International Journal of Radiation Oncology biology • physics

www.redjournal.org

Clinical Investigation

Comparing the Effectiveness of Combined External Beam Radiation and Hyperthermia Versus External Beam Radiation Alone in Treating Patients With Painful Bony Metastases: A Phase 3 Prospective, Randomized, Controlled Trial

Mau-Shin Chi, MD,[*,†] Kai-Lin Yang, MD,[*,‡,§] Yue-Cune Chang, PhD,[‖] Hui-Ling Ko, MD,[*] Yi-Hsien Lin, MD,[¶,#] Su-Chen Huang,[*] Yi-Ying Huang,[*] Kuang-Wen Liao, PhD,[**] Motoharu Kondo, MD, PhD,[††] and Kwan-Hwa Chi, MD[*,‡,¶]

Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan; †Biomedical Science and Engineering, and **Institute of Molecular Medicine and Bioengineering, National Chiao-Tung University, Hsinchu, Taiwan; ‡Institute of Biomedical Imaging and Radiological Sciences, and ¶School of Medicine, National Yang-Ming University, Taipei, Taiwan; §School of Medicine, Fu Jen Catholic University, New Taipei City, Taiwan; ‖Department of Mathematics, Tamkang University, New Taipei City, Taiwan; #Division of Radiotherapy, Cheng Hsin General Hospital, Taipei, Taiwan; and ††Kyoto Prefectural University of Medicine, Kyoto, Japan

Received Apr 25, 2017, and in revised form Sep 11, 2017. Accepted for publication Sep 13, 2017.

Summary

Bone pain recurrence after palliative radiation therapy (RT) to bony metastases is a common scenario. In this randomized phase 3 trial, we aimed to compare the rate, duration, and time to achieve complete pain relief and radiologic responses between RT alone (30 Gy/10 fractions) and hyperthermia

Purpose: To compare the response, duration of pain relief, and time to achieve complete pain relief after radiation therapy (RT) with or without hyperthermia (HT) in patients with painful bony metastases.

Methods and Materials: Cancer patients with bony metastases and pain score $\geq$4 on the Brief Pain Inventory (BPI) were randomized to RT of 30 Gy in 10 fractions combined with HT (RT + HT) versus RT alone. Hyperthermia was performed by the Thermotron RF-8, with maintenance of the target temperature for 40 minutes per treatment within 2 hours after RT, twice weekly for 2 weeks. Patients were stratified by lesion number (solitary or multiple), BPI score (4-6 vs 7-10), and primary site. The primary endpoint was complete response (CR) (BPI = 0 with no increase of analgesics) within 3 months after treatment. This study was registered with ClinicalTrials.gov.

Reprint requests to: Kwan-Hwa Chi, MD, Department of Radiation Therapy and Oncology, Shin Kong Wu Ho-Su Memorial Hospital, 95 Wen-Chang Rd, Shih-Lin, Taipei 111, Taiwan. Tel: (+886) 2-28332211, ext. 2273; E-mail: M006565@ms.skh.org.tw

Conflict of interest: none.

Supplementary material for this article can be found at www.redjournal.org.

Int J Radiation Oncol Biol Phys, Vol. 100, No. 1, pp. 78–87, 2018
0360-3016/$ - see front matter
https://doi.org/10.1016/j.ijrobp.2017.09.030

(HT) (by Thermotron RF-8) combined with RT. The addition of HT to RT significantly increases pain control and extends response duration compared with RT alone for painful bony metastases.

Results: The study was terminated early after an interim analysis of 57 patients, 3 years after the first enrollment (November 2013 to November 2016): 29 patients in the RT + HT group and 28 patients in the RT-alone group. The CR rate at 3 months after treatment was 37.9% in the RT + HT group versus 7.1% in the RT-alone group ($P = .006$). The accumulated CR rate within 3 months after treatment was 58.6% in the RT + HT group versus 32.1% in the RT-alone group ($P = .045$). Median time to pain progression was 55 days in patients with CR (n = 9) in the RT-alone group, whereas the endpoint was not reached during the 24-week follow-up in the RT + HT group ($P < .01$).
Conclusions: The addition of HT to RT significantly increases the pain control rate and extends response duration compared with RT alone for painful bony metastases.

Introduction

Bone metastases lead to significant morbidities, such as unbearable pain, pathologic fractures, or cord compression. Many randomized trials have confirmed the mainstay role of radiation therapy (RT) to alleviate pain or control the progression of osseous metastatic disease (1, 2). A dose of 30 Gy in 10 fractions is generally regarded as the standard palliative RT dose. Although symptom relief has been seen in 50% to 80% of patients who received RT, only less than 50% of patients have been reported as pain-free after 4 weeks (3), and 50% have experienced pain relapse at approximately 12 weeks (median, 9.6-15 weeks) after treatment (4). An impact of bone ossification usually has been seen at 10 to 12 weeks after RT (5).

It has long been recognized that hyperthermia (HT) in the range of 40° to 43°C and higher acts as a radio- and/or chemo-sensitizer (6, 7). The increased RT or chemotherapy effect is called thermal sensitization. The Thermotron RF-8 (Yamamoto Vinita, Osaka, Japan), which delivers 8-MHz radiofrequency (RF)-based deep HT, is one of the most commonly used HT machines. The RF-8 requires a pair of capacitive electrodes placed on opposite sides of the body to treat superficial, subsurface, or deep-seated tumors, especially at 5 to 7 cm depth; it has been used in combination with RT for the past 2 decades in Japan (8). Dielectric heat with high power has been produced after rapid changes in the electric field (8 MHz) to reach the goal temperature in a specific region (9). Since the 1990s, increased local control or overall survival by combining RF-8 with RT have been reported in multiple randomized trials in the settings of esophagus cancer (10), advanced cervical cancer (11, 12), advanced head and neck cancer (13), and advanced non-small cell lung cancer (14). Hyperthermia also stimulates osteoblast activity to improve osteogenesis and decrease fracture risk (15).

Despite the high incidence of bony metastases and the relatively short duration of treatment response, the clinical experience of combining HT with RT has never been reported. We aimed to conduct the first phase 3 study comparing the rate, duration, and time to achieve complete pain relief and radiologic responses between RT and the combination of HT with RT.

Methods and Materials

Study design

The primary objective of the study was to evaluate the rate of complete response (CR) in indicated lesions, defined as a Brief Pain Inventory (BPI) score of zero plus no concomitant increase in analgesic use within 3 months after RT. Secondary objectives included time and duration of pain relief; differences in radiologic tumor response on measurable lesions at week 12; quality of life changes recorded by the European Organization for Research and Treatment of Cancer C30 questionnaire; and treatment-related adverse events. This randomized phase 3 study was approved by the instiutional review board of Shin Kong Wu Ho-Su Memorial Hospital and is registered with ClinicalTrials.gov. NCT 01842048.

Patients

Eligible patients had a histologically or clinically (computed tomography [CT], magnetic resonance imaging, bone scan, or positron emission tomography/CT scan) confirmed solid tumor bony metastases with the index lesion involving or abutting bone; Eastern Cooperative Oncology Group performance status score of 0 to 3; age between 20 and 75 years; and life expectancy $\geq$3 months. The index lesion was defined as a lesion $<$20 cm with worst pain (BPI $\geq$4) over the last 24 hours, in the irradiated field contoured from CT simulation, and effectively covered by electrodes (maximal diameter 30 cm). Each patient could have only 1 index lesion for treatment and evaluation. Radiation to other metastatic lesions was allowed after treatment of the index lesion, to prevent the influence on analgesic dose evaluation. Systemic therapy (chemotherapy, hormonal therapy, target therapy, or bisphosphonate), analgesics, or prior surgery without metal implants were allowed. The strength of analgesics and systemic therapy should not have been changed for 4 weeks before and during RT. Exclusion criteria included index lesion involving the skull, pathologic fracture requiring immediate surgical intervention, previous RT to the lesion site,

schedule of changing systemic treatment during the study period, history of metal implant inside or outside the irradiation field, and a pacemaker insertion. All patients provided written informed consent.

Treatment plan, stratification, and randomization

Patients were randomly assigned to receive either combination treatment (RT + HT) or RT alone. Patients in the RT + HT group maintained the target temperature for at least 40 minutes per treatment by the RF-8 machine twice weekly within 2 hours after RT for a total of 4 times. The radiation protocol was 3 Gy per fraction, 5 times per week, for a total of 30 Gy (2 weeks' treatment). Patients were stratified by number of sites (solitary or multiple), primary cancer origin (breast or prostate vs other), and severity of pain. To include an equal number of patients in both treatment arms, a blocked randomization schedule was used for each stratum (16).

Radiation therapy technique

After thermoplastic mask immobilization and CT simulation, the target volume was defined after registration of the diagnostic magnetic resonance imaging, CT, or positron emission tomography/CT scan to the simulation CT scan (5-mm slice thickness). The affected bony lesions, including soft tissue parts, were delineated as the gross tumor volume. For coverage of areas with potential microscopic disease, a safety radical margin at least 20 mm around the gross tumor volume was defined as the clinical target volume. The planning target volume was generated with a 3-dimensional margin of 5 mm around the clinical target volume. Depending on the tumor location, the esophagus, lung, heart, thyroid gland, and rectum were delineated as the organs at risk. Three-dimensional conformal RT or step-and-shoot intensity modulated RT plans were generated from an Elekta (Stockholm, Sweden) machine by the Pinnacle treatment planning system (Fitchburg, Wisconsin).

Hyperthermia

The patients were treated in the supine position by the Thermotron RF-8. The Thermotron machine required paired electrodes for heating. For a proper heat-up process, tight skin contact was crucial. An anterior and posterior positioning (0°, 180°) of the electrodes was suitable for treating bone metastases in more than 80% of patients in our study. However, a tilting angle may be need for lesions over the lateral ribs or the extremities. The RF-8 was designed with double movable joints (gantry and electrodes) with a maximal tilting angle of 15°. Computed tomography films during RT simulation were used for tumor localizing. An optimal treating position of the patient was based on maximal coverage of electrodes and by his or her comfort. A smaller electrode was placed near to the tumor for focused power concentration. Electrode pairs used in our study were 25 × 21 cm (7 patients), 25 × 25 cm (6 patients), 21 × 21 cm (5 patients), 30 × 30 cm (2 patients), 25 × 30 cm (4 patients), 14 × 25 cm (2 patients), 10 × 10 cm (2 patients), and 21 × 14 cm (1 patient).

According to common practice with the Thermotron RF-8, the operator started from 150 W and increased the output by 25 to 50 W per minute until the patient complained of discomfort, which is called "output-limiting symptoms" (17). The skin cooling was set on 25°C and may gradually decreased to 10°C or lower to decrease patient discomfort. When pain occurred the output was decreased by 100 W. The output was increased by 50 W again or de-escalated back and forth depending on whether the symptoms reappeared: this was the optimal output dose maintained for the next 40 minutes. Before treatment an intratumoral or intracavitary sensor catheter with 4 temperature points was placed whenever possible, according to the lesion's localization, the patient's performance status, and the patient's agreement to invasive measurement. Intracavitary measurement close to the index lesion, such as lesions over the pelvis (intravaginal, intra-anal) or thoracic spine lesion by esophageal temperature, was performed as an alternative. If those measurements were not suitable, all patients had skin temperature measured under the electrodes and over the lateral side of the body mid-plane between electrodes. In our department the upper limit of the rectal temperature was set at 42.5°C, esophagus temperature at 41.5°C, and lateral side body temperature at +3.5°C outside the electrodes and +6.5°C inside the electrodes' coverage to prevent overheating. The increased skin temperature over the lateral side of the body mid-plane between electrodes may reflect the "estimated interval temperature," as previously reported (18).

Response assessment and toxicities

Pain relief was objectively measured before and after RT by BPI score (19). The scores were collected by a questionnaire study 15 times over a 6-month follow-up period. The pain relief score was assessed for the worst pain related to the index lesion. The first survey was performed at enrollment, the second survey on the first day of treatment, the third to sixth survey during the treatment period (2 surveys per week); the seventh and eighth surveys were performed weekly after treatment (third and fourth week); the 9th to 12th survey every 2 weeks (5th-12th week); and the 13th to 15th surveys monthly until 6 months of follow-up. Changes in the severity of pain before and after RT were statistically analyzed.

In accordance to the guidelines of the International Bone Metastasis Consensus Working Party (20), CR was defined as pain score 0 at the treated site, with no concomitant increase in analgesic intake (oral morphine equivalent dose). A partial response (PR) was defined as either pain reduction of 2 points at the treated site without increase or decrease the analgesic dosage by 25% (oral morphine equivalent dose from baseline). Pain progression was defined as an increase of BPI $\geq$2 points at the treated site without increase of the analgesic dose or a $\geq$25% increase

of dose with stable or increased pain score by 1 point. Patients with a CR or PR were considered to have a response, whereas patients with progressive or stable disease were considered as nonresponders.

All toxicities related to the HT procedure were recorded using the Common Terminology Criteria for Adverse Events, version 4.0 (21). Any toxicity of grade 3 or 4 (except elevated core body temperature after treatment) was considered as a severe adverse event. Adverse events of less severity were reported on case report forms and submitted with routine data submission.

The radiologic response was defined according to the Response Evaluation Criteria in Solid Tumors (version 1.1) (22). Measurable indicated lesions were evaluated for reduction in tumor volume as shown on CT images after treatment on week 12. A radiologic complete remission (radiologic CR) was defined as the complete disappearance of all soft tissue compartments of bony lesions regardless of radiologically assessed ossification. A radiologic partial remission (radiologic PR) was defined as at least a 30% decrease in the sum of diameters of the target lesions, using as reference the baseline sum of diameters. Radiologic progressive disease was defined as at least a 20% increase in the sum of diameters of the target lesions, taking as reference the smallest sum of diameters of study. Radiologic stable disease was defined as neither sufficient shrinkage to qualify for radiologic PR nor sufficient increase to qualify for radiologic progressive disease.

Statistical analysis

The planned sample size for a 2-sided test with $\alpha = 0.05$ and 80% power was 152 patients, which would allow the detection of a 15% difference in the CR rate. An interim analysis was planned at 3 years; the analysis was performed in conjunction with the data safety monitoring committee at 3 years after the first enrollment of the trial. The committee decided on early termination of the study on the basis of the statistical significance of the efficacy and the slow recruitment of this trial, which would require another 3 years to reach the original planned sample size.

To compare the differences between the groups, a χ^2 test was used; the Fisher exact test was used for the severity of adverse events. The Kaplan-Meier method, a log-rank test, and Cox's proportional hazard model were used for comparing the between-group differences of the CR rates and/or relapsed rates. The statistical software SPSS version 22.0 (IBM, Armonk, NY) was used for performing statistical analyses. All tests were 2-sided, and statistical significant was defined as a P value of $<.05$.

Results

From November 2013 to November 2016 a total of 67 patients were enrolled; 10 patients were ineligible, and thus 57 patients were randomized in a 1:1 fashion. All randomized patients were included for analysis. There were 29 patients in the RT + HT group and 28 in the RT-alone group (Fig. 1). The randomly assigned patients were followed and included in the primary analysis. The patients' baseline characteristics were comparable. As shown in Table 1, there were no significant differences between these 2 treatment groups in age, sex, painful sites, the primary cancer origin (breast/prostate cancer vs others), lesion location or depth, and worst BPI score. The mean maximal power delivered in our study was 559.3 W (range, 300-1250 W), and the mean specific absorption rate was 6.08×10^4 W/kg (range, 2.8-19.4 $\times$ 10^4 W/kg).

Pain reduction was more often achieved in the RT + HT group than in the RT-alone group (Table 2, Fig. 2, and Supplementary Figure E1 [available online at www.redjournal.org]). As shown in Table 2, the CR rate at the third month after treatment was 37.9% (n=11) in the RT + HT group versus 7.1% (n=2) in the RT group (P=.006). The accumulated CR rate within 3 months after treatment was 58.6% (n=17) in the RT + HT group and 32.1% (n=9) in the RT-alone group (P=.045) (Table 2). The data safety monitoring committee suggested an early termination because the CR rate at the third month was a more clinically relevant outcome than the accumulated CR rate at the first, second, and third month, and it may have been unethical to treat with the RT-only arm.

The curve of the cumulative CR rate in the RT + HT group was higher than that in the RT-alone group during the entire follow-up period (Fig. 2). The corresponding log-rank test showed that the overall comparison between these 2 treatment groups in the curves of the cumulative CR rate was borderline significant (P=.07). For comparing the instantaneous CR rates between these 2 treatment groups, the results of the Cox regression show that the hazard rate ratio of the CR rate in the RT + HT versus the RT-alone group was 2.066 (P=.08). We further presented the curves of the CR rates as a function of time (up to the 6-month follow-up, or equivalently, 15 measures) of both groups. As shown in Figure 2 there was higher frequency and longer duration of

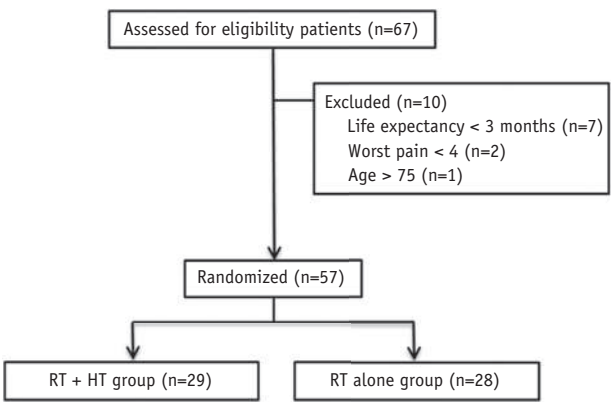

Fig. 1. Patient CONSORT flow diagram. *Abbreviations:* HT = hyperthermia; RT = radiation therapy.

Table 1 Demographic characteristics of the patients at baseline

Characteristic	RT + HT (n=29)	RT alone (n=28)	P
Age (y), mean ± SD	56.86 ± 11.06	59.04 ± 11.26	.465*
Sex			.701†
Male	17 (58.6)	15 (53.6)	
Female	12 (41.4)	13 (46.4)	
Metastatic site(s)‡			.881†
Solitary	13 (44.8)	12 (42.9)	
Multiple	16 (55.2)	16 (57.1)	
Primary cancer site‡			.284†
Breast/prostate cancer	4 (13.8)	7 (25)	
Other cancer	25 (86.2)	21 (75)	
Location of lesions			.959§
Cervical spine	3 (10.3)	4 (14.3)	
Thoracic spine	8 (27.6)	7 (25.0)	
Sternum, ribs, and extremity	7 (24.1)	5 (17.9)	
Lumbar spine	3 (10.3)	4 (14.3)	
Pelvic bones	8 (27.6)	8 (28.6)	
Depth of lesions (from tumor center to nearest electrode, cm)			
Cervical spine	7.40 ± 2.43	6.95 ± 2.07	.857‖
Thoracic spine	14.10 ± 3.42	14.83 ± 2.02	.397‖
Sternum, ribs, and extremity	4.86 ± 2.97	4.74 ± 2.35	.755‖
Lumbar spine	13.40 ± 1.04	14.95 ± 3.41	1.000‖
Pelvic bones	15.88 ± 17.13	17.13 ± 2.12	.798‖
Worst pain score (Brief Pain Inventory)‡			.707†
4-6	10 (34.5)	11 (39.3)	
7-10	19 (65.5)	17 (40.7)	
Median power of Thermotron RF-8 (W), median (range)	559.3 (300-1250)		
Specific absorption rate (W/kg), median (range)	6.08×10^4 (2.8-19.4×10^4)		

Abbreviations: HT = hyperthermia; RT = radiation therapy.
Values are number (percentage) unless otherwise noted.
* Independent *t* test.
† Pearson χ^2 test.
‡ This characteristic was used as a stratification factor at the time of randomization.
§ Fisher exact test.
‖ Mann-Whitney test.

CR after RT + HT compared with RT alone. For further comparisons, we examined the CR and non-CR mutual transition rates in the RT + HT and RT-alone groups from month 1 to month 2 and month 2 to month 3. As shown in Supplementary Table E1 (available online at www.redjournal.org), compared with the RT-alone group, the patients treated by RT + HT had not only a higher non-CR to CR transition rate but also a lower CR to non-CR transition rate.

Table 2 Comparison of CR rates between RT + HT and RT alone at 1, 2, and 3 months after treatment

Characteristic	RT + HT (n=29)	RT alone (n=28)	P
Complete response (1 mo)			.346*
CR	7 (24.1)	4 (14.3)	
Non-CR	22 (78.6)	24 (85.7)	
Complete response (2 mo)			.033*
CR	10 (34.5)	3 (10.7)	
Non-CR	19 (65.5)	25 (89.3)	
Complete response (3 mo)			.006*
CR	11 (37.9)	2 (7.1)	
Non-CR	18 (62.1)	26 (92.9)	
Best response within 12 wk			.045*
CR	17 (58.6)	9 (32.1)	
Non-CR	12 (41.4)	19 (67.9)	

Abbreviation: CR = complete response. Other abbreviations as in Table 1.
* Pearson χ^2 test.

Pain control within the RT + HT group lasted longer than that within the RT-alone group. In patients who achieved CR within 3 months, the median time to pain progression was 55 days in the RT-alone (n=9) group, whereas the median time to pain progression was not observed in the RT + HT group during the 24 weeks of the protocol follow-up period (log-rank = 5.65, P=.017; hazard ratio [HR] [95% confidence interval (CI)] 0.263 [0.081-0.852], P=.026) (Fig. 3a). In patients who had at least PR, median time to pain progression was 29 days in the RT-alone group (n=21); whereas the median time to pain progression was not reached in the RT + HT group (n=29) (log-rank = 19.17, P<.001; HR [95% CI] 0.207 [0.096-0.447], P<.001) (Fig. 3b). The median time to pain progression in all patients was 28 days in the RT-alone group (n=28) and not reached in the RT + HT group (log-rank = 25.35, P<.001; HR [95% CI] 0.178 [0.085-0.375], P<.001) (Fig. 3c).

Fifteen patients in the RT + HT group and 12 patients in the RT-alone group had measurable radiologic lesions and were assessed at week 12. One patient (6.7%) in the RT + HT group achieved radiologic CR; 10 (66.7%) versus 3 (25%) had radiologic PR; 4 (26.7%) versus 4 (33.3%) had radiologic stable disease; and 0 (0%) versus 5 (41.7%) had progression on the radiologic assessment in the RT + HT versus RT-alone groups, respectively. As shown in Figure 4, we demonstrated 3 representative cases with obvious bony ossification 8 to 12 weeks after RT + HT treatment. In the 3 cases, electrode sizes of 21 or 25 cm (25 × 25 cm in 2 patients and 25 × 21 cm in 1) were used, and the mean power measured was 590 W (570, 680, and 520 W, respectively).

Only 3 patients had directly measured intratumoral temperature. The average highest temperature measured in tumor was 41.9°C ± 1.2°C. There were 10 patients with intracavitary temperature measurement (4 by intra-anal, 2 by intra-vaginal, and 4 through the nasogastric tube). All patients had mid-plane body temperature measurement. The toxicities were generally mild and acceptable in both

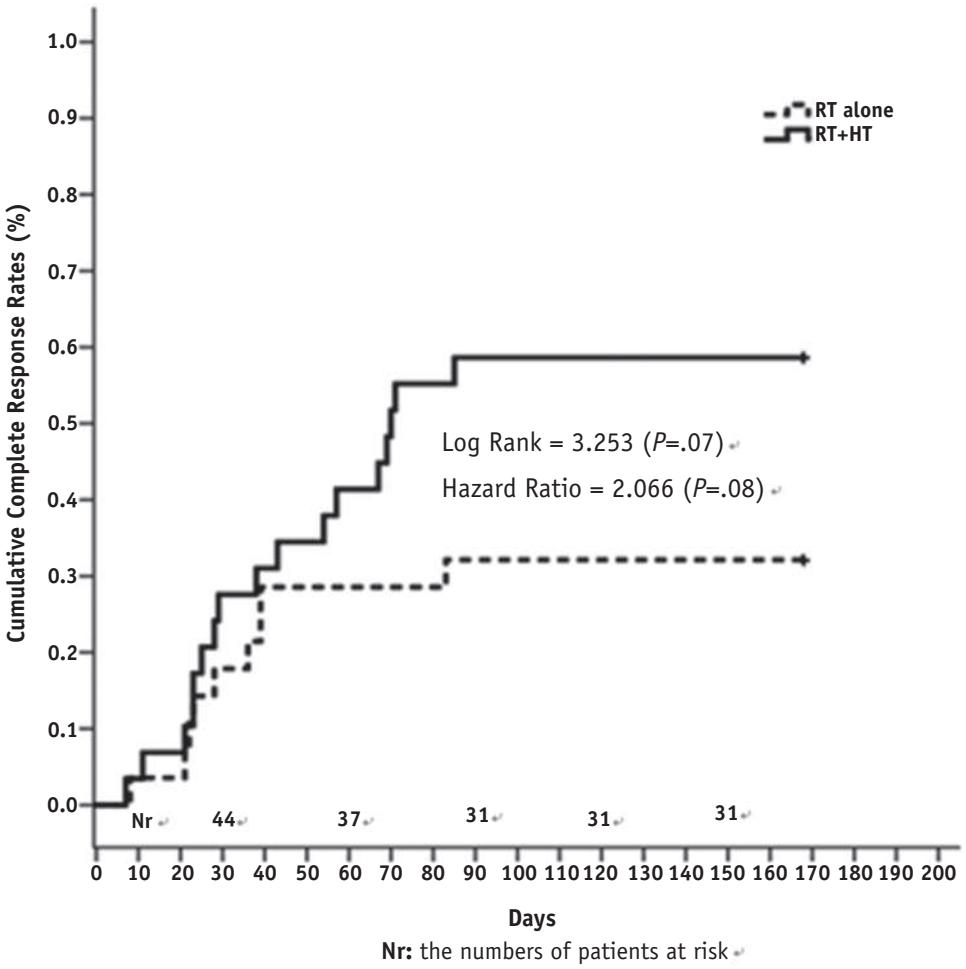

Fig. 2. Cumulative complete response rates in radiation therapy plus hyperthermia (RT + HT) and radiation therapy alone (RT-alone) group.

treatment groups, and there were no grade 3 adverse events documented during the study. The most common treatment-related adverse events were RT related, such as grade 1 skin reaction, nausea/vomiting, and diarrhea. In the RT + HT group (n = 29), a significant increase in local heating pain (48.3% [n = 14] vs 0%, $P < .001$) was observed. Skin within the treatment area often became erythematous for 1 to 2 hours after treatment. Of the patients treated with HT, 6 (20.6%) experienced elevated core body (oral) temperature (>38°C) that could be resolved shortly after HT. The obese patients were more likely to experience subcutaneous fat induration (13.7%, n = 4) persisting for several weeks (Supplementary Table E2; available online at www.redjournal.org). The quality of life assessment showed significant improvement in the first month for patients who received RT + HT. However, no statistically significant differences were seen after the third month of treatment (Supplementary Table E3; available online at www.redjournal.org).

Discussion

A significant increase in sustained CR rate, time, and duration of pain relief in the RT + HT group was observed in this study. In patients who achieved CR, more than half of the patients who received combined RT + HT treatment reported being pain-free after 24 weeks of follow-up, compared with 55 days in patients received only RT.

Nowadays RT is the most effective treatment modality for bony metastases, and pain alleviation has been achieved in 50% to 80% of patients (3). The 2016 American Society of Radiation Oncology evidence-based guideline supported equivalent pain relief and duration of different fraction sizes (8 Gy single fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions) (23). Timing of response to RT is correlated with duration of being pain-free. Patients with improved pain at day 8 after RT have been observed to have a longer pain relapse−free survival compared with patients with later response (3.38 weeks vs 0.3 weeks; $P < .001$) (24). However, in a literature review, up to 30% of patients treated with RT alone ultimately had pain relapse in 12 weeks (4). As shown in our study, the addition of HT to RT led to a significant increase of CR even in the third month after treatment (37.9% vs 7.1%, $P < .006$) (Table 2).

In our study there was a significantly higher radiologic response rate in patients who received HT compared with those who did not (73.4% in the RT + HT group and 25% in

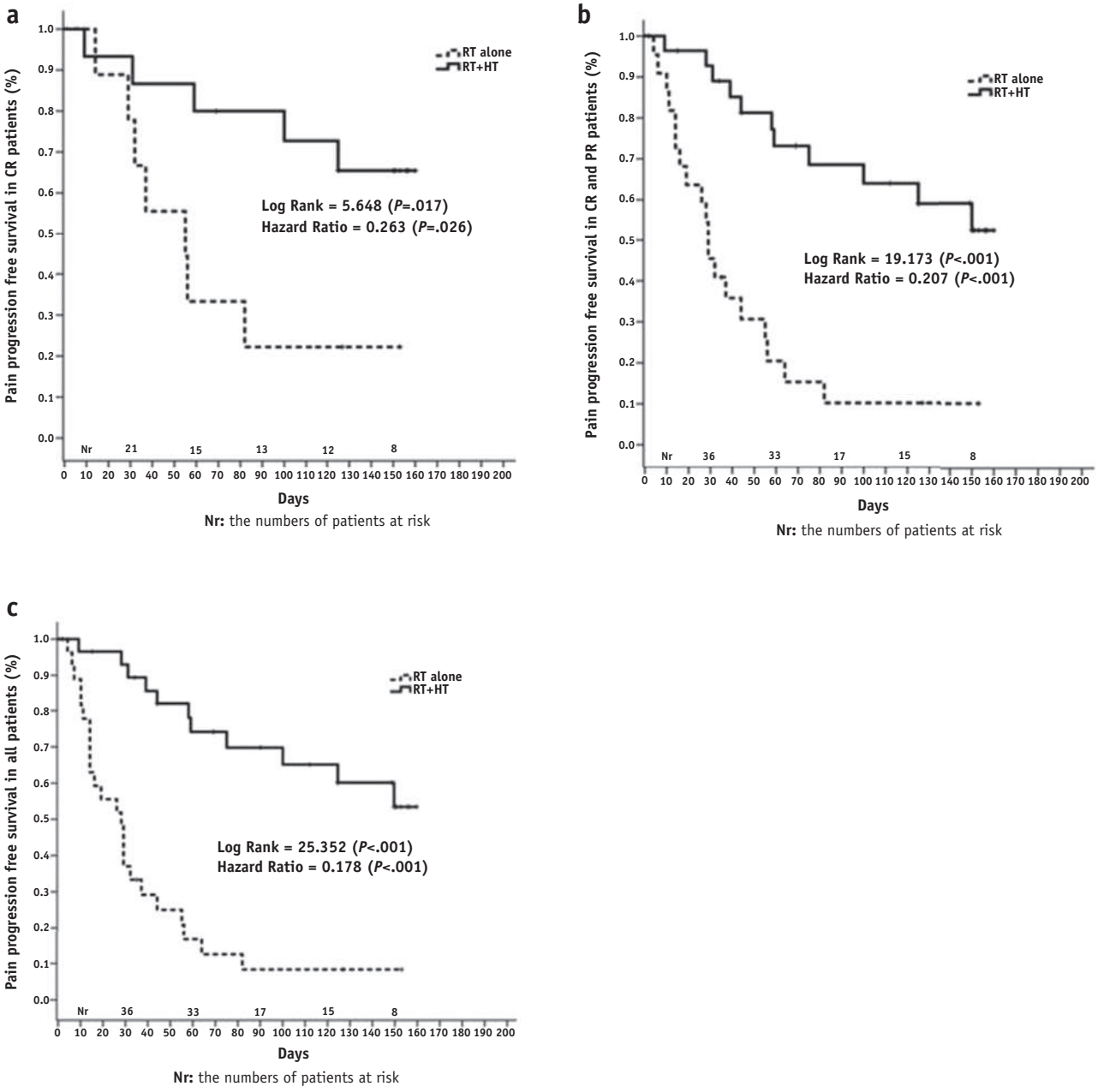

Fig. 3. Time to pain progression. (a) Time to pain progression in patients with complete response (CR). (b) Time to pain progression in patients with complete response (CR) and partial response (PR). (c) Time to pain progression in all patients. *Abbreviations:* HT = hyperthermia; RT = radiation therapy.

the RT-alone group, $P = .014$). Eight patients (53.3%) had at least partial ossification in the RT + HT group, whereas only 2 (16.7%) were observed in the RT-alone group. Pathologic fracture has been a common scenario in bone metastases, leading to significant comorbidity due to decreased bone density. Even after stereotactic body RT, the risk of vertebral compressive fracture was 14.1% and 17.3% at 3 and 12 months (25). In our study, the 30 Gy in 10 fractions schedule may not be enough for such lesions with an extensive soft tissue component, and extending HT may be particularly helpful. Thibault et al (25) reported a significant association of osteolytic percentage measures before treatment with risk of compressive fracture ($P<.001$). The osteolytic threshold was 11.6% measured by volumetric image segmentation software. Radiation therapy has improved bone stability and the density of osteolytic lesions by facilitating reossification (26). The measurement of bone density by Hounsfield unit (HU) is a practical way to determine local response of osteolytic lesions. The mean bone density in radiation-treated metastatic lesions has been increased by 145.8 HU after 3 months ($P<.0001$) and by 238.0 HU after 6 months ($P<.0001$) (27). On the other hand, heat stimulates the activity of osteoblastic cells to improve osteogenesis. In 2015 Ikuta et al (15) showed osteogenesis improvement by mild HT in a defected rat tibia model.

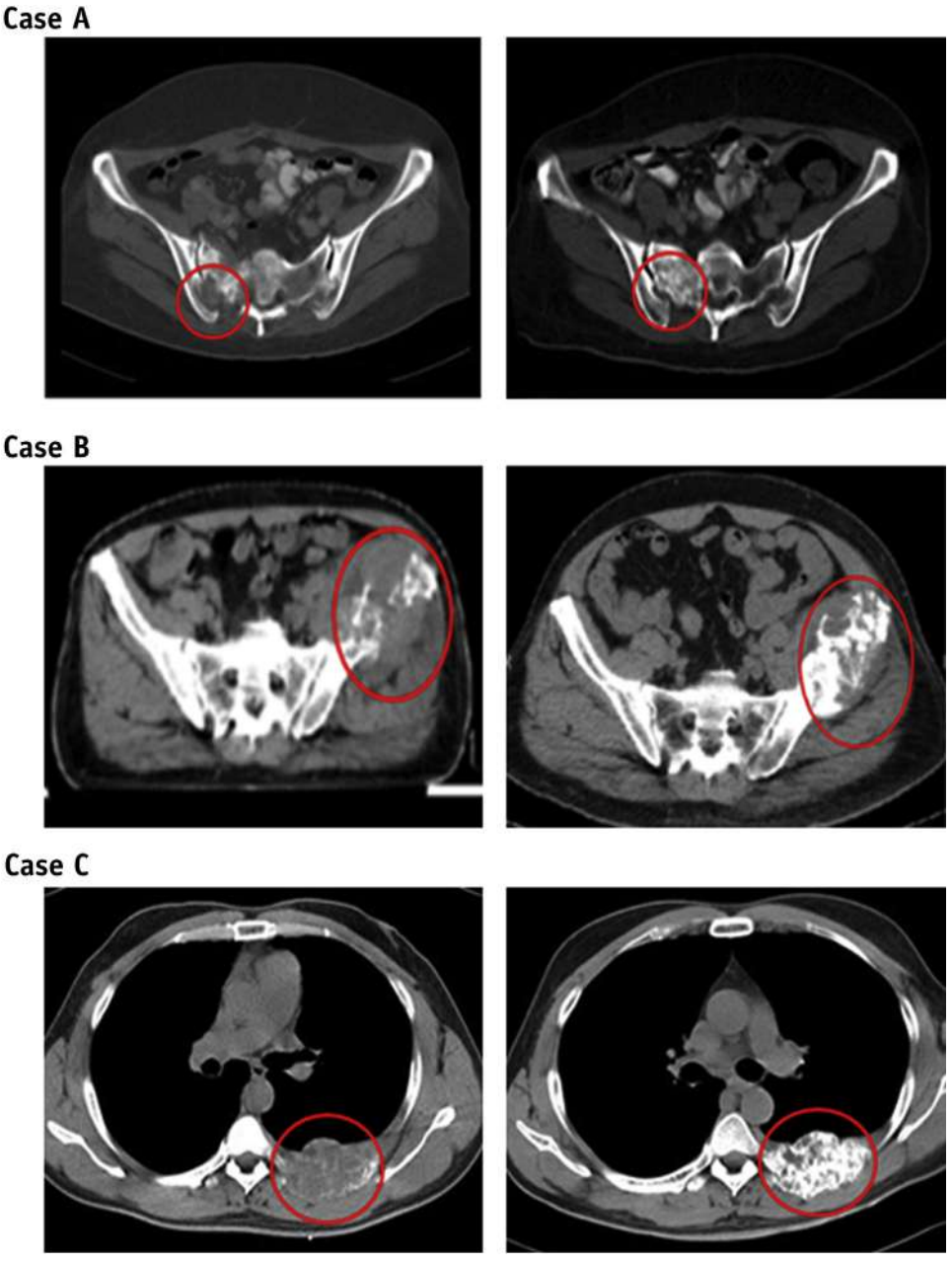

Fig. 4. Three cases of bone ossification of the osteolytic lesions after radiation therapy plus hyperthermia. Images presented were established within a 2-month period after treatment.

There was a significant increase in new bone formation after 2 weeks of treatment. Increased viability and proteoglycan metabolism in cultured chondrocytes and cartilage matrix gene expression in a rabbit knee joint model has also been reported (28, 29).

Many articles have proven the synergistic effect of heat in combination with RT (10-14). Hyperthermia can inhibit the homologous recombination repair of RT-induced DNA damage (30). Generally, the tumor microenvironment is more hypoxic owing to poor tissue penetration. Hyperthermia might increase tumor vascular perfusion as well as reduce tumor hypoxia (31). Thermal radio-sensitization is dependent on temperature. Although the knowledge of real temperature distribution is limited by imperfect thermal approximation models and the gaps between phantom and real body with blood perfusion, the good therapeutic effect of HT in our study might be due to higher temperatures around the bony metastatic sites. Bone tissue has been classified by low conductivity and low permeability compared with muscle (32). The attenuation in thermal distribution is reflected by the difference in the dielectric constant, and therefore bones absorb more heat than muscle (33). The temperature around the tumor and the destructed bone cortex would be higher than the surrounding soft tissues. We believe that the marrow cavity absorbed more heat than the cortex because of high fat content.

Hyperthermia, as an adjunctive immunotherapy strategy for cancer treatment, is supported by increased research data. Mild heat shock stimulates tumor necrosis factor–related apoptosis inducing ligand (TRAIL) to mediate apoptosis. The enhanced immune cells induce tumor apoptosis that lasts for a long time, even after heating (34). It has been found that HT induced aggregation of the most important regulator of apoptosis induced by death receptors: cellular FADD-like IL-1β converting enzyme inhibitory protein (c-FLIP) (35). Moreover, thermally enhanced immune effector cells, such as dendritic cells or natural killer cells, are generated and migrate to the tumor site for proliferation and killing (36). This HT-induced immune activation phenomenon may aid in an adjunctive explanation of the good palliative effect with RT.

Conclusions

We report the first phase 3 trial showing benefit of combined HT with RT for bony metastases. The combined treatment is safe and effective in increasing pain control and reossification rate, and prolonging treatment response duration in bony metastatic patients. Widespread variations of dose fractionation schedules have shown similar pain relief outcomes between protocols (23). It would be necessary to search for an effective modality in addition to RT besides fractionation issues in our own hands. Additional prospective trials are needed to better define the role of RT + HT on osseous metastases.

References

1. Chow E, Danjoux C, Wong R, et al. Palliation of bone metastases: A survey of patterns of practice among Canadian radiation oncologists. *Radiother Oncol* 2000;56:305-314.
2. Chow E, Harris K, Fan G, et al. Palliative radiotherapy trials for bone metastases: A systematic review. *J Clin Oncol* 2007;25:1423-1436.
3. Agarawal JP, Swangsilpa T, van der Linden Y, et al. The role of external beam radiotherapy in the management of bone metastases. *Clin Oncol (R Coll Radiol)* 2006;18:747-760.
4. Roos DE, Turner SL, O'Brien PC, et al. Randomized trial of 8 Gy in 1 versus 20 Gy in 5 fractions of radiotherapy for neuropathic pain due to bone metastases (Trans-Tasman Radiation Oncology Group, TROG 96.05). *Radiother Oncol* 2005;75:54-63.
5. Feyer PC, Steingraeber M. Radiotherapy of bone metastasis in breast cancer patients—current approaches. *Breast Care (Basel)* 2012;7:108-112.
6. Roti Roti JL. Cellular responses to hyperthermia (40-46 degrees C): Cell killing and molecular events. *Int J Hyperthermia* 2008;24:3-15.
7. Crezee J, van Leeuwen CM, Oei AL, et al. Biological modelling of the radiation dose escalation effect of regional hyperthermia in cervical cancer. *Radiat Oncol* 2016;11:14.
8. Abe M, Hiraoka M, Takahashi M, et al. Multi-institutional studies on hyperthermia using an 8-MHz radiofrequency capacitive heating device (Thermotron RF-8) in combination with radiation for cancer therapy. *Cancer* 1986;58:1589-1595.
9. Ohguri T, Imada H, Yahara K, et al. Radiotherapy with 8-MHz radiofrequency-capacitive regional hyperthermia for stage III non-small-cell lung cancer: The radiofrequency-output power correlates with the intraesophageal temperature and clinical outcomes. *Int J Radiat Oncol Biol Phys* 2009;73:128-135.
10. Kitamura K, Kuwano H, Watanabe M, et al. Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. *J Surg Oncol* 1995;60:55-58.
11. Harima Y, Nagata K, Harima K, et al. A randomized clinical trial of radiation therapy versus thermoradiotherapy in stage IIIb cervical carcinoma. *Int J Hyperthermia* 2001;17:97-105.
12. Harima Y, Ohguri T, Imada H, et al. A multicentre randomised clinical trial of chemoradiotherapy plus hyperthermia versus chemoradiotherapy alone in patients with locally advanced cervical cancer. *Int J Hyperthermia* 2016;32:801-808.
13. Huilgol NG, Gupta S, Sridhar CR. Hyperthermia with radiation in the treatment of locally advanced head and neck cancer: A report of randomized trial. *J Cancer Res Ther* 2010;6:492-496.
14. Mitsumori M, Zeng ZF, Oliynychenko P, et al. Regional hyperthermia combined with radiotherapy for locally advanced non-small cell lung cancers: A multi-institutional prospective randomized trial of the international atomic energy agency. *Int J Clin Oncol* 2007;12:192-198.
15. Ikuta K, Urakawa H, Kozawa E, et al. In vivo heat-stimulus-triggered osteogenesis. *Int J Hyperthermia* 2015;31:58-66.
16. Matts JP, Lachin JM. Properties of permuted-block randomization in clinical trials. *Control Clin Trials* 1988;9:327-344.
17. Shoji H, Motegi M, Osawa K, et al. Output-limiting symptoms induced by radiofrequency hyperthermia. Are they predictable? *Int J Hyperthermia* 2016;32:199-203.
18. Shoji H, Motegi M, Osawa K, et al. A novel strategy of radiofrequency hyperthermia (neothermia) in combination with preoperative chemoradiotherapy for the treatment of advanced rectal cancer: A pilot study. *Cancer Med* 2015;4:834-843.
19. Uki J, Mendoza T, Cleeland CS, et al. A brief cancer pain assessment tool in Japanese: The utility of the Japanese Brief Pain Pnventory–BPI-J. *J Pain Symptom Manage* 1998;16:364-373.
20. Chow E, Wu JS, Hoskin P, et al. International consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases. *Radiother Oncol* 2002;64:275-280.
21. National Cancer Institute National Institutes of Health U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0. Available at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf. Accessed July 31, 2017.
22. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer* 2009;45:228-247.
23. Lutz S, Balboni T, Jones J, et al. Palliative radiation therapy for bone metastases: Update of an ASTRO evidence-based guideline. *Pract Radiat Oncol* 2017;7:4-12.
24. Truntzer P, Atlani D, Pop M, et al. Early evaluation predicts pain relief of irradiated bone metastases: A single-center prospective study. *BMC Palliat Care* 2013;12:12.
25. Thibault I, Whyne CM, Zhou S, et al. Volume of lytic vertebral body metastatic disease quantified using computed tomography-based image segmentation predicts fracture risk after spine stereotactic body radiation therapy. *Int J Radiat Oncol Biol Phys* 2017;97:75-81.
26. Schlampp I, Rieken S, Habermehl D, et al. Stability of spinal bone metastases in breast cancer after radiotherapy: A retrospective analysis of 157 cases. *Strahlenther Onkol* 2014;190:792-797.
27. Foerster R, Eisele C, Bruckner T, et al. Bone density as a marker for local response to radiotherapy of spinal bone metastases in women with breast cancer: A retrospective analysis. *Radiat Oncol* 2015;10:62.
28. Hojo T, Fujioka M, Otsuka G, et al. Effect of heat stimulation on viability and proteoglycan metabolism of cultured chondrocytes: Preliminary report. *J Orthop Sci* 2003;8:396-399.
29. Tonomura H, Takahashi KA, Mazda O, et al. Effects of heat stimulation via microwave applicator on cartilage matrix gene and HSP70 expression in the rabbit knee joint. *J Orthop Res* 2008;26:34-41.

30. Genet SC, Fujii Y, Maeda J, et al. Hyperthermia inhibits homologous recombination repair and sensitizes cells to ionizing radiation in a time- and temperature-dependent manner. *J Cell Physiol* 2013;228: 1473-1481.
31. Sen A, Capitano ML, Spernyak JA, et al. Mild elevation of body temperature reduces tumor interstitial fluid pressure and hypoxia and enhances efficacy of radiotherapy in murine tumor models. *Cancer Res* 2011;71:3872-3880.
32. Lagendijk JJ, Nilsson P. Hyperthermia dough: A fat and bone equivalent phantom to test microwave/radiofrequency hyperthermia heating systems. *Phys Med Biol* 1985;30:709-712.
33. Hede S, Trivedi N, Mekala, et al. Thermometry studies of radiofrequency induced hyperthermia on hydrogel based neck phantoms. *J Cancer Res Ther* 2005;1:162-167.
34. Moulin M, Arrigo AP. Long lasting heat shock stimulation of TRAIL-induced apoptosis in transformed T lymphocytes. *Exp Cell Res* 2006; 312:1765-1784.
35. Morlé A, Garrido C, Micheau O. Hyperthermia restores apoptosis induced by death receptors through aggregation-induced c-FLIP cytosolic depletion. *Cell Death Dis* 2015;6:e1633.
36. Behrouzkia Z, Joveini Z, Keshavarzi B, et al. Hyperthermia: How can it be used? *Oman Med J* 2016;31:89-97.