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Evaluating the effectiveness of combined radiotherapy and hyperthermia for the treatment response of patients with painful bony metastases: A phase 2 clinical trial

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ABSTRACT

Introduction: Since the survival time of patients with bony metastases has noticeably improved in recent years, these patients are at high risk of complications associated with this metastasis. Hence, the appropriate choice of treatment modality or combination of therapeutic approaches can lead to increasing bone pain relief, improving quality of life, etc. This study is aimed to evaluate the effectiveness of combined radiotherapy and hyperthermia for the treatment response of patients with painful bony metastases.

Patients and methods: In a single-arm clinical trial, 23 eligible patients (14 female and 9 male) with the mean age of 67 years old and suffering from bony metastases were enrolled in the study. Two hours after radiotherapy, the patients underwent hyperthermia for 1 h in the supine position. All the patients completed the brief pain inventory (BPI) assessment tool and quality of life questionnaire (QLQ-C30) from the European Organization for Research and Treatment of Cancer (EORTC) at the baseline, end of the treatment and 1, 2 and 3 months thereafter. The response to the treatment was assessed as the zero score (complete response) or two or more than two-point drop of the worst pain within the preceding 24 h (partial response) during the 3-month posttreatment.

Results: All the pain intensity and interference scores, except the pain interference with the enjoyment of life score, significantly decreased. A total of 18 out of 23 patients (78%) achieved complete or partial response. The number of patients using pain relief medications decreased from 74% (n = 17) at the baseline to 48% (n = 11) 3 months later. Moreover, except for nausea and vomiting, appetite loss, diarrhea and financial impact problems, the patients' quality of life improved significantly in all the functional scales and symptoms within 3 months.

Conclusion: This study showed that using hyperthermia in combination with radiotherapy significantly ameliorated bone pain among the patients suffering from cancer with painful bony metastases.

1. Introduction

Bone is one of the most frequent sites of metastasis in advanced malignancies, which is present in almost 50–75% of patients (McDonald et al., 2015; Nguyen et al., 2011). According to autopsy studies on the patients with cancer, 85% of the patients with breast, prostate and lung cancers had bone metastases at the time of death (Nielsen et al., 1991). Bone metastases can cause considerable complications, such as intolerable pain, hypercalcemia, pathologic fractures or cord compression (Caissie et al., 2012; Chi et al., 2018b; Chow et al., 2010; Culleton et al., 2011; Zeng et al., 2012a). Pain as one of the most frequent symptoms of bone metastasis occurs in about 70% of patients, which might be localized or diffused (Mantyh, 2013; Pituskin et al., 2010). Furthermore, in most patients, bone pain leads to difficulty in the activities of daily living and reduced quality of life (Zeng et al., 2012b).

The survival time of patients following the diagnosis of bone metastases has been noticeably improved in recent years, particularly for the patients with breast and prostate cancers. In such circumstances,

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these patients are at high risk of skeletal-related symptoms and adverse side effects over long periods of time. Hence, the appropriate choice of treatment modality or combination of therapeutic approaches can lead to increasing bone pain relief, improving quality of life, decreasing medical costs, preventing the patient's disability and dependence on others as well as preventing life-threatening complications (Dennis et al., 2012; Haddad et al., 2014).

Current treatment modalities for the patients with bone metastases are mainly palliative and comprise systemic treatments (such as chemotherapy, radiopharmaceuticals and hormonal therapy), localized treatments (such as radiotherapy and surgery) and analgesics (such as opioids and nonsteroidal anti-inflammatory drugs) (Goetz et al., 2004). Radiotherapy is a standard treatment for the patients with bone metastases and localized bone pain, since the 30 Gy total dose during 10 fractions is usually considered as a standard palliative radiotherapy dose (Chi et al., 2018b; Goetz et al., 2004). There are several studies which have assessed the effectiveness of radiotherapy for the bone pain relief in the patients with bony metastases (Agarawal et al., 2006; Amouzegar-Hashemi et al., 2008; Caissie et al., 2012; Feyer and Steingraeber, 2012; Roos et al., 2005; Steenland et al., 1999; Wu et al., 2003; Zeng et al., 2012a). For example, it was reported that radiotherapy causes the palliation of bone pain in most patients. However, 20%–30% of patients did not reveal pain relief (Goetz et al., 2004). It was also shown that approximately a quarter of the patients experienced complete pain relief (Culleton et al., 2011; Zeng et al., 2012a) and about 60–70% of the patients had at least some degrees of pain alleviation following radiotherapy, regardless of the treatment regime (Caissie et al., 2012; Zeng et al., 2012a). However, it was reported that 50% of the patients experienced pain relapse at almost 12 weeks after radiotherapy (Roos et al., 2005). Furthermore, an effect of bone ossification was observed 10–12 weeks after radiotherapy (Feyer and Steingraeber, 2012). Moreover, for the patients with recurrent pain at a site previously irradiated, further radiotherapy might not be eligible due to constraints in normal tissue tolerance (Pituskin et al., 2010).

New thermo-biological studies in oncology have revealed that heat can act as a strong sensitizer for chemotherapy and radiotherapy (Bolomey et al., 1995; Cihoric et al., 2015; Crezee et al., 2016; Roti Roti, 2008; Sahinbas et al., 2017). In several randomized trials on advanced head and neck, esophagus, advanced cervical and advanced non-small cell lung cancers, it has been reported that hyperthermia or heating of tumors to the temperature of 40–43 °C in combination with radiotherapy could increase local control or overall survival (Harima et al., 2001, 2016; Huilgol et al., 2010; Kitamura et al., 1995; Mitsumori et al., 2007). Furthermore, hyperthermia stimulates osteoblast activity to recover osteogenesis and decline fracture risk (Ikuta et al., 2015).

With regard to the high incidence of bony metastases and increasing the effectiveness of radiotherapy combined with hyperthermia, the current study is aimed to evaluate the treatment response of radiotherapy along with hyperthermia in the patients with painful bony metastases. Furthermore, changes regarding bone pain relief and quality of life following these therapeutic modalities are investigated.

2. Patients and methods

2.1. Study design

After being approved by Ethics Review Board, Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1395.1532), the current study was conducted. This work was a single-arm prospective study using the patients as their own controls. The primary outcome was to evaluate the treatment response of the bony metastasis patients treated with radiotherapy and hyperthermia. The response to the treatment was assessed as the zero score (complete response) or two or more than two point drop of the worst pain during the preceding 24 h (partial response) in the 3-month post treatment. The secondary outcome was to assess the palliation of the bone pain and quality of life of the patients at the end of the treatment and 1, 2 and 3 months thereafter. All the patients completed the brief pain inventory (BPI) assessment tool and quality of life questionnaire (QLQ-C30) from the European Organization for Research and Treatment of Cancer (EORTC) at the baseline, end of the treatment and 1, 2 and 3 months thereafter.

2.2. Patients

After describing the implementation of the study by the researchers, all the participants read the participation conditions and gave their written consent. Throughout 12 months from December 2016 to December 2017, 25 patients were enrolled in this study, two of whom stopped cooperating at the end of the follow-up. All the eligible patients had bony metastases confirmed by bone scan, computed tomography (CT), positron emission tomography/CT scan or magnetic resonance imaging; age of 27–86 years old and life expectancy of more than 3 months (because the patients were followed up 3 months after the complete treatment). The exclusion criteria comprised pathologic fracture needing immediate surgery, previous radiotherapy to the proposed site of treatment, presence of metal implant within or outside the irradiation treatment field and pacemaker insertion. All the patients underwent radiotherapy and hyperthermia at Omid Radiotherapy Center, Tehran, Iran.

2.3. Radiotherapy treatment planning

At first, the gross tumor volume (GTV) was determined by a physician, which included bony lesions along with affected soft tissue parts. Then, the clinical target volume (CTV) was defined as the GTV + 2 cm safety radical margin. Finally, the planning target volume was determined as a CTV +0.2 cm three-dimensional (3D) margin. All the patients were irradiated to the total dose of 30 Gy in 10 fractions over two weeks. Furthermore, 3D conformal radiotherapy plans produced from a Siemens Primus linear accelerator (Siemens AG, Erlangen, Germany) by the TiGRT treatment planning system (Lina Tech, Sunnyvale, CA, USA) were used to deliver the radiation dose to the patients.

2.4. Hyperthermia

In the current study, the Celsius + TCS device (Celsius 42 GmbH, Cologne, Germany) was used for hyperthermia of the patients as it was convenient. This devise is a capacitive system which operates up to 600 W at 13.56 MHz (Kok et al., 2018; Sahinbas et al., 2017). The patients underwent hyperthermia for 1 h in the supine position, up to 2 h after radiotherapy. For the localization of the tumor site, the obtained CT images during radiotherapy simulation were used. A pair of capacitive electrodes was positioned on the patient's affected body site; an opposite arrangement of the electrodes (anterior-posterior) was used for the majority of the patients. The tissues under electrodes indicated the dielectric and were heated according to the adaptive orientation of ions inside the cells and in the intercellular space. There were water bags with deionized water under the electrodes, which led to better adaptation to the body's surface. The deionized water was cooled through a cooling circuit, as cooling the thermo receptors on the skin surface and subcutaneous fat regions of the patients can prevent the heat-induced pain, allowing for increased heat inputs. It is notable that in the current study, various electrode sizes were applied to obtain a selective local impact.

2.5. Evaluating response treatment, bone pain relief and quality of life

The treatment response of the bony metastases patients within 3 months after radiotherapy along with hyperthermia was assessed based on the guidelines of International Bone Metastasis Consensus Working Party (Chow et al., 2002). According to this guideline, complete

response was specified as the pain score 0 at the worst pain in the preceding 24 h; partial response was defined as two or more than two point drop of the worst pain compared to before the treatment (baseline) during the preceding 24 h; stable pain was determined as no change in the score or only the pain reduction of 1 score compared to the baseline at the worst pain during the preceding 24 h.

To investigate the pain relief of the patients, this item was calculated before and after radiotherapy along hyperthermia by the BPI scores. These scores were obtained by a questionnaire study 5 times over a three-month follow-up period. The first survey was carried out at enrollment, the second survey on the treatment complete and the third to fifth surveys 1, 2, and 3 months posttreatment. Finally, variations in the severity of pain before and after both treatment modalities were statistically analyzed.

In order to calculate the scores of each dimension of the quality of life questionnaire, first, the raw score of each dimension was calculated from the total score of the items in each dimension (in the form of Likert scale from 1 to 4 for each of the functional dimensions and symptoms or Likert scale of 1–7 for the dimension of overall quality of life) divided by the number of questions in that dimension. Then, for the functional dimensions and overall quality of life, the scores for each sub-dimension were calculated on the scale of 0–100, so that higher scores represented better quality of life in terms of function and overall quality of life:

$$score = (1 - \frac{Row \quad score - 1}{possible \quad range}) \times 100 \tag{1}$$

Moreover, for dimensions of the symptoms, the final score in each dimension was calculated on the scale of 0–100 from the following equation, so that higher scores indicated poorer quality of life in terms of the symptoms.

$$score = (\frac{Row \quad score - 1}{possible \quad range}) \times 100 \tag{2}$$

In the above-mentioned formulas, the range of values was considered 3 for functional dimensions and symptoms and 6 for the dimension of the overall quality of life.

It should also be noted that the questions related to each of the dimensions of functional and overall quality of life in the questionnaire were: physical (questions 1 to 5), role play (questions 6 and 7), cognitive (questions 20 and 25), emotional (questions 21 and 24) and social (questions 26 and 27). Moreover, questions related to the dimensions of the symptoms included fatigue (questions 10, 12 and 18), pain (questions 9 and 19), nausea and vomiting (questions 14 and 15), dyspnea (question 8), insomnia (question 11), loss of appetite (question 13), constipation (question 16), diarrhea (question 17), financial difficulties (question 28) and global health status (questions 29 and 30).

2.6. Statistical analysis

Frequency (percent), mean (standard deviation) and median (range) were used to describe the data. Because of more clear descriptions through mean ± standard deviation, the median values were discarded at posttreatment intervals. Based on the Shapiro-Wilk test, none of the quantitative variables including pain score, quality of life and age of patients had normal distribution, so non-parametric tests were carried out to analyze the data. To examine significant changes over time for the BPI and quality of life (QOL) scores, Friedman test was used. For the post-hoc pairwise comparisons, Sign rank test with Bonferroni correction (with the adjusted P value of less than 0.005) was performed. To test the significant changes in the proportion of the patients with complete response over the follow-up time, the Cochran's Q test was employed. All the analyses were two-sided and carried out by SPSS (version 21.0) (IBM) software.

It should be noted that three patients had more than one treated lesion site and independent evaluation of each site was recorded. Thus, to have simplicity and use of all data in the analyses, these assessments were considered as independent data.

Table 1
Patient's demographic and clinical characteristics.

	No. of Patients (%)
Total number of patients	23
Sex	
Male	14 (61)
Female	9 (39)
Primary cancer site	
Breast	12 (52)
Prostate	9 (39)
Lung	2 (9)
Location of lesions	
Pelvic bones	10 (43)
Lumbar spine	6 (26)
Femur	4 (17)
Scapula	2 (9)
Chest Wall	1 (4)
Age in year, mean ± SD (median, range)	62.13 ± 17.97 (67, 27–86)

SD indicates standard deviation.

3. Results

3.1. Patient's demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of the patients enrolled in the study. Twenty-three patients with the mean age of 67 years old (range: 27 to 86), including 14 men and 9 women, underwent combined radiotherapy and hyperthermia. Breast (n = 12) and prostate (n = 9) were the most common tumor types treated. For three patients, two lesions were treated. Locations of the treated lesions in two of them were on femur and scapula and, for one patient, were on pelvic bones and chest wall.

3.2. Bone pain relief

At the baseline, for all the dimensions of BPI, the median scores ranged from 6 to 8, except for pain interference with sleeping and relationships with others that scored lower (Table 2). Assessments at the end of the treatment showed that the patients experienced highly significant reductions in the worst pain, least pain, average pain and current pain ($P < .001$ for all, Table 2), which was maintained during the follow-up time (Table 2 and Fig. 1). As the main primary end point, the mean score of worst pain in a 24-h period was 8.39 at the baseline (range: 6 to 10), which significantly decreased to 4.26 (range: 0 to 9) immediately posttreatment and sustained in 3.74, 3.43 and 3.61 (range: 0 to 9 for all) 1, 2 and 3 months posttreatment, respectively. Similar results were observed for least pain, average pain and current pain, the details of which are shown in Table 2. The results of the sign rank test for pairwise comparisons showed that, compared to the baseline, all the pain scores' evaluations at different time points after the treatment showed a significant difference (all with $P < .005$). However, no significant changes were observed in the scores during the follow-up time compared with the immediately post treatment time ($P > .05$ for all, details are shown in Table 2).

For the functional interference of the pain, except for pain interference with the enjoyment of life ($P = 0.538$), for all other pain interferences including general activity, mood, walking ability, normal work, relationships with others and sleeping, the scores had significant improvement at the end of the treatment. Thus, the changes were maintained during the follow-up time ($P < .001$ for all) (Table 2 and Fig. 2). However, based on the results of the sign rank test for pairwise comparisons, it should be noted that, compared with the posttreatment time, no significant changes were observed in the scores over the follow-up time ($P > .05$ for all). Fig. 2 shows the trend of the BPI

Table 2
Median, mean and standard deviation of the pain scores at the baseline, end of the treatment, and 1-, 2- and 3-month posttreatment by the brief pain inventory–short form scale (n = 23).

Pain score dimension[a]	Baseline[b] (a)	Posttreatment (b)	Follow-up			Chi-square statistics (df)	P[c]
			1st month (c)	2nd month (d)	3rd month (e)		
Worst pain	8 [b,c,d,e], 8.39 ± 1.23	5 [d], 4.26 ± 2.68	4, 3.74 ± 3.12	4, 3.43 ± 3.34	4, 3.61 ± 3.22	67.63 (df = 4)	< .001
Least pain	5 [b,c,d,e], 4.83 ± 1.67	2, 2.3 ± 1.92	2, 2.26 ± 2.14	2, 2.17 ± 2.23	2, 2.26 ± 2.18	53.48 (df = 4)	< .001
Average pain	6 [b,c,d,e], 6.09 ± 1.04	3, 2.87 ± 2.14	3, 2.7 ± 2.36	3, 2.43 ± 2.45	3, 2.57 ± 2.39	67.84 (df = 4)	< .001
Current pain	6 [b,c,d,e], 6.35 ± 1.43	3, 3.17 ± 2.59	3, 2.96 ± 2.75	2, 2.7 ± 2.88	3, 2.83 ± 2.82	53.21 (df = 4)	< .001
Pain relief [d]	80%, 78% ± 16%	80%, 70% ± 26%	80%, 77% ± 16%	80%, 78% ± 17%	80%, 77% ± 16%	–	–
Pain interference							
General Activity	8 [b,c,d,e], 7.87 ± 1.74	5 [d,e], 4.91 ± 2.92	5, 4.35 ± 3.04	5, 4.26 ± 2.99	5, 4.26 ± 2.99	67.76 (df = 4)	< .001
Mood	8 [b,c,d,e], 6.61 ± 2.33	6, 5.09 ± 2.21	4, 4.09 ± 2.21	3, 3.91 ± 2.19	3, 3.96 ± 2.18	51.92 (df = 4)	< .001
Walking ability	7 [b,c,d,e], 6.74 ± 2.12	4, 4.22 ± 2.24	3, 3.78 ± 2.65	3, 3.61 ± 2.52	3, 3.7 ± 2.57	60.11 (df = 4)	< .001
Normal work	8 [b,c,d,e], 7.78 ± 1.51	6 [d], 5.48 ± 2.23	6, 4.78 ± 2.63	6, 4.7 ± 2.58	6, 4.74 ± 2.6	66.03 (df = 4)	< .001
Relationships with others	3 [b], 4.43 ± 2.61	3, 3.7 ± 2.05	3, 3.39 ± 1.97	3, 3.22 ± 1.81	3, 3.22 ± 1.81	24.31 (df = 4)	< .001
Sleeping	4 [b,c,d,e], 3.96 ± 2.27	3, 3.26 ± 2.28	2, 2.52 ± 1.59	2, 2.52 ± 1.59	2, 2.52 ± 1.59	39.88 (df = 4)	< .001
Enjoyment of life	7, 5.91 ± 2.68	6, 5.57 ± 2.33	6, 5.3 ± 2.9	5, 5 ± 2.95	5, 5.13 ± 2.97	3.12 (df = 4)	.538

Superscripts indicate significant difference ($P < 0.005$) between the particular score and that of the time point indicated by the superscript.
[a] Scores range from 0 to 10 with a higher score representing a higher level of pain.
[b] Median, mean ± standard deviation values were reported.
[c] *P*-values reported for comparison between assessments from Friedman tests.
[d] Pain relief was assessed in 17, 12, 10, 10 and 11 patients consuming medication at the baseline, post therapy, and 1-, 2- and 3-month post-therapy, respectively.

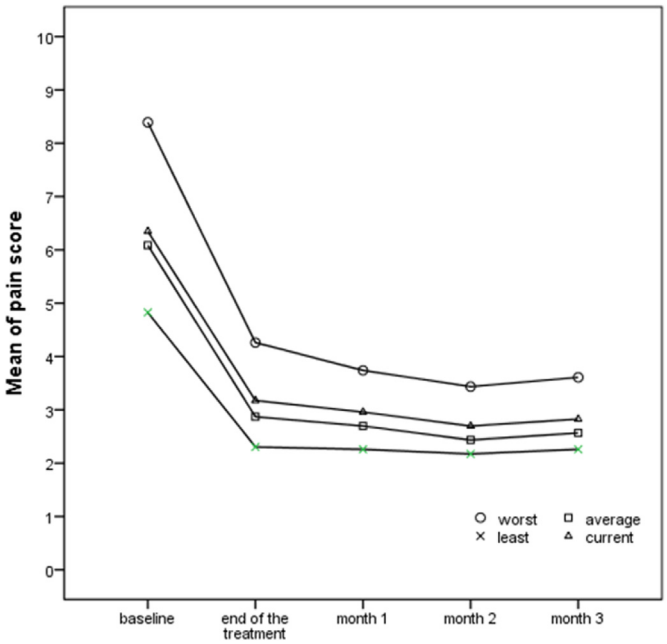

Fig. 1. Mean scores of the worst, least, average and current pain over time. There are highly significant reductions in the mean scores of the worst, least, average and current pain over time ($P < .001$ for all, details are shown in Table 2).

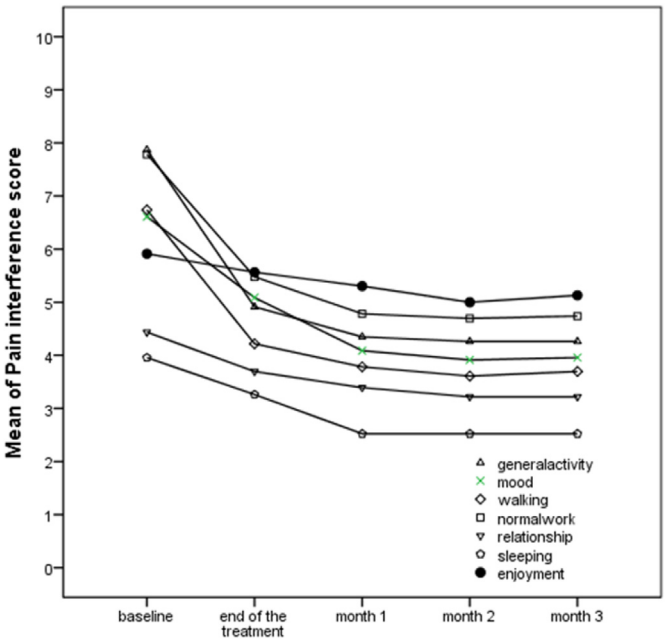

Fig. 2. The mean of pain interference scores over time. For all the pain interferences including general activity, mood, walking ability, normal work, relationships with others and sleeping (except for pain interference with the enjoyment of life [$P = 0.538$]), the scores had significant improvement over time ($P < .001$ for all, details are shown in Table 2).

functional interference items at the baseline and different follow-up times.

At the end of the follow-up time, a total of 18 of 23 patients (78%, 95%CI: 61%–95%) achieved complete or partial response (Table 3). Four patients were refractory to the treatments and had stable pain at all the assessment times and the response status of two patients was variable between stable or partial responses during the follow-up.

Furthermore, the number of patients using pain relief medications decreased from 74% (n = 17) at the baseline to 52% (n = 12) at the end of the treatment and 48% (n = 11) 3 months later.

3.3. Quality of life

The quality of life assessment of the patients at the baseline showed that the patients had lower level of role and physical functioning and greater degree of pain, fatigue and financial impact problems (Table 4). Moreover, dyspnea, nausea and vomiting and diarrhea were the least symptoms rated by the patients. Thus, 74%, 70% and 91% of the patients had no compliance with these symptoms at the baseline.

The quality of life assessments within 3 months showed that the patients had improvement in all the functional scale and symptom scales, except for nausea and vomiting ($P = 0.455$), appetite loss ($P = 0.764$), diarrhea ($P = 0.092$) and financial difficulties ($P = 0.055$) symptoms (Table 4 and Fig. 3).

Table 3
Response to the treatment at the end of the treatment as well as the 1-, 2- and 3-month posttreatment (n = 23).

Response	Posttreatment	Follow-up			Cochran's Q statistics (df)	P^a
		1st month	2nd month	3rd month		
Complete response	2 (8)	7 (30)	10 (43)	8 (35)	16.68 (df = 3)	.001
Partial response	16 (70)	11 (48)	8 (35)	10 (43)		
Stable to the treatment	5 (22)	5 (22)	5 (22)	5 (22)		

Frequency (percent) was reported.
[a] *P*-value reported for changes of complete response proportion during the follow-up time. Pairwise comparisons showed a significant difference in the complete response rate only between the posttreatment time and 2 months after the treatment ($P = 0.005$).

Table 4
Median, mean and standard deviation of the quality of life assessment at the baseline, end of the treatment, and 1-, 2- and 3-month posttreatment by the QLQ-C30 scale (n = 23).

QOL dimension[a]	Baseline[b] (a)	Posttreatment (b)	Follow-up			Chi-square statistics (df)	P^c
			1st month (c)	2nd month (d)	3rd month (e)		
Functional scales							
Physical	26.67 [b,c,d,e], 31.01 ± 23.06	44.67, 4.93 ± 21.2	53.33, 50.44 ± 29.39	53.33, 52.17 ± 27.54	53.33, 50.72 ± 29.04	48.3 (df = 4)	< .001
Role	16.67 [b,c,d,e], 25.36 ± 25.06	33.33, 35.51 ± 27.2	33.33, 41.3 ± 32.13	33.33, 43.48 ± 30.87	33.33, 40.58 ± 32.5	31.39 (df = 4)	< .001
Emotional	58.33 [c], 54.71 ± 33.88	75.00, 63.04 ± 33.69	83.33, 76.45 ± 25.58	83.33, 73.55 ± 27.48	83.33, 73.55 ± 27.48	26.71 (df = 4)	< .001
Cognitive	83.33, 75.36 ± 34.03	100.0, 77.54 ± 33.94	100.0, 86.23 ± 19.88	100.0, 86.23 ± 19.88	100.0, 86.23 ± 19.88	22.67 (df = 4)	< .001
Social	66.67 [d,e], 59.42 ± 31.71	66.67 [d,c,e], 62.32 ± 29.82	66.67, 68.84 ± 33.45	66.67, 72.46 ± 28.7	66.67, 72.46 ± 28.7	28.44 (df = 4)	< .001
Symptom scales							
Fatigue	66.67 [b,c,d,e], 65.7 ± 20.9	55.56, 51.21 ± 26.33	33.33, 37.2 ± 27.14	33.33, 39.61 ± 27.79	44.44, 40.1 ± 27.78	42.54 (df = 4)	< .001
Nausea and vomiting	0, 5.07 ± 7.84	0, 9.42 ± 17.28	0, 6.52 ± 15.68	0, 7.25 ± 15.75	0, 7.25 ± 15.75	3.66 (df = 4)	.455
Pain	100 [b,c,d,e], 82.61 ± 22.74	66.67, 56.52 ± 28.31	66.67, 50.72 ± 35.35	66.67, 50 ± 34.45	66.67, 52.17 ± 35.99	44.14 (df = 4)	< .001
Dyspnea	0, 11.59 ± 21.58	0, 5.8 ± 19.21	0, 0 ± 0	0, 0 ± 0	0, 0 ± 0	16.89 (df = 4)	.002
Insomnia	33.33, 37.68 ± 28.96	33.33, 28.99 ± 27.16	33.33, 23.19 ± 18.63	33.33, 23.19 ± 18.63	33.33, 23.19 ± 18.63	22.57 (df = 4)	< .001
Appetite loss	33.33, 34.78 ± 35.5	33.33, 39.13 ± 37.14	33.33, 31.88 ± 38.24	33.33, 33.33 ± 37.61	33.33, 33.33 ± 37.61	1.85 (df = 4)	.764
Constipation	0, 26.09 ± 38.87	0, 24.64 ± 33.66	0, 13.04 ± 21.88	0, 15.94 ± 24.35	0, 15.94 ± 24.35	13.38 (df = 4)	.010
Diarrhea	0, 2.9 ± 9.6	0, 5.8 ± 19.21	0, 0 ± 0	0, 0 ± 0	0, 0 ± 0	8.00 (df = 4)	.092
Financial difficulties	66.67, 42.03 ± 37.9	66.67, 43.48 ± 38.19	66.67, 36.23 ± 36.12	66.67, 39.13 ± 35.75	66.67, 39.13 ± 35.75	9.26 (df = 4)	.055
Global health status	33.33 [b,c,d,e], 37.32 ± 15.26	66.67 [d], 63.77 ± 18.05	66.67, 72.83 ± 21.5	66.67, 73.91 ± 20.92	66.67, 72.83 ± 21.5	70.10 (df = 4)	< .001

Superscripts indicate significant difference ($P < 0.005$) between the particular score and that of the time point that the superscript indicates.
[a] The scores range from 0 to 100 with a higher score representing a higher level of functioning and global health status but a greater degree of symptoms.
[b] Median, mean ± standard deviation values were reported.
[c] *P*-values reported for comparison between assessments from the Friedman tests.

However, it should be noted that the results of the sign rank test for pairwise comparisons demonstrated that, compared to the baseline, only the physical ($P = 0.002$) and role ($P = 0.001$) functioning, fatigue ($P < 0.001$) and pain ($P < 0.001$) symptoms along with the global health status ($P < 0.001$) improved significantly at the end of the treatment time, whereas emotional ($P = 0.002$) and social ($P = 0.004$) functioning scales were improved within the 1- and 2-month post-treatments, respectively. Moreover, for cognitive functioning ($P = 0.016$) and dyspnea ($P = 0.031$), insomnia ($P = 0.012$) and constipation ($P = 0.031$) symptoms, with the caution of acceptance of higher level of significance ($P < .03$ instead of $P < 0.005$ of Bonferroni correction), a trend of improvement was observed at the first month posttreatment.

4. Discussion

The most effective treatment modality for the patients with bony metastases is radiotherapy and pain relief has been reported in 50%–80% of patients (Agarawal et al., 2006). However, some patients (30%) treated with radiotherapy alone eventually have pain relapse (Roos et al., 2005). On the other hand, several studies have reported that hyperthermia can be one of the most effective modalities in the support of radiation/chemotherapy (Horsman and Overgaard, 2007; Issels et al., 2010; van der Zee et al., 2000; Vernon et al., 1996). In the current study, the bone pain relief and quality of life were evaluated in the patients with painful bony metastases treated with radiotherapy along with hyperthermia.

In the current study, it was observed that hyperthermia combination with radiotherapy led to rapid relief and alleviation of pain in the patients with bone metastasis at the end of the treatment, which sustained during the follow-up time. Moreover, along with significant decreases in the use of pain relief medications, 35% and 43% of the patients experienced complete and partial responses. In conjunction with the decreased pain scores, significant improvement was observed in the patients' QOL. To describe precisely, the findings showed that the use of radiotherapy + hyperthermia was efficiently able to reverse decreased ability, fatigue and loss of cognition, emotion and social activity. However, considering its low prevalence, it could not improve gastrointestinal system side effects including appetite loss, nausea and vomiting. Moreover, it seems that improvement in mental components of QOL required more time posttreatment.

Studies regarding evaluation of bone pain alleviation using

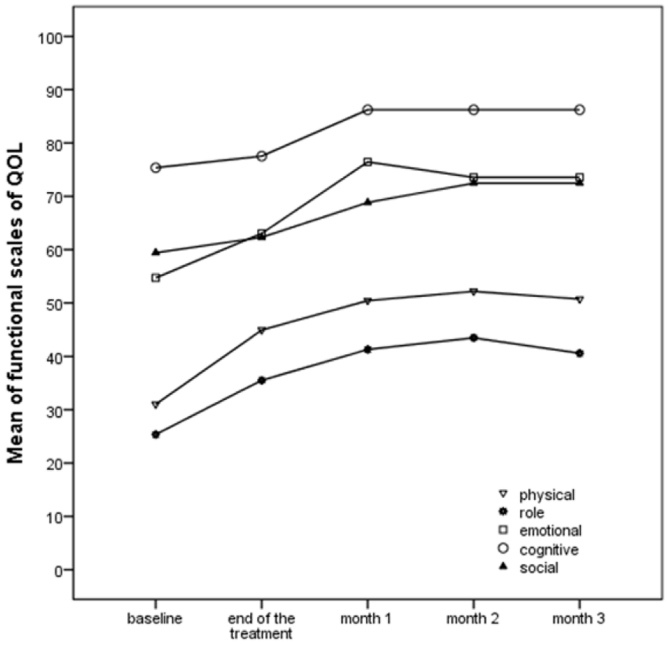

Fig. 3. The mean scores of the functional scales of QOL over time. The patients had improvements in all the functional scales including the physical, role, cognitive, emotional and social over time ($P < .001$ for all, details are shown in Table 4).

hyperthermia or combination of hyperthermia and radiotherapy are very limited. In a randomized clinical trial, Chi et al. evaluated the response treatment of patients with breast cancer metastasis treated with hyperthermia and radiotherapy combination (n = 29) compared with radiotherapy alone (n = 28). Similar to our results, their complete response rate in the third month after combination therapy was 37.9%. Furthermore, their findings revealed that hyperthermia was safe and effective treatment modality in increasing pain control and, in combination with radiotherapy, this treatment modality was able to improve complete response by more than 20% after 3 months. Moreover, their results demonstrated significantly better QOL in the first month for the patients who had undergone radiotherapy + hyperthermia compared with radiotherapy alone (Chi et al., 2018a). Another study by Kong et al. showed that hyperthermia could alleviate bone metastasis pain in combination with pamidronate disodium. Although pamidronate disodium has been used as a pain relief agent, this study showed that hyperthermia had a synergic effect on pain management (Kong et al., 2018).

The hyperthermia effects on biological structures are complex and pleiotropic. This treatment modality was a non-invasive and low toxic strategy for inducing cell killing in tumor. Molecular and cellular evaluations showed that radiotherapy stimulated several immunologic signaling pathways, leading to the upregulation of inflammatory mediators in normal tissues, as well as angiogenesis and resistance to apoptosis in tumor cells (Keywan Mortezaee et al., 2018; Najafi et al., 2018). Hyperthermia is known as an adjunctive immunotherapy strategy which is able to induce immune system mediators that mediate apoptosis in cancer cells. It has been revealed that heat shock proteins (HSPs) that are activated following exposure to hyperthermia stimulate apoptosis through the upregulation of the TNF-related apoptosis inducing ligand (TRAIL). Overexpression of TRAIL is observable for a long time after hyperthermia which, might indicate that hyperthermia induces apoptosis even after the end of the treatment (Moulin and Arrigo, 2006).

The current study was not a comparative research, so that it could be a phase III study exploring the role of the radiotherapy + hyperthermia combined treatment against radiotherapy alone; hence, it is suggested to perform a further randomized trial. Considering the limitation of our study because it was one arm, we also suggest performing a parallel randomized clinical trial to evaluate the beneficial effect of the hyperthermia treatment combined with radiotherapy compared with other modalities. Moreover, further evaluations are needed for the patients with different cancers and different stages.

5. Conclusion

This study was conducted to follow the possible pain management of hyperthermia in combination with radiotherapy for the patients with bone metastasis. Findings of the current study demonstrated that the combination of hyperthermia and radiotherapy was a promising strategy for bone pain relief in the patients with painful bony metastases. Moreover, the quality of life evaluation showed that although combination of these modalities could not improve gastrointestinal side effects such as nausea and vomiting, it is able to improve ability and cognition, emotion and social activities of the patients and also decrease their fatigue.

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