Journal of Bone Oncology 31 (2021) 100395

Contents lists available at ScienceDirect

Journal of Bone Oncology

journal homepage: www.elsevier.com/locate/jbo

Research Paper

Concurrent capecitabine with external beam radiotherapy versus radiotherapy alone in painful bone metastasis of breast cancer origin

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ARTICLE INFO

Article history:
Received 1 July 2021
Revised 26 September 2021
Accepted 2 October 2021
Available online 16 October 2021

Keywords:
Concurrent capecitabine
Palliative radiotherapy
Pain score
Breast cancer
Bone metastases

ABSTRACT

Background: In breast cancer, painful bone metastases are common. Local radiotherapy is the standard treatment of painful bone metastases. Pain control and overall response rateswere low in radiotherapy alone.

The objectives of this study were to compare the safety and efficacy of external beam radiotherapy with concurrent capecitabine vs. external beam radiotherapy alone in pain control of painful bone metastases in breast cancer patients.

Materials and methods: Eighty-four patients with painful bone metastases from breast cancer participated in this prospective study. We randomized the patients into two groups: group A treated with radiotherapy 30 Gy in 10 fractions and group B treated with capecitabine 825 mg/m^2 every 12 hrs. concurrently with the same radiotherapy dose.

Results: There was no statistically significant difference between the two groups regarding early treatment toxicity. Most of the toxicity was gastrointestinal (diarrhea and nausea) and mild (grade I or II). The median pain score decreased from week one, and there was a marked response at week4. The difference in median pain score between both groups was statistically significant with p-value = 0.045. The median analgesic score in both groups was statistically significant with a p-value = 0.032 at week 12. A complete response to pain at week 4 was 19% and 42.9% in groups A and B, respectively.

Conclusion: Concurrent chemoradiation in painful bone metastases from breast cancer origin was tolerable and safe; it had a higher overall response rate and pain palliation than radiotherapy alone.

1. Introduction

Seventy percent of advanced breast cancer patients have bone metastasis and this causes significant morbidity due to pain and skeletal-related events. Bone metastasis affects the quality of life of the patient and also decreases overall survival [1,2].

Bone is the commonest site of metastasis in breast cancer with almost one-third of metastatic breast cancer patients having bone-only metastasis [3].

Several biological factors are the cause of the high incidence of bone metastases including greater blood flow in the red bone marrow and manufacturing of adhesive molecules, which are involved in binding tumor cells with the stroma of bone marrow. Tumor cells within hematopoietic cells go through variable periods of inactivity, thus escaping the chemotherapy effect before becoming cancer-initiating cells which develop into definite metastatic colonies [4].

The trabecular bone is a vascular and preferred site to which breast cancer cells metastasize in the case of hematogenous spread. Most bone metastases seen in breast cancer patients are osteolytic. Interaction between tumor cells and the bone microenvironment stimulates osteoclast which increases bone turnover, releasing bone activity growth factor and cytokines [5].

Pain is the most common symptom of bone metastasis and the standard therapy for pain is conventional radiotherapy, which

Abbreviations: SF, single fraction; MF, multiples fraction; CR, Complete response; PR, Partial response; SP, Stable pain; PP, Progressive pain; OR, overall response rates.

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https://doi.org/10.1016/j.jbo.2021.100395
2212-1374/

improves skeletal integrity, reduces the risk of fraction, preserves physical function, and palliates pain [6].

There is worldwide variation in dose fractionation of palliative radiotherapy; it can be given in a single fraction (SF) or multiple fractions (MF). Meta-analysis of 25 trials comparing single schedule with multiple schedules showed that both had similar overall pain responses. The complete pain response was 23%-24% only for SF and MF, respectively, but there was more need for re-irradiation and more pain flare at the treated metastatic site in the case of SF [7,8].

Concurrent chemoradiation is used for many metastatic and locally advanced primary tumors to improve the local control of primary tumors and palliation of many local symptoms like pain, bleeding, and compression as in esophageal cancer, non-small cell lung cancer, and head and neck cancers [9–11].

Combining adjuvant radiotherapy with capecitabine was safe in the adjuvant treatment of breast cancer, and had comparable toxicity to radiotherapy alone [12].

Capecitabine is an oral fluoropyrimidine and a prodrug of 5-fluorouracil. It has enhanced efficacy on tumor tissue and reduces gastrointestinal tract and bone marrow toxicities with low alopecia and neuropathy. It is an interesting option for some patients due to its route of administration and favorable toxicity profile. It is a potent radiosensitizer which enhances the biologically effective dose of radiotherapy [13].

The purpose of this study is to compare the safety and efficacy of concurrent capecitabine radiotherapy with radiotherapy alone in the treatment of painful bone metastasis in breast cancer patients.

2. Materials and methods

2.1. Study design

This prospective randomized phase II study included 84 breast cancer patients with painful bone metastasis presented to the Radiotherapy Department and Pain Clinic at South Egypt Cancer Institute from January 2019 to January 2021. Patients were randomly assigned into group A in which patients received radiotherapy only and group B in which patients received the same radiotherapy schedule with concurrent capecitabine. SPSS program version 26 was used for randomizing patients by creating a categorical variable that contains two groups and assigning patients into either of the two groups based on their enrollment number in the study. We followed up the patients for 12 weeks.

2.2. Eligibility criteria

The patient must have histological confirmation of breast adenocarcinoma. Radiographic manifest of bone metastasis was required including plain radiographs, radionuclide bone scans, or magnetic resonance imaging. The patients must have pain in the sites of the radiographically documented metastasis. The patients must be $\geq$ 18 years of age. The estimated life expectancy of patients was 3 months or greater according to Rades score [14], Performance Status $\leq$ 3 according to the ECOG scoring system. Patients who had ALT and AST no greater than 3 times the normal level, serum bilirubin and creatinine no greater than 1.5 times the normal level, absolute neutrophil count $\geq$ 1500/ml, and platelets >100,000/mm^3 were included in this study. Patients were included in the study disregarding their previous exposure to chemotherapy except capecitabine.

2.3. Exclusion criteria

We excluded patients with previous radiation therapy, palliative surgery to the painful site, having a threatening fracture of the treatment site, or intended surgical fixation of the bone. In addition, patients with evidence of spinal cord or cauda equina compression clinically or radiographically were excluded from the study. We also excluded the patients who previously received capecitabine.

2.4. Radiation therapy

Treatment volume included the radiographic abnormality with at least a 2 cm margin, In the case of vertebral metastasis treatment volume was determined by adding the upper and lower vertebra to the affected vertebra. The dose of radiotherapy was 30 Gy in 10 fractions, 5 days per week. We used prophylactic antiemetic before radiotherapy in the case of the large target volume in the abdomen.

2.5. Chemotherapy

Oral capecitabine 825 mg/m^2 was administered 5 days per week, in twice-daily doses, concurrently with radiotherapy.

2.6. Evaluation of toxicity

We assessed toxicity during treatment once weekly. After the end of treatment we evaluated patients every 4 weeks until 12 weeks according to NCI common terminology criteria for adverse events (CTCAE) vertion0.5 [15].

2.7. Pain assessment

Patients were asked to describe their pain on the Visual Analogue Scale (VAS) in which scores range from zero to 10; where zero indicates (no pain) and 10 indicates (worst possible pain). Mild pain was assigned a score of 1–4, moderate pain a score of 5–6, extreme pain a score of 7–8, and heavy pain a score of 9–10 [16]. We chose the most painful sit as index sit We assessed the pain score before the onset of treatment, at week zero then at week one, week 2, week 4, week 8, and week 12 after the end of treatment in both studied groups.

2.8. Analgesic use assessment

The physician used the 5-point WHO Scale to measure analgesic use based on the medical records: Level 0 requires no analgesics; level 1 requires non-narcotic analgesics on occasion; level 2 requires non-narcotic analgesics on a regular basis; level 3 requires narcotic analgesics on occasion; and level 4 requires narcotic analgesics on a regular basis.

2.9. Response to treatment

We evaluated the response to treatment by the international bone metastases consensus [17] which takes into account both the patient's pain score and analgesic consumption. Complete response (CR) was defined as zero pain score at the treated site with no increase in analgesic intake. Partial response (PR) reduction pain score by two or more at the treated site without increase in analgesics need. Stable pain (SP) was a no change in pain score or aone-point change. Progressive pain (PP) was a two or more point increase in pain score with stable analgesic use or increased analgesic use (with stable pain score or one-point increase above baseline). Patients with complete or partial response were considered as overall response rates (OR), and patients with stable or progressive pain were considered as non-responders.

2.10. Statistical analysis:

Power Calculation

Our primary outcome parameter was the efficacy of radiotherapy concurrently with capecitabine versus radiotherapy alone in pain palliation from painful bone metastases in breast cancer patients. Secondary outcomes included the assessment of toxicity and side effect of concurrent capecitabine with radiotherapy in comparison with radiotherapy alone. Using the EBI program at a power of 80%, with 95% confidence interval and a 2-sided type I error of 5%, 40 patients in each group were required to detect a significant difference between the two studied, and this raised the sample size to 84 patients (42 patients in each group).

2.11. Data analysis

Data analysis was undertaken using SPSS version 26. Categorical data were presented in the form of frequencies, and percentages while the mean ± SD and median (range) were used to present continuous variables. Mann Whitney U Test was used to compare median pain and analgesic score between groups A and B at each time point. Chi-square was used to compare the proportion of response to treatment between groups A and B. The level of significance was considered at a P-value < 0.05. All statistical tests were two sided.

3. Ethics statement and consent to participate

The Ethical Committee of South Egypt Cancer Institute, Assiut University, approved the study protocol. It was conducted in accordance with the provisions of the Declaration of HelsinkiSECI-IRB no.174. TheEthical Committee of South Egypt Cancer Institute approved the study and an informed written consent was obtained from all patients.

4. Results

4.1. Baseline characteristics

This study included 84 metastatic breast cancer patients with painful bone metastases; each treatment group included 42 patients. The clinical characteristics are summarized in Table 1.

The mean age was 47.29 and 47.71 for groups A and B, respectively. Most of our patients were hormonal receptor-positive, while only 10 and 12 patients are negative for groups A and B, respectively. The majority of patients in both groups were suffering from grade 2 metastatic breast cancer. Only 12 patients in group A and 14 patients for a group B were HER2 positive. Patients' characteristics were comparable, and the differences were not statistically significant.

Besides bone metastases, four patients in-group A had lung metastases and four others had liver metastases, while 4 patients in group B had lung metastases and 6 others had liver metastases.

All our patients completed the treatment protocol.

Table 1
Characteristics of the studied groups.

Variables	Group A (n = 42)	Group B (n = 42)	P-value*
Age (years) Mean ± SD	47.29 ± 9.65	47.71 ± 8.82	0.832
Pathology			
IDC	38 (90.5)	38 (90.5)	1.000
LC	4 (9.5)	4 (9.5)	
Grade			
2	20 (47.6)	24 (57.1)	0.280
3	12 (28.6)	6(14.3)	
4	10 (23.8)	12 (28.6)	
Hormonal receptor			
Positive	32 (76.2)	30 (71.4)	0.620
Negative	10 (23.8)	12 (28.6)	
her2/new			
Positive	12 (28.6)	14 (33.3)	0.569
Negative	28 (66.7)	24 (57.1)	
Unknown	2 (4.8)	4 (9.5)	
NO of region treats with RTH			
Single region	28 (66.7)	30 (71.4)	0.637
Multiple regions	14 (33.3)	12 (28.6)	

Data is expressed as Mean ± SD, or frequency (%).
* Independent sample T test, Chi square test.

Table 2
Treatment related side effects in the treatment groups.

Variables	Group A (n = 42)	Group B (n = 42)	P-value*
Diarrhea			
No	38 (90.5)	34 (81.0)	0.270
Grade 1	4 (9.5)	6 (14.3)	
Grade 2	0 (0.0)	2 (4.8)	
Nausea			
No	36 (85.7)	32 (76.2)	0.266
Grade 1	6 (14.3)	10 (23.8)	
Grade 2	0 (0.0)	0 (0.0)	
Hand and foot syndrome			
No	42 (100.0)	40 (95.2)	0.152
Grade 1	0 (0.0)	2 (4.8)	
Grade 2	0 (0.0)	0 (0.0)	
Mucositis			
No	42 (100.0)	40 (95.2)	0.152
Grade 1	0 (0.0)	2 (4.8)	
Grade 2	0 (0.0)	0 (0.0)	
Weakness			
No	36 (85.7)	34 (81.0)	0.558
Grade 1	6 (14.3)	8 (19.0)	
Grade 2	0 (0.0)	0 (0.0)	
Radiation dermatitis			
No	38 (90.5)	34 (81.0)	0.212
Grade 1	4 (9.5)	8 (19.0)	
Grade 2	0 (0.0)	0 (0.0)	

Data is expressed as frequency (%).
*Chi square test.

4.2. Toxicity

Early Treatment related toxicity according to the NCI CTCAE version5 was summarized in Table 2. Concurrent chemoradiation was generally well tolerated and side effects were mild. All the side effects were (grade I or II).Most of the capecitabine side effects were gastrointestinal. Grade 2 diarrhea occurred in two patients (4.8%) in group B, and grade I nausea occurred in 10 patients (23.8%) of group B versus 6 patients (14.3%) in group A. There was no grade 3 or 4 toxicity in both treatment groups. Only two patients in group B developed hand and foot syndrome which was grade I. There was no statistically significant difference between the two groups regarding treatment toxicity. Within two weeks from the end of treatment, all toxicities improved.

4.3. Pain score

The median pain score was seven for both groups before the start of treatment. The median pain score decreased from week one to week 12 in both groups, but the reduction was more in

group B as illustrated in Table 3. There was a statistically significant difference in the median pain score between groups A and group B from week one after treatment (8.00 compared to 5.00, respectively, and p-value = 0.008),at 4 weeks after treatment (5.00 compared to 2.00, respectively, and a p-value = 0.005), and at 12 weeks after treatment (4.00 compared to 1.00, respectively, and a p-value = 0.001) as shown in Table 3.

4.4. Analgesic score

An analgesic score of zero was documented in one patient in group B and no patient in group A before the initiation of treatment. After 4 weeks an analgesic score of zero was documented in 8 patients in group A and 22 patients in group B. The use of analgesics decreased with time and the main changes were noted during the first 4 weeks as shown in Figure 1.

Before the start of treatment and at week one after treatment, there was no statistically significant difference in the median analgesic score between both groups with a p-value greater than 0.05. However, there was a statistically significant difference in the median analgesic score between groups A and B from week two to week 12 after treatment with a p value = 0.001 at week 4 as shown in Table 4.

4.5. Response to treatment

The response to treatment was determined based on pain scores and analgesic scores.After one week PR was documented in 10 (23.8%) and 18(42.9%) patients in groups A and B, respectively. At week 4 CR was determined in 8(19%) patients in group A and 18 patients (42.9%) in group B. The rate of overall response (OR) increased over time and then stabilized at weeks 8 and 12. At week one OR was 12 (28.6%) and 24 (57.1%) for groups A and B, respectively, while at week 4 it became 20 (47.6%) and 34 (81%) for groups A and B, respectively. The difference in response between both groups was statistically significant from week one to week12 with a p-value = 0.012 at week 4 as shown in Table 5.

Table 3
Median pain score between the two studied groups.

Pain score	Group A	Group B	P-value*
Week 0	7.00 (4–10)	7.00 (4–10)	0.942
Week 1	8.00 (0–10)	5.00 (0–10)	**0.008**
Week 2	5.00 (0–10)	2.00 (0–9)	**0.001**
Week 4	5.00 (0–9)	2.00 (0–9)	**0.005**
Week 8	4.00 (0–9)	2.00 (0–9)	**0.002**
Week 12	4.00 (0–9)	1.00 (0–9)	**0.001**

Data expressed as median (range).
*Man-Whitney *U* test.

Table 4
Analgesic score between the two studied groups.

Analgesic score	Group A	Group B	P-value*
Week 0	2.00 (1–4)	3.00 (0–4)	0.970
Week 1	2.00 (0–4)	2.00 (0–4)	0.112
Week 2	2.00 (0–4)	1.00 (0–4)	**0.012**
Week 4	1.00 (0–4)	0.00 (0–4)	**0.001**
Week 8	1.00 (0–4)	0.00 (0–4)	**0.005**
Week 12	1.00 (0–4)	0.00 (0–4)	**0.002**

Data expressed as median (range).
*Man-Whitney *U* test.

5. Discussion

Despite advances and improvements following breast cancer treatment, a large proportion of patients develop metastatic disease, especially bone which is the most common first site for distant metastasis. Due to interactions between the tumor and hematopoietic stem cells [18].

Radiotherapy is a key treatment modality for painful bone metastasis; it was highly effective in relieving pain independently of whether single or multiple fractions were prescribed [19]. The effect of radiotherapy on bone pain was due to its ability to produce ossification and reduced osteoclast activity of tumor cells [20].

We used a radiotherapy dose of 30 Gy delivered in 10 fractions to avoid higher incidence of reirridiation and pain flare that occur more with single fraction radiotherapy courses although there is no difference between SF and MF radiotherapy in pain palliation. We suggested that concurrent chemoradiation had more pain con-

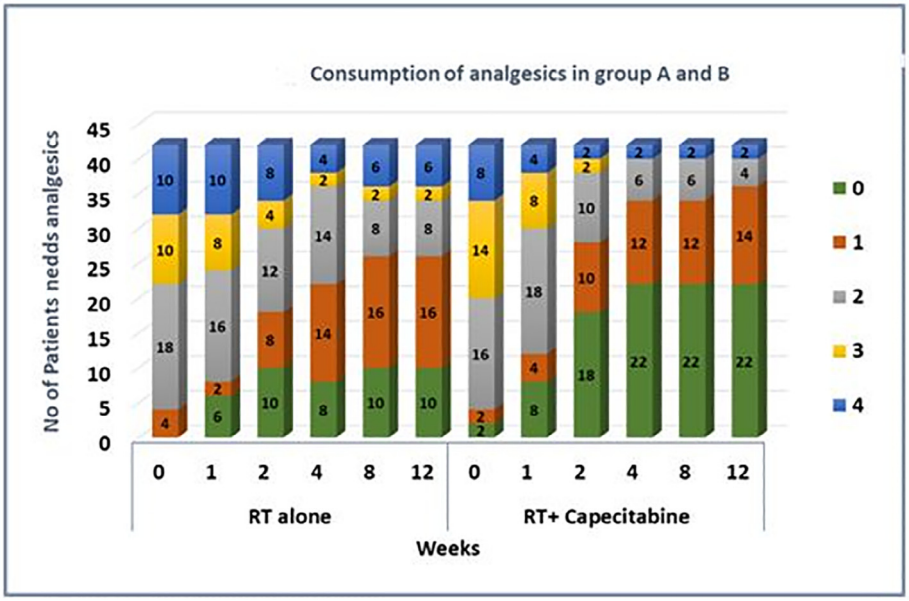

Fig. 1. Consumption of analgesics in groups A and B.

Table 5
Response to treatment between the two studied groups.

Response	Group A (N = 42)	Group B (N = 42)	P-value*
Week 1			
CR	2 (4.8)	6 (14.3)	**0.018**
PR	10 (23.8)	18 (42.9)	
SP	20 (47.6)	16 (38.1)	
PP	10 (23.8)	2 (4.8)	
Week 2			
CR	6 (14.3)	14 (33.3)	**0.001**
PR	10 (23.8)	20 (47.6)	
SP	18 (42.9)	6 (14.3)	
PP	8 (19.0)	2 (4.8)	
Week 4			
CR	8 (19.0)	18 (42.9)	**0.012**
PR	12 (28.6)	16 (38.1)	
SP	16 (38.1)	6 (14.3)	
PP	6 (14.3)	2 (4.8)	
Week 8			
CR	8 (19.0)	18 (42.9)	**0.004**
PR	10 (23.8)	16 (38.1)	
SP	18 (42.9)	6 (14.3)	
PP	6 (14.3)	2 (4.8)	
Week 12			
CR	8 (19.0)	18 (42.9)	**0.004**
PR	10 (23.8)	16 (38.1)	
SP	18 (42.9)	6 (14.3)	
PP	6 (14.3)	2 (4.8)	

Data is expressed as frequency (%).
*Chi square test.
Complete response (CR), defined as no pain and no need for analgesics; partial response (PR), defined by a decrease of 2 points in the pain score and no change in analgesics consumption; stable pain (SP), defined as a decrease of one point or no change in the pain score and no change in analgesics.

trol than radiotherapy alone because concurrent chemoradiation was used for the palliation of many local symptoms in metastatic primary tumors. Therefore, our study aimed to compare the safety and efficacy of radiotherapy concurrently with capecitabine versus radiotherapy alone in palliating pain resulting from bone metastases in breast cancer patients. Reviewing published literature, we do not find any similar publications that made this comparison.

In our study, capecitabine with local radiation was well tolerated and associated with mild side effects, which resolved within 2 weeks from the end of treatment with no treatment interruption. There was no statistically significant difference in toxicity between the two groups.

These results are consistent with the results of a study conducted by Kundel et al, which was a phase II prospective study. They used capecitabine concurrent with radiotherapy to treat painful bone metastasis of breast cancer origin. They reported no grade III or IV toxicity although they used a higher dose of capecitabine in comparison to our study. Most of the toxicities observed were gastrointestinal symptoms such as diarrhea and nausea (either grade I or II). Grade I diarrhea was reported in 24% of the patients versus 14.3% in our study. Grade I hand and foot syndrome was reported in 7 % versus 4.8 % in our study, while grade I weakness was reported in 21 % versus 19 % in our study, and mucositis was reported in 10% [21].

Several studies showed that palliative radiotherapy alone was associated with a decrease in mean pain score and a decrease in analgesic consumption which reflected on the quality of life of patients. For instance, McDonald et al reported that 40% of the patients experience pain reduction at day 10 with further improvement in pain response at day 42 [22]. It was similar to our result ingroup A

In our study, the median pain score in group B who received radiotherapy concurrently with capecitabinedecreased from 7 to 5 after one week and then to 2 after 2 weeks of treatment. This finding is in line with the finding reached by Kundel et al. who reported a decrease in mean pain score from 2.93 to 2.28 after one week, then to 1.45 after 2 weeks of treatment with a p-value < 0.0001. Kundel et al documented an analgesic score of zero in one patient, a score of 1 in 9 patients, a score of2 in 8 patients, and a score of4 in 3 patients before the start of treatment. After 4 weeks of treatment, a score of zero was documented in15 patients, a score of1in 5 patients, a score of2 in 6 patients and a score of3 in 3 patients. In our study after 4 weeks of treatment, we documented an analgesic score of zero in 22 patients, a score of1one in 12 patients, a score of2 in 6 patients, and a score of 4 in 2 patients [21].

The results of our research indicated that at week 12the CR ratewas19.0%and the OR rate was 42.9% in group A, who received palliative radiotherapy alone. These rates were lower than those found by Wu et al. who reported CR rates of 32% and OR rates72 % in patients with painful bone metastasis [23]. Also, these rates were lower than those found by Van et al. who reported OR rates of 61 %, and the median response time was 4 weeks, but CR rates were 13 % which were lower than the rates found in our research [24]. Saito et al. reported CR rates of26% and OR rates of67% [25]. These rates were higher than our rates because a larger number of patients participated in these studies. However, our results were consistent with those reached by Chow et al. who reported CR rates of23% and OR rates of50% [26]. Our results were also consistent with those reached by ForoArnalot et al. who reported CR rates of 13% and OR rates of55% [27].

We reported CR and OR rates of 42.9% and 81.0%, respectively, at weeks 12 in group B, who received concurrent chemoradiation. This finding was consistent with that reached by Kundel et al. who reported CR rates of48 % and OR rates of 86% in patients who received capecitabine concurrently with palliative radiotherapy at weeks 12. In the phase II trial of Kundel et al., they reported that14 % of the patients had CR at week 1, 38 % at week 2, and 48 % at weeks 12 [21].

6. Limitations of the study

This study was limited to a small number of subjects and a short follow-up period, so we cannot assess the rate of recurrence in pain and long-term toxicities.

7. Conclusion

Concurrent capecitabine with external beam radiotherapy in painful bone metastases was safe. The toxicity was mild and comparable to that which occurred in palliative external beam radiotherapy alone. It was effective in the palliating of pain from bone metastases in breast cancer patients in comparison to palliative external beam radiotherapy alone and associated with higher CR and OR rates regarding pain control. This decreased analgesic consumption and improved the quality of life.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

Shimaa, made contribution to protocol design, analyzed and interpreted the patient data regarding the radiation oncology spectrum. And was a major contributor in writing the manuscript

Ayatallah, analyzed and interpreted the patient data and manuscript revision. Shereen , assessed the pain and analgesic score. Tarek, made manuscript editing and preparation all authors read and approved the final manuscript.

References:

[1] N. Sathiakumar *et al.*, "Mortality following bone metastasis and skeletal-related eventsamong women with breast cancer: a population-based analysisof U.S. Medicare beneficiaries, 1999–2006 Title," *Breast Cancer Res Treat*, vol. 131, no. DOI 10.1007/s10549-011-1721-x, pp. 231–238, 2012.

[2] R.E. Coleman, "Clinical Features of Metastatic Bone Disease and Risk of Skeletal Morbidity," 2006, doi: 10.1158/1078-0432.CCR-06-0931.

[3] F. Macedo *et al.*, Bone metastases: an overview, *Oncol. Rev.* 11(1) 2017, doi: 10.4081/oncol.2017.321.

[4] A.L. Allana, S.A. Vantyghem, A.B. Tuck, A.F. Chambers. Tumor dormancy and cancer stem cells: implications for the biology and treatment of breast cancer metastasis, *Breast Dis.* 26(1) 2006 87-98. IOS Press, doi: 10.3233/bd-2007-26108.

[5] R.L. Theriault, R.L. Theriault, Biology of bone metastases, *Cancer Control* 19(2) 2021 92-101. H. Lee Moffitt Cancer Center and Research Institute, doi: 10.1177/107327481201900203.

[6] S. Lutz, L. Berk, E. Chang, E. Chow, C. Hahn, P. Hoskin, D. Howell, A. Konski, L. Kachnic, S. Lo, A. Sahgal, L. Silverman, C. von Gunten, E. Mendel, A. Vassil, D.W. Bruner, W. Hartsell, Palliative radiotherapy for bone metastases: An ASTRO evidence-based guideline, Int. J. Radiat. Oncol. Biol. Phys. 79 (4) (2011) 965–976, https://doi.org/10.1016/j.ijrobp.2010.11.026.

[7] A. Fairchild, E. Barnes, S. Ghosh, E. Ben-Josef, D. Roos, W. Hartsell, T. Holt, J. Wu, N. Janjan, E. Chow, International patterns of practice in palliative radiotherapy for painful bone metastases: evidence-based practice?, Int J. Radiat. Oncol. Biol. Phys. 75 (5) (2009) 1501–1510, https://doi.org/10.1016/j.ijrobp.2008.12.084.

[8] S.E. Rich, R. Chow, S. Raman, K. Liang Zeng, S. Lutz, H. Lam, M.F. Silva, E. Chow, Update of the systematic review of palliative radiation therapy fractionation for bone metastases, Radiother. Oncol. 126 (3) (2018) 547–557, https://doi.org/10.1016/j.radonc.2018.01.003.

[9] H.H. Strøm, R.M. Bremnes, S.H. Sundstrøm, N. Helbekkmo, Ø. Fløtten, U. Aasebø, Concurrent palliative chemoradiation leads to survival and quality of life benefits in poor prognosis stage III non-small-cell lung cancer: a randomised trial by the Norwegian Lung Cancer Study Group, *Br. J. Cancer 2013 1096*, 109(6) 2013 1467–1475, doi: 10.1038/bjc.2013.466.

[10] E. Ikeda, T. Kojima, K. Kaneko, K. Minashi, M. Onozawa, K. Nihei, N. Fuse, T. Yano, T. Yoshino, M. Tahara, T. Doi, A. Ohtsu, Efficacy of concurrent chemoradiotherapy as a palliative treatment in stage IVB esophageal cancer patients with dysphagia, Jpn. J. Clin. Oncol. 41 (8) (2011) 964–972, https://doi.org/10.1093/jjco/hyr088.

[11] M.E. Poole, S.L. Sailer, J.G. Rosenman, J.E. Tepper, M.C. Weissler, W.W. Shockley, W.G. Yarbrough, H.C. Pillsbury III, M.J. Schell, S.A. Bernard, Chemoradiation for locally advanced squamous cell carcinoma of the head and neck for organ preservation and palliation, Arch. Otolaryngol. Neck Surg. 127 (12) (2001) 1446, https://doi.org/10.1001/archotol.127.12.1446.

[12] A.D. Sherry, I.A. Mayer, D.N. Ayala-Peacock, V.G. Abramson, B.N. Rexer, A.B. Chakravarthy, Combining adjuvant radiotherapy with capecitabine in chemotherapy-resistant breast cancer: feasibility, safety, and toxicity, Clin. Breast Cancer 20 (4) (Aug. 2020) 344–352.e1, https://doi.org/10.1016/j.clbc.2020.02.010.

[13] W. Yin, G. Pei, G. Liu, L. Huang, S. Gao, X. Feng, Efficacy and safety of capecitabine-based first-line chemotherapy in advanced or metastatic breast cancer: a meta-analysis of randomised controlled trials, Oncotarget 6 (36) (2015) 39365–39372, https://doi.org/10.18632/oncotarget.5460.

[14] D. Rades, J. Dunst, S.E. Schild, The first score predicting overall survival in patients with metastatic spinal cord compression, Cancer 112 (1) (2008) 157–161, https://doi.org/10.1002/cncr.23150.

[15] "Common terminology criteria for adverse events - version 0.5," Nov. 27, 2017. https://www.uptodate.com/contents/common-terminology-criteria-for-adverse-events (accessed Mar. 26, 2021).

[16] R.C. Serlin, T.R. Mendoza, Y. Nakamura, K.R. Edwards, C.S. Cleeland, When is cancer pain mild, moderate or severe? Grading pain severity by its interference with function, Pain 61 (2) (1995) 277–284, https://doi.org/10.1016/0304-3959(94)00178-H.

[17] E. Chow, P. Hoskin, G. Mitera, L. Zeng, S. Lutz, D. Roos, C. Hahn, Y. van der Linden, W. Hartsell, E. Kumar, Update of the international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases, Int. J. Radiat. Oncol. Biol. Phys. 82 (5) (2012) 1730–1737, https://doi.org/10.1016/j.ijrobp.2011.02.008.

[18] L.A. Kingsley, P.G.J. Fournier, J.M. Chirgwin, T.A. Guise, Molecular biology of bone metastasis, Mol Cancer Ther. 6(10) 2007 2609–2617, doi: 10.1158/1535-7163.MCT-07-0234.

[19] W.M. Sze, M.D. Shelley, I. Held, T.J. Wilt, M.D. Mason, Palliation of metastatic bone pain: Single fraction versus multifraction radiotherapy - A systematic review of randomised trials, Clin. Oncol. 15 (6) (2003) 345–352, https://doi.org/10.1016/S0936-6555(03)00113-4.

[20] M.J. Goblirsch *et al.*, Biology of bone cancer pain, *Clin. Cancer Res.* 12(20 PART 2) 2006, doi: 10.1158/1078-0432.CCR-06-0682.

[21] Y. Kundel *et al.*, Phase II study of concurrent capecitabine and external beam radiotherapy for pain control of bone metastases of breast cancer origin, *PLoS One* 8(7) 2013 doi: 10.1371/journal.pone.0068327.

[22] R. McDonald, K. Ding, M. Brundage, R.M. Meyer, A. Nabid, P. Chabot, G. Coulombe, S. Ahmed, J. Kuk, A.R. Dar, A. Mahmud, A. Fairchild, C.F. Wilson, J.S. Y. Wu, K. Dennis, C. DeAngelis, R.K.S. Wong, L. Zhu, S. Chan, E. Chow, Effect of radiotherapy on painful bone metastases: a secondary analysis of the NCIC Clinical Trials Group Symptom Control Trial SC.23, JAMA Oncol. 3 (7) (2017) 953, https://doi.org/10.1001/jamaoncol.2016.6770.

[23] J.S.Y. Wu, R. Wong, M. Johnston, A. Bezjak, T. Whelan, Meta-analysis of dose-fractionation radiotherapy trials for the palliation of painful bone metastases, Int. J. Radiat. Oncol. Biol. Phys. 55 (3) (2003) 594–605, https://doi.org/10.1016/S0360-3016(02)04147-0.

[24] J.M. van der Velden, Y.M. van der Linden, A.L. Versteeg, J.-J. Verlaan, A. Sophie Gerlich, B.J. Pielkenrood, N. Kasperts, H.M. Verkooijen, Evaluation of effectiveness of palliative radiotherapy for bone metastases: a prospective cohort study, J. Radiat. Oncol. 7 (4) (2018) 325–333, https://doi.org/10.1007/s13566-018-0363-6.

[25] T. Saito, K. Yamaguchi, R. Toya, N. Oya, Single- versus multiple-fraction radiation therapy for painful bone metastases: a systematic review and meta-analysis of nonrandomized studies, *Adv. Radiat. Oncol.* 4(4) 2019 706-715. Elsevier Inc, doi: 10.1016/j.adro.2019.06.003.

[26] E. Chow, K. Harris, G. Fan, M. Tsao, W.M. Sze, "Palliative radiotherapy trials for bone metastases: a systematic review, *J. Clin. Oncol.* 25(11) 2007 1423–1436, doi: 10.1200/JCO.2006.09.5281.

[27] P. Foro Arnalot *et al.*, "Randomized clinical trial with two palliative radiotherapy regimens in painful bone metastases: 30 Gy in 10 fractions compared with 8 Gy in single fraction, *Radiother. Oncol.* 89(2) 2008 150–155, doi: 10.1016/j.radonc.2008.05.018.