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Clinical evaluation of efficacy and safety of ^{177}Lu-EDTMP in patients with Painful Skeletal Metastasis: a multiparametric comparison with ^{153}Sm-EDTMP on equidose basis

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ABSTRACT

The purpose of the study was to assess the efficacy and safety profile of ^{177}Lu-EDTMP in patients with painful skeletal metastasis and make a comparative evaluation of the efficacy with that of ^{153}Sm-EDTMP. **Methods:** A total of 32 patients with painful skeletal metastases were prospectively evaluated (26 men and 6 women; mean age of 46.19 years; age range: 33-84 years). Patients were divided in two groups, one treated with ^{177}Lu-EDTMP (n=16) and other treated with ^{153}Sm-EDTMP (n=16). In both the groups, patients were treated with dose of 37MBq/kg body weight for both the radionuclide (dose range of ^{177}Lu-EDTMP varied from 1295 MBq to 2701 MBq depending on the weight of patient, whereas in ^{153}Sm-EDTMP the dose range varied from 1258 MBq to 2553 MBq). The following evaluation scores were adopted to examine the efficacy: [i] Analgesic score, [ii] pain scale (visual analogue scale or VAS), [iii] quality of life evaluation using 3 assessment scales (EORTC, Karnofsky and ECOG assessment scales), [iv] bone proliferation marker (estimation of bone alkaline phosphatase or BAP). The hematological toxicity was evaluated using *NCI*-Common Terminology Criteria for Adverse Events (*CTCAE*) and was compared between both groups at baseline and each monthly till 3 months post therapy. For the assessment of pain response post-therapy, a pre-defined criteria was followed used in this study protocol that considered both the VAS and analgesic score change on a sliding scale (rather than a single parameter or an absolute value), and the response was subdivided into 4 categories: complete response (CR), partial response (PR), minimal response (MR) and no-response (NR). **Results:** The overall pain relief in patients treated with ^{177}Lu-EDTMP was 80%. Among the responders, 50% of patients had complete response (CR), 41.67 % had partial response (PR) and 8.33% had minimal response (MR). The overall pain relief in patients treated with ^{153}Sm-EDTMP was 75%. Among these, 33.33% of patients had complete response (CR), 58.33% had partial response (PR) and 8.33% had minimal response (MR). The difference in pain relief between these two groups was not significant (p=

1.000). There was significant improvement in quality of life post therapy at 3 month in both group of patients as assessed by ECOG (p =0.014 and 0.005) and Karnofsky indices (p =0.007 and 0.023) respectively for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP. There was significant improvement in quality of life (pain free survival) post therapy at 3 month in both group of patients as assessed by EORTC QLQ BM22 score (p = 0.004 and <0.001) respectively for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP. Bone proliferation marker in responders showed significant reduction in both groups [^{177}Lu-EDTMP (p =0.008) and ^{153}Sm-EDTMP (p =0.019)], parallel to the clinical response. In patients treated with ^{177}Lu-EDTMP non-serious (Grade I / II) anemia, leucopenia and thrombocytopenia was noted in 46.67%, 46.67% and 20% respectively. In patients treated with ^{177}Lu-EDTMP serious (Grade III / IV) anemia, leucopenia and thrombocytopenia was noted in 20%, 6.67% and 0% respectively. In patients treated with ^{153}Sm-EDTMP non-serious (Grade I / II) anemia, leucopenia and thrombocytopenia was noted in 62.5%, 31.25% and 18.75% respectively. In patients treated with ^{153}Sm-EDTMP serious (Grade III / IV) anemia, leucopenia and thrombocytopenia was noted in 18.75%, 0% and 6.25% respectively. Only 1 patient treated with ^{153}Sm-EDTMP showed Grade IV thrombocytopenia, however no blood transfusion was required. No statistically significant difference noted in non-serious toxicity between two groups with respect to anemia (p= 0.571), leucopenia (p= 0.511) and thrombocytopenia (p= 0.561). No statistically significant difference noted in serious toxicity between two groups with respect to anemia (p= 0.671), leucopenia (p= 0.334) and thrombocytopenia (p= 0.739). 3 out of 12 responders (25% of the responders) treated with ^{177}Lu-EDTMP reported incidence of flare phenomenon, on 3rd day post therapy and 1 (8.33%) reported on 5th day post therapy, showing no response to therapy. In ^{153}Sm-EDTMP group, 2 out of 12 responders (16.66% of the responders) reported incidence of flare phenomenon, reported on 3rd day post therapy. **Conclusions:** The present study documented a similar pain response efficacy

of 177Lu-EDTMP coupled with improvement in the quality of life when compared to that of ^{153}Sm-EDTMP. Similar hematological toxicity profile and absence of renal toxicity demonstrated with ^{177}Lu-EDTMP would indicate that this agent is a feasible and safe alternative to ^{153}Sm-EDTMP for treatment of painful skeletal metastasis with minimal side effects especially in the setting of centers having no nearby accessibility for ^{153}Sm-EDTMP because of its longer half life. This is an important consideration taking into account that 177Lu is a popular radionuclide for PRRT in many centres across the world.

Keywords: - ^{177}Lu-EDTMP, ^{153}Sm-EDTMP, Bone pain palliation, Bone alkaline phosphates (BAP), Skeletal metastases.

INTRODUCTION

With the increasing incidence of cancer (one of the contributory factors being increase in the life expectancy due to better health care services), every year there is rising demand in terms of managing various advanced malignancies and their complications. Skeletal metastasis is a frequent accompaniment in the patients with end stage malignancies. Bone metastases are most frequent in patients with advanced prostate or breast carcinoma (60-80% of patients). Such metastasis can cause debilitating pain and limit daily activities in these patients with significant burden in terms of healthcare management and costs to the society. The most typical locations are vertebrae, ribs, pelvic bones and skull (*1,2,3*). The therapeutic options are rarely (if ever) curative and at some point of time the vast majority of these patients suffering from osseous metastasis develop progressive disease, leading to a series of disease related events that have the most significant impact on quality of life in these patients (*4*).

The symptomatic treatment of skeletal pain due to metastases is a complex task which may require administration of drugs, including bisphosphonates and analgesics, and use of external beam radiotherapy (*5,6,7*). Of the various treatment options available for the treatment of painful bone metastases, analgesics are the first step in treatment cascade. In case of nociceptive pain, paracetamol and other non-steroidal anti-inflammatory drugs are the first line agents. They usually provide relief in pain in the initial phase but as the disease progresses, increased dose or opioid analgesics are required either orally or intravenously. The use of high doses is associated with severe adverse side effects, particularly with opioid analgesics like nausea, constipation, confusion, drowsiness, dry mouth etc. Similarly, neuropathic pain is first treated as nociceptive pain, but can be supplemented by tricyclic antidepressants and anti-epileptic medications if there is no relief in pain. The hormonal therapy and chemotherapy may be effective in alleviating the pain but eventually the disease becomes refractory to these agents also (*4*). In limited metastatic disease, external beam radiotherapy provides effective pain control with short course of high dose per fraction and low toxicity, however there is rapid increase in toxicity with increasing field of irradiation (*7,8*).

In patients with multiple skeletal lesions with osteoblastic lesions on skeletal scintigraphy, systemic radiotherapy with radionuclides linked to bone-seeking agent is an effective treatment options, owing to its efficacy, low cost and comparative low toxicity (*7,9*). Various radionuclides which are commercially available for systemic metabolic radiotherapy of bone pain includes

Phosphorus-32 (P-32), Strontium-89 (Sr-89), Rhenium-186 (Re-186) chelated with hydroxyethylidene diphosphonate (HEDP) and ^{153}Samarium (^{153}Sm) chelated with ethylene diamine tetramethylene phosphonate (EDTMP) (*4,10-12*). Radionuclide with high energy beta-radiation have higher tissue range, hence high anti-tumor potential, but there is proportionate increase in bone marrow suppression. It is one of the major constraint towards the widespread use of P-32 (Mean β=695 keV, t1/2= 14.3 days) and Sr-89 (Mean β=583keV, t1/2=50.5 days), other being long half life (Sr-89) and absence of gamma photons for imaging (*4*).

^{153}Sm-EDTMP (Mean β=233keV, t 1/2=1.9 days, γ=103keV) with short beta range emission have advantages over radionuclides with high beta energy in terms of reduced incidence of bone marrow suppression. ^{177}Lutetium (^{177}Lu) chelated with EDTMP is a new and relatively inexpensive bone seeking radiopharmaceutical, and can be potentially useful radionuclide for systemic radionuclide therapy in patients with bone metastases (*13,14,15*). ^{177}Lu-EDTMP (Max β=497 keV, t1/2=6.7 days, γ=208 keV) with short beta range emission and half life of 6.7 days may be a useful alternative to ^{153}Sm-EDTMP for systemic radionuclide therapy with logistical advantage due to the relatively longer half life of ^{177}Lu; furthermore, ^{177}Lu labeling with other ligands such as DOTATATE (for Neuroendocrine tumors) and PSMA (for prostatic carcinoma) make it more attractive for an active therapeutic Nuclear Medicine programme. This prospective study was undertaken to investigate the efficacy and safety of ^{177}Lu-EDTMP in patients with painful bone metastases caused by tumours and compare these parameters with that of ^{153}Sm-EDTMP.

METHODS: This was a prospective study of 32 patients divided into two groups, receiving either of two radiopharmaceuticals and was carried over a period of 18 months.

Patient Inclusion and Exclusion criteria

The patients selected for the study fulfilled the following criteria i.e. having bone pain due to skeletal metastasis due to any malignancy and bone scan demonstrating multiple osteoblastic lesions corresponding to the sites of pain.

The exclusion criteria included the standard criteria (*16*) that are advocated in the guidelines such as absolute e.g. pregnancy, breastfeeding and relative such as Haemoglobin < 9 gram%, Total white cell count < 3500/cubicmillimeter, platelet count < 100000/cubicmillimeter, acute or chronic spinal cord compression or in treating pathological fracture, neurogenic pain and pathological fractures, life expectancy less than 4 weeks. Also, the patients with the need for surgical procedures were excluded

from this study.

Evaluation of patients prior to inclusion

The study protocol was approved by the Institutional Medical Ethics Committee. All eligible patients were explained about the procedure in detail regarding both benefits and possible adverse effects of the therapy along with radiation precautions and follow up requirements following therapy. Written informed consent was taken prior to the administration of radionuclide. All patients underwent routine workup including clinical examination, bone scan and routine laboratory blood tests as part of their pre-therapy investigations.

All relevant study data from the detailed study proforma was entered into an excel sheet and then analyzed.

Study procedure

A total of 32 patients were evaluated in this prospective study: Sixteen patients were treated with ^{177}Lu-EDTMP and 16 cases were administered ^{153}Sm-EDTMP. To avoid the selection bias, patients were randomly allocated into two different groups with the help of random table generation, with the odd number patient given one agent and even number patient given the other. Patients considered for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP therapy had documented bone metastasis with significant pain at corresponding metastatic sites. Pain was severe enough to limit normal activities (appropriate objective scale e.g. Visual analogue scale (VAS), Karnofsky scale was utilized for this assessment) and/or required regular analgesics. Patients underwent recent [within 4 weeks or less] bone scintigraphy documenting increased osteoblastic activity at the painful sites.

At the time of inclusion in the study, an explanation of the procedure was given to the patients in detail regarding both benefits and possible adverse effects of the therapy along with radiation precautions and follow up requirements following therapy. Written informed consent was taken prior to the administration of radionuclide. As per the limit stipulated by Atomic Energy Regulatory Board (AERB), in India, an activity of 1.1 GBq (30 mCi) of ^{131}I is specified as the discharge limit. 30 mCi of ^{131} I retained in the body in an adult patient corresponds to an exposure-rate of about 5-6 mR/h (=50-60 Sv/h) at a distance of one metre. Using this parameter, the pain palliation therapy

with either of the radiophamaceuticals can be undertaken on outpatient basis.

Patients' pain level was evaluated using a visual analogue pain scale (VAS). The patients were asked to score the pain on the scale of 10 where 0 being no pain and 10 being the worst pain possible. The patients were also instructed to fill the same every monthly for the 3 months in the post-therapy period. Similarly patients' performance parameters were also evaluated using ECOG scale and Karnofsky's indices both pre-therapy and every monthly for 3 months post-therapy.

Patient's pre-therapy analgesic score was computed using product of analgesic type used and frequency of administration (Table 1). Similarly the post therapy analgesic score was evaluated at 3 months using the same scale.

The patient was instructed to note down the time interval during the post-therapy period, they started feeling relief of pain: this was to evaluate the onset of pain relief with each radiopharmaceutical. Similarly patients were also instructed to note the phenomenon of flare phenomenon (increase in pain intensity especially during the initial few days post therapy).

Standardized therapy protocol and post treatment procedures were maintained for both radiopharmaceuticals. Abnormalities on bone scintigraphy were correlated with appropriate examination and correlation to exclude other causes of chronic pain which would be unlikely to respond to treatment using bone seeking radiopharmaceuticals. Neurogenic pain and pathological fracture was specifically excluded. Absence of use of wide field [hemibody] radiotherapy within 3 months of ^{177}Lu-EDTMP and ^{153}Sm-EDTMP was ensured. Long-acting myelosuppressive chemotherapy (e.g. nitrosoureas) was discontinued at least 4 weeks prior to administration of ^{177}Lu-EDTMP and ^{153}Sm-EDTMP and was withheld for 6–12 wk post therapy to avoid concomitant myelosuppression. A full haematological and biochemical profile was obtained within 7 days of the proposed treatment. Disseminated intravascular coagulation (DIC), a definitive risk factor for severe thrombocytopenia post-therapy, was excluded by performing pre treatment clotting studies to identify patients with subclinical DIC. An interval of at least 48 hrs was ensured between bisphosphonate administration and ^{177}Lu-EDTMP and ^{153}Sm-EDTMP treatment.

In both the groups, patients were treated with dose of 37MBq/kg body weight for both the radionuclide (dose range of ^{177}Lu-EDTMP varied from 1295 MBq to 2701 MBq depending on the weight of patient, whereas in ^{153}Sm-EDTMP the dose range varied from 1258 MBq to 2553 MBq.)

The result was analyzed and compared for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP at 3 months for the following aspects as effectiveness in relieving pain, side effects associated with the therapy, reduction in amount of analgesics intake and measuring efficacy of anti-tumor effects in terms of reduction of tumor markers (bone fraction of alkaline phosphatase, etc.) and bone scan lesions.
Patient was asked to perform complete blood count every 15 days post therapy for 3 months to evaluate hematological toxicity and hematological toxicity was evaluated using NCI-Common Terminology Criteria for Adverse Events v4.0 (CTCAE).

Patients were asked to fill a QOL form EORTC (EORTC QLQ BM22) to evaluate quality of life in terms of pain parameters both at baseline and 3 months after therapy.

Assessment of Pain Response: Methodology and Rationale

We used a pre-defined sliding scale considering both the VAS and analgesic score change (rather than a single parameter) during the post therapy pain response assessment, which would make it possible a global assessment.

In a study by Yuan et al. (*15*) evaluating the efficacy and safety of ^{177}Lu-EDTMP in bone metastatic pain palliation in breast cancer and hormone refractory prostate cancer, the response criteria were defined as complete response (CR, disappearance of all bone pain, freely mobile, and at least a 50 % use of pain medication), partial response (PR, some improvement in bone pain), and no response (no change in pain or mobility). In another conducted by Baczyk et al. (*3*) comparing treatment efficacy of ^{89}Sr and ^{153}Sm-EDTMP in bone metastases in prostate and breast cancer, a complete analgesic effect was established if the VAS score decreased below score 2, a partial effect was defined as a decrease of VAS score after therapy to 2-4 points and unsatisfactory response who had no decrease of VAS score below 5. In study conducted by Tripathi et al. (*4*) bone pain palliation in skeletal metastases using ^{153}Sm-EDTMP, patient was considered as a responder if pain intensity on VAS decrease for at least two steps for two weeks, while the analgesic score remained at least constant. Complete response was recorded if patient was completely relieved of pain. If the pain score or analgesic score increased during follow up period, the patient was considered as a non-responder.

Based on the aforementioned logic, the present study design considered both the VAS and analgesic score change post therapy on a sliding scale, and the response was subdivided into categories as

complete response (CR) was defined as either pain scale of zero at 3 months or more than 75% decrease in analgesic score with a change in pain score, partial response (PR) in pain relief was defined as either change in pain scale by > 3 or 50- 75% decrease in analgesic score post therapy with a change in pain score, minimal response (MR) in pain relief was defined as either change in pain scale by 1-3 or 25-50% decrease in analgesic score post therapy with a change in pain score, no response (NR) was defined as no change in pain score or less than 25% decrease in the analgesic score.

RESULTS:

The patient population consisted of 32 patients, age range of 33 to 84 years with a mean of 58.38 years. It included 26 males (81.25%) and 6 females (18.75%). Based on the histopathology of the primary, 17 patients had adenocarcinoma prostate (53.12%), 5 patients had carcinoma of breast (15.62%), 3 patients had medullary carcinoma of thyroid (9.37%), 4 patients had non-small cell lung carcinoma (12.5%), and 1 patient each of neuroendocrine tumor, renal cell carcinoma and metastatic adenocarcinoma with unknown primary (3.12% each). The distribution of primary cancer in individual group based on the histopathology of the primary were 6 patients had adenocarcinoma prostate (37.5%), 4 patients had carcinoma of breast (25%), 3 patients had medullary carcinoma of thyroid (18.75%), 1 patient each of non-small cell lung carcinoma, neuroendocrine tumor and renal cell carcinoma (6.25% each) in ^{177}Lu-EDTMP group and 11 patients had adenocarcinoma prostate (68.75%), 3 patients had carcinoma of lung (18.75%), 1 patient each of carcinoma breast and metastatic adenocarcinoma with unknown primary (6.25% each) in ^{153}Sm-EDTMP group.

The table for patient demographics with respect to the mean pre-therapy performance characteristics (with either of the agents) is depicted in Table 2.

Hematological toxicity was evaluated using Common Terminology Criteria for Adverse Events v4.0 (NCI-CTCAE score). In both groups, transient reduction in the blood counts was noted post therapy with nadir between 4-6 weeks with gradual recovery by 8 weeks. In patients treated with ^{177}Lu-EDTMP non-serious (Grade I / II) anemia, leucopenia and thrombocytopenia was noted in 46.67%, 46.67% and 20% respectively. In patients treated with ^{177}Lu-EDTMP serious (Grade III / IV) anemia, leucopenia and thrombocytopenia was noted in 20%, 6.67% and 0% respectively (Table 3). In patients treated with ^{153}Sm-EDTMP non-serious (Grade I / II) anemia,

leucopenia and thrombocytopenia was noted in 62.5%, 31.25% and 18.75% respectively. In patients treated with ^{153}Sm-EDTMP serious (Grade III / IV) anemia, leucopenia and thrombocytopenia was noted in 18.75%, 0% and 6.25% respectively. Only 1 patient treated with ^{153}Sm-EDTMP showed Grade IV thrombocytopenia, however no blood transfusion was required (Table 3).

No statistically significant difference noted in non-serious toxicity between two groups with respect to anemia (p= 0.571), leucopenia (p= 0.511) and thrombocytopenia (p= 0.561). No statistically significant difference noted in serious toxicity between two groups with respect to anemia (p= 0.671), leucopenia (p= 0.334) and thrombocytopenia (p= 0.739).

Bone Alkaline Phosphatase (BAP) Parameters. For ^{177}Lu-EDTMP, there was significant difference in mean (SD) value of pre-therapy (34.83 ±31.21), and post-therapy (29.04±24.42) (p= 0.008) with most of responders (83.33%) showing reduction in BAP value [Fig 1] compared to baseline where as only 16.6% showed increase in BAP value compared to baseline.

For 153Sm-EDTMP, there is a significant difference in mean (SD) value of pre-therapy (54.49 ±32.82)) and post-therapy (46.57±25.46) (p= 0.019) with most of responders (92.31%) showing reduction in BAP value [Fig 1] compared to baseline where as only 7.69% showed increase in BAP value compared to baseline.

Pain Score Assessment. Patients treated with ^{177}Lu-EDTMP showed significant reduction in mean (SD) pain score assessed by visual analogue pain scale at 3 month post therapy (3.75±1.82)) compared to baseline (8.25±0.75)) in responders [Fig 2], which is statistically significant (p= 0.002). Similarly in patients treated with ^{153}Sm-EDTMP showed significant reduction in mean (SD) pain score assessed by visual analogue pain scale at 3 month post therapy (4.5±1.78)) compared to baseline (7.67±0.78)) in responders [Fig 2], which is statistically significant (p= 0.002).

Quality Of Life Score Assessment. There was significant improvement in the quality of life (pain free

survival) in responders as assessed by mean (SD) EORTC score between, pretherapy (52.42±12.52) and post therapy (42.92±11.74) level in patients treated with 177Lu-EDTMP (p=0.004) [Fig 3].

Similarly, in patients treated with 153Sm-EDTMP, there was significant improvement in the quality of life in responders (pain free survival) as assessed by mean (SD) EORTC score between pretherapy (54.49±32.82) and post therapy (47.57±11.42)) level (p<0.001) [Fig 3].

In patients treated with ^{177}Lu-EDTMP, significant improvement in mean (SD) ECOG scale level between baseline (1.92±1.0)) and 3 month post therapy (1.17±0.39)) noted, which is statistically significant (p= 0.014). Similarly in patients treated with ^{153}Sm-EDTMP, significant improvement in ECOG scale level between baseline (2.42±1.0)) and 3 month post therapy (1.42±0.51)) noted, which is statistically significant (p= 0.005). [Fig 4]

In patients treated with ^{177}Lu-EDTMP showed significant improvement in mean (SD) Karnofsky's scale level at baseline (65.83±16.21) and 3 month post therapy (80±8.53) which was statistically significant (p= 0.007). Similarly in patients treated with ^{153}Sm-EDTMP showed significant improvement in mean (SD) Karnofsky's scale level at baseline (62.17±16.24) and 3 month post therapy (75.83±9.96)) which is statistically significant (p= 0.023). [Fig 5]

A total of 12 patients showed pain relief post ^{177}Lu-EDTMP therapy [Fig 6], whereas 3 patients did not show any response and one patient was lost to follow up. The pain relief started post therapy as early as 3 days to up to 18 days post therapy. The response was initially mild which gradually increases over the period and plateauing around 6-8 weeks. The duration of response varied from 3 months to upto around 13 months.

Out of 12 responder patients, 6 patients showed complete response (CR) in pain relief. 5 patients showed partial response (PR) in pain relief 1 patient showed minimal response (MR) in pain relief.

All patients with prostate cancer (osteoblastic metastases), showed response in pain relief.

A total of 12 patients showed pain relief post ^{153}Sm-EDTMP therapy [Fig 7], whereas 4 patients did not show any response. The pain relief started post therapy as early as 5 days to up to 12 days post therapy. The response was initially mild which gradually increases over the period and plateuing

around 6-8 weeks. The duration of response varied from 3 months to around 15 months.

Out of 12 patients, 4 patients showed complete response (CR) in pain relief. 7 patients showed partial response (PR) in pain relief. 1 patient showed minimal response (MR) in pain relief.

Out of 11 patients with prostate cancer (osteoblastic metastases), 7 patients showed response.

The change in response parameters in non-responders with either radiopharmaceutical is depicted in Table 4a and 4b.

Flare Response, Pain Response and Duration of Response to Therapy. In group of patients treated with ^{177}Lu-EDTMP, 3 out of 12 responders (25% of the responders) reported incidence of flare phenomenon, on 3rd day post therapy and 1 (8.33%) reported on 5th day post therapy, showing no response to therapy.

In ^{153}Sm-EDTMP group, 2 out of 12 responders (16.66% of the responders) reported incidence of flare phenomenon, reported on 3rd day post therapy.

The duration of response varied from 3 months to upto around 15 months in patients treated with ^{177}Lu-EDTMP, which was the maximum follow up period during this study period. The duration of response varied from 3 months to around 15 months, in patients treated with ^{153}Sm-EDTMP, which was the maximum follow up period during this study period. Hence, a further follow up of the patients responding to therapy needs to be carried on for evaluating the advantage of one agent over the other with regards to pain free survival.

DISCUSSION:

Systemic therapy with bone seeking radiopharmaceuticals is advantageous for treatment of multiple sites painful skeletal metastases and refractory to conventional modes of treatment. Treatment with systemic radionuclide agents is mainly palliative leading to reduction in bone pain and prevention of disease progression thus preventing associated complications (*3*). Accumulation of radionuclide at the metastatic foci leads to irradiation of pathological tissue, leading to destruction of cells in metastatic foci by beta rays with minimal effect on surrounding normal tissue. Shrinkage of metastatic tumor decreases the mechanical stimulation of periosteal pain receptors (*3,17,18,19*).

Various bone seeking radiopharmaceuticals used currently used includes Phosphorus-32, ^{89}Strontium chloride, ^{153}Sm-EDTMP etc. Recently US FDA has approved another therapeutic agent for bone pain palliation, Radium-223 chloride. Radium-223 chloride is an alpha emitting radio-isotope, is similar to calcium ions, accumulates in the bone and targets osteoblastic metastatic sites. Due to alpha radiation, it has short tissue penetration (maximum range less than 10μm) and delivers high energy per track length. Side effects are mild and predominantly gastrointestinal with minimal myelosuppression. This agent has demonstrated promising results in castrate resistant prostate cancer patients with bone metastases.

^{177}Lu, a β emitter radionuclide, in addition to its present popularity for peptide receptor radionuclide therapy (PRRT), is also considered useful a potential bone pain palliation agent owing to its suitable nuclear decay characteristics (T1/2 = 6.73 days, E ß (max) = 497 keV, E gamma = 113 keV [6.4%] and 208 keV [11%]) and the feasibility of large-scale production with adequate specific activity using moderate flux research reactors. The photons of 113 keV (6.4%) and 208 keV (11%) and is suitable for imaging. EDTMP, as one of the most widely used ligands, forms stable complexes with various radiometals and these EDTMP-radiometal complexes concentrate in the skeleton, in proportion to osteoblastic activity, and exhibit other favorable pharmacological characteristics in biological systems. Thus, ^{177}Lu-EDTMP has favorable physical and biological characteristics for the treatment of painful bone metastases (*15,20,21,22*).

^{177}Lu-EDTMP animal studies have shown significant uptake of activity in the skeleton within 1 hr post-injection. There is no significant background activity 3 hrs post-injection suggesting rapid clearance of complex from the circulation. The skeletal activity was found to be retained until 7 days post-injection (*14,23*).

Our present study aimed to study the clinical efficacy and safety of ^{177}Lu-EDTMP in patients with painful skeletal metastasis from various malignancies in comparison with ^{153}Sm-EDTMP. The results showed significant pain relief, improvement in quality of life, reduction in tumor marker in majority of the patients with no significant hematological toxicities. The present study documented overall response in pain relief in 80 % of the patients treated with ^{177}Lu-EDTMP which is comparable to that reported in two phase II clinical studies where the reported response rate was 86 % (*23*). The dose of ^{177}Lu-EDTMP used in those studies was 1295 MBq and 2590 MBq (*15,23*). In our study we administered ^{177}Lu-EDTMP in a dose of 1 mCi/kg body weight to be comparable to

dose of ^{153}Sm-EDTMP. The overall response in patients treated with ^{153}Sm-EDTMP was 75 % which was comparable to rate reported by controlled clinical trials and the other uncontrolled studies, ranging from 61-95 % (*24-29*).

In the study done by Yuan et al (*15*), complete response in pain relief was observed in 55 % and 80 % of patients in group 1 and 2 treated with 1295 MBq and 2590 MBq of ^{177}Lu-EDTMP respectively. In this study (*15*) there was an improvement in the Karnofsky index which paralleled bone pain relief observed with mean (SD) Karnofsky indices of 58.18 (9.82) and 56 (8.94) at baseline in group 1 and 2 respectively which increase to 82.73 (9.05) at 6 weeks in group 1 and 85 (5.77) in group 2.

In another study conducted by Agarwal et al (*23*), the overall response rate was 86 %. Complete, partial and minimal responses were seen in 6 patients (13 %), 21 patients (48 %) and 11 patients (25 %), respectively. A favourable response was seen in 27 patients (84 %) with prostate cancer and in 11 patients (92 %) with breast cancer. There was an improvement in quality of life of the patients as reflected by an increase in mean karnofsky indices of from 56 ± 5 to 75 ± 7 ($p < 0.0001$).

Quality of life as assessed using EORTC-QLQ-BM22 forms in the present study clearly showed significant improvement in the quality of life of patients compared to pretherapy status in both groups ($p = 0.004$ and 0.024) for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP respectively). The pain relief was also associated with significant improvement in Karnofsky and ECOG score in both groups of patients compared to pretherapy status. ($p = 0.007$ and 0.023; $p = 0.014$ and 0.05 for ^{177}Lu-EDTMP and ^{153}Sm-EDTMP respectively). In the study by Tripathi et al (*4*) with ^{153}Sm-EDTMP, an improvement in Karnofsky index was observed in all responders with mean pretherapy score 70.83 (8.74) and post therapy at 16 weeks score of 79.16 (9.06).

Bone Alkaline Phosphatase (BAP) which is currently regarded as one of the most sensitive indices of bone formation in patients with prostate cancer and skeletal metastases (*30,31*). In our study there was a significant reduction in the BAP levels post-therapy in responders in both groups of patients. Only 2 patients treated with ^{177}Lu-EDTMP and 1 patient treated with ^{153}Sm-EDTMP showed increase in BAP level from the baseline, however in all these patients the BAP was within the normal range. Interestingly, in case of non-responders in both groups, BAP levels demonstrated

a rising trend. The reduction of BAP levels in responders need to be further examined with respect to their overall survival statistics compared to the non-responders.

The major limiting factor in therapy using bone seeking radiopharmaceuticals is bone marrow toxicity. In the study conducted by Yuan et al (*15*), grade II hematological toxicity occurred in 3 of 16 and grade III hematological toxicity occurred in 1 patient. In addition, grade I, II and III platelet toxicity occurred in 5, 3 and 1 patient, respectively, and grade I and II leucocyte toxicity occurred in 6 and 5 patients respectively. In the study conducted by Agarwal et al (*23*), non-serious haematological toxicity (grade I/II) was observed in 15 patients (34 %) and serious toxicity (grade III/IV) occurred in 10 patients (23 %). No statistically significant difference in haematological toxicity between the groups treated with 1295 MBq and 2590 MBq of ^{177}Lu-EDTMP.

In study by Dolezal et al (*7*), 32 patients with bone disseminated hormone-refractory prostate cancer and bone pain treated with ^{153}Sm-EDTMP, mild and transient bone marrow suppression was observed as a side effect of treatment. None of the patients showed hematological toxicity grade 4, and only 2 showed grade 3 (NCI-CTC). The majority of the patients had hematological toxicity grade 1 or 2. In the study by Tripathi et al (*4*) on 86 patients with painful skeletal metastases treated with ^{153}Sm-EDTMP, 5 patients had leucopenia of grade I and 3 patients had grade II toxicity. 3 patients each, showed grade I and Grade II thrombocytopenia. 18 patients had grade I, and 8 patients had grade II anaemia. Grade III and IV haematological toxicity was not seen in any patient.

In our study non-serious haematological toxicity (grade I/II) was observed in 8 patients (53.33 %) and serious toxicity (grade III/IV) occurred in 4 patients (26.67 %) treated with ^{177}Lu-EDTMP. In patients treated with ^{153}Sm-EDTMP non-serious haematological toxicity (grade I/II) was observed in 10 patients (62.5 %) and serious toxicity (grade III/IV) occurred in 3 patients (18.75 %) No statistically significant difference in haematological toxicity between the groups treated with ^{177}Lu-EDTMP and ^{153}Sm-EDTMP in relation to anaemia, leucopenia and thrombocytopenia.

No statistically significant difference in nephrotoxicity between the groups treated with ^{177}Lu-EDTMP and ^{153}Sm-EDTMP.

One shortcoming of the study has been that the patients were included through the random

table generation of odd and even numbers and were allocated to either group for therapy and this might have resulted in some difference in distribution of primary malignancies, though the maximum fraction in either group belonged to prostate carcinoma. The findings, however, indicate that that ^{177}Lu-EDTMP may be an attractive alternative that ought to be considered.

CONCLUSION:

The present study documented a similar pain response efficacy of ^{177}Lu -EDTMP coupled with improvement in the quality of life when compared to that of ^{153}Sm-EDTMP. Similar hematological toxicity profile and no renal toxicity demonstrated with ^{177}Lu-EDTMP would indicate that this agent is a feasible and safe alternative to ^{153}Sm-EDTMP for treatment of painful skeletal metastasis with minimal side effects especially in the setting of centers having no nearby accessibility for ^{153}Sm-EDTMP because of its longer half life. This is an important consideration taking into account that ^{177}Lu is a popular radionuclide for PRRT in many centres across the world.

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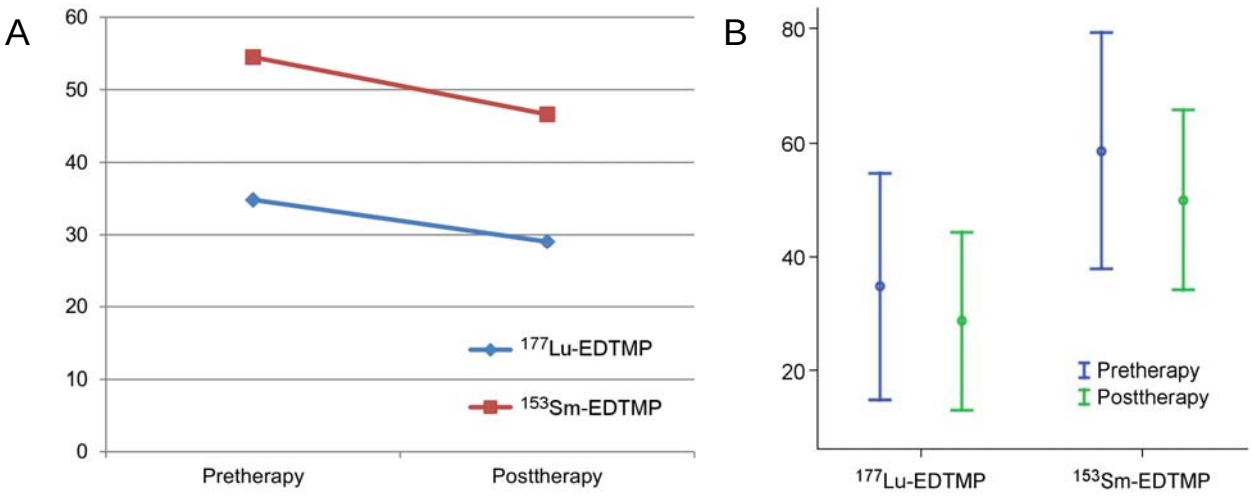

Fig 1a. Graph demonstrating BAP parameters in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP

Fig1b: Error Bar Graph demonstrating Bone Alkaline phosphatase (BAP) parameters in responders

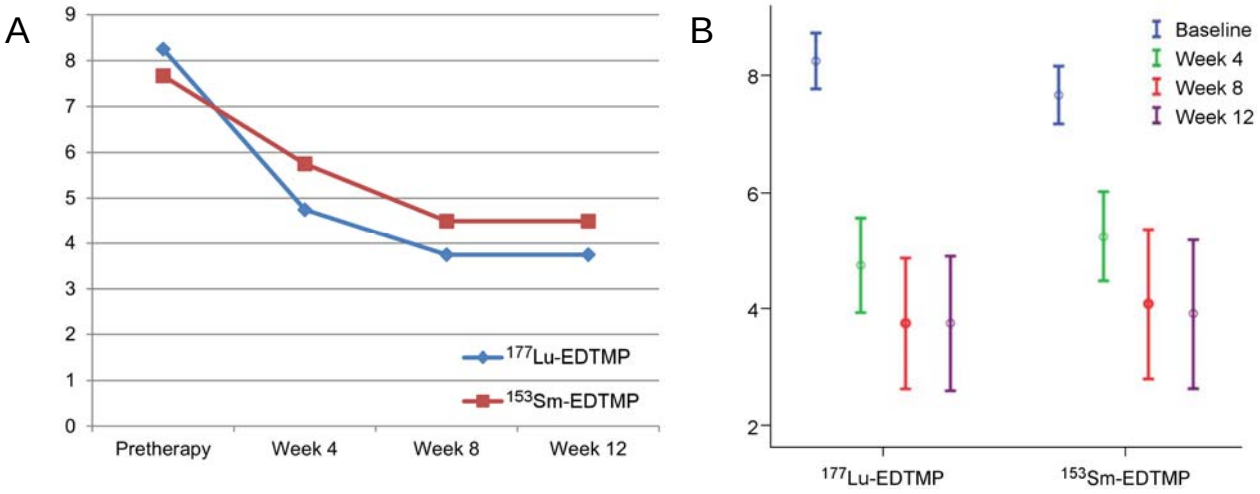

Fig 2a**:** Mean VAS pain score in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP

Fig 2b**:** Mean VAS pain score in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP

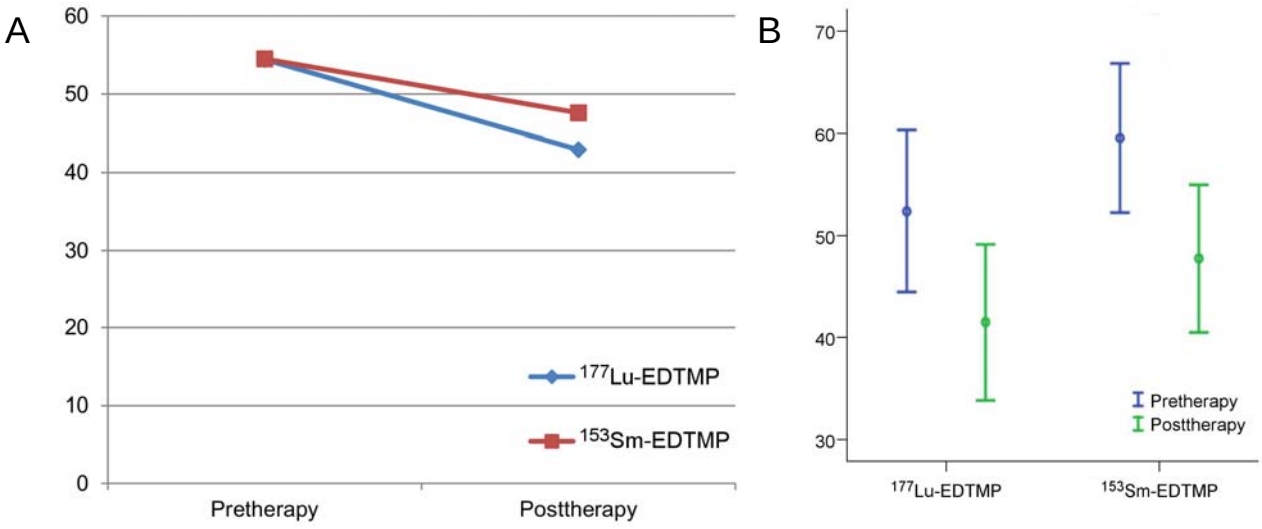

Fig 3a**:** Mean EORTC Indices in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP:

Fig 3b: Error bar graph illustrating mean EORTC Indices in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP

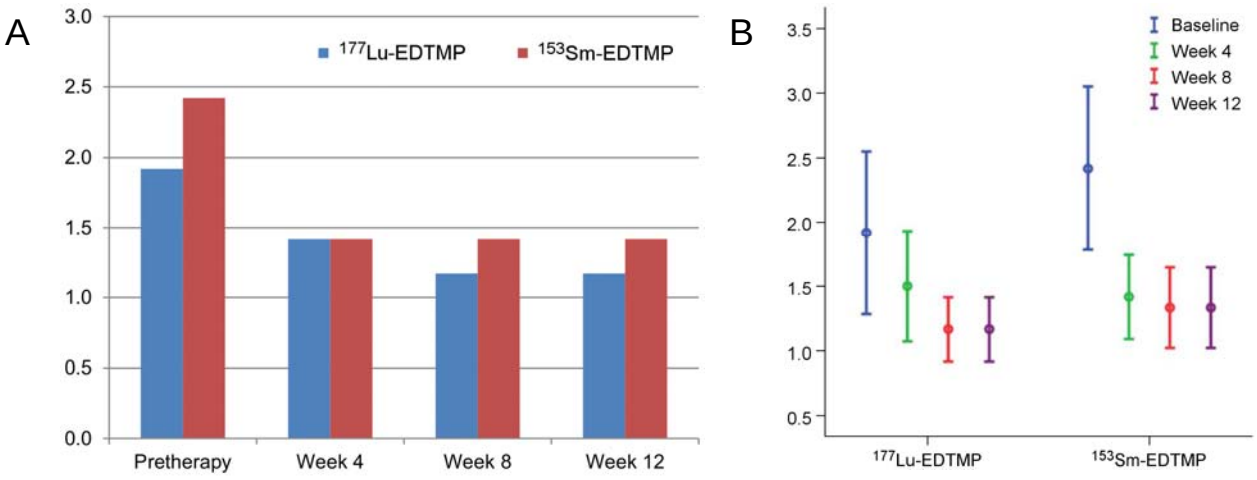

Fig 4a. Mean ECOG Indices in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP:

Fig 4b: Error bar graph illustrating mean ECOG Indices in responders treated with ^{153}Sm-EDTMP and ^{177}Lu-EDTMP:

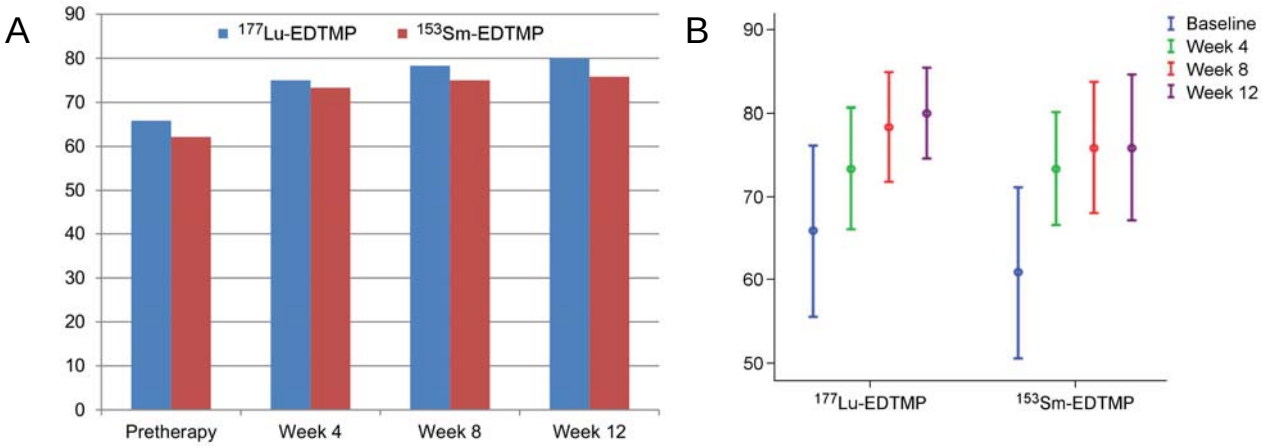

Fig 5a. Graph illustrating Mean Karnofsky's indices in responders treated with ^{153}Sm-EDTMP and ^{177} Lu-EDTMP

Fig 5b: Error bar graph illustrating mean Karnofsky's indices in responders treated with ^{153}Sm-EDTMP and ^{177} Lu-EDTMP:

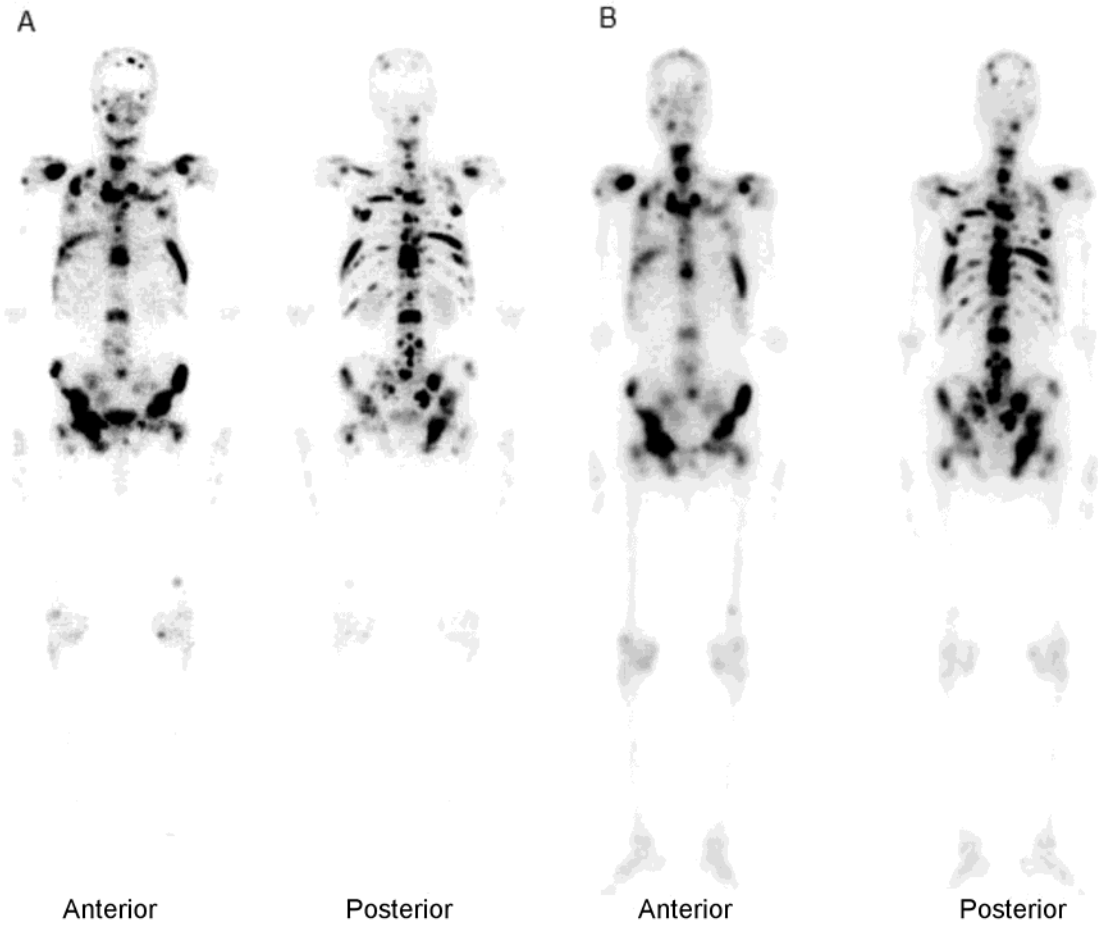

Figure 6: A) Tc-99m MDP Bone Scan. B) Post Therapy ^{177}Lu-EDTMP Scan.

Fig 6. 69 yr old male, known case of adenocarcinoma of prostate (Gleason's score 9) (operated primary) presented with multiple painful skeletal metastases. Patient was on oral NSAIDS thrice a day (analgesic score 3) and had already received RT to pelvis 6 months back. Pre-therapy parameters were: VAS- 9, BAP- 109.6, EORTC- 68, Karnofsky- 80 and ECOG- 2. Corresponding post ^{177}Lu-EDTMP therapy value were: VAS- 4, BAP- 87, EORTC- 40, Karnofsky- 80 and ECOG- 1. Post therapy analgesic score was zero.

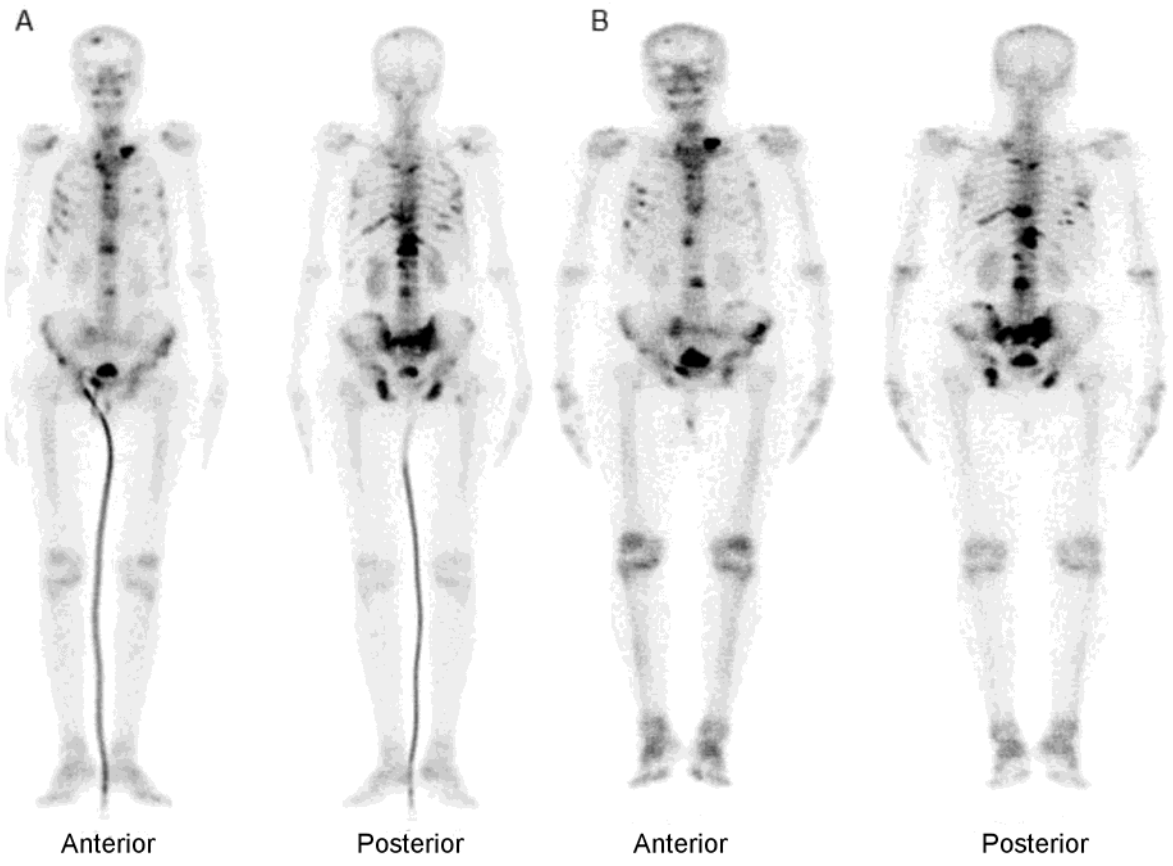

Fig 7. A) Tc-99m MDP Bone scan. B) ^{153}Sm-EDTMP post therapy scan.

Fig 7. 59 yr old male, known case of adenocarcinoma prostate (Gleason's score 8) (operated primary) presented with multiple painful skeletal metastases. Patient was on oral tablet Narcodol twice a day (analgesic score 6) and had already received RT to pelvis 9 months back. Pre-therapy parameters were: VAS- 8, BAP- 63.2, EORTC- 62, Karnofsky- 60, ECOG- 3. Corresponding post 153Sm-EDTMP therapy value were: VAS- 3, BAP- 56, EORTC- 54, Karnofsky- 80 and ECOG- 1. Post therapy analgesic score was zero.

Table 1: Analgesic Score (*4,15*):

Drugs	Score
No drug	0
Paracetamol / Aspirin	1
Other NSAIDs (Etoricoxib, rofecoxib, etc)	2
Atypical Opioids and Non morphine opioids (Tramadol, Narcogen)	3
Morphine	4

Quantity	Score
No drugs	0
Single tablet per day	1
Two tablets per day	2
Three tablets per day	3
Four tablets per day	4

Table 2. Patient demographics of mean pre-therapy performance characteristics

Study Parameter	^{177}Lu-EDTMP	^{153}Sm-EDTMP
Mean Analgesic Score	5.3	5.7
Mean EORTC	50.9	62.2
Mean BAP	35.1	60.9
Mean ECOG	2.1	2.4
Mean Karnofsky	62.7	63.5
Mean VAS	8.3	7.8

Table 3: Hematological toxicity

	Hb		WBC		Platelets	
	Lu177	**Sm153**	**Lu177**	**Sm153**	**Lu177**	**Sm153**
Normal	5/15 (33.33%)	3/16 (18.75%)	8/15 (53.33%)	11/16 (68.75%)	12/15 (80%)	12/16 (75%)
Grade I	0/15 (0%)	1/16 (6.25%)	5/15 (33.33%)	4/16 (25%)	3/15 (20%)	3/16 (18.75%)
Grade II	7/15 (46.67%)	9/16 (56.25%)	2/15 (13.33%)	1/16 (6.25%)	0/15 (0%)	0/16 (0%)
Grade III	3/15 (20%)	2/16 (12.5%)	1/15 (6.67%)	0/16 (0%)	0/15 (0%)	0/16 (0%)
Grade IV	0/15 (0%)	1/16 (6.25%)	0/15 (0%)	0/16 (0%)	0/15 (0%)	1/16 (6.25%)

Table 4. The response parameters observed in non-responders with either radiopharmaceutical:

4a. ^{177}Lu-EDTMP group (n=3):

Study Parameter	Pre-Therapy	Post-Therapy
Mean Analgesic Score	8.0	8.0
Mean EORTC	45	48.67
Mean BAP	38.37	44.23
Mean ECOG	3.0	3.3
Mean Karnofsky	50	43.3
Mean VAS	8.3	10

4b. ^{153}Sm-EDTMP group (n=4):

Study Parameter	Pre-Therapy	Post-Therapy
Mean Analgesic Score	8.75	8.75
Mean EORTC	70	72.5
Mean BAP	80.26	85.57
Mean ECOG	2.25	3.25
Mean Karnofsky	67.5	52.5
Mean VAS	8.0	8.75