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Pain Assessment after Short Course versus Long Course Palliative Radiation of Painful Bony Metastasis

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ABSTRACT

Background: the most common cause of pain in cancer patients is bone metastases. **Objective:** to evaluate the different fractionation schedules. **Patients and Methods:** this is a prospective cross sectional study conducted at Ain-Shams University Hospitals and Nasser Institute Cancer Centre, to assess the equivalence of two fractionation regimens (20 Gy over 5 fractions versus 30 Gy over 10 fractions) as regard pain relief in painful bony metastases. Over 6 months fifty patients were assigned to either fraction arms using consecutive sampling. **Results:** both fractionation regimens were effective at palliating pain from bone metastases. Pain score was consistently going down from week 0 to week 12, although maximum benefit was reached earlier in the shorter arm (at week 8), both comparison groups leveled a favourable response at week 12. At 3 months, the observed overall response rate was 88% versus 84% and complete response rate was achieved in 44% versus 36% in both short- and long fractionation course respectively, with no statistical difference was found in terms of pain relief. With the median time to pain progression was 79.0 days for the short arm versus 77.0 days for the protracted arm. **Conclusion:** lower dose of radiotherapy may provide equivalent outcomes to higher ones in palliating bone pain. So, the the surrounding normal tissue role in pain process caused by bone metastases as well as the effect of radiation in this environment has to be furtherly investigated, which may lead to pain control augmentation.

Keywords: Pain Assessment; Palliative Radiation; Painful Bony Metastasis

INTRODUCTION

The most common cause of pain in cancer patients is bone metastases [(1)]. Among solid cancers, prostate, breast, thyroid, lung, and renal cell carcinoma account for 80 percent of all skeletal metastases [(1)].

The primary disease site determines the prognosis for patients with bone metastases; patients with breast and prostate cancer have a longer median survival when it's compared with lung cancer [(2)].

Bone metastases can be categorized as complicated or uncomplicated, where uncomplicated generally refers to the absence of: impending or established pathological fracture, previous surgical fixation, impending or established spinal cord compression, impending or established cauda equina or nerve root compression (including cranial nerves), neuropathic pain, previous radiation, or associated soft tissue mass. Approximately one-third of bone metastases are considered to be 'complicated' [(3)]. oligometastatic disease describes an intermediate state between disease that is localized to the primary site, and widespread metastases [(4)]. the definition of oligometastases varies means five or fewer metastatic lesions. skeletal-related events typically encompass pathologic fracture, spinal cord compression, surgical intervention or use of palliative radiotherapy (RT) [(5)].

The treatment of an asymptomatic bone metastasis may be deferred unless the patient develops pain or is at risk for a skeletal-related event. The treatment of bone metastases may involve several types of systemic interventions, including chemotherapy, hormonal therapy, bisphosphonates, or radioisotopes, in addition to local interventions such as external beam radiotherapy (EBRT), stereotactic body radiotherapy (SBRT) hemi-body irradiation (HBI), radioisotopes, surgery, or percutaneous vertebral augmentation depending on the site and extent of disease, histology and biomarker profile of the metastasis [(2)].

AIM OF THE WORK

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To assess the equivalence of short term radiation therapy (20 Gy of radiation therapy delivered over 5 treatment fractions) and long term radiation therapy (30 Gy of delivered over 10 treatment fractions) as regard pain relief in painful bony metastases.

PATIENTS AND METHODS

This is a prospective, cross sectional study conducted at Ain-Shams University Hospitals and Nasser Institute Cancer Centre, over 6 months.

From the first of October-2017 till the 30th of April -2018, fifty patients (25 patients in each arm) presenting with painful bony metastases were assigned to either fraction arms using consecutive sampling. **The study was approved by the Ethics Board of Ain Shams University and an informed written consent was taken from each participant in the study.**

Eligibility criteria included the following:

- age of 18 years or older,
- pathological evidence of malignancy,
- or combined imaging and laboratory evidence as in HCC,
- radiographic evidence of bone metastases,
- moderate to severe pain corresponding to the area of bone metastasis,
- bone metastases that were previously un-irradiated or causing recurrent pain after radiation therapy,
- Karnofsky performance status of at least 40,
- treatment with external beam RT (EBRT), with or without bisphosphonates, radiopharmaceuticals, kyphoplasty, or vertebroplasty,
- an estimated life expectancy of at least 3 months,
- patients receiving bisphosphonates or systemic therapy (hormonal therapy, chemotherapy, immunotherapy, or systemic radioisotope therapy),
- adequate CBC, and
- A verbal informed consent approval from the patient to accept participating in the study.

Patients were ineligible if there is a pathologic fracture or an impending fracture of the treatment site, and the patient is planned for surgical intervention.

Verbal informed consent was taken before participation and all patients' information was kept confidential.

Required information before involvement into the study included history and physical examination, Karnofsky performance status, radiologically documented bone metastases within 8 weeks before randomization, and completed Brief Pain Inventory assessments.

Data was collected using data collection questionnaire with Visual Analogue Scale [22] was used to assess the pain. Pain was assessed with the worst pain score from the Brief Pain Inventory [23], requiring a score of at least 4 on a scale of 10 (or a score of less than 4 but taking narcotic medications with a daily oral morphine equivalent dose of at least 60 mg), i.e., moderate to severe pain.

Patients were stratified by age, gender (male or female), performance status, pathological diagnosis, radiotherapy fractionation course (short 400cGy x 5 fractions) versus long (300 cGy x 10 fractions), number of painful sites (solitary or multiple), treatment site (peripheral or central), pain score (no pain (0), mild (1-2), moderate (4-6) or severe (7-10) and use of narcotics before starting palliative radiotherapy (yes or no), and use of narcotics 3 months after completing radiation (yes or no).

Simulation was done while the patient was lying in either supine or prone position. In most of cases treatment was delivered in supine position - lying on his/ her back- with head and neck masks were used for fixation and immobilization in case of treating affected cervical vertebrae, knee support while treating dorso–lumbar vertebrae, and prone head rest if the patient was treated in a prone position.

CT simulation (using Siemens CT Scanner - SOMATOM Force) was done was performed with contiguous slices of 5 mm. then a three dimensional plans -using XIO planning system- were implemented. With PA, AP/PA, or posterior oblique fields were commonly used, depending on the tumour site

and separation. opposed lateral fields for mid/upper cervical spine were occasionally be used.

Treatment volume included the radiographic abnormality with at a margin of at least 2 cm was required. And in case of treating affected vertebrae, two additional vertebral bodies (one above and other below) the level of bony involvement were included in the treatment fields. When treating Lumbar vertebrae, both kidneys were delineated as organs at risk.

Linear accelerators -Siemens; linear Oncor impression and Variant linear unique - (6-15MV, 6-8-9-10-12-15Mev) were used to deliver a total radiation dose of either 30 Gy or 20 Gy according to the prescribed dose.

Response was determined by follow-up questionnaires and telephone interviews with poor-compliance patients, when necessary for completeness. Questionnaires and visual analogue scale were collected at intervals of 0, 2, 4, 8, and 12 weeks.

Statistical Methods

Data were collected, tabulated and statistically analyzed using a personal computer with (SPSS) version 22 program; (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY, USA: IBM Corp.). the Kaplan–Meier survival method is a non-parametric estimator of survival function. Mann–Whitney U test is a non-parametric test that is equivalent to a two-sample t-test. Wilcoxon test is a non-parametric equivalent of the paired t-test. P value of ≤ 0.05 was considered significant.

RESULTS

Pain relief was assessed after receiving palliative radiotherapy; with overall response rate was 88% and 84% in treatment regimens 400 cGy x 5 fractions and 300 cGy x 10 fractions respectively. With complete pain relief was reached in 44% of patients who were receiving 400 cGy x 5 fractions versus 36% in patient who were receiving 300 cGy x 10 fractions (table 1).

Table (1): Response rate within both groups

	400 cGy x 5 fx	300 cGy x 10 fx.
Overall RR	88 %	84 %
Complete RR	44 %	36 %
Mean time to achieve maximum response (±SD) (Days)	39.2 (±18.0)	45.0 (±22.6)

Table 2 shows that the mean pain score was not statistically significantly different between both treatment arms at baseline assessment (week 0) as well as at the determined assessment intervals.

Table (2): Comparison of mean pain score within both groups through determined pain assessment intervals

Variable		Fractionation		Mann-Whitney U value	P-value
		300 cGy x 10 fractions No (%)	400 cGy x 5 fractions No (%)		
Baseline pain assessment (week 0)					
	Mean (±SD)	8.3 (±1.4)	7.9 (±1.8)	281.5	0.521
	Median (Range)	8 (6-10)	8 (4-10)		
Pain assessment at week 2					
	Mean (±SD)	5.5 (±1.6)	5.2 (±1.9)	288.5	0.625
	Median (Range)	6 (2-8)	6 (2-8)		
Pain assessment at week 4					
	Mean (±SD)	4.0 (±2.0)	3.1 (±2.1)	243.0	0.163
	Median (Range)	4 (0-8)	2 (0-7)		
Pain assessment at week 8					
	Mean (±SD)	2.8 (±2.3)	2.1 (±2.2)	258.5	0.277
	Median (Range)	2 (0-7)	2 (0-7)		
Pain assessment at week 12					
	Mean (±SD)	2.3 (±2.3)	1.9 (±2.2)	280.5	0.515
	Median (Range)	2 (0-7)	2 (0-7)		

Continued benefit as regard pain relief was observed in both treatment arms over the follow up period from week 0 through week 2, 4, 8 and week 12 as observed in tables 3 and 4. Despite that both treatment arms achieved similar pain improvement at the last assessment point determined in the study protocol (week 12), the shorter fractionation schedule (400 cGy x 5 fractions) achieved maximum response earlier.

Table (3): Comparison of mean pain score through determined pain assessment intervals in patients receiving 300 cGy x 10 fractions

		Week 0	Week 2	Week 4	Week 8	Week 12
	Median	8	6	4	2	2
	Mean (SD)	8.3 (1.4)	5.5 (1.6)	4.0 (2.0)	2.8 (2.3)	2.3 (2.3)
Z (Wilcoson) value	Week 2 Vs. Week 0	-3.99				
P –value		< 0.001				
Z (Wilcoson) value	Week 4 Vs. Week 2		-4.23			
P-Value			< 0.001			
Z (Wilcoson) value	Week 8 Vs. Week 4			-3.41		
P-value				0.001		
Z (Wilcoson) value	Week 12 Vs. Week 8				-2.44	
P-value					0.014	

Table (4): Comparison of mean pain score through determined pain assessment intervals in patients receiving 400 cGy x 5 fractions

		Week 0	Week 2	Week 4	Week 8	Week 12
	Median	8	6	2	2	2
	Mean (SD)	7.9 (1.8)	5.2 (1.9)	3.1 (2.1)	2.1 (2.2)	1.9 (2.2)
Z (Wilcoson) value	Week 2 Vs. Week 0	-3.98				
P –value		< 0.001				
Z (Wilcoson) value	Week 4 Vs. Week 2		-4.27			
P-Value			< 0.001			
Z (Wilcoson) value	Week 8 Vs. Week 4			-3.60		
P-value				< 0.001		
Z (Wilcoson) value	Week 12 Vs. Week 8				-1.41	
P-value					0.157	

Palliative radiotherapy to painful bony metastases resulted in reduction in narcotic use by a percentage of 29.3% to 40% with no statistically significant difference between the 2 comparison arms. Table 5 summarizes the use of narcotics in both groups before and 3 months after palliative radiotherapy in both treatment arms.

Table (5): Use of narcotics before & after 3 months of radiotherapy

	400 cGy x5	300 cGy x 10	X^2	P-value
No. (%) of patients using Narcotics before radiotherapy	24 (96%)	25 (100.0%)	1.02	0.312
No. (%) of patients still using Narcotics 3 months after radiotherapy	16 (66.7%)	15 (60%)	0.08	0.771
No. (%) of narcotic free patients after 3 months from radiotherapy	8 (33.3%)	10 (40%)		

Sub-analysis of pain response as regard age (younger or older than 60 years) (tables 6) revealed non statistically significant differences between both treatment arms.

Table (6): Comparison of pain response according to fractionation schedule in 15 patients 60 years old or older

Variable		Fractionation		Mann-Whitney U value	P-value
		400 cGy x 5	300 cGy x 10		
Baseline pain score (week 0)					
	Mean (±SD)	9.2 (1.0)	8.5 (1.5)	21.0	0.361
	Median (Range)	10	8.0		
Pain assessment at week 2					
	Mean (±SD)	6.3 (1.9)	5.7 (1.7)	21.0	0.399
	Median (Range)	7.5	6.0		
Pain assessment at week 4					
	Mean (±SD)	3.7 (2.8)	4.0 (2.3)	27.0	0.902
	Median (Range)	4.0	4.0		
Pain assessment at week 8					
	Mean (±SD)	3.2 (2.7)	3.4 (1.9)	26.0	0.809
	Median (Range)	3.0	4.0		
Pain assessment at week 12					
	Mean (±SD)	3.0 (2.9)	2.2 (1.7)	25.0	0.717
	Median (Range)	3.0	2.0		

DISCUSSION

Bone metastases are a common manifestation of malignancy that can cause severe and debilitating effects including pain, spinal cord compression, hypercalcemia, and pathological fracture. Radiation therapy (RT) provides successful time-efficient palliation of painful bone metastases with very few side effects, reduce analgesic requirements, maintain skeletal function, and improve quality of life [(6)].

Radiotherapy is usually given as an outpatient treatment, however, it requires daily hospital attendance, usually at a specialised centre that may be some distance away from patient's home. If the course of radiotherapy is protracted, it may cause considerable problems for the patient, especially those with poor performance status and limited life expectancy. From a health economic point of view, radiotherapy for bone pain constitutes a significant workload of a radiotherapy centre. It is, therefore, important to strike a balance between the treatment efficacy, patient convenience and cost. There is yet no consensus regarding the most appropriate way of delivering radiotherapy for metastatic bone pain. The practice differs significantly among different countries [(7)].

The optimal fractionation schedule is still an unresolved issue. In clinical practice, the selection of the fractionation schemes is often influenced by patient characteristics (performance status, compliance to treatment, life expectancy), tumor-related factors (histology of the primary tumor, interval time from primary diagnosis to bone metastases, time of developing pain or neurologic deficits before RT) and logistic issues (treatment duration time, validity of family members assistance, hospital location, cost of therapy) [(8)].

Continuous efforts have been done to reach a consensus about the most appropriate fractionation regimen. Many Studies Comparing different fractionation protocols have been conducted. Based on high-quality published evidence, many guidelines have been published to guide the choice of the most suitable treatment protocol. For example, The American Society for Radiation Oncology (ASTRO) initially published a guideline in palliative radiotherapy for bone metastases in March 2011 was followed by two updates in June 2014 and Augest 2016 [(9)].

In this prospective study, the efficacy of two different fractionation protocols (400cGy in 5 treatment fractions versus 300cGy in 10 treatment fractions) in palliating pain from painful bony metastases in 50 Egyptian patients treated at Ain-Shams Clinical Oncology department and Nasser Institute has been evaluated.

We found that both external beam radiation therapy fractionation regimens (30 Gy in 10 treatment fractions and in the arm receiving 20 Gy in five treatment fractions), were effective at palliating pain from bone metastases. Pain score was consistently going down in the responders from week 0 to week 12, although maximum benefit was reached earlier in the shorter arm (at week 8), both

comparison groups levelled a favourable response at week 12. At 3 months, the observed overall response rate was 88% versus 84% and complete response rate was achieved in 44% versus 36% in both short- and long fractionation course respectively, With no statistical difference was found in terms of pain relief. With the median time to pain progression was 79.0 days for the short arm versus 77.0 days for the protracted arm.

Sub-analysis was tried to highlight any strata difference between the two groups as regard gender, type of malignancy (solid further haematological, with further sub-analysis for breast and prostate), site of metastases, presence of extra-osseous component, or age. All the results has revealed non-statistical difference between the two groups whatever the stratification used. With exception that females reached an earlier pain relief (at week 8) and that bony metastases caused by prostate cancer has demonstrated a better response when treated with 400cGy over 5 fractions, yet strong conclusion can't be announced due to paucity of the involved patients with cancer prostate in the study cohort, being only 6 cases.

Although patients presented with moderate-to-severe pain before treatment with radiation therapy, a substantial proportion patients had experienced improvement in pain 3 months after treatment, and nearly one-third (33.3 – 40 %) no longer required narcotic pain medication, with a non-significant P-value = 0.771 when comparing the two groups in terms of narcotic discontinuation after the end of radiotherapy.

An updated ASTRO evidence-based guideline for palliative radiation therapy for bone metastases in 2017 of high-quality data continues to show pain relief equivalency following a single 8 Gy fraction, 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions for patients with previously un-irradiated painful bone metastases. Patients should be made aware that single-fraction (SF) RT is associated with a higher incidence of retreatment to the same painful site than is fractionated treatment [9].

There have been multiple randomized comparisons of one or a few treatments to more standard, longer courses of radiation therapy for palliation of bone metastases. Most of these studies have shown no statistically significant difference in pain relief between shorter-duration, lower-dose treatments and longer-duration, higher-dose treatments [28].

Ozsaran ***et al.*** [10] had evaluated the use of 8 Gy x 1 versus 4 Gy x 5 versus 3 Gy x 10 in 109 patients with primary tumours of origin was either prostate, breast, or lung. Evaluation of the palliation rate was in favor of 30 Gy/10 fractions after 10 days, but the difference disappeared after the first- and third-month follow-up. Single fractions could decrease the treatment burden for patients and departments. Those with a short life expectancy should be treated during as short a time period as possible. Kagei et al., recorded no difference in the incidence of pain relief, speed of onset, or acute morbidity was found between the two treatment regimens (8, 10, 12, or 15 Gy single versus 20 Gy/4 or 25 Gy/5 or 30 Gy/6 fractions). No severe morbidity was seen in either arm [11].

Foro et al had compared the efficacy of 8 Gy single versus 15 Gy/3 fractions or 30 Gy/10 fractions in 75 patients with painful bone metastasis, including those at risk of pathological fracture or cord compression. No superiority observed between treatment arms as regard pain control [12].

Koswig and Budach [13] also found no significant difference in pain reduction between the two arms (8 Gy single versus 30 Gy/10 fractions). Single treatment is advantageous because it minimizes the burden. However, multiple is optimal for remineralization. Therefore, prognosis of the patient should be taken into account.

Hartsell et al recorded equivalent rates of pain relief, narcotic use, and pathological fracture incidence between arms (8 Gy single versus 30 Gy/10 fractions). Substantial difference in number of patients needing re-treatment; substantially more patients in the single arm required re-treatment [14].

Price,et al. and Cole [24,25] found no statistically significant differences in response rates between arms (5 or 8 Gy single versus 30 Gy/10 fractions); however, more single fraction patients needed re-treatment.

Many other randomized trials had confirmed the same results that treatment with single fraction provides a non-inferior pain

control in comparison with multi-fractionation regimens, with more retreatment was needed in patients treated with single fraction [16].

In the opposite side Kirkbride et al found that multiple fractionation radiotherapy over superior to a single fraction, as regard pain control [17]. Also, Roos et al record that single fraction is not as effective multiple for neuropathic pain relief, but also not significantly worse, with single fraction was poorer in general, but the differences were quantitatively small. Although they generally recommended multiple fractionation, but the use of single fraction for patients with expected short survival and at treatment centres with long wait times [18].

Ratanatharathorn et al. reviewed many of these studies and concluded that higher-dose, longer-course regimens provided better pain outcomes than low-dose regimens. In contrast, Wu et al. performed a meta-analysis of studies comparing single versus multiple fractions of radiotherapy for palliation of painful bone metastases. They found a complete response rate of 32%–33%, an overall response rate of 72%–73%, and no difference in response rates comparing a single treatment with multiple treatments. The primary difference between the two arms was the higher rate of retreatment in the patients receiving a single fraction (11%–25%) compared with those receiving multiple fractions (0%–12%) [19].

Why should a lower dose of radiotherapy be as effective as higher doses in palliating bone pain? If the response depends solely on decreasing the tumour cell burden, then the higher-dose regimens should be more effective than the lower-dose regimens.

The complete response rate in the RTOG 9714 trial [29] was 16%, substantially lower than the previous RTOG [30] study. The reasons for this difference may include the assessment method used and the severity of pain or extent of disease. For the RTOG 7402 trial [30], physicians scored pain with a four-point scale, whereas patients in our study scored pain by use of a more sensitive 10-point scale in the Brief Pain Inventory. In addition, the cohort of patients treated in this study is different from that treated 40 or more years ago. Although there were few systemic therapy options during the RTOG 7402 trial, second-, third-, and fourth line chemotherapy options are currently available for breast cancer. In addition, multiple hormonal manipulations are available for the treatment of both breast and prostate cancer, and bisphosphonates are used in many of these patients. Pain control is better understood, with much more emphasis on adequate pain management now than 4 decades ago. Thus, the patients who are referred for palliative radiation therapy now may have more widespread disease that has become resistant to other therapies, as reflected in our study by the severity of pain scores (76% patients in our study had severe pain at study entry), and the percentage of patients how presented by multiple bony metastases (96 %).

A shorter fraction provides non-inferior pain relief compared with a more prolonged RT course in both centrally or the peripheral located painful bony metastases.

Howell et al evaluated the subset of patients with painful vertebral metastases in the Radiation Therapy Oncology Group 97-14 trial and found they were comparable to the entire population, with partial or complete pain response in 70% versus 62% for SF versus MF arms (not significant) [6].

Series from Gutierrez Bayard [26], Howell [6], and Majumder [27] all evaluated the efficacy of treatment of symptomatic bone metastases with 8 Gy/1 fraction versus 30 Gy/10 fractions and demonstrate these regimens are effective for pain relief, with response rates of 70% to 80% and decreased pain scores and narcotic use. Chow ***et al.*** [20] documented similar findings with comparison of 8 Gy/1 fraction and 24 Gy/6 fractions. Meta-analyses by Chow et al confirm these results using combined data from 5617 patients in 25 RCTs with overall response rates of 60% versus 61% for SF and multiple fraction (MF) regimens [20].

We have to clarify that our study has several limitations. We included patients with solid and haematological malignancies with bone metastases, with a relatively small sample size. However, the outcomes may be differing among patients with bone metastases according to their primary of origin, for example in our study, pain relief in bone

metastases originating from the prostate was in favour of the shorter fractionation arm at W 8, so for better sub-analysis, a larger sample size is needed. A second limitation of the study involves completion of the assessment tool. The Brief Pain Inventory was completed by only 41 (82%) of the 50 patients at the 3-month assessment point. As would be expected in this group of patients, 9 of the 50 patients had died or were too ill to complete the form at 3 months. Thus, the Brief Pain Inventory was completed by 41 (82 %) of the 50 patients who were alive and able to complete the form.

CONCLUSION

As noticed in this study, lower dose of radiotherapy may provide equivalent outcomes to higher ones in palliating bone pain. So, the role of the surrounding normal tissue in the pain process caused by bone metastases as well as the effect of radiation in this environment has to be furtherly investigated, which may lead to pain control augmentation.

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