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Comparison of the Effect of Combined Treatment with Radiotherapy and Hyperthermia versus Exclusively Radiotherapy to Reduce Pain in Patients with Bone Metastases

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Authors' contributions

This work was carried out in collaboration among all authors especially author BK. The reason is that the article is an extraction of her Doctoral Specialty Thesis. Author BK designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author AN acted as the role of the main supervisor and advisor. Author SRM acted as the main consultant. Authors MS and MBT advised and suggested improving the quality of work. Authors LK and TA made comments for modification. All authors read and approved the final manuscript.

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ABSTRACT

Based on the extant studies conducted by scholars, recognizing the best and practical treatment methods in patients with bone metastases is an important and conspicuous focus in improving and amelioration of the treatment and prognosis of patients. Ergo, this study aims to compare the effects of radiotherapy and hyperthermia with radiotherapy only to reduce pain in one of the oncology centers located in Tehran (the capital city of Iran). In this randomized clinical trial study, patients with bone metastases were randomly assigned to one of two group's radiotherapy and hyperthermia or radiotherapy exclusively and the collected data were processed through Statistical Package of Social Science (SPSS). Thenceforth, findings were evaluated and compared between the two groups. A total of 60 patients inclusive of 34 women and 26 men were investigated. In the

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baseline, 20 patients in the case group (67%) and 21 patients in the control group (70%) used palliative drugs. At the end of the trial, the consumption of palliative drugs was decreased in the case group (12 patients, 43%) but, no change was observed in the control group. After treatment, complete response to treatment (27% vs. 13%), experienced a decrease in the clinical pain (57% vs. 83%) and did not respond to treatment in a stable mode (17% vs. 4%) of which were different between case and control groups, respectively. Regardless of the difference in the ratio of partial response in two groups, there was no significant difference between the two groups in terms of response to treatment. Although the effect of radiotherapy and hyperthermia in comparison with radiotherapy exclusively was more efficacious in some aspects of the intervention of pain with sleep. However, there was no remarkable and significant difference in other cases.

Keywords: Radiotherapy; hyperthermia; bone metastases; pain.

1. INTRODUCTION

The most common symptom of bone metastases considers as ambiguous pain with a gradual progression that is relatively localized. The pain of femur or acetabulum worsens with mobility, but the pain caused by lower ischium or sacrum worsens while sitting and reduce with an intensity of mobility [1]. Mechanisms of pain due to bone metastases have not been fully determined, and possible mechanisms consist mechanical instabilities, stimulation of periosteal tensile receptors, osteolysis of tumor-induced osteoclasts, tumor-induced neurological damage, or the presence of tumor cells themselves, production of neural growth factor, or stimulation of other receptors of cytokine. The pathophysiology of bone metastases is based on the spread of hematogenous tumor cells, and many patients with bone metastases simultaneously develop in different sites of the body [2-4].

The response to treatment relies on different factors including gender, histology and primary tumor site, patient's functional status, type of lesion (osteolytic or osteoblastic), metastasis site, place of tolerance or non-accepting weight, the extent of the disease, number of painful sites and the severity of pain before treatment [5].

Achieving sufficient knowledge about the best therapy practices in patients with bone metastases is a principal focus in increasing treatment and prognosis in patients. The efficacy and effectiveness of medication also rely on the purpose of the treatment, that is, relieving pain, preventing pathologic fracture, avoiding ensuing therapies, or controlling the position of the disease [6]. Palliative radiotherapy is very effective for patients with bone metastases, and the pain of many patients after treatment is eliminated and the response rate to palliative radiotherapy for localized painful patients is significantly higher than the response rate resulting from palliative systemic treatments. Hence, radiotherapy is the basis of localized bone metastases. One striking point to mention is that due to the mechanism of pain which may be multifactorial for exemplification combined therapies, especially the combination of radiotherapy and hyperthermia, that acts as one of the important radiolaborant sensitivities, may be referred to any of the treatments alone. It is worthwhile mentioning that in contrast to the mentioned view, it might increase the therapeutic side effects [7,8]. It is noteworthy that according to the review in related literature which will be stated later in this research paper, It can be asserted that researchers who are implicated with this research era have pursued advanced studies and in line with previous studies, the current study aims to compare the effect of combined treatment with radiotherapy and hyperthermia versus with radiotherapy only to reduce pain in patients with bone metastases in one selective oncology center in Tehran, Iran.

The remainder of this research is delineated as follows; firstly, previous relevant studies will be reviewed and a conclusion from them will be explained. Secondly, some noticeable concepts will be defined. Thirdly, research methodology including sample size, target population, questionnaire development, and data processing will be interpreted. Thenceforth, results will be brought into the discussion, and recommendations for future studies development will be explicated.

2. REVIEW OF FORMER EXPEDIENT STUDIES

Kaur et al. [9] in a review study published in the United States found that the simultaneous use of radiotherapy and hyperthermia increased the

response to treatment of bone metastases, the most important of which was the effect of hyperthermia on HSP70, which increased therapeutic response to radiotherapy.

Matsumine et al. [10] conducted an interventional study in Japan, by examining 15 patients with bone metastases; the use of hyperthermia with the alternating electromagnetic field method increased the response rate to 91%.

In another study, the use of hyperthermia with alternating electromagnetic field method has been shown to increase the therapeutic response to bone metastases [11].

A review article reported that the simultaneous use of radiotherapy and hyperthermia could significantly increase the therapeutic response to bone metastases [12].

Sakurai et al., in an interventional study in Japan, 26 patients with bone marrow metastases were diagnosed with lung cancer that the use of hyperthermia with radiotherapy caused a therapeutic response up to 76% compared with 17% response therapeutic in radiotherapy only [13].

Recently, in a clinical trial in Taiwan, 57 patients with bone marrow metastases were found that adding hyperthermia to radiotherapy increased the therapeutic response rate and also improved pain control in patients [14].

Also, Van Rhoon et al. [15] in the Netherlands stated that adding hyperthermia to radiotherapy was only effective in a group of patients with high life expectancy and those with resistance to treatment.

2.1 Conclusion of In-depth Review in Literature

By reviewing previous studies as stated in section 2, it can be deduced that inadequate researches in metastatic bone marrow patients have been conducted and the need for an optimal palliative care outbreak in these patients and the hyperthermia augmentation and supplementation in combination with radiotherapy will be an invaluable contribution to the body of knowledge in this research era of which will be pragmatic for patients who are suffering from illness as stated earlier, academicians all over the world and providing salutary and salubrious impacts and confirmation for doctors who are engaged in the relevant clinical centers. Moreover, a review of conducted studies in Iran literature in this research era recapitulates and supports the notion that no study has been done by scholars in Iran and stated point is a chief impetus to conduct a study in order to contribute not only in Iran literature but also a contribution to the academic community, rectorates of hospitals and clinical centers and most importantly patient who are suffering from this illness.

As a result of stated important points, the authors of the present research has been motivated to conduct this study in Omid Tehran Radiation Oncology center in Tehran, Iran with the primary purpose of evaluating and comparing the effects of radiotherapy and hyperthermia with radiotherapy only in the treatment of bone metastases to knowledge contribution in this research era.

2.2 Explication of Concepts

2.2.1 Pain control

The majority of patients with bone metastases improve pain during their illness, and pain control in these patients greatly increase their quality of life. In many patients, pain control can be obtained using the World Health Organization (WHO) Pandemic Protocol. Stage I is the use of nonopioid antiemetics, such as asthenophenone or NSAIDs. Stage II uses weak opiates like codeine and stage III is the use of strong opioids such as morphine. Medications should be prescribed according to a routine and scheduled procedure (based on hours) rather than until a patient achieves a certain amount (based on the patient's need). In this way, in 76-70% of patients, the pain is well controlled. Auxiliary medications such as gabapentin or amitriptyline may also be added to neuropathic pain. Antidepressants and anxiolytics may also be useful in some patients. Antiemetics medications often cause constipation and sometimes anorexia. These patients should be treated with laxatives or fiber-containing diets. Other side effects of opioid analgesia include sleep deprivation, changes in consciousness, and mood disorders [16].

2.2.2 Radiotherapy

Radiotherapy is effective in relieving bone metastases, in the majority of patients (80-90%) causes the partial relief of pain and complete

pain relief in 50% of patients. The response to treatment depends on several factors, including gender, histology and primary tumor site, patient's functional status, type of lesion (osteolytic or osteoblastic), location of the metastasis, place of tolerance or non-accepting weight, extent of the disease, number of painful places and severity of pain before treatment. The efficacy and effectiveness of treatment are also dependent on the purpose of the treatment, that is, relieving pain, preventing pathologic fracture, avoiding subsequent therapies, or controlling the position of the disease. For each of these goals, the required dose and appropriate volume of treatment are different. The use of bisphosphonates along with radiotherapy may improve the treatment outcomes in terms of pain control and bone repair. Many patients with bone metastases have different lesions that there are two methods for treating metastatic bone leakage; hemibody irradiation and radiopharmaceuticals. The partial contra-indications of this treatment include kidney and liver dysfunction or inadequate hematologic storage [16,17].

2.2.3 Combination and hyperthermia treatments

Today, attention is paid to combining treatments to remove cancerous tumors and increase the outcome of the treatment; Kai et al. [18] undoubtedly; the use of other therapeutic regimens along with radiation therapy is to prevent the recurrence of the tumor. One of the most important reasons for tumor recurrence is the presence of hypoxic cells in the central region of tumors. These cells have fewer PHs than peripheral tumor cells. These conditions make the central tumor cells more resistant to X and gamma rays. To create a certain number of injuries in a hypoplastic condition, it has to increase the radiation dose by 2-3 times, which also increases the dose of healthy tissues [19]. Many attempts have been made to solve this problem, most notably includes 1) the use of high-pressure oxygen during radiotherapy, 2) use of sensitizers, 3) use of Hypothermic [20].

2.2.4 Hyperthermia methods

Hyperthermia means an increase in temperature from 37 to 40 to 45 Celsius for the treatment of toners. As indicated in the study by Van der Zee et al. [21], the first International Congress about hyperthermic oncology was held in Washington, DC in 1975 and this conference ignited worldwide interest in hyperthermia, and most importantly, scientists reported that the application of heat as a therapeutic method along with common therapies consider an effective method to treat tumors. Hyperthermia is done in different ways: 1) local hyperthermia in this method of microwave antennas, ultrasound applicators, and RF applicators that use most of the world's centers of the same type 2) the regional hyperthermia and 3) the whole-body hyperthermia.

3. MATERIALS AND METHODS

This study is trial phase 3 and patients were referred to the hyperthermia (HT) department by different physicians and among the referred patients some of them are randomly selected for HT and the physicians have been blinded to patients. Patients were examined for pain relief and HT were done maximum one hour after radiotherapy with radiofrequency capacitive HT machine (Celsius42+ GmbH, Germany). The painful area of the patient was positioned between two electrodes and only one part of the body was treated by HT. The same HT protocol (Praxis- Klinik Hperthermie & Support Care, Institut Fur Hyperthermieforschung des Marien hospitals Herne, Klinikum der Ruhr-Universitat Bochum) was used for all patients. For further explication, in this interventional trial, the research population consisted of patients with bone metastases. The research samples were selected from patients who had including criteria of the study, which were willing to participate in the study, and signed written informed consent. The inclusion criteria of the study are bone metastases with pain, but not surgical. The exclusion criteria were the presence of diseases that were contraindicated for hyperthermia. Sixty (60) patients were randomly assigned to either radiotherapy or hyperthermia or radiotherapy only group. Five randomized blocks were used for randomization. Improvement of bone metastases and postoperative complications in two groups were compared by brief pain inventory (PBI) pain questionnaires proposed by Cleeland and Ryan [22] that is a highly cited scale and scholars have utilized it in their researches in the world. Notably, another section of the survey instrument in the current research was related to the measurement of quality of life and this scale was adopted from EORTC QLC-C30 introduced by Kaasa et al. [23] and the scale consists of (30) thirty items with intensifying labeling from (1. Not at all, 2. A little, 3. Quite a bit, 4. Very Much) and this scale is reliable and

valid among scholars all over the world. Another consequential point to be mentioned is that questionnaire in this research consist of demographic items such as gender, date of birth as usual of each standard survey instrument.

Data were analyzed using SPSS 21 software. Descriptive statistics (percentage), mean (standard deviation), and middle (minimum-maximum) with tables were used to describe the data [24]. Shapiro-Wilks test was used to assess the normal distribution of manifest variables including pain scores and age scores of patients, which was not found for any normal distribution [25]. Therefore, a nonparametric method was used to analyze the data. To compare the mean score of pain dimensions in both groups, the Mann-Whitney test was run, and additionally, the Wilcoxon test was used to compare the scores before and after treatment in each group. Considering the difference between the two groups in the baseline, the analysis of covariance was used to adjust the baseline values and also to calculate the percentage difference before and after the treatment compared to the baseline values [25,26]. According to the lack of changes in the results, the details of this analysis in the text are not mentioned. Chi-Square test was used to compare the distribution of response to treatment between the two groups. The significance level was considered to be less than 0.05, that is, P-value <0.05 represents and supports a statistically significant relationship [26].

4. DATA PROCESSING AND RESULTS

In this section, firstly, the demographic and clinical characteristics of the patients in the two intervention and control groups will be explained by running descriptive statistics in SPSS and the representation of findings with supporting tables. Then, after the interpretation of the results, the difference between the two intervention and control groups will be elucidated at a significant level of less than 0.05.

4.1 Individual and Clinical Characteristics of the Patients

Describing the individual and clinical characteristics of the patients, including gender, age, primary cancer site, and location of lesions were categorized into two groups of intervention and control as shown in Table 1. In total, 60 patients with bone marrow metastasis with a mean and standard deviation of 59.72 ± 14.78 years were included. 34 patients were female (57%) and 26 males (43%). Patients in both intervention and control groups did not differ significantly in terms of age (P = 0.222) and gender (P = 1.000). In the intervention group, the highest incidence of cancer was 13 cases of breast cancer (43%), 12 cases of prostate cancer (40%) and 2 cases of lung cancer (7%), while in the control group, the highest incidence of cancer-related to 10 cases of breast cancer (33%), 6 cases of prostate cancer (20%), 2 cases of bladder cancer (7%) and 2 cases of pancreatic cancer (7%). In general, the diagnostic variability was higher in the control group. In the intervention group, the lesions sites were mainly in pelvic bones (37%), lumbar spine (33%), and femur (20%). In the control group, the lesions sites were mainly in the lumbar spine (43%), pelvic bones (30%), femur (10%), and thoracic (10%). Table 1 describes the demographic characteristics of patients in two groups (n = 60).

4.2 Comparison of the Pain Scores between the Two Groups

Explication of patients' status for each sensory and reactive dimensions of pain at the beginning of the study and after treatment is presented in Tables 2 and 3. For further explanation, the scores of the patients in the sensory aspect of pain indicate that based on the Mann-Whitney test in the underlying condition patients in the control group have significantly higher mean scores than the intervention group as can be seen in Table 2. The mean values in the underlying condition, in the same way in both groups, were in the range of 6 to 10 in all items evaluated by the sensory dimension of pain.

After treatment (radiotherapy in the control group and radiotherapy-hyperthermia in the intervention group), although the patients in both control and intervention groups had a significant reduction in all sensory aspects of pain, including the highest pain intensity in the last 24 hours, the lowest pain intensity experienced in the last 24 hours, the average pain intensity in the last 24 hours and the intensity of the current pain (for all cases, P <0.001, based on the Wilcoxon test). However, according to the Mann-Whitney test, mean scores after treatment in both intervention and control groups did not differ significantly (P> 0.05 for all cases). The mean values after treatment are similar in both groups less than 3.

Table 1. Description of the demographic characteristics of patients in two groups

Variable	Levels	Total (N=60)		RT-HT (n=30)		RT (n=30)	
		Frequency	Percentage	Frequency	Percentage	Frequency	Percentage
Gender	Female	34	57	17	57	17	57
	Male	26	43	13	43	13	43
Primary cancer site	Breast	23	38	13	43	10	33
	Prostate	18	30	12	40	6	20
	Lung	3	5	2	7	1	3
	Bladder	2	3	0	0	2	7
	Colon	2	3	1	3	1	3
	Pancaras	2	3	0	0	2	7
	cervix	1	2	0	0	1	3
	CUP	1	2	0	0	1	3
	Endometr	1	2	0	0	1	3
	Endometrial sarcoma	1	2	0	0	1	3
	Esophagus	1	2	0	0	1	3
	Gastric	1	2	0	0	1	3
	Multiple myeloma	1	2	0	0	1	3
	Ostmeosarcoma	1	2	1	3	0	0
	Rectum	1	2	0	0	1	3
	Thyroid	1	2	1	3	0	0
Location of lesions	Lumbar spine	23	38	10	33	13	43
	Pelvic bones	20	33	11	37	9	30
	Femur	9	15	6	20	3	10
	Thoracic	3	5	0	0	3	10
	Scapula	2	3	2	7	0	0
	Cervical Vertebra	1	2	0	0	1	3
	Chest Wall	1	2	1	3	0	0
	Knee	1	2	0	0	1	3
Age (years)	Middle	62.0		66.0		58.5	
	Mean (sd)	60(15)		62(17)		58(13)	
	Minimum – Max	27-86		27-86		30-82	

RT: Radiotherapy, HT: Hyperthermia

Table 2. Description of pain in terms of severity (sensory dimension) in two groups of patients

Pain score	RT-HT (n=30)		RT (n=30)		P-value	
	Baseline	After	Baseline	After	Baseline	After
Highest pain, middle	9.0	2.5	10.0	3.0	0.023	0.525
Mean (sd)	9(1)	3(3)	9(1)	3.3 (2.6)		
Minimum – Max	6-10	0-9	6-10	0-8		
Lowest pain, middle	5.0	2.0	8.0	2.0	<0.001	0.398
Mean (sd)	5.8(2.3)	1.9(2.1)	7.9 (1.3)	2.3(2.2)		
Minimum – Max	2-10	0-7	5-10	0-7		
Medium Pain, middle	6.0	2.0	9.0	3.0	<0.001	0.222
Mean (sd)	6.8(1.6)	2.3 (2.2)	8 (1)	3(2)		
Minimum – Max	5-10	0-7	5-10	0-7		
Current pain, middle	7.0	1.5	9.0	2.0	<.001	0.308
Mean (sd)	7(2)	2.3(2.7)	8.6(1.3)	2.6(2.2)		
Minimum – Max	4-9	0-8	5-10	0-8		
Pain relief, Middle **	80.0	90.0	20.0	90.0	<0.001	0.181
Mean (sd)	67.7(26. 4)	82.9(16.8)	29(21)	88 (16)		
Minimum – Max	20-100	40-100	10-100	50-100		

RT: Radiotherapy, HT: Hyperthermia

** The range of values in all dimensions is from 0 to 10.*

*** The values for the patients who took the drug were 21 (70%) and 21 (70%) of the patients in the control group and 21 (70%) and 14 (47%) of the patients in the intervention group, in periods before and after treatment have been reported*

Table 3. Description of the pain in term of pain interferes with daily activities (after reaction), in two groups of patients

Score of pain	RT-HT (n=30)		RT (n=30)		P-value	
	Baseline	After	Baseline	After	Baseline	After
Normal activities	9.0	3.0	9.0	3.0	.012	.858
Mean (sd)	8.2(1.7)	4(3)	9 (1)	3.4 (2.2)		
Minimum – Max	4-10	0-10	7-10	0-9		
Mood	8.0	3.0	9.0	3.5	.013	.260
Mean (sd)	7.3(2.4)	3.6(2.1)	8.7(1.2)	4.2(2.3)		
Minimum – Max	2-10	1-9	5-10	1-10		
Walking ability	8.0	2.0	9.0	3.0	.013	.535
Mean (sd)	7.3(2.1)	3.1(2.6)	8.6 (1.1)	3.3(2.1)		
Minimum – Max	3-10	0-9	6-10	0-10		
Common work	8.0	5.0	8.0	3.0	.656	.332
Mean (sd)	8.1 (1.5)	4(3)	8 (1)	3.2 (2.2)		
Minimum – Max	4-10	0-9	6-10	0-10		
Communication with others	7.0	2.0	8.0	3.0	.017	.129
Mean (sd)	6(3)	3(2)	8(1)	4(2)		
Minimum – Max	1-9	0-8	6-10	0-9		
Sleep	6.0	2.0	7.0	3.0	.004	.040
Mean (sd)	5.1(2.9)	2.3(1.6)	7.2(1.5)	3.2 (2.1)		
Minimum – Max	0-10	0-7	3-10	0-8		
Enjoyment of life	8.0	3.5	8.0	4.0	.837	.823
Mean (sd)	6.7(2.8)	4.6(2.9)	7 (1)	4.1 (1.9)		
Minimum – Max	2-10	1-10	5-9	1-10		
Total of reactive dimension	6.9	3.7	8.2	3.6	.003	.689
	6.89(1.65)	3.41(1.94)	8.16(0.83)	3.59(1.91)		
Minimum – Max	4-9.57	0.71-8.43	6.14-9.86	0.43-9.14		

RT: Radiotherapy, HT: Hyperthermia

** The range of values in all dimensions is from 0 to 10*

Table 4. Description of the frequency of use of analgesics and its types in two groups of patients

Analgesics	RT-HT (n=30)		RT (n=30)	
	Baseline	After	Baseline	After
No drug intake	9(30)	16(53)	9(30)	9(30)
Taking medication	21(70)	14(47)	21(70)	21(70)
Name of the drug				
Dexamethasone	5(17)	3(10)	0(0)	0(0)
Tramadol	4(13)	4(13)	1(3)	1(3)
Gelofen	3(10)	2(7)	0(0)	0(0)
Diclofenac	2(7)	1(3)	3(10)	3(10)
Acetaminophen	2(7)	1(3)	0(0)	0(0)
Oxycodone	1(3)	1(3)	4(13)	3(10)
Alfnix	1(3)	0(0)	0(0)	0(0)
Aspirin	1(3)	1(3)	0(0)	0(0)
Methadone	1(3)	0(0)	0(0)	0(0)
Acetaminophen codine	0(0)	0(0)	7(23)	7(23)
Morphine	0(0)	0(0)	4(13)	4(13)
Gabapentin	0(0)	0(0)	1(3)	2(7)
Naproxen	0(0)	0(0)	1(3)	1(3)

RT: Radiotherapy, HT: Hyperthermia

Table 5. Description of the response to treatment one month after treatment in two groups of patients

Reply to treatment	RT-HT (n=30)	RT (n=30)	Q test statistic (degree of freedom)	P-value
complete response	8(27)	4(13)	5.52 (2)	0.063
partial response	17(57)	25(83)		
Resistant to treatment	5(17)	1(4)		

RT: Radiotherapy, HT: Hyperthermia
Values are frequency (percentages)

The scores of patients in the reactive dimension of pain indicate that based on the Mann-Whitney test in the underlying condition patients in the control group except for common work items and enjoyment of life reported significantly higher mean scores than the intervention group as represented in Table 3. The mean values in the underlying condition in the same way in both groups were in the range of 6 to 9 in all evaluated items of the pain response.

After treatment (radiotherapy in the control group and radiotherapy-hyperthermia in the intervention group), although the patients in both control and intervention groups had a significant decrease in all the items of the pain response, including pain interference with normal activities, mood, walking ability, common work, communication with others, pain interference with sleep and enjoyment of life (for all cases, $P < 0.001$, based on Wilcoxon test). However, the mean scores of pains in the reactive items according to the Mann-Whitney test show that there was not a significant difference between case and control groups except for interference pain with sleep ($P > 0.05$ for all cases). Patients in the combination therapy group reported a significantly lower score for sleep interference ($P = 0.04$). The mean values after treatment were similar in both groups which had a result of less than 4.

The results of covariance analysis in comparison of sensory and reactive dimensional scores in two intervention and control groups showed that the mean scores of pain in both intervention and control groups after adjustment to the difference between the two groups in the underlying condition are not significantly differed (for all cases, $P < 0.01$). The description of the frequency of pre-treatment and post-treatment analgesics in the two groups of patients is presented in Table 4. At the beginning of the study, 20 patients in the intervention group (67%) and 21 patients in the control group (70%) used the analgesics which was reduced to 43% (12 patients) after treatment, while in the control group without changing 70% (21 patients). Also, the most commonly used analgesics were dexamethasone, tramadol and gelofen in the intervention group, while the most commonly used analgesics were acetaminophen codeine, morphine, and diclofenac respectively.

It is notable that in the patients who consumed the analgesics, the mean of pain relief with medication in the intervention group before and after the treatment was approximately the same and on average 66% and 83%, respectively, while in the control group the mean partial pain relief was reported before and after treatment (29%) (88%) as delineated in Table 2. The ensuing Tables 2, 3, and 4 contain comprehensive information relevant to the interpretation of results in this section.

4.3 Elucidation of the Response to Treatment in Two Groups

The response to the treatment or the clinical effectiveness of treatment in the patients who were considered in the current study is as follows: (1) complete response (zero scores in describing the worst pain situation in the last 24 hours), (2) partial response (reduction of 2 scores and more relative to the baseline before treatment in describing the worst pain situation in the last 24 hours), and (3) stable pain (no change in score or only a reduction score relative to baseline before treatment describing the worst pain situation in the past 24 hours). The frequency of response to treatment is represented in Table 5.

After treatment, 27% and 13% of patients in the intervention group and the control group had a complete response to treatment, while 57% and 83% of patients in the two intervention and control groups experienced a decrease in the clinical pain and 17% in contrast, 4% of the patients in the two intervention and control groups did not stably respond to treatment. Chi-

square test results revealed that there is no significant difference between the two groups in terms of response to treatment despite the difference in partial response ratio in two groups (P = 0.063).

5. DISCUSSION AND CONCLUSION

At this stage, it is noteworthy to remind that the fundamental premises behind the stimulus of conducting present research stem from some pronounced pints as mentioned earlier in the present original research article. For the recapitulation of literature in this research era, the efficacy of treatment is dependent on the purpose of the treatment that is, relieving pain, preventing pathologic fracture, avoiding subsequent therapies, or controlling the position of the disease [6].

Notably, palliative radiotherapy is very efficacious and pragmatic for patients with bone metastases, and the pain of many patients after treatment is alleviated and the response rate to palliative radiotherapy for localized painful patients is significantly higher than the response rate ensuing from palliative systemic treatments and ergo, radiotherapy is the basis of localized bone metastases, but because the mechanism of pain may be multifactorial, combined therapies, especially the combination of radiotherapy and hyperthermia, which acts as one of the important radiolaborant sensitivities, may be referred to any of the treatments exclusively; on the other hand, it may increase the therapeutic side effects [7,8].

Based on studies as reviewed earlier by Sakurai et al. [13], Matsumine et al. [11], Kaur et al. [9], Matsumine et al. [11], Zagar et al. [12], Chi et al. [14], Van Rhoon et al. [15], we can assert that as the nature of each research in which the findings are different, this study in Iran had its results and findings are synchronized and consistent with exemplary researches by scholars as delineated earlier.

5.1 Major Conclusions

Right off the bat, we compared the effects of radiotherapy and hyperthermia with radiotherapy only in the treatment of bone metastases in the Omid Tehran radiation oncology center. At the first, 20 patients in the intervention group (67%) and 21 patients in the control group (70%) used palliative drug, which was reduced to 43% (12 patients) after treatment, while in the control group without changing 70% (21 patients) were remained. After treatment, 27% and 13% of patients in the intervention group and the control group had a complete response to treatment, while 57% and 83% of patients in the two intervention and control groups experienced a decrease in the clinical pain and 17% in contrast of 4% of the patients in the two intervention and control groups did not respond to treatment in a stable mode. Regardless of the difference in the ratio of partial response in two groups, there is no significant difference between the two groups in terms of response to treatment.

To make a long story short, according to the results of this interventional study, it can be asserted that in some aspects of interference with sleep pain, the efficacy of combined therapy is higher and in other cases, there is no significant difference, and since the treatment of these patients is palliative, therefore adding hyperthermia to improve and ameliorating their sleep patterns is not useful, so using combination therapy based on patient conditions, patient preference, economic status, hyperthermia availability is not a waste of benefit.

5.2 Recommendations for Future Studies Development

This research like any research had limitation which was ineluctable. The most remarkable limitation was the willingness of the target population or patients because the sampling technique was randomized. That was problematic due to not being able to have a large sample size. However, the current sample population was adequate and reliable for achieving accurate findings as mentioned earlier, and the consistency of them by the results of former studies.

The current research implies outstanding messages to academicians, doctors, and those who are implicated in this subject. Admittedly, findings can play a pivotal role in this research era to apprise and keeping updated those who are implicated in this subject and also providing practical ways to mount further studies and reaching solid conclusions. Furthermore, it is worthwhile mentioning that conducting studies with larger sample sizes and basing data analysis on a sound methodological foundation is highly suggested. Last but not least, assessment of the effects of treatment on patients who suffer from bone metastases could be a favorable and fortunate value to improve our insight and realization to ponder on this subject.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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