COMPARISON OF LOW vs. HIGH DOSE ^{177}Lu-EDTMP THERAPY FOR PALLIATION OF PAINFUL BONE METASTASES: RCT

THESIS

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DECLARATION

I hereby declare that the thesis titled **"Comparison of Low Vs. High Dose ^{177}Lu-EDTMP Therapy for Palliation of Painful Bone Metastases: RCT"** embodies the original work carried out by the undersigned in All India Institute of Medical Sciences, Jodhpur.

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CERTIFICATE

This is to certify that the thesis titled **"Comparison of Low Vs. High Dose ^{177}Lu-EDTMP Therapy for Palliation of Painful Bone Metastases: RCT"** is the bonafide work of Dr. Rakesh Ramprakash Pandey, carried out under guidance and supervision, in the Department of Nuclear Medicine, All India Institute of Medical Sciences, Jodhpur.

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177-Lu	177-Lutetium
EDTMP	Ethylenediamine tetramethylene phosphonate
RANKL	Receptor activator of nuclear factor kappa-B ligand
18-F FDG	18-Florine Florodeoxy Glucose
PET-CT	Positron Emission Tomography-Computed Tomography
WHO	World Health Organisation
NSAIDs	Non-Steroidal Anti-inflammatory drugs
P-32	Phosphorus-32
Sr-89	Strontium-89
Sm-153	Samarium-153
Re-186	Rhenium-186
Ho-166	Holmium-166
Ra-223	Radium-223
Tc-99m	Technetium-99m
HEDP	Hydroxyethylidene Diphosphonate
DOTMP	1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonate
MDP	Methylene Diphosphonate
OR	Overall Response
CR	Complete Response (Assessable)
VAS/NRS	Visual Analogue Scale/Numeric Rating Scale
AS	Analgesic Score
KPS	Karnofsky Performance Score
ECOG	Eastern Cooperative Oncology Group
BLS	Bone Lesion Score
CTCAE	Common Terminology Criteria for Adverse Events
DNA	Deoxyribonucleic Acid
DSBs	Double Strand Breaks

SUMMARY

INTRODUCTION:

Patients with bone metastasis usually presents with bone pain. Bone pain is an important reason for decrease in quality of life in cancer patients. In 1986, WHO defined a sequential approach for relief in pain due to metastases ranging from non-opioid to strong opioid. Many different therapies are available for relief of bone pain like analgesics, antitumor agents, hormones, chemotherapy, steroids, local surgery, bisphosphonates (zoledronic acid), anaesthesia, radiation therapy (local and systemic), and bone targeted radionuclide therapy.

Bone targeted radionuclide therapy is preferred in those with relapse after an initial line of treatment with hormonal or chemotherapy or those who have previously been irradiated to the maximum limit of their tissue tolerance, or those with progressive or recurrent symptoms at treated sites. Radionuclides available for pain palliation are P-32, Sr- 89, Sm-153, Re-186, Re-188, Ra-223, Lu-177 and Sn-117. Properties of radionuclide like half-life, particle energy play important role in clinical characteristic, onset and duration of palliative effect and also on the toxic effect of the therapy. Due to its medium range energy and long half-life ^{177}Lu (6.73 days), the tumour cells are irradiated at a slower rate with relatively lower dose per cycle. Also ^{177}Lu-EDTMP can be supplied to regions far from the site of production.

AIMS AND OBJECTIVES:

The aim of the study is to assess outcome of low vs. high dose ^{177}Lu-EDTMP therapy for palliation of painful bone metastases.

The primary objective of the study was to find difference in pain relief in patients of bony metastases receiving high dose vs low dose ^{177}Lu-EDTMP therapy. The secondary objectives are to find and compare the improvement in quality of life assessed by KPS and ECOG, compare reduction in analgesic dose post therapy, change in haematological parameters between two groups.

METHODOLOGY:

From March 2021 to September 2022, 15 eligible patients with metastatic bone pain were enrolled in the study after taking informed consent and explaining about the methodology & objectives of the study. Their baseline VAS, AS, KPS, ECOG and haematological parameters were documented and bone scan was done to look for the osteoblastic metastasis. The patients were randomised into two groups, group A and group B. The patients were administered either 1 mCi/kg or 0.5mCi/kg of ^{177}Lu-EDTMP based on the allotted group. The patient, physician and investigator were blinded about the dose received by the patients.

After administration of ^{177}Lu-EDTMP, follow up was done in the patients at 2, 4, 8 and 12 weeks following therapy. Their VAS, AS, KPS, ECOG and haematological parameters were documented at every follow-up.

RESULTS:

From March 2021 to September 2022, 15 patients were recruited in the study: 7 in Group A and 8 in group B. Two patients were excluded, one in each group due to lack of follow-up in them. Thus the final number of patients included were 13: 6 in Group A and 7 in group B. There were 8 patients of prostate cancer, 2 patients of carcinoma breast and 3 patients of carcinoma lung.

Overall response:

The overall analysis of 13 patients showed, decrease in mean VAS score and AS from baseline to each point time at follow-up, and was statistically significant. The mean VAS score came down from 8.15 $\pm$ 1.28 at baseline to 2.31 $\pm$ 3.01 at 3 months ($p<0.001$). Similarly, the mean AS came down from 3.31 $\pm$ 0.751 in baseline to 1.62 $\pm$ 1.66 at 3 months ($p<0.001$). The percentage decrease in mean VAS score was 42% at 15 days, 51% at 1 month, 67% at 2 months and 72% at 3 months. Both ECOG and KPS did not have Gaussian distribution and therefore were median were calculated and compared. There was improvement in Quality of life in most of the patients responding to the therapy however there was no significant difference in the medians of KPS and ECOG as compared to baseline and at follow-ups.

Overall response rate (ORR) was calculated by including patients showing complete response, partial response and minimal response, ORR was 76.9%.

The maximum pain relief was achieved at 15 days in 1 patient (10%), 30 days in 2 patients (20%), at 60 days in 5 patients (50%) and at 90 days in 2 patients (20%). The median being 60 days. The haematological parameters including haemoglobin, WBC and platelets decreased significantly from the baseline post administration of ^{177}Lu-EDTMP. According to Common Terminology Criteria for Adverse Events (CTCAE) grading, 2/13 patients had grade III anaemia, 3/13 had grade II anaemia and 3/13 patients experienced grade I anaemia. 3/13 patients had grade I leukopenia, while 1/13 experienced grade II leukopenia. 4/13 patients had grade I thrombocytopenia while 1/13 patient experienced grade II thrombocytopenia.

Inter-group analysis between group A and group B:

There was progressive decrease in VAS score from baseline at each point time of follow-up in both the groups. The mean VAS score came down from 8.33 $\pm$ 1.03 at baseline to 1.50 $\pm$ 2.51 at 3 months (p=0.002) in group A, while it came down from 8.00 $\pm$ 1.52 at baseline to 3.00 $\pm$ 3.41 at 3 months (p=0.006) in group B. The mean AS came down from 3.33 $\pm$ 0.82 in baseline to 1.17 $\pm$ 1.33 at 3 months (p=0.010) in group A, while it came down from 3.29 $\pm$ 0.76 at baseline to 2.00 $\pm$ 1.91 at 3 months (p=0.049) in group B. However, there was no statistically significant difference in mean VAS and AS between the two groups at any point of follow-up. The percentage change in VAS score at 15 days, 30 days, 60 days and 90 days, in group A was 38%, 56%,72% and 81% respectively, while in group B was 45%, 47%, 63% and 65% respectively. There was improvement in Quality of life in most of the patients responding to the therapy in both the groups. However, there was no statistically significant difference between the groups.

Overall response rate in group A was 83.33% while it was 71.42% in group B. There was no statistically significant difference between overall response rates in two groups (p=0.503). In group A, time to achieve maximum pain relief was 60 days (30-90 days) and in group B, time to achieve maximum pain relief was 60 days (15-60 days).

The haematological parameters including haemoglobin, WBC and platelets decreased from the baseline in both the groups. For haemoglobin and WBC values, there was no

statistically significant difference in the values between Group A and Group B at any point time of follow-up. The decline in platelet values was more in Group A than Group B and the difference between Group A and Group B values was significant at 15 days and 2 months. There was no significant difference in CTCAE grade of haematological toxicity between both the groups.

CONCLUSION:

^{177}Lu-EDTMP is an effective radiopharmaceutical for palliation of metastatic bone pain. In the limited number of patients, we found efficacy of low dose (0.5 mCi/kg) therapy was similar to high dose therapy (1.0 mCi/kg) with less platelet toxicity in patients with low dose. Hence, low dose ^{177}Lu-EDTMP therapy may be preferred in these patients.

INTRODUCTION

Neoplasm means an abnormal growth of tissue resulting from autonomously proliferating cells even after cessation of initiating stimulus. Neoplasm may be benign (localised) or malignant in nature. Metastases in Greek means 'Migration'. While benign tumours are restricted at the site of their origin, malignant tumours are known to spread and involve distant organs and sites in the body. For a tumour to metastasise, various physiological and pathological processes are involved like loss of intracellular cohesion, cell migration, angiogenesis, invasion of systemic circulation, evasion of local immune response, surviving in the circulation, seeding at a distant tissue, and ability to grow at distant site(1).

The pathways for metastasis include, haematogenous spread (most common)(1), lymph nodal spread(2) and transcoelomic, i.e. direct seeding into body cavities(3). The route of spread depends upon the histological type and site of cancer. Carcinomas generally spread by lymphatic route (except renal cell carcinoma and hepatocellular carcinoma) while sarcomas generally metastasise using haematogenous route.

The site of distant metastasis is also dependent on the type and origin of the primary malignancy. The most common organ system involved in metastasis include lung, liver, skeletal and brain. Some cancer type predominantly metastasizes to specific organ as prostate cancer metastasise to bones. Few cancers follow a sequential pattern of spread as colorectal cancer spreads first to liver followed by lungs and brain(4). Although the pattern of spread is influenced by organ specific circulation pattern and anatomy of the vascular supply but there is discrepancy between anatomy and metastasis in various cancers. This confirms Steven Paget's 'seed and soil' hypothesis suggesting cancer cell are like 'seeds' that have intrinsic compatibilities with certain, welcoming organ microenvironment 'soil' provided by the specific organ(5).

Bony metastasis is most common type of metastasis(6). The incidence of bony metastasis varies among different cancers like myeloma (90-100%), prostate (65-75%), breast (65-75%), lung (30-40%), renal (20-25%), thyroid (60%), melanoma (14-45%) depending on the advanced state of disease(6). Cancers responsible for 80% of bony metastasis include prostate, breast and lung cancers. The site of bony metastasis can

involve any of the bone but the most commonly affected areas are vertebrae, pelvis, ribs, femur, humerus and skull.

Metastasis in bone can be osteoblastic or osteolytic or mixed due to uncoupling of osteoblast mediated bone formation and osteoclast mediated bone resorption(7). The type of lesion depends on the site and type of primary tumour. Osteolytic lesions are generally seen in multiple myeloma, renal cell carcinoma, non-Hodgkin's lymphoma, thyroid cancer, melanoma, non-small cell lung cancer, and langerhans-cell histiocytosis. Osteoblastic lesions are seen in prostate, carcinoid, small cell lung cancer, Hodgkin lymphoma and medulloblastoma. Mixed (osteoblastic and osteolytic) lesions are seen in breast carcinoma, gastrointestinal cancer and squamous cell cancer(8). However, it should be noted that bone formation and resorption are a part of spectrum and therefore both the processes are going on simultaneously in most of the cancers(9).

For a tumor to grow and metastasise in bone, it involves an important pathway of RANK-RANKL-Osteoprotegerin (OPG) cascade. RANKL is a ligand which is expressed on cells of osteoblastic lineage. It binds to its natural receptor which is present on osteoclastic cells and helps in osteoclasts activation, survival and proliferation(10). A positive shift towards RANK-RANKL axis helps in promoting tumorigenesis and metastases in bone. On the other hand, OPG is expressed by osteoblast and vascular cells. It counteracts the action of RANK and therefore oppresses bone resorption and prevents osteolysis(11).

Clinical features of bony metastasis:

Skeletal metastatic disease leads to considerably increased morbidity and mortality in cancer patients. The frequency of skeletal complications (also known as skeletal-related events) varies across a range of tumor types.

Pain: Pain in bony metastasis might develop slowly over weeks to months, and it increases in intensity with time. Pain might be constantly present, increasing at night, exacerbated on movement, pressure or weight bearing.

Hypercalcemia: It is seen in patients with small cell carcinoma lung, breast and renal cell carcinoma. In most cases, hypercalcemia is a result of bone destruction, and osteolytic metastases are present in 80% of cases(12). The signs and symptoms of

hypercalcemia are nonspecific (fatigue, anorexia, and constipation). If untreated, can lead to deterioration of renal function and mental status.

Pathological fracture: Metastatic disease in bone leads to destruction of bone trabeculae and thereby reduces the load-bearing capabilities resulting in microfractures initially and pathological fractures in long-term. Mirel's proposed a scoring system to categorise bony metastasis and accordingly decide further management (Table 1& 2), [(13),(14)].

Others: Compression of spinal cord, cauda equina, bone marrow suppression, etc.

Diagnosis of bone metastases is done using various imaging modalities, plane radiography, computed tomography (CT) and magnetic resonance imaging (MRI), as well as functional imaging with a wide range of targeted radioligands using gamma and PET camera(15).

Table 1. Variables for calculation of Mirels score

	Score		
Variable	1	2	3
Site	Upper limb	Lower limb	Per trochanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	<1/3	1/3-2/3	>2/3

Table 2. Mirels clinical recommendations

Score	Recommendation
<7 (6 month fracture risk 5% or less)	Radiotherapy and observation
8 (6 month fracture risk 15%)	Use clinical judgement
>9 (6 month fracture risk 33% or more)	Prophylactic fixation

Mechanism of metastatic bone pain:

The pathophysiology of pain in bone metastasis is quite varied. The pain can be due to inflammatory mediators or mechanical factors. The inflammatory pain is due to local release of cytokines and chemical mediators from cancer cell and periosteal irritation(8). Tumor induced osteolysis is an important pathology causing pain in patients with bony metastasis. These osteolysis is due to activation of osteoclasts which produce an acidic environment. This acidic environment stimulates the nocireceptor causing pain perception(16). The severity of pain depends on the number of neurochemical changes at the dorsal root ganglia in the spinal cord(17). Various pain

effects like spontaneous pain, hyperalgesia, and allodynia are also dependent on these neurochemical release (like substance P, c-Fos and Dynorphin). The mechanical factors that can be associated with bone pain are pathological fracture, decrease in bone density due to activation of osteoclasts, microfractures in the bony trabeculae causing bone distortion, stretching of periosteum by the expanding tumour, entrapment of any nerve, weakening and collapse of the bone(18).

It is important to differentiate Nociception pain versus neuropathic pain. Nociceptive pain is a result of activity in the neural pathways caused by actual tissue damage or any stimuli which could potentially damage tissue(19). Neuropathic pain is caused due to lesion or disease in the somatosensory nervous system(20). Cancer patients can have nociceptive, neuropathic or mixed nociceptive plus neuropathic pain. The prevalence of pure neuropathic pain, mixed pain and pure nociceptive pain are 19%, 20% and 59%(21). Different drugs/therapies act at different level of pain cascade and one may be better for nociceptive pain while other are directed towards relieving neuropathic pain.

Management of metastatic bone pain:

Pain is a complex symptom which impacts the patient in physical, psychological, emotional and economical terms. It hampers the daily routine activities of the patient and thereby restricting their social life. Various treatments approaches have been tried and tested over the years in formulating the protocol to achieve pain relief in these patients. The WHO analgesic ladder (Figure. 1), formulated by WHO provides the strategy for adequate pain relief in cancer patients. It focuses on escalating the pain therapy according to the degree of pain from non-opioid analgesics to mild opioids or opioids. Studies suggest that, if correctly used, this three-step WHO approach can prove to be 80%-90% effect(22).

The pain palliation approaches can be broadly categorised as medical and surgical. There are many different available medical therapies for relief of bone pain like analgesics, antitumor agents, hormones, chemotherapy, steroids, bisphosphonates (zoledronic acid), anaesthesia, radiation therapy (local and systemic), and bone targeted radionuclide therapy(18). Surgical management is rarely considered as an option for treatment of metastatic pain. Neourodestruction and neuromodulation are some of the

techniques used(16). Physiotherapy and occupational therapy can be given to improve mobility and help in physical adaptation.

There are many side effects of the drugs for pain palliation. And therefore many patients suffer from resistant cancer pain along with other complications of the treatment such as mirror pain, morphine tolerance, constipation & respiratory depression for opioid drugs and stomach ulcers & kidney toxicity for NSAIDs(23). The chronic use of these drugs is limited due to these side effects. There is no consensus on single best therapy for palliation of metastatic bone pain, usually a combination of multiple therapy (systemic and local) is needed(24).

Systemic radionuclide therapy:

Bone targeted radionuclide therapy has been used since many decades. Various radiopharmaceuticals have been developed over time (Table 3). Bone-pain palliation radionuclides have advantages like easy-to-administer, offers simultaneous treatment of multiple painful metastatic foci, the repeatability and can be combined with other treatments(25). However, it is not the first line of management. The common indications of radionuclide bone pain palliation therapy include: 1. Painful metastatic bone lesions with intense uptake in osteoblastic lesions seen on radionuclide bone scans. 2. Primary painful bone tumours with osteoblastic lesion showing intense uptake on radionuclide bone scan(25). It is preferred in those with relapse after an initial line of treatment with hormonal or chemotherapy, in patients with multiple painful metastatic sites with mild or temporary relief in pain on systemic analgesics and in whom local radiotherapy cannot be adequate due to multiple lesions at different sites of body.

These agents substitute calcium or bind to hydroxyapatite in bones and deliver ionizing radiation to areas with increased osteoblastic activity(26). The mechanism of action for pain reduction may involve reduction in pain mediators (histamine, prostaglandin E, interleukin, substance P) produced by the tumour and radiation induced mechanical factors like reduction of periosteal reaction(27). The target of radionuclide therapy is to administer sufficient dose to the metastatic foci while minimising the dose to the normal tissue. Properties of individual radionuclide like half-life, particle energy plays important role in clinical characteristic, onset and duration of palliative effect and also

on the toxic effect of the therapy. The particle emission energy of ^{32}P and ^{89}Sr is high, so they are associated with greater marrow toxicity. Samarium-153 has short physical half-life of 1.9 days resulting in more rapid delivery of radiation(28). The maximal β energy of Samarium-153 is 0.81 MeV compared to 0.437 of Lutetium-177. The higher energy leads to higher range for electrons which is 4 mm and 2 mm respectively in normal bony tissue(29).

The physical half-life of Lutetium-177 is 6.73 days. It is a β and γ emitter. The γ emitting property can be used to acquire scintigraphic images. The absorbed dose coefficient for endosteum is 4 $\pm$ 2.5 mGy/MBq, for red bone marrow is 1.4 $\pm$ 0.6 mGy/MBq, and for urinary bladder wall is 0.644 $\pm$ 0.334 mGy/MBq(30). Due to long half-life and low beta energy, the tumour cells are irradiated by ^{177}Lu-EDTMP at a slower rate with relatively lower dose per cycle. Also ^{177}Lu-EDTMP can be supplied to regions far from the site of production. In terms of its physical and biological properties ^{177}Lu-EDTMP appears to be a good agent for palliation therapy in the patients of bone pain due to metastasis(31).

Rationale behind the study

^{177}Lu-EDTMP is an important bone pain palliation radiopharmaceutical which is used widely. There are studies proving its good efficacy and safety in setting of multiple painful bone metastasis. However, there is no consensus on right dose of ^{177}Lu-EDTMP to be administered. Many patients with metastatic bone pain, have ongoing chemotherapy. These patients generally have marrow suppression due to toxicity of the chemotherapy drugs(32). Myelosuppression is also seen with various therapeutic radiopharmaceuticals and is usually dose related. It would be prudent to explore any correlation in ^{177}Lu-EDTMP therapy.

Therefore, it is of utmost importance to decide an adequate dose with maximum efficacy and minimum toxicities which can prove to be of great importance in patients. There is only one study comparing high versus low dose of ^{177}Lu-EDTMP, but in this study fixed dose of 35 mCi or 70 mCi was administered to the patients in either of the groups(29).

Till date comparison of weight-based low and high dose ^{177}Lu-EDTMP therapy for bone pain palliation has not been done to the best of our knowledge. Hence, we propose

to conduct a double blinded randomised control trial to compare the efficacy and safety profile of two different weight-based dosage of ^{177}Lu-EDTMP: 1 mCi/kg and 0.5 mCi/kg.

Figure 1: Cancer pain management—three step WHO analgesic "ladder"

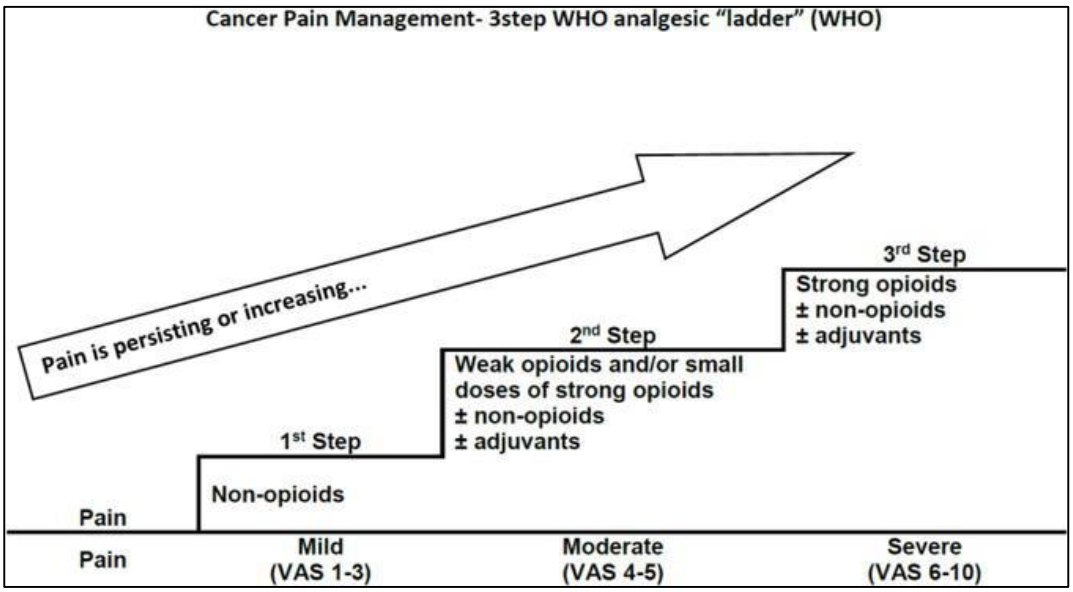


Table 3. Various Radiopharmaceuticals used for bone pain palliation(33),(34),(35).

Radioisotope	Pharmaceutical	Half-life (Days)	Emission	β Energy Max/Mean	Range Max/mean	Excretion (main)	Dose administered (MBq)	Response duration (Months)
[^{32}P] Phosphorus	-	14.3	β^-	1.71/0.695	8/2.7	Renal	185	3
[^{89}Sr] Strontium	Dichloride	50.5	β^-	1.46/0.583	6.7/2.4	Renal	150	3-6.5
[^{153}Sm] Samarium	EDTMP	1.93	β^-	0.81/0.233	2.5/.06	Renal	37MBq/kg	2-3
[^{186}Re] Rhenium	HEDP	3.7	β^-, γ	1.07/0.349	4.5/1.1	Renal	1295	5-12
[^{188}Re] Rhenium	HEDP	0.7	β^-, γ	2.12/0.64	11/3	Renal	1100-3300	3-6
[^{177}Lu] Lutetium	EDTMP DOTMP	6.73	β^-, γ	0.489/0.133	1.7/0.23	Renal	1295-2590	1-4
[^{166}Ho] Holmium	EDTMP DOTMP	1.12	β^-, γ, x	1.84/0.67	8.7/4.0	Renal	1110/<55,500	-
[^{223}Ra] Radium	Dichloride	11.4	α,β^-, γ	α – 7.53	<0.1/0.05-0.08	Gastrointestinal	55KBq/Kg x 6	1.5
[^{117m}Sn] Tin	DTPA	13.6	β^-, γ	Conversion electron - 0.129, 0.152	0.3	Renal	327 or 4.7MBq/kg	-
DOTMP—1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylene phosphonate; EDTMP—ethylene diamine tetramethylene phosphonate; HEDP—hydroxyethylidene diphosphonate.								

REVIEW OF LITERATURE

The existing literature demonstrates range of response to various radionuclide therapy for bone pain palliation in metastatic bone pain patients. There are various studies determining the efficacy and safety profile of different radiopharmaceuticals, including ^{177}Lu-EDTMP. It has been studied in some studies across the globe and a few Indian studies. In addition, there is limited literature available comparing the dose range of radiopharmaceuticals. There was no trial in literature comparing the weight based doses of ^{177}Lu-EDTMP.

Various prospective studies and some meta-analyses & systemic reviews have been included in this literature review. We reviewed the efficacy and safety of different radiopharmaceuticals and also dose related response rate and side effects as well.

Epidemiology

Rohini K. et. al. analysed oncology electronic medical records in the United States, to look for incidence of bone metastasis in solid tumors, in a record of 382733 patients they found cumulative incidence of bone metastasis (95% CI) was 2.9 % (2.9-3.0) at 30 days, 4.8% (4.7–4.8) at one year, 5.6% (5.5–5.6) at two years, 6.9% (6.8–7.0) at five years, and 8.4% (8.3–8.5) at ten years. They also concluded that incidence varied according to the cancer type with prostate cancer showing highest risk of 18-29%. It was followed by lung, renal and breast cancer. Also the cumulative incidence of bone metastasis is related to stage at diagnosis. The incidence among patients diagnosed at Stage IV is higher of whom 11% had bone metastases diagnosed within 30 days(36).

Soojung Hong et. al. analysed bone metastasis and skeletal related events in a database of 21562 Korean patients. The incidence of bone metastasis was 18.8% in breast cancer, 17.5% in prostate cancer and 13.7% in lung cancer patients. The median time to develop bone metastasis was 18.9 months from primary cancer diagnosis. Additionally, Cumulative incidence of skeleton related events (SREs) was 45.1% in all bone metastasis patients and the time to develop SRE after bone metastasis was almost 1 month for most cancers except 5.9 months in breast cancer and 4.7 months in prostate cancer(37).

Diagnosis:

A meta-analysis by Ming-che Chang et. al. comparing diagnostic performance of PET-CT with bone scan for detection of bone metastasis in patients of lung cancer showed pooled sensitivity and specificity of FDG PET-CT, 0.93 and 0.95 respectively while it was 0.87 and 082 for bone scan(38). While a meta-analysis by Sungmin Woo analysed diagnostic performance of MRI for detection of bone metastasis in prostate cancer which showed pooled sensitivity and specificity of MRI in detection of bony metastasis was 0.96 and 0.98 respectively(39).

Management of metastatic bone pain:

Analgesic drug therapy:

In a meta-analysis by Eisenberg E et. al. to study the efficacy and safety of NSAIDs for cancer pain management, concluded that NSAIDs produced 60% decrease in pain relief in majority of patients with moderate to severe pain. They analysed different pain intensity differences like peak pain intensity difference, summed pain intensity difference, peak pain relief and total pain relief and concluded that there was statistically significant difference between NSAIDs and placebo while there was no statistically significant difference while comparing the different NSAIDs. Analgesic effect of NSAID was equivalent to that of 5 mg of intravenous morphine. There is a difference of 8-12% in pain relief between low versus high dose of NSAID. The incidence of side effect to repeated dose of analgesics is about 59 episodes per 100 patient with gastrointestinal side effects being the most common(40).

Satoshi Hara studied role of opioids in management of metastatic bone pain, and found that analgesic effect was achieved in 80% of the 32 patient. However, 12 patients required supplementary analgesics (antidepressant and anticonvulsant – 5, palliative radiotherapy – 6 & extradural anesthesia – 2) (41).

In a systematic review and meta-analysis by McNicol ED et. al. including 28 studies to assess the efficacy and safety of opioids suggested the incidence of common adverse events in the opioid group were: constipation 34%, drowsiness 29%, nausea 27%, dizziness 22% and vomiting 12%. Additionally, the proportion of participants who withdrew from opioid treatment due to adverse events was about 13%(42).

Palliative Radiotherapy:

Kristopher Dennis et. al. did a systemic review of 26 articles of which 24 were randomised trial to determine the optimal dose of single fraction conventional palliative radiation therapy for the relief of metastatic bone pain. The various response rates for different single fraction dose were as: 4 Gy - OR(ITT) = 23–47%, OR(A) = 44–47%, CR(ITT) = 15–18%, CR(A) = 15–26%, 5 Gy - OR(A) = 72%, CR(A) = 55%, 6 Gy - OR(ITT&A) = 65%, CR(ITT&A) = 21%, 8 Gy - OR(ITT) = 21–81%, OR(A) = 31–93%, CR(ITT) = 9–52%, CR(A) = 14–57%, 10 Gy - OR(A) = 84%, CR(A) = 39%(43).

A systemic review by Ronald Chow et. al. studying efficacy of single fraction radiotherapy in patients with bony metastasis showed overall response rates of 81%, 74%, 60% and 54% for 10 Gy, 6, 8 and 4 Gy respectively. While complete response rates were 37%, 30%, 22% and 21% for 10 Gy, 6, 8 and 4 Gy respectively. The need of retreatment after single fraction radiotherapy varied between 9 to 44%, the reasons being spinal cord compression in 2% - 8% patients and pathological fracture in 0% to 16% patients. Also there were some acute toxicities were reported in the studies included: hematologic, lung, central nervous system, gastrointestinal, nausea, vomiting, diarrhoea and fatigue/tiredness. There was intial flare up of pain post radiotherapy as reported by some studies and ranged from 10% to 57% with overall combined rate of 25% at about 3 days' post radiotherapy(44).

Table 4. Response to single fraction radiotherapy (8 Gy) seen in different studies.

Study	OR(ITT)	OR(A)	CR(ITT)	CR(A)
Foro-Arnalot et. al(45)	75%	78%	15%	16%
Hamouda et. al(46)	77%	80%	38%	40%
Hartsell et. al(47)	41%	65%	10%	15%
Roos et. al.(48)	53%	57%	26%	28%
El-Shenshawy et. al.(49)	78%	78%	18%	18%

OR(ITT): Overall Response (Intention to treat); OR(A): Overall Response (Assessable); CR(ITT): Complete Response (Intention to treat); CR(A): Complete Response (Assessable);

Table 5. Flare in bone pain post radiotherapy seen in different studies

Study	Dose	Pain flare seen [%]	Duration for pain flare
Gomez –Itturiaga et.al (50)	8 Gy	14/42 [33%]	Mean : 3 days
Hird et. al.(51)	8 Gy	27/70 [39%]	N/A
Loblaw et. al.(52)	8 Gy	13/23 [57%]	Median : 3 days
Roos et. al.(48)	8 Gy	14/137 [10%]	N/A

A prospective study by Takuma Nomiya et. al. in 91 patients to study the time course of pain relief in patients of metastatic bone pain receiving radiotherapy concluded that mean pain score reduced significantly every week for about 4 to 5 weeks. The mean time to achieve 50 % (n = 83) pain relief was 13 days while mean time to achieve complete pain relief (n = 45) was 24 days. Additionally, the doses of analgesics were successfully reduced in 28/64 (44%) of the patients after radiotherapy(53).

Jackson Sai-Yiu Wu et. al. did a meta-analysis to study and compare pain relief in various fractionation scheduled radiotherapy for treatment of painful bone metastasis doing a literature review of 16 trials. Results showed pooled complete response (intention to treat) 33.4% (539 of 1613) after single-fraction and 32.3% (523 of 1618) after multifraction treatment and pooled overall response rates (intention to treat) 62.1% (1011 of 1629) after single-fraction and 58.7% (958 of 1631) after multifraction treatment(54).

Bisphosphonate therapy:

Charles L. Vogel et. al. did a prospective, multicenter study in 638 patients with breast cancer, prostate cancer, or multiple myeloma to study the safety and pain palliation of Zolendronic acid. Patients were given 6 cycle of zolendronic acid. Patients experienced statistically significant significant decrease in mean pain scores at every visit. In the ITT population mean VAS pain score decreased from baseline at all assessments after the second visit, with statistically significant reduction at visits 4 and 5(55).

Radionuclide bone pain palliation therapy:

Rosa Sciuto et. al. evaluated therapeutic efficacy of Strontium-89-chloride and 186-Re-HEDP in palliation of painful bone metastases from breast cancer. 50 patients were randomised to receive either 148 MBq of 89-Sr (25 patients) or 186-Re-HEDP (25 patients). Pain response was evaluated using Wisconsin Pin test. They found a global response rate of 88%; 84% for 89-Sr compared to 92% for 186-Re-HEDP. The onset of pain relief was significantly early in 186-Re-HEDP group (median 4 days) compared to 89-Sr (median 21 days). The karnofsky performance scale was used to see the improvement in both the groups and it significantly increased in both the groups post treatment. 30% of the patients experienced mild transient increase in pain: 8/25 in 89-Sr group and 7/25 in 186-Re-HEDP group. In 89-Sr group there was 20% mean decrease in platelets and 21% mean decrease in leukocytes at 3 and 4 weeks. However, platelet and leukocyte counts returned to baseline levels within 12 weeks in all patients. The time to recovery after the nadir was 51± 17 days for platelet and 59± 16 days for leucocytes. While in 186-Re-HEDP there was 20% mean decrease in platelets and 15% mean decrease in leukocytes at 3 and 4 weeks. However, platelet and leukocyte counts returned to baseline levels within 6 weeks in all patients. The time to recovery after the nadir was 11 ± 4 days for platelets and 14 ± 6 days for leucocytes(56).

Rosa Sciuto et. al. compared the effect of low dose cisplatin plus 89-Sr versus 89-Sr alone in treatment of painful bone metastases in 70 patients of prostate cancer, 35 patients in each arm. 32/35 (91%) patients in low dose cisplatin plus 89-Sr had overall pain relief, while 22/35 in the 89-Sr alone showed overall pain relief. The relapse of pain was seen in 1 month to one year in low dose cisplatin plus 89-Sr group while it was 1 month to 7 months in 89-Sr alone group. In low dose cisplatin plus 89-Sr group – 1 patient had WHO grade 1 platelet toxicity, 8 patients had WHO grade 1-2 leukocyte toxicity, 14 patients had haemoglobin toxicity of WHO grade 1-4. In 89-Sr alone group - 2 patient had platelet toxicity of Who grade 1-2, 2 patients had leukocyte toxicity of grade 2, 13 patient had haemoglobin toxicity of grade 1-4(57).

Hélène Kolesnikov-Gauthier et. al. did a prospective study to evaluate efficacy and safety of 153-Sm-EDTMP in patients with painful bone metastasis. Patients experienced subjective clinical benefit in 128/292 (43.8%) at D15 and 127/239 (53.1%) at D30. 41/312 (13.1%) patients experienced flare phenomenon. Haematological

toxicity like Grades 3 or 4 anaemia occurred in 9/242 (3.7%) patients at D30 and 6/146 (4.1%) at D45. Grades 3 and 4 thrombocytopenia occurred in 14/248 (5.6%) at D30 and 2/150 (1.3%) at D45. Grades 3 and 4 neutropenia occurred in 7/228 (3.1%) and 3/ 138 (2.2%)(58).

A metaanalysis by G D'angelo et. al. did a systematic review and metaanalysis of 57 studies using 89Sr-chloride and 153Sm-EDTMP for palliation therapy of pain from bone metastases. The pooled overall efficacy of radiopharmaceuticals as a single agent was 70%, and when combined with other therapies it was 74%. The overall toxicity of radiopharmaceuticals was 15%(59).

Knut Liepe and Joerg Kotzerke did a comparative study to determine the efficacy and toxicity of 188-Re-HEDP, 186-Re-HEDP, 153-Sm-EDTMP and 89-Sr in treatment of painful skeletal metastases. Pain relief was defined decrease of pain symptoms at two steps on the VAS at least in two consecutive weeks without any increase in the analgesic intake. 58/79 (73%) of patient achieved pain relief: 24/31 (77%) in patients receiving 188-Re-HEDP, 10/15 (67%) in patients receiving 186-Re-HEDP, 11/15 (73%) in patients receiving 153-Sm-EDTMP and 58/79 (73%) in patients receiving 89-Sr. The duration of response was > 12 weeks in 14/24 patients with 188-Re-HEDP, 5/10 for 186Re-HEDP, 6/11 for 153-Sm-EDTMP and 6/13 for 89-Sr. Patients with response < 12 weeks, the duration was 9 ± 2 weeks for 188-Re-HEDP, 10 ± 2 weeks for 186-Re-HEDP, 10 ± 1 weeks for 153-Sm-EDTMP and 9 ± 2 weeks for 89-Sr. In haematological toxicities: 10% (8/79) patients had thrombocytopenia grade I, 2% (2/79) a thrombocytopenia grade II. There was no significant anaemia or leukopenia noted(60).

Nilsson et. al. investigated pain relieving effect of radium-223 in castration resistant prostate cancer patients in a multicentre phase II study. They randomised 100 patients to receive single dose of 5 or 25 or 50 or 100 k Bq/kg of radium-223. Significant response in pain was observed in all the groups at 8 weeks, 40%, 63%, 56% and 71% reduction in pain was observed in 5, 25, 50 and k Bq/kg group respectively. A significant improvement in the brief pain inventory functional index was also observed for all-dose groups. Most of the patients (~97%) reported adverse events. Most frequent adverse effects being nausea, fatique, vomiting, diarrhoea, constipation, etc. Haematological side effects were mild with no significant difference between the groups(61).

Parker et. al. did a double blind randomised, multicentre phase 2 study to evaluate efficacy and safety of different doses of 223-Radium chloride in patients with castration resistant prostate cancer and bone metastasis. 112 patients were randomised to receive 25, 50 or 80 k Bq/kg of 223-Radium. They concluded that significant dose response relationship is seen in these patients. Pain index data was available for 86 of 112 patients. There was significant reduction in pain in all the groups with maximum response rate in 50 k Bq/kg group(62).

Table 6. Response rate to various radionuclide therapy: 89-Sr, 153-Sm-EDTMP and 186-Re-HEDP.

Radionuclide	Study	No. Patients	Dose	Pain relief
89-Sr	Dafermou et al(63)	527	4 mCi	59.8%
	Baczyk et al(64)	70	4 mCi	88%
	Ma et al(65)	116	40-60 uCi/kg	83.6%
153-Sm-EDTMP	Serafini et al(66)	118	0.5-1 mCi/kg	62%-82%
	Sartor et al(67)	152	1 mCi/kg	65%
	Dolezal et al(68)	32	1 mCi/kg	75%
186-Re-HEDP	Tennvall et al(69)	14	70 mCi	79%
	Dafermou et al(63)	58	35 mCi	86%
	Leondi et al(70)	24	35 mCi	62%

^{177}Lu-EDTMP for metastatic bone pain palliation therapy:

Hesham et. al. did a comparative study on potential use of ^{177}Lu radiopharmaceuticals for palliative therapy of bone metastases and concluded that with ^{177}Lu-EDTMP, we see a more rapid therapeutic effect after injection compared with the ^{89}SrCl2. Also the dose load to red bone marrow with ^{177}Lu-EDTMP is lower than that from ^{153}Sm-EDTMP and thus ^{177}Lu EDTMP is more effective. The dose per tumor is much greater than the dose per organ for ^{177}Lu-EDTMP in comparison to other radionuclides(71).

Mehrosadat Alavi, et al. did a phase I trial to determine efficacy and safety of ^{177}Lu-EDTMP in metastatic bone pain. 30 patients were administered a dose of 0.8 mCi/kg body weight. The results revealed complete palliative pain response in 53% while 30% showed a partial response, and no response was noted among 17% patients. 70% of the patients reported flare phenomenon. Patient reported pain relief from 2.53 ± 2.08 weeks after the injection, and the duration of response lasted for 4.38 ± 3.34 weeks. There was significant reduction in haemoglobin and platelet at 4 week following therapy(31).

A study was conducted by Ajit S. Shinto, et al. to evaluate the role of ^{177}Lu-EDTMP for bone pain palliation in skeletal metastases. 10 patients were administered 100 mCi dose and the result showed significant decrease in mean pain score from 8.44 to 5.73 in one-month period. The mean score at 12 weeks was just 20.2% of the baseline mean pain score. And an increase in mean karnofsky score from 45 to 65 in 4 weeks was also noted. They concluded that ^{177}Lu-EDTMP therapy effective, feasible, safe and well tolerated with less haematological toxicity(72).

Krishan Kant Agarwal et. al. conducted a phase II study to evaluate efficacy and safety of ^{177}Lu-EDTMP for pain palliation in patients of prostate and breast cancer with bony metastases and a secondary objective to compare low dose and high dose ^{177}Lu-EDTMP where low dose was 35 mCi and high dose as 70 mCi. The overall response rate was 86% (38/44) among which complete response was seen in 13% (6/44), partial response was seen in 48% (21/44) and 25% showed minimal response. Among responders VAS decreased significantly from 6.8±1.5 at baseline to 3.5±1.7 during follow-up after radionuclide therapy and there was significant decrease in AS from baseline 1.8±0.7 to 1.2±0.9. Grade I/II haematological toxicity was seen in 34% (15/44) patients, while 23% (10/44) patients showed grade III/IV haematological toxicity. Among the two

groups: group A (low dose) versus group B (high dose), the overall response was 77% in group A and 95 % in group B with no statistically significant difference between the two. There was no significant difference in fall of VAS score or analgesic score between the two groups neither any difference in improvement in KPS score between the two groups. Additionally, there was no statistically significant difference in toxicity between the groups(29).

Jie Yuan, et al. conducted a phase 2 study with 11 patients to study efficacy and safety of ^{177}Lu-EDTMP using two different doses 35 mCi and 70 mCi. There was significant reduction in pain score among both the groups in the first six weeks after treatment but there was no statistically significant difference in pain reduction between the two groups. The Karnofsky index increased from 58.18 (9.82) to 82.73 (9.05) at 6 weeks in group 1 and from 56.00 (8.94) to 85.00 (5.77) at 8 weeks in group 2. They concluded that ^{177}Lu-EDTMP was effective and feasible for bone pain palliation in bone metastases. A dose of 35 mCi was sufficient for palliation and increase till 70 mCi is well tolerated. Haematological nadir was observed at 1 week in high dose group as compared to 4 weeks in low dose group(73).

In a prospective study Pradeep Thapa et. al. compared efficacy of ^{177}Lu-EDTMP and 153-Sm-EDTMP by administrating 16 patients with 1mCi/kg ^{177}Lu-EDTMP and another 16 with 153-Sm-EDTMP. Overall pain relief in ^{177}Lu-EDTMP group was 80%: among which 50% had complete pain relief, 41.67% had partial relief and 8.33% had minimal relef. Whereas in ^{153}Sm-EDTMP group overall pain relief was 75%: 33.33% complete, 58.33% partial, and 8.33% minimal. There was no statistically significant difference between the two. Hematological toxicity including anemia, leukopenia, and thrombocytopenia of grade I/II were 46.67%, 46.67%, and 20% respectively in ^{177}Lu-EDTMP group patients, while grade III/IV were 20%, 6.67%, and 0%, respectively. For ^{153}Sm-EDTMP, anemia, leukopenia, and thrombocytopenia of grade I/II were 62.5%, 31.25%, and 18.75%, respectively, and grade III/IV were 18.75%, 0%, and 6.25%, respectively. There was no statistically significant difference between them. They concluded that ^{177}Lu-EDTMP has a similar pain relief efficacy and safety as ^{153}Sm-EDTMP and can be a feasible alternative(74).

A comparative study (by Sarika Sharma, et al.) between ^{153}Sm-EDTMP and ^{177}Lu-EDTMP was done by administering dose of 1 mCi/kg body weight of both the drugs.

Both the radioisotopes delivered similar absorbed dose to the metastatic lesion. A complete response was observed in 80% of the patients in both the groups: 16/20 patients who received ^{153}Sm-EDTMP showed response while 8/10 in ^{177}Lu- EDTMP group had response. With a mean pain score declining from 7.2 $\pm$ 1.72 to 1.31 $\pm$ 0.48 in patients with samarium therapy, and from 7.9 $\pm$ 1.55 to 1.63 $\pm$ 0.52 in patients with Lutetium therapy. They concluded that both the radionuclides have comparable efficacy in bone pain palliation in bony metastases(75).

Mehrosadat Alavi et. al. did a clinical trial in 25 patients to determine the safety and efficacy of ^{177}Lu/153-Sm-ethylenediamine tetramethylene phosphonic acid (EDTMP) cocktail therapy. All patients received a total dose of 37 MBq (18.5 MBq of each compound), with a maximum allowed dose of 70 mCi. 18 patients (72%), showed complete response, 6 patients (24%) showed acceptable response and 1 patient had minimal response. There was no grade IV toxicity noted while 1 patient had grade III toxicity. They concluded that this cocktail therapy is an effective and safe treatment for bone pain palliation in patients with bony metastases(76).

Emran Askari et. al. did a systematic review and meta-analysis to evaluate the efficacy, safety and toxicity of ^{177}Lu-EDTMP in patients with metastatic bone pain. The pooled overall pain response was 84% while 32% of the patients had a complete palliative pain response rate. There was grade I/II anemia in 24% of patients, while 19% of patients showed grade III/IV anemia. Similarly, the incidence of leukopenia and thrombocytopenia of grade I/II was 26% and 21% respectively while of grade III/IV was 4% and 4 % respectively. They concluded that ^{177}Lu-EDTMP can be an effective, safe and feasible alternative treatment option for metastatic bone pain palliation in patients with disseminated skeletal metastases(77).

Table 7. Response rates of ^{177}Lu-EDTMP in different studies

Study	Patients	Dose	Bone palliation response			
			CRR	PRR	MRR	ORR
Yuan et. al.(73) Ψ	HDG - 5 LDG - 11	HDG – 70 mCi LDG – 35 mCi	HDG – 80% LDG – 18%	HDG – 20% LDG – 82%	-	HDG – 100% LDG – 100%
Agarwal et. al.(29) τ	HDG - 22 LDG - 22	HDG – 70 mCi LDG – 35 mCi	HDG – 18% LDG – 9%	HDG – 50% LDG – 45%	HDG – 27% LDG – 23%	HDG – 95% LDG – 77%
Thapa et. al.(74) ϕ	16	1 mCi/kg	40%	33.3%	6.6%	80%

ΨComplete response (CR) defined as disappearance of all bone pain, freely mobile, and at least a 50% decreased use of pain medication; partial response (PR) defined as some improvement in bone pain.

τCR defined as >70% decrease in VAS and PR defined as 40%–70% decrease in VAS, minimal response (MR) 20%–40% decrease in VAS.

ϕCR defined as either pain score of 0 at 3 month or >75% decrease in analgesic score with change in pain score, PR defined as either change in pain score by >3 or 50%–75% decrease in analgesic score with change in pain score, and MR defined as either change in pain score by 1–3 or 25%–50% decrease in analgesic score with change in pain score.

Table 8. Incidence of haematological toxicities using ^{177}Lu-EDTMP in studies

Study	Anaemia		Leukopenia		Thrombocytopenia	
	Grade I/II (%)	Grade III/IV (%)	Grade I/II (%)	Grade III/IV (%)	Grade I/II (%)	Grade III/IV (%)
Thapa et. al.(74)	46.7%	20%	46.7%	6.7%	20%	0%
Bal et. al.(78)	33%	24%	14.2%	4.7%	0%	0%
Yuan et. al.(73)	HDG:40% LDG:9%	HDG:0% LDG:9%	HDG:40% LDG:81%	HDG:0% LDG:0%	HDG:80% LDG:36%	HDG:0% LDG:9%
Agarwal et. al.(29)	HDG:18.2% LDG:27.3%	HDG:18.2% LDG:27.3%	HDG:18.2% LDG:9.1%	HDG:0% LDG:0%	HDG:18.2% LDG:4.5%	HDG:0% LDG:4.5%

HDG, high-dose group; LDG, low-dose group.

AIMS AND OBJECTIVES

Aim

To assess outcome of low vs. high dose ^{177}Lu-EDTMP therapy for palliation of painful bone metastases.

Objectives

Primary:

1. To find difference in pain relief in patients of bony metastases receiving high dose vs low dose ^{177}Lu-EDTMP therapy.

Secondary:

1. To find and compare improvement in quality of life as assessed by KPS/ECOG scale between the two groups.
2. To compare reduction in analgesic dose post therapy in both groups.
3. To find and compare the duration of pain relief achieved between the two groups.
4. To evaluate change in haematological and biochemical parameters post therapy between both the groups.
5. To look for any other adverse effect.
6. Bone scan quantification for response assessment and comparison between two groups.

MATERIALS AND METHODS

STUDY SETTING:

All patients with multiple metastatic bone pain who came for pain palliation therapy to Department of Nuclear Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan were recruited for the study.

STUDY DESIGN:

A randomised controlled trial will be conducted by dividing the patients into two groups on basis of the administered dose of ^{177}Lu-EDTMP.

Study Type: Interventional (Clinical Trial)

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Primary Purpose: Palliation of metastatic bone pain.

Official Title: Comparison of low vs. high dose ^{177}Lu-EDTMP therapy for palliation of painful bone metastases: RCT.

Table 9. Arms and Interventions:

ARMS	INTERVENTION
Group A- High dose ^{177}Lu-EDTMP therapy.	Patients receiving a dose of 1.0 mCi/kg body weight of ^{177}Lu-EDTMP.
Group B- Low dose ^{177}Lu-EDTMP therapy.	Patients receiving a dose of 0.5 mCi/kg body weight of ^{177}Lu-EDTMP.

Outcome Measures:

Primary Outcome Measures:

1. VAS/NRS and Analgesia score: VAS/NRS score and Analgesia score for measurement of pain pre and post therapy was used. The scores were measured at the time of therapy, 2,4,8,12 weeks following therapy.

Secondary Outcome Measures:

1. Analgesic use: The reduction in dose and frequency of Analgesic drugs used prior to therapy and 2,4,8,12 weeks following therapy were noted.
2. Quality of life (KPS score and ECOG score): The KPS score and ECOG status of the patients was evaluated prior to therapy and 2,4,8,12 weeks following therapy.
3. Duration of pain relief: The period for which the patient experienced a reduction in pain as compared to baseline VAS/NRS score evaluated at 2,4,8,12 weeks following therapy.
4. Time of initiation of response and Time for maximum response: The time when the VAS/NRS score starts to decrease and Time to reach the minimum VAS/NRS score achieved.
5. Absolute values and Percentage change of Haematological parameters (haemoglobin, WBCs counts, platelet counts) prior to therapy and 2,4,8,12 weeks following therapy.
6. Absolute values and Percentage change of Biochemical parameters (Sr. Creatinine, estimated GFR, ALP) prior to therapy and 2,4,8,12 weeks following therapy.

STUDY PARTICIPANTS:

INCLUSION CRITERIA:

1. Patients with greater than 18 years of age, with HPE confirmed cancer.
2. Patients having painful metastatic bone lesions with osteoblastic response, as confirmed by areas of intense uptake on 99m-Tc-MDP bone scans at painful sites.
3. The patients on naive or prior analgesic therapy.

4. The minimum VAS/NRS score without medication should be $\geq$ 4.
5. The patient's KPS score should be $\geq$ 30 and ECOG $\leq$ 3.
6. Time interval between ^{177}Lu-EDTMP therapy and prior chemotherapy or radiotherapy should be greater than four weeks.

EXCLUSION CRITERIA:

1. Patients with the following cell count limits will not be considered for the therapy:

   Haemoglobin < 9 g/dL

   Total white cell count < 3000/μL

   Platelet count < 60000/μL
2. Patients with poor renal function i.e. estimated glomerular filtration rate < 30 mL/ min.
3. Patients with life expectancy less than 3 months.
4. Pregnant or lactating females if any.

SAMPLING AND SAMPLE SIZE:

Sample size was calculated keeping 20% attrition.

$$n = \frac{(Z_{(1-\alpha/2)} + Z_{(1-\beta)})^2 \, 2Sp^2}{d^2}$$

where,

$$Sp = \frac{S_1 + S_2}{2}$$

d = difference in means

$Z_{(1-\alpha/2)} = 1.96$

$Z_{(1-\beta)} = 0.842$

During the given time period a total of 15 patients were recruited however 2 patients could not complete the required follow-up. So the total number of patients included for analysis are 13.

Ethical clearance was taken and the patients were recruited after taking informed consent.

STUDY DURATION:

12th March 2021 to 31st December 2022

OPERATIONAL DEFINITIONS:

Response:

Complete response: Decrease in VAS/NRS score ≥ 70% from baseline.

Partial response: Decrease in VAS/NRS score ≥ 50% but < 70% from baseline.

Minimal response: Decrease in VAS/NRS score > 20% but < 50% from baseline.

No response: Decrease in VAS/NRS score ≤ 20% from baseline.

Best existing standard of care:

Drug: Best standard of care (BSoC)

Best standard of care is regarded as the routine standard of care at each centre, like analgesics, antitumor agents, hormones, chemotherapy, steroids, local surgery, bisphosphonates (zoledronic acid), anaesthesia, radiation therapy (local and systemic).

DATA TOOLS:

1. **Clinical profile sheet:** Patient demographics and clinical information.
2. **Visual Analogue Score (VAS)**(79)**:** It is a psychometric response scale used to quantify the pain. It is a 10 cm long scale demarcating no pain at origin towards left and gradually increasing pain to highest pain at 10 cm mark at the right.
3. **Analgesic score (AS)**(80)**:** It is a score graded from 1 to 6 according to the dose and type of analgesics administered by the patient for pain relief where 1 corresponds to no pain and no use of analgesics, 2 – using non-narcotic analgesic, 3 – occasional oral narcotics, 4 – Regular oral narcotics, 5 – parenteral narcotics and 6 – uncontrollable with parenteral narcotics.
4. **ECOG**(80)**:** It is a score describing the functioning of the patients in terms of their ability to take care of themselves. It is classified from 0,1,2,3,4 & 5, with 0 denoting patient's performance as fully active, patient's condition worsening as the score increases and 5 denoting Dead.

5. **Karnofsky Performance Status (KPS) scale**(81)**:** It is a score describing the functioning of the patients in terms of their ability to take care of themselves. It is classified from 100 to 0, with scale decreasing by a factor of 10 at each step. 100 denoting patient's performance as fully active, patient's condition worsening as the score decreases and 0 denoting Dead.
6. **Bone Lesion Score (BLS)**(29)**:** It was calculated on the basis of extent and number of lesions on the findings of scintigraphy. The entire skeleton was divided into five anatomical regions, namely skull, spine, thorax, extremities and pelvis. The grading of 1 to 4 was done on the basis of number of lesions for skull, thorax extremities and spine and percentage of bone involvement for the pelvis.

PROCEDURE:

Patients:

Patients of either sex, greater than 18 years of age who were diagnosed to have bone pain due to metastatic lesion of bone were approached for participating in the study. The patient was primed about the study procedure, the possible benefits, and any adverse outcomes, through a patient information sheet (in English/Hindi). They were enrolled after taking valid informed consent. The family members /guardians were also explained about the same and were also informed that no loss of benefit from routine care be experienced if they refuse to take part in the study.

All the patients who were diagnosed to have bone pain due to metastatic bone disease were taken for the study. The patients had undergone bone scan within 8 week showing osteoblastic lesion with increased radiotracer uptake at the site of bone pain. A detailed haematological and biochemical profile were obtained within 1 week prior to the therapy. A list of procedures as described by Handkiewicz-Junak D et. al. in the EANM guidelines were followed (Table 10)(25).

Table 10. Mandatory procedures to be performed before ^{177}Lu-EDTMP Therapy[25]

Procedure	Objective	Timing
Medical history	To obtain patient demographics, indication for therapy, concomitant medications	Qualification for treatment on day of treatment
Life expectancy estimation	To confirm at least 4–6 weeks (preferably 3 months)	Qualification for treatment
Bone scan	To evaluate extent of disease	No longer than 4–8 weeks prior to therapy
Radiological imaging	To exclude severe lytic lesions with risk of pathological bone fracture or cord compression	As required
Complete blood count, d-dimer, serum creatinine	To exclude haematological, biochemical contraindication to therapy	No longer than 1–2 weeks prior to therapy; If required repeat on day of treatment
Pregnancy test		On day of treatment

The estimated GFR was calculated according to Cockraft and Gault formula(82):

eGFR (mL/min) = [(140 - age) × Wt / (72×S.Cr in mg/dl)] × (0.85 if female) [eGFR has to be corrected for surface area]

Randomisation:

The randomisation of the patients was done on the basis of following characteristics: Sex, VAS score and whether previous treatment was received.

Doses:

The patients were randomized into two groups:

1. Group A received 1 mCi/kg body weight of ^{177}Lu-EDTMP was administered to these patients.
2. Group B received 0.5 mCi/kg body weight of ^{177}Lu-EDTMP was administered to these patients.

The dose was administered slowly over a period of 1 minute by an indwelling iv cannula. 10 ml normal saline was flushed following the administration of dose.

Imaging:

Planar anterior and posterior images were acquired after 3 hours of dose administration using gamma camera.

Response assessment:

A detailed evaluation of the patient's condition was done. Patients pain was rated on basis of VAS/NRS score. A multisite VAS/NRS analysis was done for several body regions (head, upper spine, lower spine, arms, legs, ribs, sternum, clavicle, pelvis) to get the region wise baseline VAS/NRS score. Pain was also assessed on the basis of Analgesic score ranging from 1 to 6. Quality of life was assessed on the basis of Karnofsky Performance Score (KPS) and ECOG. Bone scan quantification parameters were compared in pre and post therapy images. The side effect to the therapy were assessed using CTCAE Version 5. This scores and parameters were reassessed at 2,4,8 and 12 weeks after therapy.

STASTICAL ANALYSIS:

Analysis among patients belonging to same group:

Difference between pre-therapy and post-therapy VAS, AS, serum haematological values were analysed by paired sample t-test. Pre-therapy and post-therapy difference in ECOG and KPS were evaluated by Friedman's test.

Analysis between patients belonging to two groups:

Difference in response rates, degree of response and degree of haematological toxicity between two groups were evaluated using chi square test and confidence interval analysis. Difference between pre-treatment and post treatment variables were evaluated using t-test for unpaired data. For ordinal data, intergroup comparison was done using Wilcoxon sign rank test.

RESULTS

From March 2021 to September 2022, 15 patients were recruited in the study: 7 in Group A and 8 in group B. Two patients were excluded, one in each group due to lack of follow-up in them. Thus the final number of patients included were 13: 6 in Group A and 7 in group B. There were 8 patients of prostate cancer, 2 patients of carcinoma breast and 3 patients of carcinoma lung. The mean age of patients was 62. 42 ± 13.57 and the mean bone lesion score was 12.37 ± 4.24. The baseline characteristics of all 13 patients is described in table 11.

Table 11. Baseline characteristics of all patients:

Variable	
Patients, *n*	13
Primary (Prostate/breast/lung), *n*	8/2/3
Age (years)	62.42 ± 13.57
Bone lesion Score, mean±SD	12.37 ± 4.24
Latency time from diagnosis (months), median (range)	15 (4-72)
Previous Radiotherapy (yes/no), *n*	7/6
Previous Chemotherapy (yes/no), *n*	10/3
Previous Hormonal therapy (yes/no), *n*	7/6
Baseline Visual Analogue Score (VAS), mean+SD	8.15 ± 1.28
Baseline Analgesic score (AS), mean+SD	3.31 ± 0.75
Baseline ECOG, median (range)	1 (1-3)
Baseline Karnofsky performance score (KFS), median (range)	80 (50-90)
Baseline Hemoglobin (g/dL), mean±SD	11.85 ± 1.52
Baseline WBC (per microlitre), mean±SD	8750.00 ± 2788.26
Baseline Platelets (per microlitre), mean±SD	324846.15 ± 136531.34

Overall analysis:

Pain Relief:

The decrease in mean VAS score from baseline to each point time at follow-up was statistically significant (Table 12). The mean VAS score came down from 8.15 ± 1.28 at baseline to 2.31 ± 3.01 at 3 months ($p<0.001$). Similarly, the mean AS came down from 3.31 ± 0.751 in baseline to 1.62 ± 1.66 at 3 months ($p<0.001$). There was progressive decrease in VAS from baseline till 3-month follow-up. However,

statistically significant fall between two consecutive follow-ups was seen between baseline and 15 days (p=0.01) and between 1 month and 2-month follow-up (p=0.012). The percentage decrease in mean VAS score was 42% at 15 days, 51% at 1 month, 67% at 2 months and 72% at 3 months (Figure 2). There was progressive decrease in analgesic score in each follow-up. There was statistically significant difference between AS score at each follow-up in comparison to baseline (Table 13). Statistically significant decline in analgesic score was seen at between baseline and 15 days (p=0.012) and between 1 month and 2-month follow-up (p=0.027).

Table 12. Decrease in mean VAS from baseline in follow-up:

Time period	VAS, mean + SD	p-Value
Baseline	8.15 + 1.28	
15 days	4.85 + 3.05	0.001
1 Month	4.15 + 2.82	<0.001
2 Month	2.85 + 3.36	<0.001
3 Month	2.31 + 3.01	<0.001

Figure 2. Percentage change in mean VAS score in follow-up.

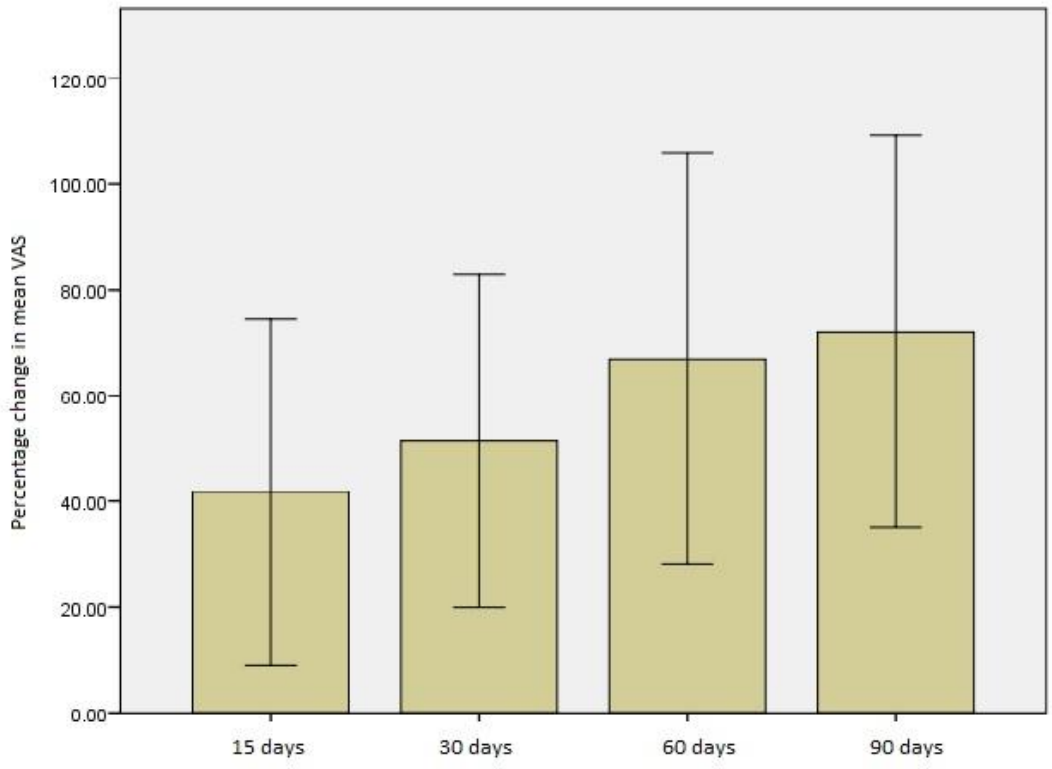


Table 13. Decrease in mean AS from baseline in follow-up:

Time period	AS, mean ± SD	p-Value
Baseline	3.31 ± 0.751	
15 days	2.15 ± 1.59	0.012
1 Month	2.15 ± 1.34	0.005
2 Month	1.69 ± 1.60	0.001
3 Month	1.62 ± 1.66	0.001

Quality of life assessment:

Both ECOG and KPS did not have Gaussian distribution and therefore their median were calculated and compared. There was improvement in Quality of life in most of the patients responding to the therapy however there was no significant difference in the median KPS and median ECOG at baseline as compared to medians at subsequent follow-ups (Table 14 & 15).

Table 14. Change in median KPS from baseline in follow-up:

Time period	KPS, median (Range)	p-Value
Baseline	80 (50-90)	
15 days	80 (50-100)	0.785
1 Month	80 (60-100)	0.279
2 Month	80 (60-100)	0.068
3 Month	80 (50-100)	0.103

Table 15. Change in median ECOG from baseline in follow-up:

Time period	ECOG, median (Range)	p-Value
Baseline	1 (1-3)	
15 days	1 (1-3)	0.317
1 Month	1 (1-2)	0.564
2 Month	1 (1-2)	0.180
3 Month	1 (1-3)	0.414

Overall Response rates:

Overall response rate (ORR) was calculated by including patients showing complete response, partial response and minimal response. Ten among the thirteen patients showed response i.e ORR was 76.9%. The baseline characteristics including, VAS, AS, ECOG, KPS and haematological parameters among the responders and non-responders were comparable (Table 16). The VAS in responders came down from 8.20 ± 1.3 to 0.9 ± 1.52 while in non-responders it came from 8.0 ± 1.0 to 7.00 ± 1.00. The difference in VAS score between responders and non-responders at 12 weeks was statistically significant ($p<0.01$). Similarly, the Analgesic score in responders came down from 3.3 ± 0.58 to 1.1 ± 1.52 while in non-responders it did not change much, from 3.3 ± 0.82 in baseline to 3.3 ± 0.57 at 12 weeks. The difference in AS score between responders and non-responders at 12 weeks was statistically significant ($p<0.03$).

Table 16. Baseline characteristics between responders and non-responders

Variable	Responders	Non Responders	p-value
Patients, *n*	10	3	
Primary (Prostate/breast/lung), *n*	8/1/1	0/1/2	0.04
Age (years)	60.4±12.43	50.00± 14.17	0.33
Bone lesion Score, mean±SD	15.33±2.08	11.8±3.93	0.081
Latency time from diagnosis (months), median (range)	6 (4-23)	15 (7-72)	
Previous Radiotherapy (yes/no), *n*	4/6	3/0	0.067
Previous Chemotherapy (yes/no), *n*	7/3	3/0	0.279
Previous Hormonal therapy (yes/no), *n*	7/3	0/3	0.03
Baseline Visual Analogue Score (VAS), mean+SD	8.20± 1.3	8.0±1.0	0.747
Baseline Analgesic score (AS), mean+SD	3.3±0.58	3.33±0.82	0.278
Baseline ECOG, median (range)	1 (1-3)	1 (1-2)	1
Baseline Karnofsky performance score (KFS), median (range)	80 (50-90)	80 (60-80)	1
Hemoglobin (g/dL), mean±SD	11.80±1.68	12.00±1.00	0.875

Response in different cancers group:

In the patients with prostate cancer, 8/8 showed favourable response, 1 of the 2 breast cancer patients had no response (ORR = 50%) while 2 of the 3 lung cancer patients showed no response (ORR = 33.33%) (Figure 3, 4, 5 & 6). The mean VAS in patients with prostate cancer came down from 8.63+ 0.916 to 1.13+1.64 and in non-prostate cancer patients came down from 7.4 + 1.51 to 4.2 +3.99. There was no statistically significant difference between them (p = 0.07) (Fig. 7).

Figure 3. Response rates in all the patients:

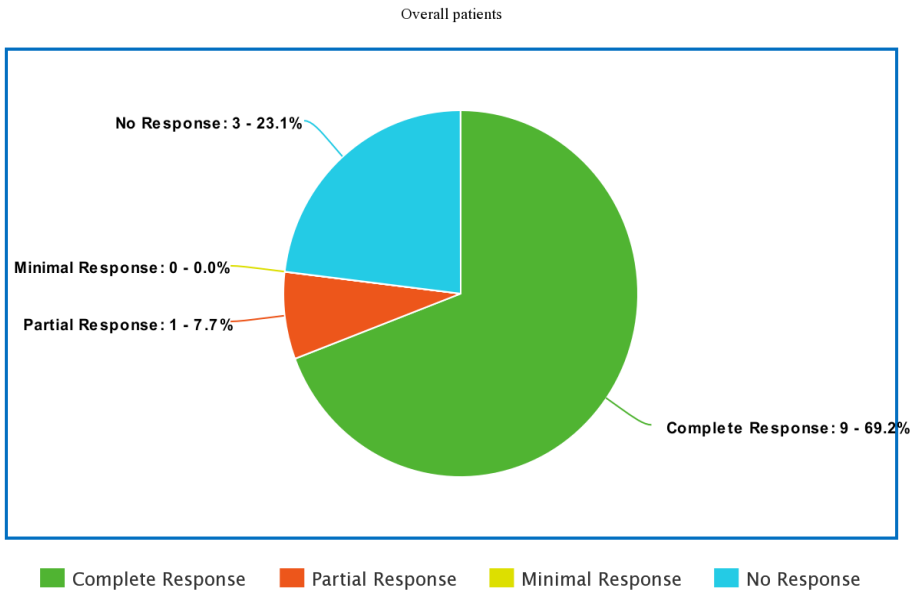


Figure 4. Response rate in prostate cancer patients

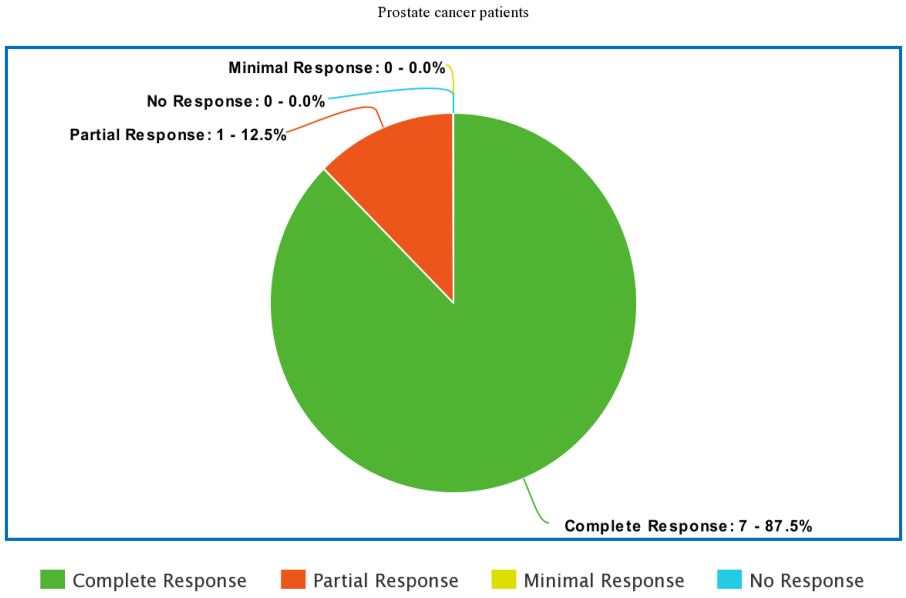


Figure 5. Response rate in breast cancer patients

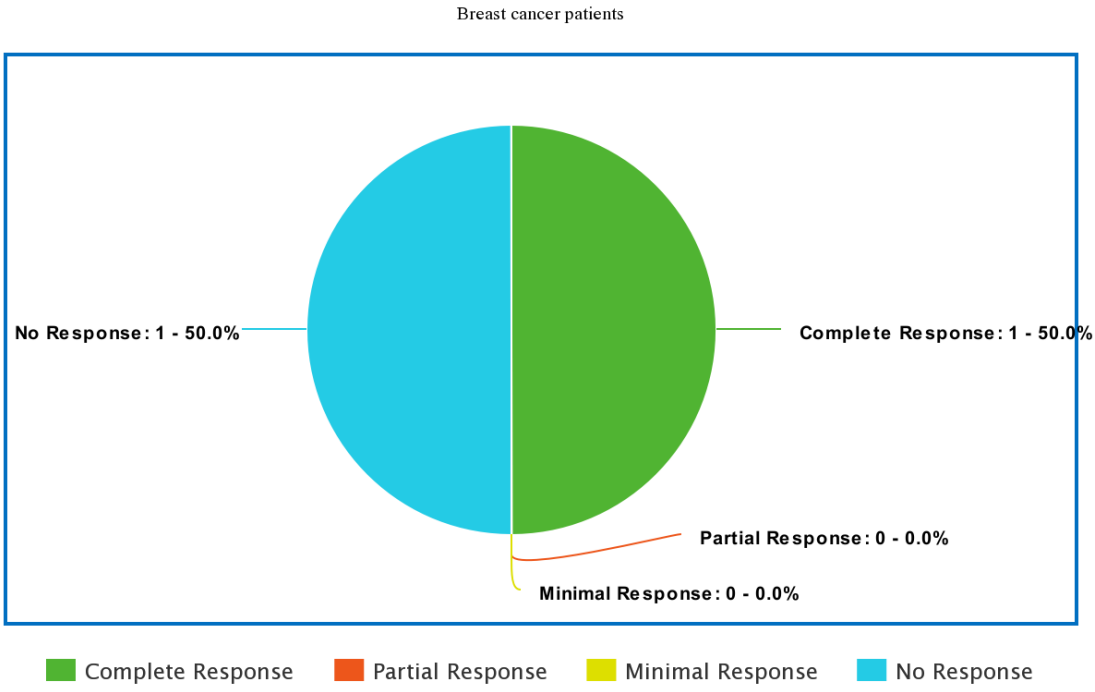


Figure 6. Response rate in lung cancer patients

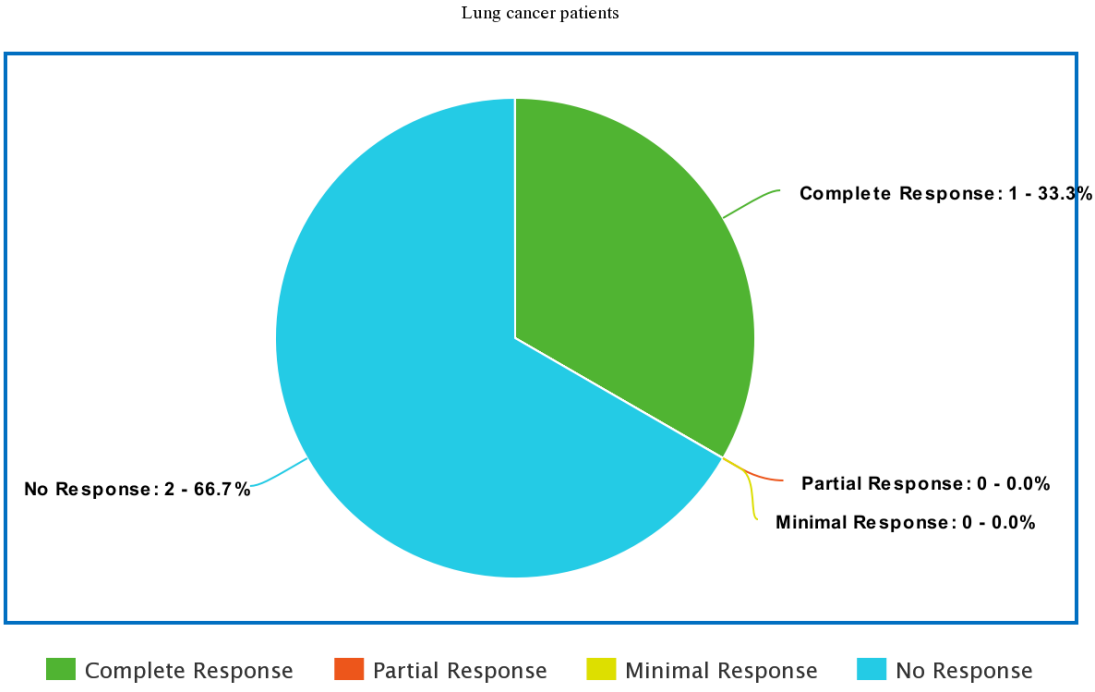
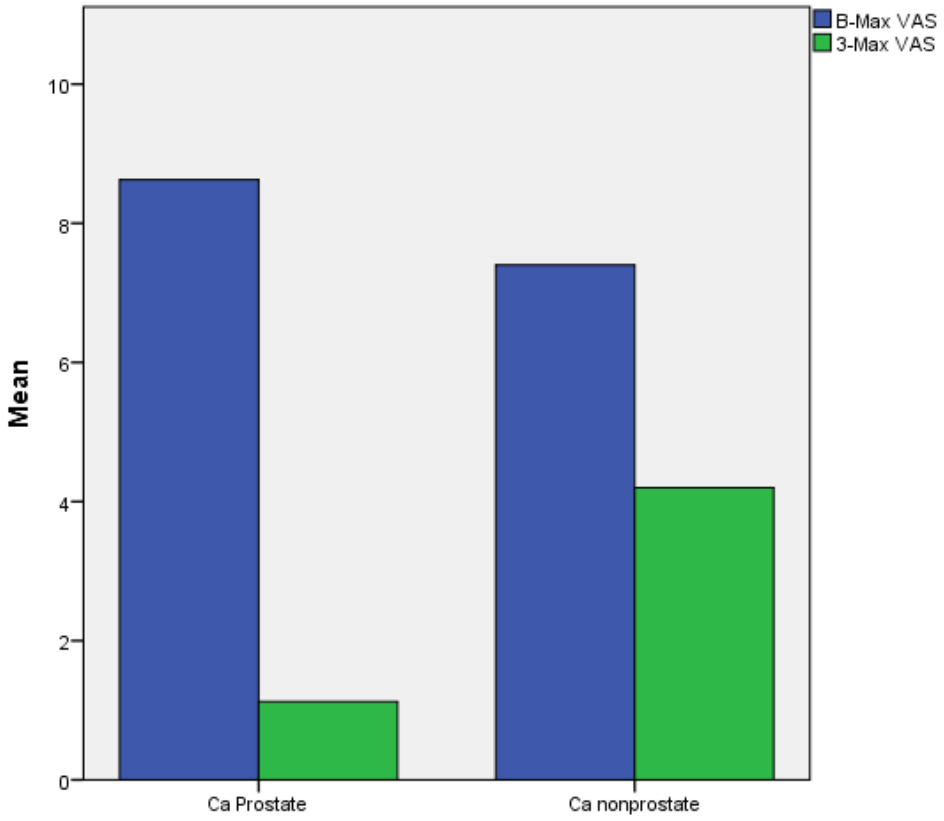


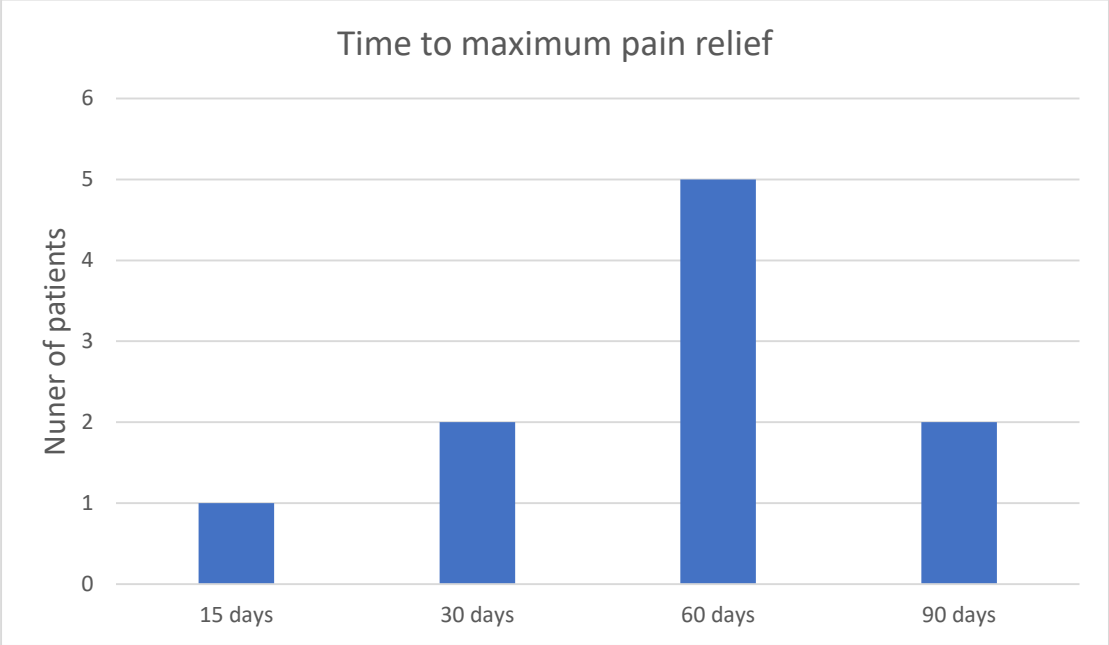
Figure 7. Decrease in mean VAS from baseline to 3 months in prostate cancer versus other cancers



Time to maximum pain relief:

The maximum pain relief was achieved at 15 days in 1 patient (10%), 30 days in 2 patients (20%), at 60 days in 5 patients (50%) and at 90 days in 2 patients (20%). The median being 60 days (Figure 8).

Figure 8. Time to maximum pain relief



Haematological Toxicity:

The haematological parameters including mean haemoglobin, WBC and platelets decreased significantly from baseline post administration of ^{177}Lu-EDTMP (Table 17, 18 & 19). However, statistically significant difference from the previous value was seen for haemoglobin and WBC at 15 days' follow-up (p=0.012, p=0.013). For platelet counts statistically significant decline from previous value was seen at each follow-up at 15 days and subsequently at 1,2 and 3 months. According to Common Terminology Criteria for Adverse Events (CTCAE) grading, 2/13 patients had grade III anaemia, 3/13 had grade II anaemia and 3/13 patients experienced grade I anaemia. 3/13 patients had grade I leukopenia, while 1/13 experienced grade II leukopenia. 4/13 patients had grade I thrombocytopenia while 1/13 patient experienced grade II thrombocytopenia. None of the patient developed life threatening complications or required blood transfusion. Different haematological toxicities experienced by the patients are categorised according to CTCAE in table 20.

Table 17. Decrease in mean Haemoglobin from baseline in follow-up:

Time period	Haemoglobin, mean + SD	p-Value
Baseline	11.85 + 1.52	
15 days	10.85 + 1.28	0.012
1 Month	10.54 + 1.33	0.001
2 Month	10.31 + 1.97	0.004
3 Month	10.08 + 1.71	0.005

Table 18. Decrease in mean WBC from baseline in follow-up:

Time period	WBC, mean + SD	p-Value
Baseline	8750.00 + 2788.26	
15 days	6084.62 + 2147.33	0.013
1 Month	5486.92 + 1634.02	<0.001
2 Month	6188.31 + 2350.42	0.022
3 Month	5680.77 + 1872.48	0.004

Table 19. Decrease in mean platelet counts from baseline in follow-up:

Time period	Platelet mean $\pm$ SD	p-Value
Baseline	324846.15 $\pm$ 136531.34	
15 days	233692.31 $\pm$ 85490.14	0.003
1 Month	190569.23 $\pm$ 86210.860	0.002
2 Month	24884.62 $\pm$ 121897.18	0.037
3 Month	213692.31 $\pm$ 118269.03	0.002

Table 20. CTCAE grading of Haematological toxicities in all patients:

CTCAE grade:	Anaemia	Leukopenia	Thrombocytopenia
Grade I	3	3	4
Grade II	3	1	1
Grade III	2	0	0
Grade IV	0	0	0
Total	8	4	5

Inter group analysis between group A (High dose, 1 mci/kg) and group B (Low dose, 0.5 mCi/kg):

The mean age of patients in group A was 62.17 ± 8.88 years and Group B was 54.43 ± 15.56 years. The mean VAS at baseline of Group A and Group B was 8.33 ± 1.03 and 8.00 ± 1.52, respectively. The median latency duration from initial diagnosis of skeletal metastases to treatment for bone pain palliation was 25 (4-72) months for Group A and 15 (6-23) months for Group B. There was no significant difference in pre-therapy variables between the two groups. The pre-therapy characteristics between the two groups are illustrated in Table 21.

Pain Relief:

There was progressive decrease in mean VAS score from baseline at each point time of follow-up. The mean VAS score came down from 8.33 ± 1.03 at baseline to 1.50 ± 2.51 at 3 months (p=0.002) in group A, while it came down from 8.00 ± 1.52 at baseline to 3.00 ± 3.41 at 3 months (p=0.006) in group B. However, there was no statistically significant difference in mean VAS between the two groups at any point of follow-up (Table 22, Figure 9). Similarly, the mean AS came down from 3.33 ± 0.82 in baseline to 1.17 ± 1.33 at 3 months (p=0.010) in group A, while it came down from 3.29 ± 0.76 at baseline to 2.00 ± 1.91 at 3 months (p=0.049) in group B (Table 23, Figure 10). However, there was no statistically significant difference in mean AS between the two groups at any point of follow-up. The percentage change in VAS score at 15 days, 30 days, 60 days and 90 days, in group A was 38%, 56%,72% and 81% respectively, while in group B was 45%, 47%, 63% and 65% respectively (Figure 11). There was no significant difference between the two groups.

Table 21. Pre-therapy characteristics between Group A and Group B:

Variable	Group A (1mCi/kg, high dose)	Group B (0.5mCi/kg, low dose)	P-value
Patients, *n*	6	7	0.906
Primary (Prostate/breast/lung), *n*	5/1/0	3/1/3	0.179
Age (years)	62.17 ± 8.88	54.43 ± 15.56	0.29
Bone lesion Score, mean±SD	13.167 ± 4.53	12.143 ± 3.43	0.453
Latency time from diagnosis (months), median (range)	25 (4-72)	15 (6-23)	0.201
Radiotherapy (yes/no), *n*	2/4	5/2	0.17
Chemotherapy (yes/no), *n*	5/1	5/2	0.612
Hormonal therapy (yes/no), *n*	5/1	2/5	0.048
Baseline Visual Analogue Score (VAS), mean ± SD	8.33 ± 1.03	8.00 ± 1.52	0.651
Baseline Analgesic score (AS), mean ± SD	3.33 ± 0.82	3.29 ± 0.76	0.916
Baseline ECOG, median (range)	1 (1-2)	1 (1-3)	1
Baseline Karnofsky performance score (KFS), median (range)	80 (60-80)	80 (50-90)	1
Haemoglobin (g/dL), mean ± SD	11.83 ± 1.83	11.86 ± 1.34	0.979

Table 22. Change in mean VAS between Group A and Group B:

Time period	Group A (1mCi/kg) VAS, mean + SD	Group B (0.5mCi/kg) VAS, mean + SD	p-Value
Baseline	8.33 + 1.03	8.00 + 1.52	0.715
15 days	5.17 + 2.23	4.57 + 3.78	0.733
1 Month	3.67 + 2.80	4.57 + 2.99	0.585
2 Month	2.33 + 2.94	3.29 + 3.86	0.624
3 Month	1.50 + 2.51	3.00 + 3.41	0.383

Figure 9. Change in mean VAS between Group A and Group B

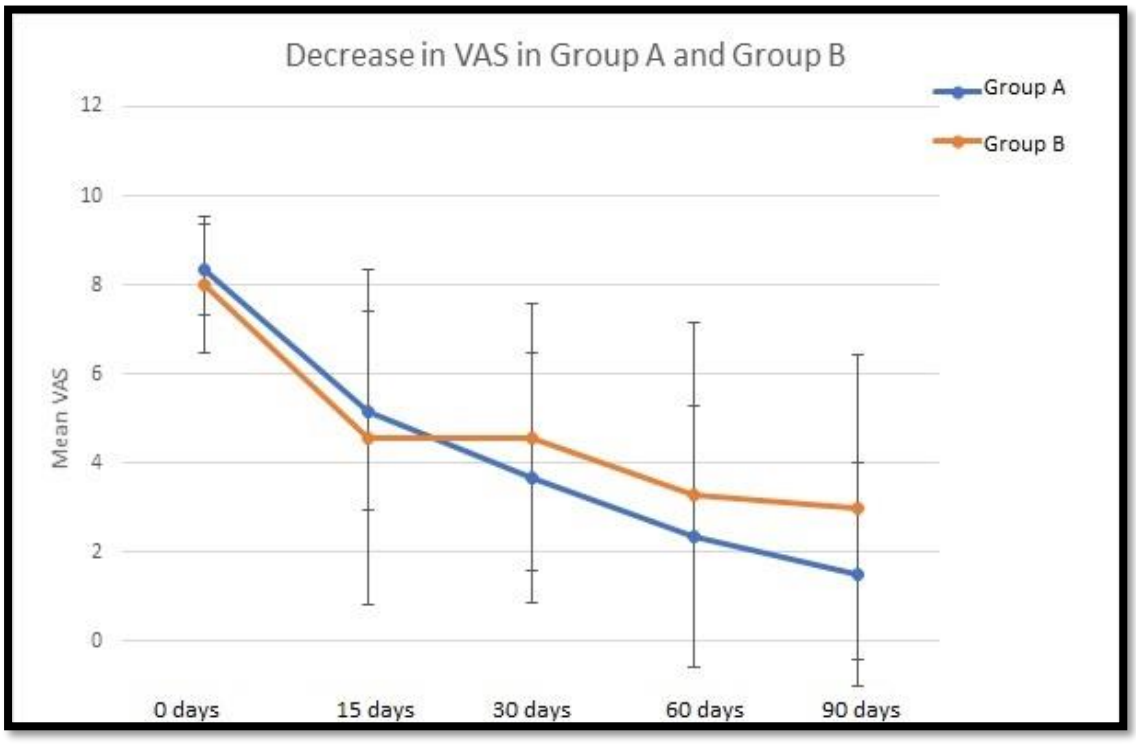


Table 23. Change in mean AS between Group A and Group B:

Time period	Group A (1mCi/kg) AS, mean ± SD	Group B (0.5mCi/kg) AS, mean ± SD	p-Value
Baseline	3.33 ± 0.82	3.29 ± 0.76	0.916
15 days	2.00 ± 1.41	2.29 ± 1.70	0.747
1 Month	1.83 ± 1.17	2.43 ± 1.51	0.441
2 Month	1.33 ± 1.21	2.00 ± 1.91	0.464
3 Month	1.17 ± 1.33	2.00 ± 1.91	0.377

Figure 10: Change in mean AS between Group A and Group B

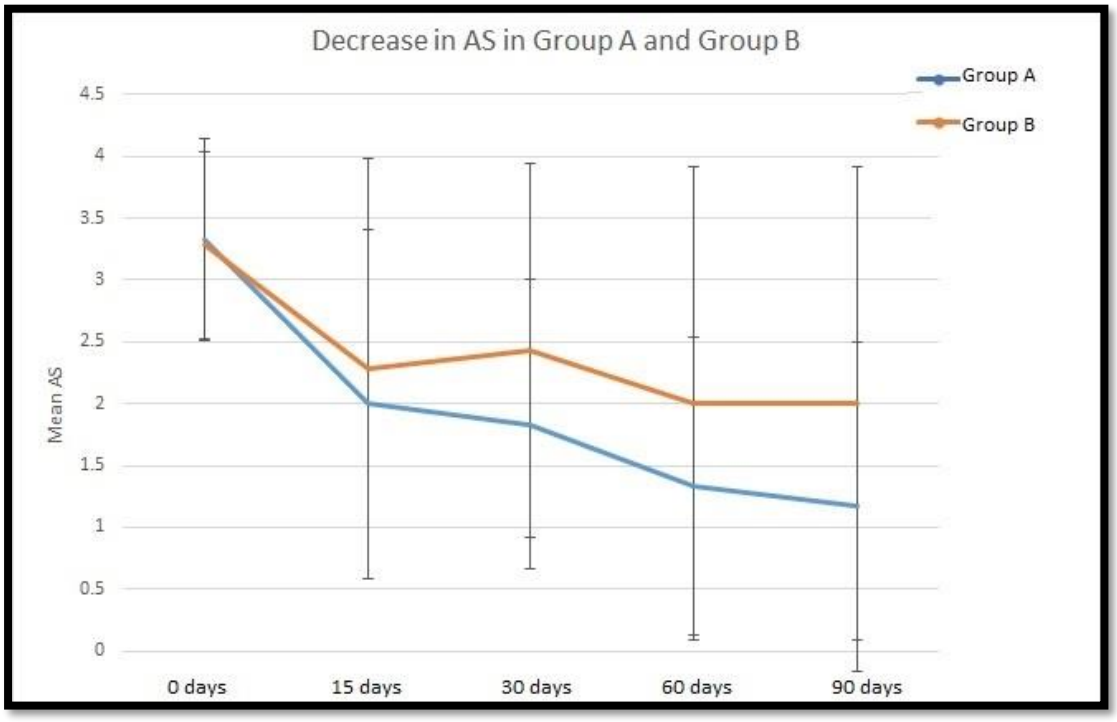
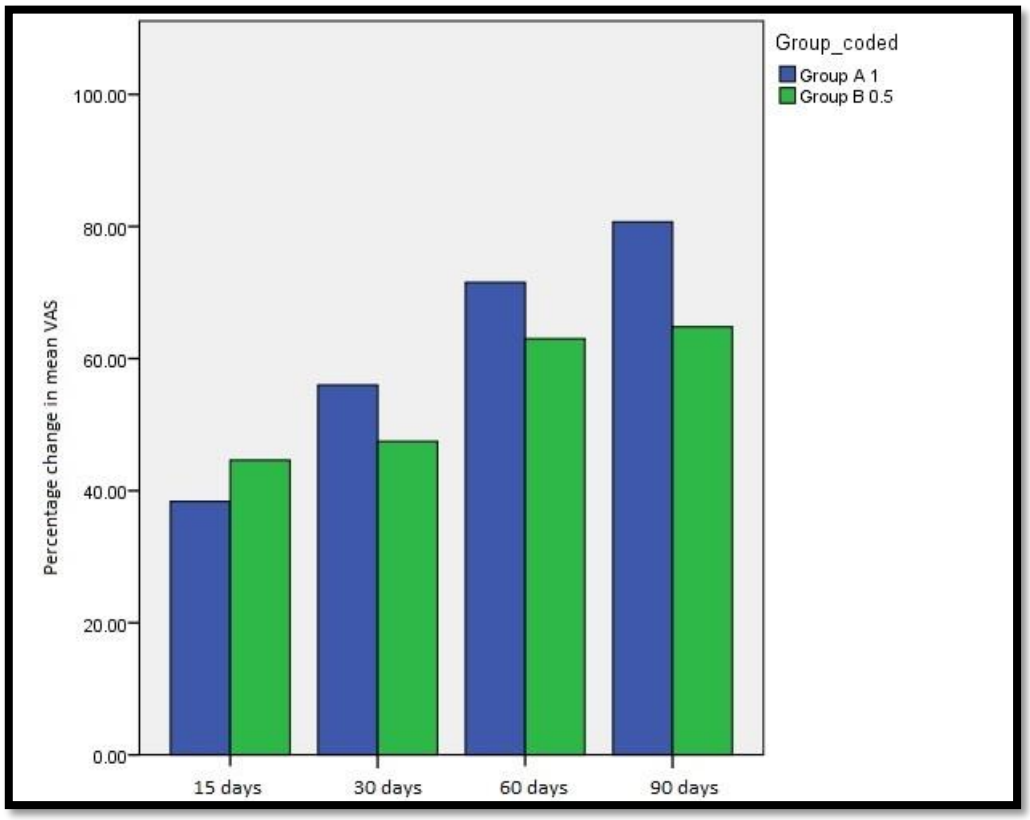


Figure 11. Percentage change in VAS between group A and Group B.



Quality of life assessment:

Both ECOG and KPS did not have Gaussian distribution and therefore there median were calculated and compared. There was improvement in Quality of life in most of the patients responding to the therapy in both the groups. However, there was no statistically significant difference between the groups (Table 24 & 25).

Table 24. Change in KPS between Group A and Group B:

Time period	Group A (1mCi/kg) KPS, median (Range)	Group B (0.5mCi/kg) KPS, median (Range)	p-Value
Baseline	80 (60-80)	80 (50-90)	1.00
15 days	70 (60-100)	80 (50-90)	0.559
1 Month	75 (60-100)	80 (60-90)	0.559
2 Month	85 (60-100)	80 (60-100)	0.592
3 Month	85 (50-100)	80 (60-100)	0.592

Table 25. Change in ECOG between Group A and Group B:

Time period	Group A (1mCi/kg) ECOG, median (Range)	Group B (0.5mCi/kg) ECOG, median (Range)	p-Value
Baseline	1 (1-2)	1 (1-3)	1.00
15 days	1.5 (1-2)	1 (1-3)	1.00
1 Month	1.5 (1-2)	1 (1-2)	0.592
2 Month	1 (1-2)	1 (1-2)	0.559
3 Month	1 (1-3)	1 (1-2)	0.559

Overall Response rates:

Overall response rate in group A was 83.33%. 1/6 patient had no response and 5/6 patients showed complete response (Figure 12). Overall response rate in group B was 71.42%. 2/7 (28.57%) had no response, 1/7 (14.28%) patient had partial response and 4/7 (57.14%) patients had complete response (Figure 13). There was no statistically significant difference between overall response rates in two groups (p=0.503). The mean percentage decrease in VAS score from baseline at 12 weeks follow-up was 80.71% + 34.68% for group A, and for group B it was 64.80% $\pm$ 40.38%. The percentage decrease was comparable between the two groups (p=0.461).

Figure 12. Response rate in Group A (high dose) patients:

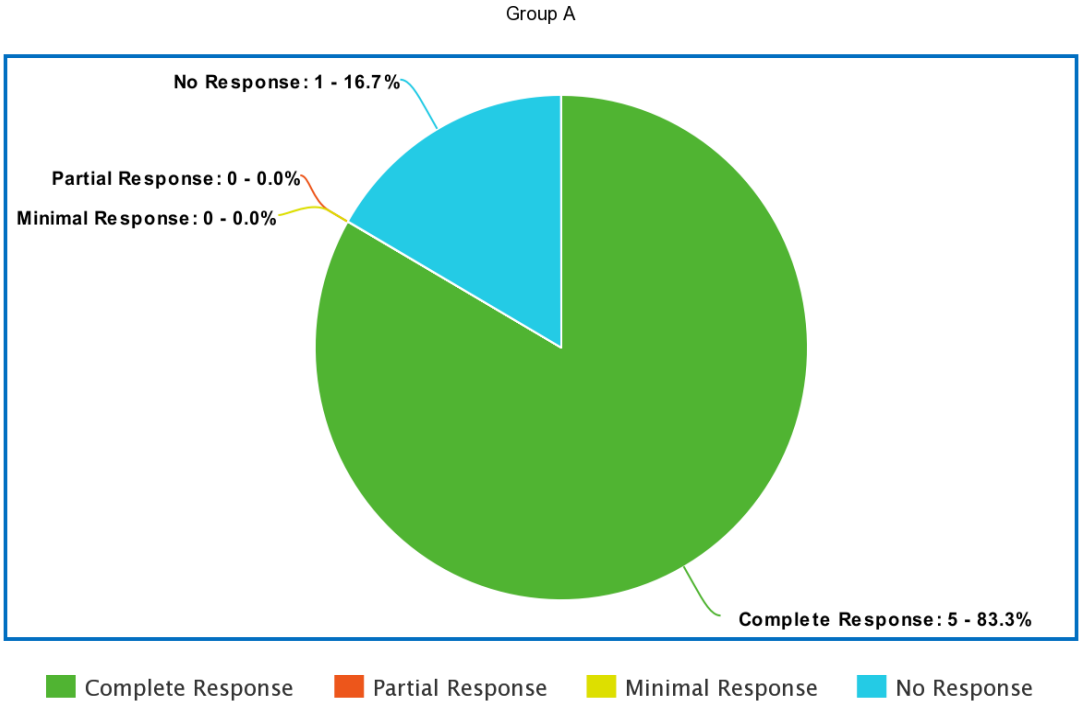


Figure 13. Response rate in Group B (low dose) patients:

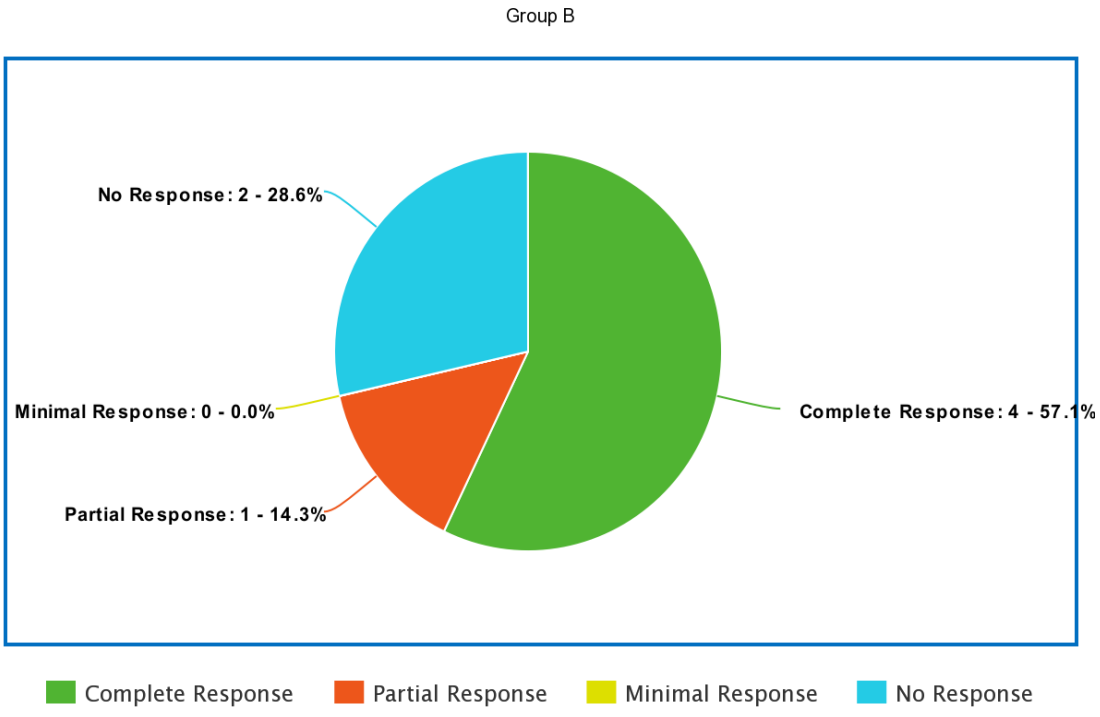
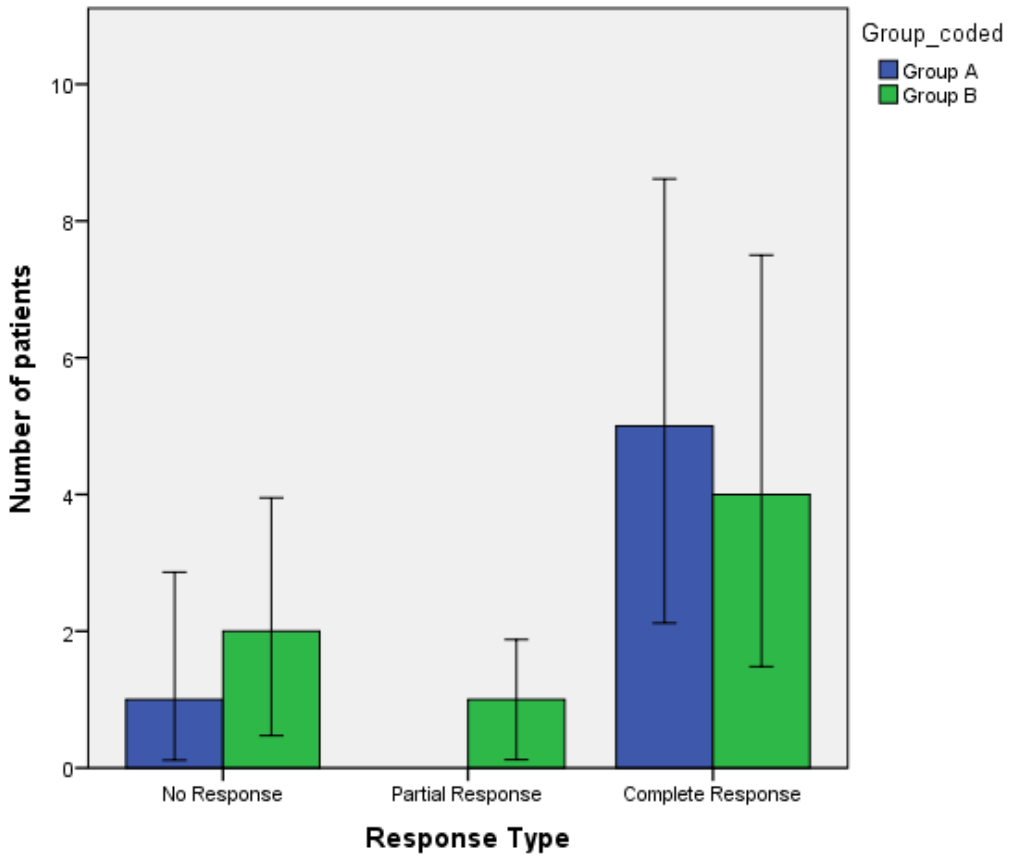


Figure 14. Response rates between Group A and Group B



Time to maximum pain relief:

In group A, median time to achieve maximum pain relief was 60 days (30-90 days) and in group B, median time to achieve maximum pain relief was 60 days (15-60 days). The time to maximum pain relief was comparable between the two groups (p=0.444). None of the patients who responded to the therapy had any recurrence in pain during the follow-up period of 12 weeks.

Haematological Toxicity:

The haematological parameters including haemoglobin, WBC and platelets decreased from the baseline in both the groups. The lowest value of haemoglobin in Group A was reached at 1 month after which it started normalising, however the fall in haemoglobin was slow and comparatively less in the Group B, the lowest values were reached at 3 months. However, there was no statistically significant difference in the values between

Group A and Group B at any point time of follow-up (Table 26, 27 and 28) (Figure 15, 16 and 17).

There lowest value of WBC was reached at 1 month in both the groups. Also, there was no statistically significant difference in WBC values between Group A and Group B at any point time of follow-up.

There was significant decline in the platelet counts in both the groups, the lowest value was reached at 1 month in both the groups. The decline in platelet values was more in Group A than Group B and the difference between Group A and Group B values was significant at 15 days and 2 months.

According to CTCAE grading, in group A, 1/6 patients had grade III anaemia, 2/6 had grade II anaemia and 1/6 patients experienced grade I anaemia. 1/6 patients had grade II leukopenia, while 2/6 experienced grade I leukopenia. 1/6 patients had grade II thrombocytopenia while 2/6 patient experienced grade I thrombocytopenia. None of the patient developed life threatening complications or required blood transfusion.

Similarly, in group B, 1/7 patients had grade III anaemia, 1/7 had grade II anaemia and 2/7 patients experienced grade I anaemia. 1/7 experienced grade I leukopenia. 1/6 patients had grade II thrombocytopenia while 2/6 patient experienced grade I thrombocytopenia. None of the patient developed life threatening complications or required blood transfusion. The haematological toxicities were comparable in both the groups (Table 29 and 30).

Table 26. Change in mean Haemoglobin between Group A and Group B:

Time period	Group A (1mCi/kg) Haemoglobin, mean ± SD	Group B (0.5mCi/kg) Haemoglobin, mean ± SD	p-value
Baseline	11.83 ± 1.83	11.86 ± 1.34	0.980
15 days	10.33 ± 1.37	11.29 ± 1.11	0.204
1 Month	9.83 ± 1.47	11.14 ± 0.90	0.094
2 Month	10.00 ± 1.41	10.57 ± 2.44	0.611
3 Month	10.50 ± 1.64	9.71 ± 1.79	0.428

Figure 15. Change in mean Haemoglobin between Group A and Group B:

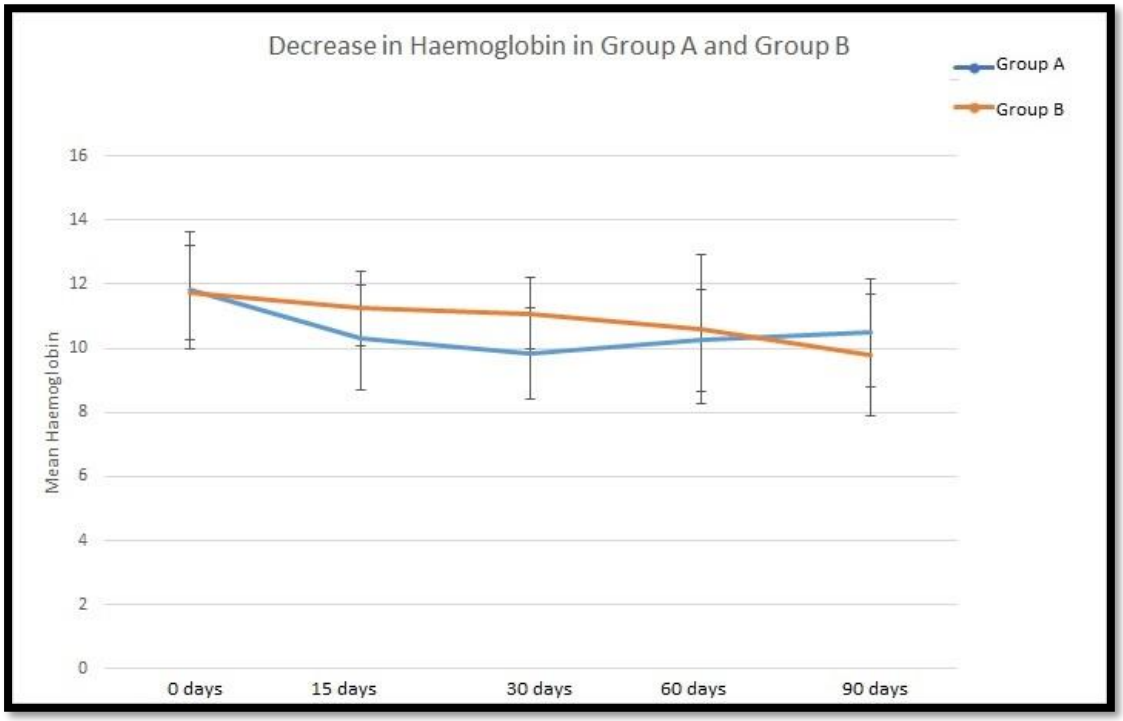


Table 27. Change in mean WBC between Group A and Group B:

Time period	Group A (1.0mCi/kg) WBC, mean + SD	Group B (0.5mCi/kg) WBC, mean + SD	p-value
Baseline	8928.33 + 3218.93	8597.14 + 2618.24	0.841
15 days	5236.67 + 2122.16	6811.43 + 2033.18	0.202
1 Month	5248.33 + 1410.78	5691.43 + 1890.96	0.639
2 Month	5231.67 + 1623.06	7008.29 + 2674.71	0.172
3 Month	5640.00 + 1895.53	5715.71 + 2024.71	0.946

Figure 16. Change in mean WBC between Group A and Group B:

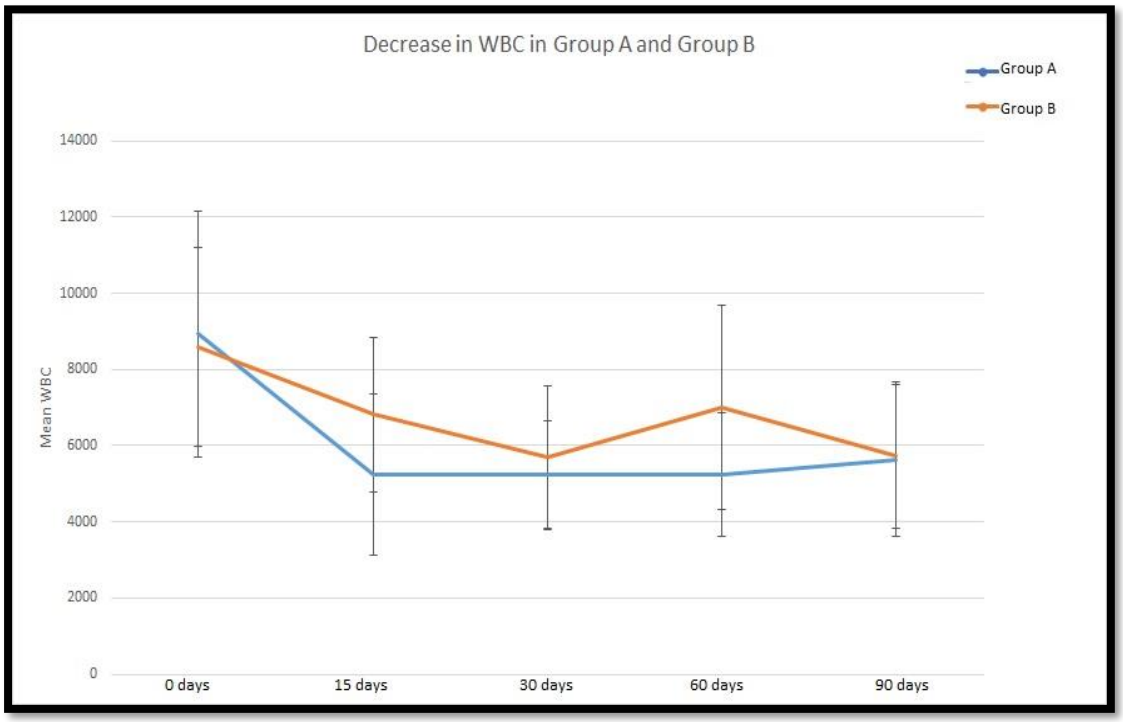


Table 28. Change in mean Platelet between Group A and Group B:

Time period	Group A (1mCi/kg) Platelets, mean + SD	Group B (0.5mCi/kg) Platelet, mean + SD	p-value
Baseline	261833.33 + 78468.890	378857.14 + 157405.45	0.117
15 days	180166.67 + 68531.50	279571.43 + 73366.33	0.028
1 Month	145566.67 + 74213.25	229142.86 + 80708.17	0.078
2 Month	177583.33 + 99687.72	310000.00 + 109521.68	0.044
3 Month	152833.33 + 68271.27	265857.14 + 131196.32	0.077

Figure 17. Change in mean Platelet between Group A and Group B:

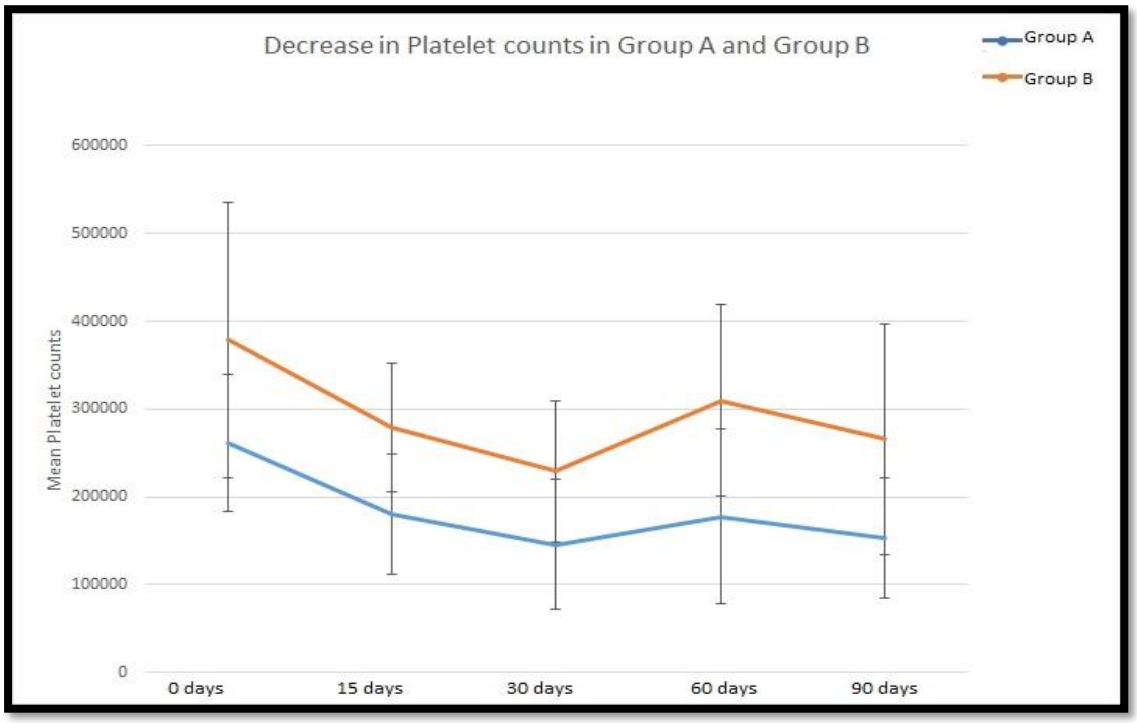


Table 29. CTCAE grading of Haematological toxicities between Group A and Group B:

	Group A				Group B				p-value
CTCAE grade:	Grade I	Grade II	Grade III	Grade IV	Grade I	Grade II	Grade III	Grade IV	
Anaemia	1	2	1	0	2	1	1	0	0.851
Leukopenia	2	1	0	0	1	0	0	0	0.321
Thrombocyto-penia	2	1	0	0	2	0	0	0	0.489

Table 30. Haematological toxicity in individual patients in Group A and Group B:

		Anaemia	Leukopenia	Thrombocytopenia
Group A	A1	Grade III		
	A2	Grade II	Grade II	
	A3	Grade I	Grade I	
	A4			Grade I
	A5	Grade II	Grade I	Grade II
	A6			Grade I
Group B	B1			
	B2	Grade I		
	B3	Grade III	Grade I	
	B4	Grade II		Grade I
	B5			
	B6	Grade I		Grade I
	B7			

DISCUSSION

Patients with cancer spread to bones usually presents with pain of intense severity. Most of them are on chronic pain medication, which not only adds to the economic burden of the patients but also have their unique toxicities affecting other organs of the body. Similarly, pain affects the quality of life in these patients and often it hinders the routine activities of self-care. Radionuclide therapy for bone pain palliation is considered as a potent alternative in patients with multiple sites of bone metastasis with bone pain.

The mechanism of bone pain palliation is less understood. However various theories have been proposed, accumulation of radionuclide in the pathological tissue leads to shrinkage of the metastatic tumour and thus decreasing the periosteal pain receptor stimulation(83). but the most accepted explanation include radiation induced decrease in pain related chemokine secretion and inhibition of osteoclasts(84).

Due to their reported high efficacy and less toxicities, radionuclide therapies are used in setting of metastatic bone pain. Radionuclides including, 89-Sr chloride, 186Re-HEDP and 153-Sm-EDTMP have been used for bone pain palliation resulting from osteoblastic metastatic bone cancer. 89-Sr is not readily available and therefore is not widely used. It also does not allow for post therapy imaging in the patients as it does not emit any gamma photon which can be used for imaging. The half-life of 153Sm-EDTMP and 186Re-HEDP are1.9 days and 3.7 days, respectively and maximal beta-energy of 0.81 MeV and 1.07 MeV, respectively. These properties pose challenges like increased radiation exposure to surrounding bone, short duration of exposure and transport to farther areas. Alpha therapy using 223-Ra, which is an osteomimetic radionuclide has shown decrease in tumor markers due to resolution of tumor along with decrease in pain in the setting of metastatic bone pain in patients of castration resistant prostate cancer. Studies have reported improvement in survival among the patients receiving 223-Ra(62),(61). 223-Radium being a pure alpha emitters, elicits cancer cell death through DNA DSBs, it also disrupts the function of both osteoblasts and osteoclasts cells, and thereby simultaneously breaks at least two links of the metastasis cycle(85).

^{177}Lu has a low electron energy, βmax 0.497 MeV, which ensures a low tissue penetration, thus ensuring minimal radiation exposure to surrounding tissue and

effectively less bone marrow suppression compared to other bone palliation radionuclides. ^{177}Lu is a β as well as γ emitter. γ ray emission allows post-therapy imaging as well as makes dosimetry possible (86).

^{177}Lu-EDTMP has a longer half-life 6.73 days and lower maximum electron energy, βmax 0.497 MeV. These properties add to the advantage of ^{177}Lu. The decrease in energy of electron results in lower range of ^{177}Lu electron (2 mm) in normal osseous tissue and bone marrow. And therefore possibly less irradiation of the normal surrounding bone marrow. Due to longer effective half-life ^{177}Lu-EDTMP irradiates tumor cells at a low dose rate, with a relatively low dose per cycle for a longer duration as compared to other radiopharmaceuticals with shorter half-life which deliver radiation at high dose rate. Another advantage of longer half-life, it provides the ability to deliver the radiopharmaceutical to farther locations from the reactor. Other advantages of ^{177}Lu-EDTMP, include the feasibility of large scale production and radionuclide purity can be determined using a moderate flux reactor that produces sufficiently high specific activity.

Imtiaz Ahmed Abbasi studied ^{177}Lu labelled methylene diphosphonates and found selective bone accumulation with relative low uptake in soft tissue and higher skeletal uptake(87). Sudipta Chakraborty et. al. studied ^{177}Lu-EDTMP and concluded that complex had excellent in vitro stability. There was accumulation of the activity in the skeleton with rapid blood clearance and insignificant retention of the activity in other vital organs(88).

1. Analysis of all patients

1.1 Overall Efficacy:

In our study the mean VAS of all patients came down from 7.2 $\pm$ 2.7 in baseline to 2.3 $\pm$ 2.8 at 12-week follow-up ($p<0.001$). Our results were consistent with the existing literature. In a study by Shinto et. al. the mean VAS score significantly came down from 8.4 $\pm$ 1 to 1.7 $\pm$ 0.44 ($p<0.001$) in 10 patients after administration of ^{177}Lu-EDTMP(72). Similarly, Bal et. al in a study reported fall in mean VAS score from 6.6 $\pm$ 2.4 in baseline to 3.6 $\pm$ 3.1 ($p<0.0001$)(78).

In this study, on overall analysis of all patients who received ^{177}Lu-EDTMP therapy, we found overall response of 76.9% while complete response was seen in 69.2% of all the patients. Our results on overall efficacy are consistent with the previously reported literature.

The response rate of various bone palliation radionuclides including, 89-Sr, 153-Sm-EDTMP, 186-Re-HEDP has been reported between 60% – 85% in various studies [(60), (63), (67),(69)]. In a comparative study of 153-Sm-EDTMP and ^{177}Lu-EDTMP, Sharma et. al. reported a response rate of 80% for both the pharmaceuticals(75). In a trial, Mehrosadat Alavi et. al. showed overall response of 96% with 72% patients showing complete response(76). In the only meta-analysis on ^{177}Lu-EDTMP, Emran Askari et. al. showed a pooled overall response of 84 % with 32 % patients showing complete response(77).

In different cancer type, our study showed 100% overall response in prostate cancer patients, 50% in breast cancer patients and 33% in lung cancer patients. Agarwal et al. showed overall response of 84% in patients of prostate cancer while it was 92% in patients of breast cancer. Similarly, the reduction in mean VAS score was comparable between both the cancer types(29). Carlo et. al. reviewed studies of 153-Sm-EDTMP in breast cancer patient and found response rate of 75-90%(89).

The reason for the difference in our study may be due to heterogeneous type of bone lesions seen in different cancer groups. Where most of the prostate cancer patients produce osteoblastic metastasis to bone, breast and lung cancer osseous metastasis is of mixed type. Also the number of patients of breast and lung cancer recruited in the study were significantly low. An analysis on subgroups of prostate versus non-prostate cancer we found that the mean VAS in patients with prostate cancer came down from 8.63+ 0.916 to 1.13+1.64. While in non-prostate cancer patients it came down from 7.4 + 1.51 to 4.2 +3.99. There was no statistically significant difference between them ($p = 0.07$).

The mean bone lesion score for responders was 15.33 ± 2.08 while it was 11.8 ± 3.93 in the non-responders which was comparable among both the groups ($p=0.081$) and hence the probability of response was not dependent on the baseline number of osteoblastic lesions in the patients. Previous treatment like radiotherapy and chemotherapy did not show any effect on the outcome. Seven out of ten responders had

received hormonal therapy while none of the non-responders had received hormonal therapy (p=0.03).

1.2 Analgesic score:

In our study the mean AS came down from 3.3 in baseline to 1.62 at 12-week follow-up (p<0.001). Analgesic scores have been calculated using different methodology in different studies on pain palliation. In the study of Agrawal et. al. the AS decreased from 1.8 to 1.2 (p<0.0001) among the responders(29).

1.3 Quality of life index:

Various studies have used different performance scales for evaluation of improvement in quality of life due to reduction in pain among the patients. KPS and ECOG scores were used in our study. In our study, there was improvement in performance score in patients who responded to treatment however no statistically significant change could be noted. Shinto et. al. reported significant increase in mean KPS of patients after administration of ^{177}Lu-EDTMP from 45 in baseline to 69 in follow-up (72). In a study by Tripathi et. al. on 153-Sm-EDTMP, the mean KPS increased from 70 .83 in baseline to 79.16 in follow-up(90).

The reason for the difference in findings of our study was that most of the patients recruited had baseline scores close to normal (Median KPS 80 and Median ECOG 1) and therefore no much difference was seen between the baseline value and the subsequent follow-up values. Also the total number of patients recruited were less, so the data on ECOG and KPS score did not follow normal distribution.

1.4 Onset and duration of pain relief:

In our study most of the patients had onset of pain relief by 15 days and maximum pain relief was achieved in about 60 days. None of the patient who responded to treatment had a relapse in pain during the entire follow-up period of 12 weeks. A longer follow up of these patients can unfold the exact time of relapse of pain following therapy. The results of our study showed results similar to other studies on ^{177}Lu-EDTMP.

Thapa et. al. reported that effect of on ^{177}Lu-EDTMP and on ^{153}Sm-EDTMP developed gradually and peaked and plateaued at around 6-8 weeks and lasted for around 3-15

months(74). Agrawal et. al in their study on ^{177}Lu-EDTMP noted that response was seen by 8 days in some patients and it lasted for 2-4 months(29).

Yuan et. al. reported a response duration of about 4 months in their study with ^{177}Lu-EDTMP(73). Studies using other radionuclide for bone pain palliation have reported varied range of duration of pain palliation from 2 weeks to 9 months[(91),(92),(93)].

1.5 Haematological toxicities:

The major limiting factor in therapy using bone-seeking radiopharmaceuticals is bone marrow toxicity leading to significant bone marrow suppression and thereby decrease in the peripheral blood counts. All previous studies have reported decrease in haematological parameters after giving different radionuclide therapy for bone pain palliation.

In our study, 10 events of CTCAE grade I haematological toxicity were observed, among which 3 were Grade I anaemia, 3 were Grade I leukopenia and 4 were grade I thrombocytopenia. 5 events of CTCAE grade II haematological toxicity were seen, among which 3 were grade II anaemia, 1 was grade II leukopenia and 1 was grade II thrombocytopenia. 2 events of CTCAE grade III haematological toxicity were seen, both of which were grade III anaemia. Overall 5 patients (38.5%) showed grade I haematological toxicity, 3 patients (23%) showed grade II haematological toxicity and 2 patients (15.4%) showed grade III haematological toxicity. None of the patients experienced any serious toxicity. There was decrease in mean haemoglobin, leukocytes and platelets from baseline in most of the follow-up visit. The percentage decrease from baseline was significant for platelets in most of the follow-up visits up to 12 weeks.

Other studies have reported similar haematological toxicity rates. In a study by Dolezal et. al. using ^{153}Sm-EDTMP in 32 patients, none of the patient had grade IV hematologic toxicity, 2 patients (6.25%) showed grade III toxicity and most of the patient showed grade I or grade II haematological toxicity(94).

In the study by Thapa et. al. nonserious hematologic toxicity (grade I/II) was observed in 53.33% patients and serious toxicity (grade III/IV) in 26.67% patients in patients administered ^{177}Lu-EDTMP. While in patients receiving ^{153}Sm-EDTMP, nonserious hematologic toxicity (grade I/II) was observed in 10 (62.5%) and serious toxicity (grade

III/IV) in 3 (18.75%)(74). In a study by Agarwal et al., nonserious hematologic toxicity (grade I/II) occurred in 34% patients and serious toxicity (grade III/IV) in 23% patients(29).

2. Inter-group analysis:

2.1 Efficacy:

In our study, overall response rate in group A was 83.33%, among them complete response was noted in 83% patients and 17% had no response. While, overall response rate in group B was 71%, among which complete response was seen in 57% patients, patients, partial response in 14% and no response in 29% patients. The mean VAS score came down from 8.33 at baseline to 1.50 (p=0.002) in group A, while it came down from 8.00 at baseline to 3.00 (p=0.006) in group B. The response rate and decline in VAS were comparable in both groups.

Similar results are reported in other studies. Yuan et. al. in a study comparing outcomes with different dose of ^{177}Lu-EDTMP, divided patients to receive either 1290.00 MBq in low dose group-1 patients(n=11) and 2626.4 MBq in high dose group-2 patients (n=5). Complete Response in bone pain palliation was noted in 55% of patients in group 1 and 80% of patients in group 2. No significant difference in efficacy were noted between the two groups(73).

Similarly, Agrawal et. al. in a study comparing outcomes with different dose of ^{177}Lu-EDTMP, divided patients to receive either 1295 MBq in low dose Group-A (22 patients) and 2590 MBq in high dose Group-B (22 patients). Overall response rate in group A was 77% as compared to 95 % in group B. Complete response was seen in 9% patients in group A and 18% patients in group B. The VAS decreased from 6.5 to 3.8 in group A and from 7.0 to 3.3 in group B. The outcomes and decrease in VAS was comparable between the two groups at each point time of follow-up(29).

2.2 Analgesic score:

In our study, the mean AS came down from 3.33 in baseline to 1.17 (p=0.010) in group A (high dose), while it came down from 3.29 at baseline to 2.00 in group B (low dose). The change in VAS was comparable between the two groups at each point of follow-up. Our study results were consistent with the results of study by Agrawal et. al. in

which the analgesic score decreased from 1.7 to 1.1 in group A (low dose), while it changed from 1.9 to 1.3 in group B (high dose). The percentage change between group A and group B was comparable.

2.3 Quality of life outcomes:

In our study, we found improvement in KPS and ECOG score with decrease in pain relief in both high dose and low dose groups with no statistically significant difference between them. Similarly, in Yuan et. al. study, mean (SD) Karnofsky indices increased from 58.18 (9.82) and 56.00 (8.94) at baseline to 82.73 (9.05) at 6 weeks in group 1(low dose), and 85.00 (5.77) at 8 weeks in group 2(high dose), respectively. There KPS outcome in both the groups were comparable(73). Study by Agrawal et. al. demonstrated increase in KPS from a baseline score of 56 to 73 in group A (low dose) and from a baseline score of 57 to 76 in group B (high dose). There was no statistical difference between the two groups (29).

2.4 Onset and duration of pain relief:

Median time to achieve maximum relief in pain was 60 days (30-90 days) for group A (high dose) patients and 60 days (15-60 days) in group B (low dose) patients, with no significant difference between the two group. There was no relapse in pain up to 3-month follow-up in patients who responded to therapy in both the groups till 12-week follow-up.

2.5 Haematological toxicities:

In our study, grade III haematological toxicities was seen in 2 patients, one in each group. Grade II haematological toxicity was noted in 5 patients, 4 in high dose group and 1 in low dose group. And grade I toxicity was noted in 10 patients, 5 in high dose group and 5 in low dose group. There was no statistically significant difference between the two groups. There was decrease in haemoglobin, leucocytes and platelet counts in both the groups. There was no difference in values at any point of follow-up of haemoglobin and leucocytes between high dose group and low dose group. However, we found significant difference between the values of platelet counts at 15 days and 2-month follow-up ($p=0.028$, $p=0.044$, respectively). High dose group showed greater decrease in platelet counts as compared to low dose group.

Similarly, Yuan et. al. in their study found Grade I, II & III platelet toxicity in 1,3 & 1 patient in group 1(low dose) and in 4,0 & 0 patient in group 2(high dose) respectively. There was no significant difference in reduced blood counts between high and low dose groups(73). In study by Agrawal et. al. grade III/IV haematological toxicity was seen in 10 patients (23 %): 6 (27%) in high dose group and 4 (18%) in low dose group. There was no statistically significant difference in haematological toxicity between the groups(29).

CONCLUSION

This study concludes that use of ^{177}Lu-EDTMP as a systemic radionuclide therapy for pain palliation in patients with metastatic bone pain is a safe, effective and feasible alternative to conventional therapy options and other radiopharmaceuticals for pain palliation. It is an easy to administer, simple OPD based therapy and a single dose provides good pain palliation. It is also well tolerated by the patients.

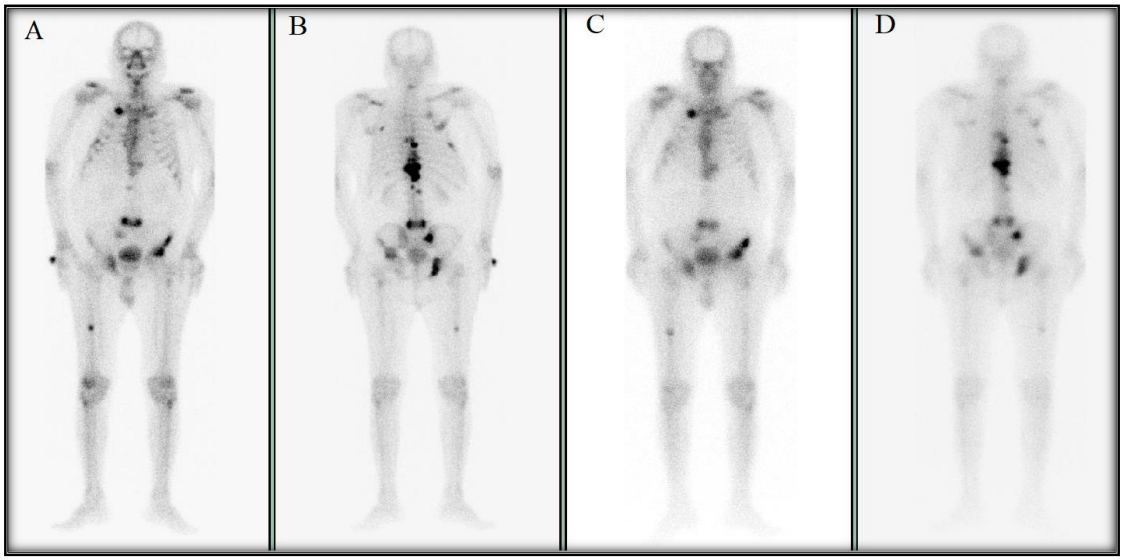
In the limited number of patients, we found low-dose (0.5mCi/kg) therapy is as effective as high-dose (1mCi/kg) for reducing the pain. The platelet toxicity with low dose therapy is also comparatively less as compared to high dose therapy and is transient. Low dose therapy would provide lower radiation exposure to the patient & personnel and is more economical as well.

We therefore conclude that low dose 177Lu-EDTMP therapy (0.5mCi/kg) may be preferred in the patients.

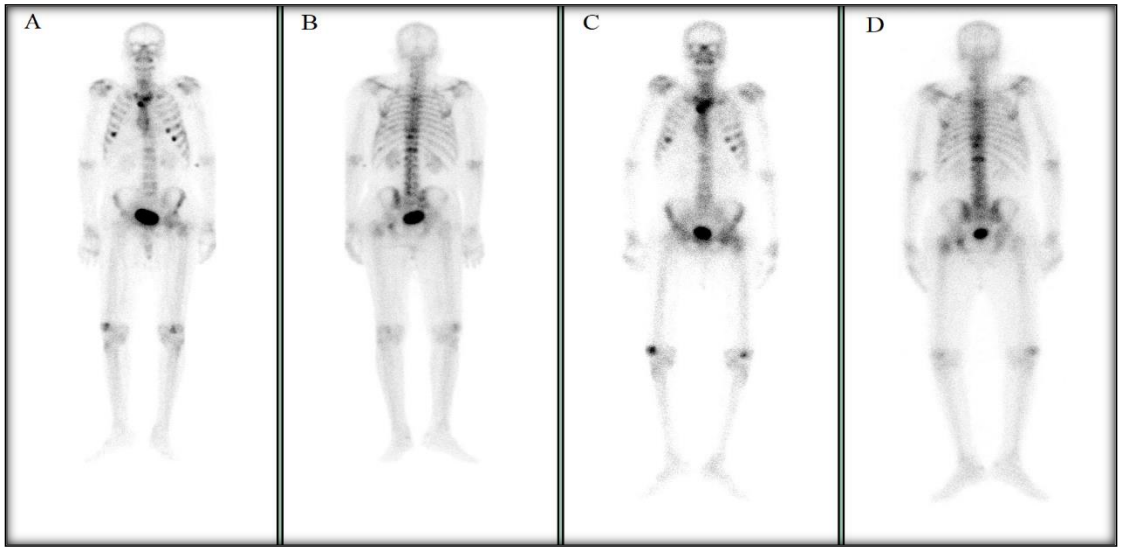
LIMITATIONS OF THE STUDY

Our study is limited by a small sample size, which may be attributed to the covid pandemic. Secondly, most of our patients were of prostate cancer. Other types of cancer were few in number. A data with equal number of different cancer types would have helped in better commenting the response in each cancer. Additionally, long term follow-up of the patients was not available, considering the limited time period of study and thus survival curves could not be derived.

COLOUR PLATES



Colour plate 1. 73 years/Male, K/c/o carcinoma prostate (GS – 5+3 = 8) with complains of bone pain in back and pelvis. A & B, anterior and posterior images of bone scan, 3 hours post injection of 99m-Tc-MDP show increased radiotracer uptake in few bilateral ribs, lower thoracic vertebrae, lumbar vertebrae, sacrum, pelvic bone and shaft of right femur. C & D, anterior and posterior post therapy images, acquired 4 hours post ^{177}Lu-EDTMP administration show increased radiotracer accumulation in the sites corresponding to metastasis on bone scan.



Colour plate 2. 72 years/Male, K/c/o carcinoma prostate (GS – 5+4 = 9) with complains of bone pain in back and sternum. A & B, anterior and posterior images of bone scan, 3 hours post injection of 99m-Tc-MDP show increased radiotracer uptake in sternum, few bilateral ribs, upper & lower thoracic vertebrae, lumbar vertebrae and pelvic bone. C & D, anterior and posterior post therapy images, acquired 4 hours post ^{177}Lu-EDTMP administration show increased radiotracer accumulation in the sites corresponding to metastasis on bone scan.

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Annexure 1

ETHICAL CLEARANCE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2021/2497 **Date: 12/03/2021**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2021/3332**

Project title: **"Comparison of low vs high dose ^{177}Lu-EDTMP therapy for palliation of painful bone metastases: RCT"**

Nature of Project:	**Research Project Submitted for Expedited Review**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr. Rakesh Pandey**
Guide:	**Dr. Rajesh Kumar**
Co-Guide:	**Dr. Arun Prashanth K & Dr. Sameer Taywade**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.
- In case of any issue related to compensation, the responsibility lies with the Investigator and Co-Investigators.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member secretary
Institutional Ethics Committee
AIIMS, Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

Annexure-2

CLINICAL SHEET

Name: Patient ID:

Age/Sex: Height/Weight:

Clinical history:

Evaluation of pain:

VAS/NRS:

	With Meds	without meds		With meds	without meds		With Meds	without meds
Head			Arms			Sternum		
Upper spine			Legs			Clavicle		
Lower spine			Ribs			Pelvis		

Analgesia Score:

ECOG Score: **Karnofsky Score:**

Investigations:

Bone scan:

CT/MRI:

Biopsy:

Haematological	**Biochemical**
1. Hb	1. ALP
2. WBC	2. eGFR
3. Platelets	**3.** S. Creatinine
4. PT: 5.INR:	

Tumor Markers:

Examination:

Treatment received:

Previous chemotherapy: YES/NO

If yes: No. of cycles:

Last cycle on:

Previous radiotherapy: YES/NO

If yes: No. of cycles:

Last cycle on:

Hormonal therapy:

Targeted therapy (monoclonal antibodies, etc):

Others:

Current medication

Annexure-3

PATIENT INFORMATION SHEET

Name of the patient: **Patient ID:**

1. **Aim of the study:** To assess outcome of low vs. high dose ^{177}Lu-EDTMP therapy for palliation of painful bone metastases.
2. **Study site:** Department of Nuclear Medicine, All India Institute of Medical Sciences, Jodhpur, Rajasthan.
3. **Study procedure:** The participants will be stratified randomly into two groups receiving high dose (1mCi/kg) vs low dose (0.5mCi/kg) of ^{177}Lu-EDTMP therapy. The patient will be blinded to the dose. The response to the therapy will be assessed at 2,4,8 and 12 weeks following the therapy. The patients haematological and biochemical parameters will be assessed in the follow-up visits.
4. **Likely benefit:** ^{177}Lu-EDTMP therapy helps in palliation of pain of the patient. Time of initiation of relief from pain is greater than 1 week.
5. **Confidentiality:** All the data collected from each study participant will be kept highly confidential.
6. **Risk:** There can be an initial increase in pain after 48-72 hr of therapy. There is risk of myelosuppresion after giving therapy, with decrease in WBC and platelet counts. Time for beginning of pain relief is more than 1 week.

For further information or questions, the following personnel can be contacted:

Dr. Rakesh Pandey, Junior Resident, Department of Nuclear Medicine, All India Institute of Medical Sciences, Jodhpur. Mobile Number: 9527199687, Email: pandeyrakesh2@gmail.com

Annexure-4

रोगी सूचना पत्र

रोगी का नाम: रोगी आईडी:

1. अध्ययन का उद्देश्य: उच्च खुराक बनाम कम खुराक ^{177}Lu-EDTMP थेरेपी प्राप्त करने वाले बोनी मेटास्टेसिस के रोगियों में दर्द से राहत पाने की तुलना।

2. अध्ययन स्थल: परमाणु चिकित्सा विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर, राजस्थान।

3. अध्ययन प्रक्रिया: प्रतिभागियों को ^{177}Lu-EDTMP थेरेपी की उच्च खुराक (1mCi / kg) बनाम कम खुराक (0.5mCi / kg) प्राप्त करने वाले दो समूहों में बेतरतीब ढंग से स्तरीकृत किया जाएगा। रोगी को खुराक के लिए अंधा कर दिया जाएगा। चिकित्सा के बाद 2,4,8 और 12 सप्ताह में चिकित्सा की प्रतिक्रिया का मूल्यांकन किया जाएगा। अनुवर्ती यात्राओं में रोगियों के हेमेटोलॉजिकल और जैव रासायनिक मापदंडों का मूल्यांकन किया जाएगा।

4. संभावित लाभ: ^{177}Lu-EDTMP थेरेपी रोगी के दर्द को कम करने में मदद करती है।

5. गोपनीयता: प्रत्येक अध्ययन प्रतिभागी से एकत्र किए गए सभी डेटा को अत्यधिक गोपनीय रखा जाएगा।

6. जोखिम: चिकित्सा के 48-72 घंटे के बाद दर्द में प्रारंभिक वृद्धि हो सकती है। WBC और प्लेटलेट काउंट में कमी के साथ, थेरेपी देने के बाद मायलोस्पुप्रेसियन होने का जोखिम है। दर्द से राहत की शुरुआत के लिए समय 1 सप्ताह से अधिक है।

अधिक जानकारी या प्रश्नों के लिए, निम्नलिखित कर्मियों से संपर्क किया जा सकता है:
डॉ। राकेश पांडे, जूनियर रेजिडेंट, परमाणु चिकित्सा विभाग, अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर। मोबाइल नंबर: 9527199687, ईमेल: pandeyrakesh2ngpr@gmail.com

Annexure-5

All India Institute of Medical Sciences Jodhpur, Rajasthan

INFORMED CONSENT FORM

Title of Thesis/Dissertation: **Comparison of low vs. high dose ^{177}LU-EDTMP therapy for palliation of painful bone metastases: RCT.**

Name of PG Student: Dr. Rakesh Pandey Tel. No. 9527199687

Patient/Volunteer Identification No. :_____

I,_____S/o or D/o_____

R/o_____ give my full, free, voluntary consent to be a part of the study "**Comparison of low vs. high dose ^{177}LU-EDTMP therapy for palliation of painful bone metastases: RCT."**, the procedure and nature of which has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary and am aware of my right to opt out of the study at any time without giving any reason. I understand that the information collected about me and any of my medical records may be looked at by responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____

Place: _____ Signature/Left thumb impression

This to certify that the above consent has been obtained in my presence.

Date: _____ _____

Place: _____ Signature of PG Student

1. Witness 1 2. Witness 2

_____ _____

Signature Signature

Name: _____ Name: _____

Address: _____ Address: _____

Annexure-6

अखिल भारतीय आयुर्विज्ञान संस्थान जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस / शोध प्रबंध का शीर्षक: **उच्च अस्थि मेटास्टेसिस के उपशमन के लिए उच्च खुराक तथा कम खुराक ^{177}Lu-EDTMP चिकित्साविधान की तुलनात्मक: आर सी टी**।

पीजी छात्र का नाम: **Dr. Rakesh Pandey** **Tel. No. 9527199687**

रोगी/स्वयंसेवक पहचान संख्या: _____

मैं, _____ पिता का नाम _____

पता_____ मेरी पूर्ण, मुक्त, स्वैच्छिक सहमति " **उच्च अस्थि मेटास्टेसिस के उपशमन के लिए उच्च खुराक तथा कम खुराक ^{177}Lu-EDTMP चिकित्साविधान की तुलनात्मक: आर सी टी**।" अध्ययन का एक हिस्सा बनने के लिए देता हूँ, जिसकी प्रक्रिया और प्रकृति मुझे अपनी भाषा में मेरी पूर्ण संतुष्टि के लिए समझाया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और बिना किसी कारण के किसी भी समय अध्ययन से बाहर निकलने के मेरे अधिकार से अवगत हूं।

मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारी को AIIMS Jodhpur या नियामक अधिकारियों के जिम्मेदार व्यक्ति द्वारा देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

दिनांक: _____ _____

जगह: _____ हस्ताक्षर / बाएं अंगूठे का निशान

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है।

दिनांक: _____ _____

स्थान: _____ पीजी छात्र के हस्ताक्षर

1. साक्षी 1 2 साक्षी 2

_____ _____

हस्ताक्षर हस्ताक्षर

नाम :_____ नाम : _____

पता :_____ पता : _____

Annexure-7

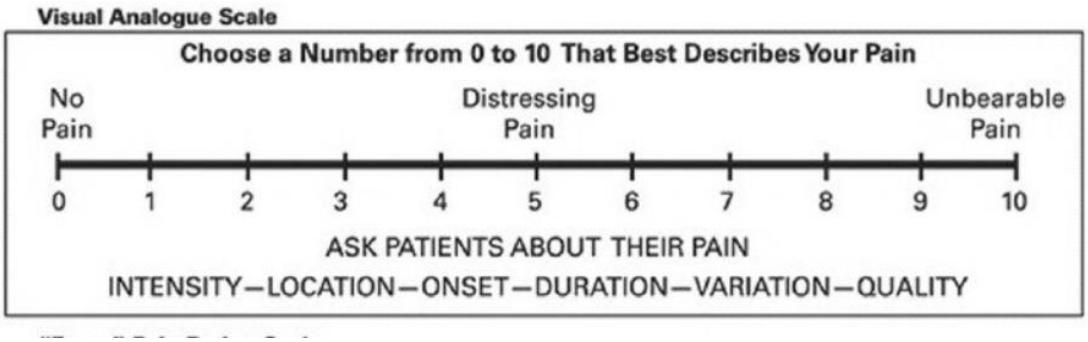
Mandatory procedures to be performed before ^{177}Lu-EDTMP Therapy

(EANM guidelines for radionuclide therapy of bone metastases with beta-emitting radionuclides)

Procedure	Objective	Timing
Medical history	To obtain patient demographics, indication for therapy, concomitant medications	Qualification for treatment on day of treatment
Life expectancy estimation	To confirm at least 4–6 weeks (preferably 3 months)	Qualification for treatment
Bone scan	To evaluate extent of disease	No longer than 4–8 weeks prior to therapy
Radiological imaging	To exclude severe lytic lesions with risk of pathological bone fracture or cord compression	As required
Complete blood count, d-dimer, serum creatinine	To exclude haematological, biochemical contraindication to therapy	No longer than 1–2 weeks prior to therapy; If required repeat on day of treatment
Pregnancy test		On day of treatment

Annexure-8

VISUAL ANALOGUE SCORE



ANALGESIA SCORE

1	No pain
2	Mild, e.g asprin
3	Occasional oral narcotic
4	Regular oral narcotics
5	Parenteral narcotics
6	Uncontrollable

Annexure-9

ECOG and KPS scores

	ECOG	Karnofsky	
0	Fully active, able to carry on all pre-disease performance without restriction.	Normal, no complaints; no evidence of disease	100
		Able to carry on normal activity; minor signs or symptoms of disease	90
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work.	Normal activity with effort, some sign or symptoms of disease	80
		Cares for self but unable to carry on normal activity or to do active work	70
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours	Requires occasional assistance but is able to care for most of personal needs	60
		Requires considerable assistance and frequent medical care	50
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	Disabled; requires special care and assistance	40
		Severely disabled; hospitalization is indicated although death not imminent	30
4	Completely disabled. Cannot carry on any self-care, totally confined to bed or chair	Very ill; hospitalization and active supportive care necessary	20
		Moribund	10
5	Dead	Dead	0

Annexure-10

Patient Instruction Sheet

1. Throughout the procedure, you are requested to remain inside the isolation room, you must not go to the corridor outside, except in case of emergency, with permission of the treating team.
2. The patient should continue normal diet.
3. No soiling of underdressing for 2 weeks post injection.
4. Toilets should be flushed 2-3 times after urination.
5. Consume plenty of fluid and urinate frequently during your stay in hospital.
6. Sleep alone for 3-4 days and maintain a distance of distance of at least 6 feet from your home members, pregnant woman or child below 18 years of age.
7. If planning for pregnancy, you should wait at least 6 months after treatment.

रोगी निर्देश शीट

1. आपके पूरी प्रक्रिया के दौरान, आपसे अनुरोध किया जाता है कि आप आइसोलेशन रूम के अंदर रहें, आपको बाहर के गलियारे में बाहर नहीं जाना चाहिए, सिवाय उभार के मामले में, इलाज करने वाली टीम की अनुमति से।

2. रोगी को सामान्य आहार जारी रखना चाहिए।

3. 2 सप्ताह के बाद के इंजेक्शन के लिए किसी भी प्रकार की कमी नहीं।

4. पेशाब के बाद 2-3 बार टॉयलेट बहना चाहिए।

5. बहुत सारे तरल पदार्थों का सेवन करें और अस्पताल में रहने के दौरान बार-बार पेशाब करें।

6. 3-4 दिनों के लिए अकेले सोएं और अपने घर के सदस्यों, गर्भवती महिला या 18 वर्ष से कम उम्र के बच्चे से कम से कम 6 फीट की दूरी बनाए रखें।

7. यदि गर्भावस्था की योजना बना रहे हैं, तो आपको उपचार के बाद कम से कम 6 महीने इंतजार करना चाहिए।