changes converged as well as persisted thereafter. It is expected that an appropriate temperature can be maintained for a sufficient duration via control of the RF generation output.

When measuring the temperature change at each site on the bone models in the current study, rapid temperature increases were observed at the early stages, which may be caused by the high dielectric constant of the moisture contained in the bone that increases the efficiency of dielectric heating. Thereafter, as the moisture inside the bone decreases owing to phase changes, the permittivity of the bone decreases and temperature converges to a state at which the amount of dielectric heating and heat loss to the outside are in equilibrium. Meanwhile, the temperature in the diaphysis increases to the maximum value because the bone is composed of a mixture of various components that form several layers with different thicknesses, thereby resulting in an uneven dielectric constant depending on the sites. However, the most substantial cause is that the electric field intensity may not be spatially uniform within the material. Solving this problem in three dimensions by an analytical solution is often too complex, especially when a dielectric material is added. In such cases, numerical techniques such as the finite element method are used. Experiments can be conducted using the COMSOL Multiphysics 5.6 software (COMSOL AB), and the distributions of the electric field and temperature changes were simply simulated as a reference for follow-up research. As in the actual experiments, the simulation results showed that the temperature is highest in the diaphysis of the bone model and that the intensity of the electric field was also concentrated therein. While the electric field strength was higher in the gap region between the bone and the electrode, a fringing field with curved field lines was observed near the edges of the electrode and the bone. In addition, the results demonstrated that inserting bones could result in loss of the original field uniformity between the electrodes, such that the sharp edges of the electrodes may be another cause of the nonuniformity (Fig. 4).

Optimal design of the electrode shape and spacing can hence improve the uniformity of the electric field intensity. The characteristics of RF heating are mainly influenced by shape parameters, such as the distance between the electrode and the object, the distance between the electrodes, and the size of the electrode. Sensitive shape parameters can be selected as the design variables and optimized through the design of experiments. The finite element analysis software analyzes the heat transfer behavior for each combination of the design variables and utilizes the results as the objective function of optimization. We plan to verify the improved performance through experiments after fabricating the optimally designed structures.

The present biomechanical study demonstrates that the median compressive and bending stiffnesses of RF-heated bones were higher than those of pasteurized bones, although the differences were not statistically significant. An experimental study[29] reported that the compressive strengths of bone grafts harvested and reimplanted after pasteurization at 70 °C for 20 minutes and irradiation at 50 Gy one fraction for 20 minutes decreased by 40%–67% than the controls immersed in a saline dish for 20 minutes at 12 weeks after implantation; the pasteurized autograft was also observed to have the lowest compressive strength. Another clinical study[30] with 278 pasteurized autografts showed the development of major complications, including graft fracture in 16 cases (16%), failure of fixation in 13 cases (5%), and graft resorption in 14 cases (5%), over a follow-up period of longer than 2 years, suggesting that pasteurized autogenous bone grafts should be used with caution in young patients, in the pelvic region, and in au-

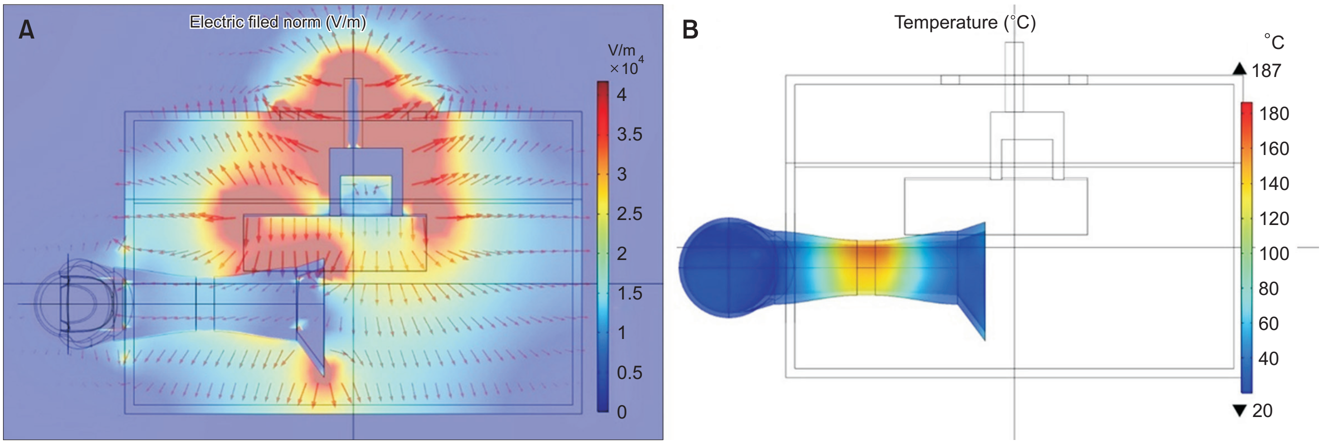

Fig. 4. Simulations demonstrate the distributions of temperature and electric field intensity. (A) Magnitude and direction of the electric field indicated by color contour and arrows. (B) Distribution of the bone temperature during heating, expressed as a colored contour.

tograft-prosthesis composite form. The results suggest that pasteurized autografts could be considered for small intercalary or distal long bone reconstructions and may be best indicated after hemicortical excision of the long bones.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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