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# COMPARATIVE EVALUATION OF EFFICACY OF PALLIATIVE RADIATION THERAPY WITH DEXAMETHASONE VERSUS PALLIATIVE RADIATION THERAPY ALONE FOR PAIN FLARES IN PAINFUL BONE METASTASIS

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## ABSTRACT

Development of pain flares is a common association with palliative radiotherapy for management of bone metastasis. Dexamethasone, a hydrocortisone with anti-inflammatory property, holds a potential for prevention of pain flare in these patients when used as an adjuvant therapy. The study was conducted on 60 patients divided randomly into 2 groups of 30 patients each. Group I patients received palliative external radiation therapy 20 Gy in 5 fractions for 5 days with tablet dexamethasone 8mg orally one to five days while group II patients received palliative radiation therapy only. All the patients were followed every day for 5 days and then monthly for 6 months for occurrence of pain flare. Group I patients were observed to have reduced pain flare ($p<0.05$), less requirement of analgesics ($p<0.05$), overall better pain relief ($p<0.05$) and lesser need of re-irradiation as compared to those in group II. Thus, dexamethasone may be used as an adjuvant to standard palliative radiotherapy for the management of painful bone metastasis though the claim is still debated and needs substantiation with more supportive studies.

**KEYWORDS:** Pain flare, Dexamethasone, Palliative Radiotherapy, Painful bone metastasis.

## INTRODUCTION

Metastatic bone disease is a common situation encountered in oncology practice. About 50% of all cancer patients develop metastases in their lifetime. Bones are the third most common site of metastases after liver and lungs in advanced cancer.[1] Bony metastases may be osteoblastic and osteolytic or of mixed variety depending upon the primary site. The most common site of bone metastases is the axial skeleton and generally at multiple sites. It is associated with considerable morbidity and mortality including bone pain, reduced mobility, anaemia, fatigue, hypercalcemia, pathological fractures and spinal cord compression.[2] Pain may be caused directly through local invasion or indirectly through alteration of the remodelling activity of osteoblasts and osteoclasts.[3] Different mechanisms involved in development of pain may be the release of chemical mediators, increased pressure due to tumour, micro-fractures and stretching of the periosteum. Nerve involvement in the disease may present as radicular or referred.[4]

Proper care of bone metastases requires inter-disciplinary co-ordination among radiologists, radiation oncologists, medical oncologists, surgeons, pain medical specialists and palliative care professionals.[5] The management of bone metastases includes radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide and supportive therapy alone or in combination. The treatment intent is usually palliative with the goals being prevention of pain flares, preservation of function, mobility, and quality of life in painful bone metastases.[6]

Radiotherapy (RT) is the most effective treatment for bone metastases. External beam radiotherapy (EBRT) for bone metastases is one of the most common uses of palliative radiation therapy. It provides effective and time-efficient pain control with improvement in quality of life. Between 60-80% of patients respond to EBRT and 25- 30% of patients have a complete response to treatment.[4] It has been suggested by few reports that dexamethasone, as an adjuvant treatment with palliative RT, might be effective in the prophylaxis of radiation-induced pain flare by decreasing the periosteal edema.[7,8]

Pain flare is defined as a two point increased in the worst pain or a 25% increase in the analgesic intake when compared with the baseline.[9] It has a negative impact on daily functioning, mood and convenience of patients as well as their attendants. The opinion regarding use of dexamethasone as an adjuvant to standard palliative treatment for painful bone metastasis is still debatable.[10]

Therefore, the present study was designed to conduct the comparative evaluation of palliative radiation therapy using 20 Gy/5 fraction in 5 days with tablet dexamethasone 4mg 1 BD × 5 days versus palliative radiation therapy alone for the prevention of pain flares in painful bone metastases.

## MATERIALS AND METHODS

The study was conducted on 60 adult patients of histopathologically proven malignancy with painful bone metastases from any primary site after obtaining informed consent and approval from the institutional board of studies. The pretreatment evaluation in all patients included complete history, general physical examination and complete systemic examination. The assessment of patient's functional outcome was done by Eastern Cooperative Oncology Group (ECOG) performance scale and Karnofsky performance scale (KPS).[11,12] Radiological assessment using X-ray of the involved site was done in all patients while bone scan or positron emission tomography computed tomography (PET CT) scan was advised as per requirement. Pain score was calculated using Glasgow Pain scale and only patients with pain intensity on a numeric rating scale of 4-10 were enrolled. The exclusion criteria included patients with haematological malignancy, patients who have been treated before with palliative radiotherapy for painful bone metastases, current use of steroids for any other medical condition or contraindications for the use of dexamethasone.

The study was designed as a randomized prospective trial and was conducted on 60 patients divided into 2 groups of 30 patients each by draw of lots. Group I patients received palliative external radiation therapy 20 Gy in 5 fractions for 5 days with tablet dexamethasone 8mg orally one to five days while group II patients received palliative radiation therapy 20 Gy in 5 fractions for 5 days only.

Patients were followed every day for 5 days during their palliative radiotherapy course for occurrence of pain flare if any, in both the groups, then monthly for 6 months. At each follow up, patients were assessed for pain flare, pain palliation using the Glasgow Pain scale, analgesic requirement and functional outcome using the ECOG performance scale and Karnofsky performance scale. Pain response was defined as a decrease in pain score by at least two points with respect to the pre-treatment value, complete pain response was defined as achieving a pain score of 0 at any point during follow up and duration of overall pain response was defined as time from initial response till return of pain to its baseline value. Improvement in performance status was defined as a decrease in ECOG functional outcome score or Karnofsky performance score by at least one grade with respect to pre-treatment value.

Data was entered in Microsoft excel spreadsheet and analyzed with Statistical Package for Social Sciences (SPSS) software version 21.0. Quantitative data was presented as mean and standard deviation. Qualitative data was presented as ratios and proportions. Comparison of quantitative data was done by analysis of variance (ANOVA) test after confirming the normality of the data. Chi square test was applied between qualitative variables to see the association. Chi square test for proportions was applied to compare the proportions between the groups. Point of statistical significance was set as $p<0.05$.

## RESULTS

The age of patients in group I ranged from 35 to 82 years (mean 59.46 ±13.03 years) while in group II, patients' age ranged from 35 to 84 years (mean 58.20±12.65 years). Seventy five percent of all the patients were males and the remaining 25% were females. There was male predominance in both the groups (76.67% and 73.3% in group I and II respectively). Out of a total of 60 patients, 47 patients (78.33%) belonged to rural background and the remaining 13 (21.67%) were from urban area. The predominance of rural population was also evident in each group (76.67% in groups I and 80% in group II). Overall 15 (25%) patients had primary in the prostate, 14 (23.33%) patients were of lung cancer and 7 (11.67%) patients were of breast cancer. Metastatic of unknown origin was observed in 11 (18.33%) patients and other primary comprised of cervix (4 patients), Renal Cell Carcinoma (2 patients), thyroid (1 patient), Non-Hodgkin's lymphoma (2 patients), Multiple Myeloma (2 patients) and Larynx (2 patients). There was no significant statistical difference in site of primary among the groups ($p>0.05$). In group I and II, most patients presented with bony metastases of spine (36.67% and 43.3% respectively) followed by pelvis (33.33% and 26.67% respectively), multiple sites (13.33% and 20.0% respectively), axial skeleton (13.33% and 6.67% respectively) and sternum (3.33% each). There was no significant statistical difference in site of bone metastases among the groups ($p>0.05$). KPS ($<60$ or $\geq 60$) and ECOG status ($>2$ or $\leq 2$) was comparable in both the groups before and after treatment ($p>0.05$). In group I and II, moderate pain scale (5-6) was observed in 26 (86.67%) and 22 (73.33%) patients respectively while severe pain scale (7-10) was observed in 4 (13.33%) and 8 (26.67%) patients respectively. There was no significant statistical difference in Glasgow pain scale after radiotherapy among the groups ($p=0.197$). In group I, 4 (13.33%) patients were irradiated again compared to 7 (23.33%) patients in group II ($p=0.317$). The comparison of duration of pain flare, patients with analgesic requirement and overall pain relief in the two groups is shown in tables 1, 2 and 3 respectively.

**Table 1: Comparison of duration of pain flare in group I and II for 5 days of treatment.**

| No of days | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 |
|---|---|---|---|---|---|
| Group I Number of patients (%) | 3 (10%) | 3 (10%) | 3 (10%) | 2 (6.67%) | 2 (6.67%) |
| Group II Number of patients (%) | 11 (36.67%) | 11 (36.67%) | 12 (40%) | 10 (33.33%) | 11 (36.67%) |
| p value | 0.015 | 0.015 | 0.007 | 0.010 | 0.005 |

**Table 2: Comparison of analgesic requirement by the patients in both the groups (n=30).**

| Analgesic requirement | 1st Day | 2nd Day | 3rd Day | 4th Day | 5nd Day | 1st month | 2nd month | 3rd month | 4th month | 5th month | 6th month |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group I Number of patients (%) | 2 (6.67%) | 3 (10%) | 2 (6.67%) | 3 (10%) | 2 (6.67%) | 3 (10%) | 3 (10%) | 3 (10%) | 3 (10%) | 3 (10%) | 3 (10%) |
| Group II Number of patients (%) | 10 (33.33%) | 9 (30%) | 9 (30%) | 10 (33.33%) | 9 (30%) | 10 (33.33%) | 10 (33.33%) | 10 (33.33%) | 10 (33.33%) | 10 (33.33%) | 10 (33.33%) |
| p Value | 0.010 | 0.05 | 0.020 | 0.028 | 0.020 | 0.028 | 0.028 | 0.028 | 0.028 | 0.028 | 0.028 |

**Table 3: Comparison of overall pain relief in both the groups (n=30).**

| Pain relief | 1st day | 2nd Day | 3rd Day | 4th Day | 5th Day | 1st month | 2nd month | 3rd month | 4th month | 5th month | 6th month |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Group I Number of patients (%) | 26 (86%) | 27 (90%) | 28 (93%) | 28 (93%) | 28 (93%) | 27 (90%) | 27 (90%) | 27 (90%) | 27 (90%) | 27 (90%) | 27 (90%) |
| Group II Number of patients (%) | 21 (70%) | 21 (70%) | 21 (70%) | 20 (66.67%) | 21 (70%) | 20 (66.67%) | 20 (66.67%) | 20 (66.67%) | 20 (66.67%) | 20 (66.67%) | 220 (66.67%) |
| p Value | 0.117 | 0.053 | 0.020 | 0.010 | 0.051 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 | 0.053 |

## DISCUSSION

Reduction of analgesic requirement was evident during treatment and follow up period of post-radiotherapy where 89.67% and 65.56% of patients in group I and group II, respectively, had analgesic requirement. There was statistically significant decrease in patients with analgesic requirement at any time during treatment and follow up ($p < 0.05$). The Bone Trial Working Party Study Group (BTWPG) reported a decrease in analgesic use from 86% to 50% patients in the single fraction arm and from 84% to 30% in the multifraction arm.[13] In a study conducted by Hartsell et al, 20% and 22% of patients were free of analgesic use at 3 months in the single fraction and multifraction arm respectively.[14] These studies compared the efficacy of multifraction over single fraction RT and not the effect of adjuvant dexamethasone with multifraction regimen though. Dexamethasone, a well known adjuvant analgesic, antiemetic and anti-inflammatory, is a good choice as a prophylactic agent because of its long half life (36-54 hours) that corresponds to the time frame following RT in which pain flare incidence is greatest.[15]

In group I, palliative RT induced pain flare was less as compared to group II. In group I, for first 3 days, these were observed to be 10% each day. While on 4th and 5th day, these were 6.67% each day. However, in group II, these were 36.67% each day for first 2 days while on 3rd, 4th and 5th day were found to be 40%, 33.3% and 36.67% respectively. There was statistically significant difference ($p<0.05$) in duration of pain flare after palliative radiotherapy among the groups. In the present study, group I pain flare incidence was 6% to 10%, while in group II, pain flare incidence was 33% to 40% within day 1 to 5 after RT. Dexamethasone has shown potential for preventing this occurrence from 27% to 33%. There was significant statistically difference in duration of pain flare after palliative radiotherapy among the groups (p value<0.05). Adjuvant dexamethasone with RT has been reported to have benefit against pain flare.[8,16,17]

In group I, 4 patients were irradiated again compared to 7 patients in group II though the difference in the number of patients who underwent re-irradiation among these groups was not found to be significant statistically ($p>0.05$). The efficacy of multifraction over single fraction palliative RT for painful bone metastasis has been reported in terms of reduced requirement of re-irradiation in few studies but not with adjuvant dexamethasone.[13,14,17] The findings of the present study suggest the higher rate of re-irradiation required in the group II as compared to Group I though the claim needs to be substantiated by further supporting studies.

In group I and II, spine was the most common site of metastases (36.67% and 43.33% respectively). This has been reported by other studies also.[13,18] In groups I and II, prostate remained the most common primary site comprising 26.67% and 20% of patients respectively as has been reported by other researchers.[19,20] The predominance of rural population was also evident in each group (76.67% in groups I and 83.33% in group II)

which may be explained by the fact that our institute is the only postgraduate institute in the state with a functional Radiotherapy Department catering to the patients from this agricultural area.

## CONCLUSIONS

Thus, it may be concluded that adding dexamathasone to palliative radiotherapy treatment bears a potential to provide relief to the patients against palliative RT induced pain flare by reducing the duration, requirement of analgesics, need for re-irradiation and improving the overall pain relief. Though further studies with larger sample size are needed before this claim may be utilized to reform supportive care in these patients with conviction.

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