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Chapter 7

Samarium-153 Therapy and Radiation Dose for Prostate Cancer

Yasemin Parlak, Gul Gumuser and Elvan Sayit

Additional information is available at the end of the chapter

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Abstract

Prostate cancer (PC) is one of the most frequent malignancies in Western countries. At initial diagnosis, bone metastases are present in 15–30% of cases. These metastases cause some complications including bone fracture, hypercalcemia, and bone pain, which significantly affect patients' quality of life. Radionuclide treatment was created as an alternative to external palliative radiotherapy in the treatment of bone pain arising from bone metastasis of PC. The basic principle of the radionuclide treatment of pain is that the uptake of radioactive material is kept in a high amount that is enough to constitute a proper clinical impact in the tumor, and it is kept at a low dose enough to avoid the occurrence of significant adverse effects in other organs (commonly in the bone marrow). Samarium-153 ethylenediaminetetramethylenephosphonic acid (153Sm-EDTMP) is a radiopharmaceutical compound that has an affinity for skeletal tissue and concentrates in areas of increased bone turnover, localizes in the skeleton, and is excreted via glomerular filtration. Medical staff preparing and administering radiopharmaceuticals in nuclear medicine, whether for diagnostic imaging or for therapeutic application, may receive significant radiation doses to their hands, particularly the fingers. Sm-153 treatment can be used as an effective and safe treatment alternative in the management of metastatic bone pain. Radiation protection of the public and the environment after Sm-153 EDTMP therapy is important.

Keywords: Sm-153 therapy, radiation dose, bone palliation, prostate cancer, radionuclide therapy

1. Introduction

Prostate cancer is one of the most common malignancies worldwide and the third most common cause of death from cancer in men. In advanced prostate cancer, spread of the disease to the

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skeleton occurs in the majority of patients, with skeletal metastases being predominantly osteoblastic in nature [1, 2]. Bone metastasis is a common sequela of solid malignant tumors such as prostate, breast, lung, and renal cancers, which can lead to various complications, including fractures, hypercalcemia, and bone pain, as well as reduced performance status and quality of life [3]. A multidisciplinary approach is often required not only to differentiate the specific cause of the pain but also for appropriate patient management. Several radiopharmaceuticals for treating painful bone metastases have been developed [3]. Radiation is of proven benefit for pain palliation, and there is growing interest in the therapeutic potential of bone-seeking radiopharmaceuticals [4]. Radionuclide therapy has been proposed as an alternative modality for the management of bone pain. These radiopharmaceuticals localize preferentially in active bone and, mainly, at metastatic lesions, allowing site-directed radiotherapy [1].

The basic principle of the radionuclide treatment of pain is that the uptake of radioactive material is kept in a high amount that is enough to constitute a proper clinical impact in the tumor, and it is kept at a low dose enough to avoid the occurrence of significant adverse effects in other organs (commonly in the bone marrow where more side effects were seen) [5]. One of the most important advantages of the pain treatment with radionuclide agents is the repeatability of the procedure [3]. The radioactive isotopes of P-32 and Sr-39 are the initial radiopharmaceuticals in radionuclide treatment of painful bone metastasis and most recently, Sm-153[4]. Sm-153 EDTMP is an effective treatment of painful bone metastases from different neoplasms. However, there are few studies describing clinical experience with this therapeutic modality. Medical staff preparing and administering radiopharmaceuticals in nuclear medicine, whether for diagnostic imaging or for therapeutic application, may receive significant radiation doses to their hands, particularly to the fingers. People occupationally exposed to radiation must have the relevant technical knowledge and competence, that is, must at least be aware of radiation protection rules and dose-optimized work practices.

The aim of this chapter was to evaluate the efficacy of Sm-153 EDTMP. The objective is to evaluate extremity doses and dose distributions across the hands of the medical staff working in Nuclear Medicine departments.

2. Main text

2.1. Prostate cancer

Prostate cancer is the most commonly diagnosed male malignancy. Prostate cancer is the most prevalent nonskin cancer among men in the United States and is the second leading cause of cancer deaths in men [6].

Prostate-specific membrane antigen (PSMA) is a cell surface protein with a significantly increased expression in prostate cancer cells when compared to other PSMA-expressing tissues such as the small intestine, renal tubular cells, or salivary glands. It therefore provides a promising target for prostate cancer–specific imaging and therapy. Recently, procedures have been developed to label PSMA with 68Ga, 99mTc, and radioiodine for positron emission

tomography (PET) or single photon emission computed tomography (SPECT) imaging and therapy [7].

Choline-PET/CT is the most promising whole-body imaging modality in detecting distant metastases of prostate cancer, because of its ability to depict small pathological lymph nodes and bone metastases with a high sensitivity, specificity, and accuracy. This feature is of primary importance on management of patients with prostate cancer and for evaluating their prognosis, thanks to the possibility to assess in a single session both anatomic and metabolic information about the disease [8]. There are several papers about the role of Ch-PET in primary prostate cancer detection and its role in staging prostatic disease before treatment. However, since the Ch uptake can occur in some benignant conditions, such as prostatitis or prostatic hyperplasia, the role of this technique in this field is still not well clear.

The 11C-Ch is characterized by a short half-life (approximately 20.4 min), and for this reason, its use is allowed only in centers provided with a cyclotron. In consideration of the logistical limitations of the use of 11C-Ch, Ch was subsequently labeled with 18F, which, thanks to the increased half-life (109.8 min), allows storage and transport. However, 18F-Ch radiotracer is characterized by an increased urinary excretion compared to 11C-Ch [9].

Bone metastases are the most common and severe complication in patients diagnosed with primary tumors. Skeletal metastases are clinically significant because of associated symptoms, complications such as pathological fracture significance for staging, treatment, and prognosis. It develops in up to 70% of patients diagnosed with prostate cancer and breast cancer. Skeletal-related events can reduce the health-related quality of life secondary to debilitating pain, paralysis, loss of mobility, and hospitalization. Systemic palliative-targeted therapy with suitable radiopharmaceuticals has emerged as a particularly appealing and efficient treatment modality for patients with multiple skeletal metastases [9].

There are essentially three main types of particulate radiations that are of interest for palliative treatment of bone metastasis using radiopharmaceuticals: beta (β^-) particles, alpha (α) particles, and Auger electrons. Traditionally, tumor-targeted radiotherapy has used β^--emitting radionuclides. However, high-energy β^- particles, with a range of several millimeters in tissues, can irradiate cells nearby the targeted tumor. Conversely, α particles (typical penetration range of <100 μm) and Auger electrons (penetration range of several nanometers to micrometers) have shorter penetration ranges and higher linear energy transfer (LET) [9].

In recent years, several reports have been published describing the use of multiple radionuclides in the context of palliative treatment of bone metastases.

2.2. Radionuclide therapy

Pain is the most common symptom in the prostate cancer patients. The incidence and severity of pain in the last period of the life is increasing. Patients and their relatives may adversely be affected from the quality of life as a major fear source. However, pain related to prostate cancer can be treated effectively about 85–90% by applying correct approaches. The remaining 5–15% of patients with pain can be achieved by applying appropriate surgical techniques. The severity and frequency of pain in cancer patients depends on many factors such as age of the patients,

the stage of the disease, and the site of bone metastases. For effective pain treatment, accompanying medical and psychosocial problems of the patients should be evaluated, and then, appropriate treatment should be done [10].

In recent years, there has been a much greater emphasis on "radionuclide therapies" that are designed to damage only the cancerous cells. At present, effective targeted radiopharmaceutical therapeutics have been developed. Radionuclide therapy uses ionizing radiation to minimize tumors and kill cancer cells. The basic principles in the treatment of radioactive elements in nuclear medicine, to benefit from the devastating effects generated in the cells. Therefore, many radionuclides have oncological applications of many proven efficacy and safety. Radionuclide therapy uses radioactive isotopes, administered either orally or intravenously, to deliver highly targeted therapy for a range of disorders, enabling the delivery of a high dose to the target, while minimizing normal tissue toxicity [11].

In targeted radionuclide therapy, the biological effect is obtained by energy absorbed from the radiation emitted by the radionuclide. Whereas the radionuclides used for diagnostic nuclear medicine procedures emit gamma rays, which can penetrate highly into the body, the radionuclides used for radionuclide therapy must emit radiation with a comparatively short range. Radionuclides emitted beta particles, alpha particle, and Auger electrons for radionuclide therapy use due to short range and high ionization capability. In some cases, mixed emitters are used to perform both imaging and therapy with the same radionuclide (e.g., Samarium-153) [11].

Various radiopharmaceuticals have been advanced for the treatment of painful bone metastases (**Table 1**). The physical characteristics of these radionuclides are different and have specific benefits. These radionuclides are administered intravenously or orally and localize the painful bone metastases with a high target-to-nontarget tissue ratio and a very low concentration in the normal bone, especially bone marrow. The therapeutic suitability of the radionuclides is important. So the penetration range of the radionuclides is concerned with the energy of the electrons. The applications of the radiopharmaceuticals are easily performed without the need for expensive high-technology equipment. Thus, these agents can be applicable not only in major medical centers but also in minor hospitals, and the workers have to be educated to comply with Nuclear Regulatory Commission requirements. These agents target not only osteoblastic lesions but also lesions containing osteolytic and osteoblastic components. Most of the patients who are treated observed reduce of pain, thus reducing their need for analgesics and improving the quality of life and mobility [3, 4].

The studies regarding metastatic bone pain have particularly focused on the metastases of hormone refractory prostate cancer, which was resistant to the treatment of opioid analgesic. While radiotherapy is more appropriate in the palliative treatment of localized, regional metastatic lesions, this management is less applicable in the treatment of diffuse metastatic lesions. The type of metastatic bone pain is different from other somatic pains, such as visceral, neuropathic, arthritic, and neuropathic pain. While the severity of pain is less intensive initially, it will progress a chronicle process including acute pain episodes with increasing severity subsequently. In this process, the pathophysiology of pain cannot be clearly explained, and various theories have been proposed [12].

Isotopes	T1/2 (days)	Max. energy (MeV)	Gamma-emission, keV (%)	Abundance (%)	Soft-tissue range (mm) (maximum/minimum)
P-32	14.3	1.7			8/3
Sr-89	50.5	1.4			2.4
Re-186	3.7	1.07	137	9	2.4
Re-188	16.9	2.1	155		3
Sm-153	1.9	0.81	103	29	0.6

Table 1. Physical properties of therapy isotopes for bone pain palliation.

A study reported that the maximal pain response to the treatment occurred at 4–6 weeks after the treatment [13]. In another study, Silberstein [14] declared that the complete or partial response to 153Sm treatment was obtained in 62–74% of patients, and this response was commonly seen 5–10 days after the treatment.

The study investigated the efficacy of 153Sm treatment; complete response rate was found 12.4% and the partial response rate was found 73.4%.

Gul et al. determine the reduction in the analgesic consumption and improvement in the performance and mobility score of the patients (10).

Alleviating of pain can occurred about within 2–7 days depending on the agent after the first injection. The repeating injections should be performed as soon as possible after the occurrence of pain recurrence, if bone marrow reserve is adequate. The clinical usage of radionuclides is not only limited to the opioid resistant pain. As the result of some trials, it was obviously clear that the expected long-term efficacy and tolerance could be achieved without requirement of opioid analgesics. The primary goal of the treatment is to provide better quality of life in daily activities by minimal drug usage [3].

2.2.1. Therapy radionuclides for bone pain palliation

In the past few years, several radiopharmaceuticals have been improved with bone-seeking properties that provide palliation of pain to multiple bone metastasis. The most of these are beta electrons, depositing highly their energy over up to millimeters in the surrounding tissues. A few of the therapeutic radionuclides emit small amounts of gamma-radiation, allowing for a scintigraphic imaging. The commonly used radiopharmaceutical for pain palliation is samarium-153 HEDP. Hematopoietic suppression is the major side effect of radionuclide therapies, with leukopenia and thrombocytopenia more likely to be clinically significant than anemia. The physical properties of radiopharmaceuticals are discussed in detail in the following sections.

2.2.2. Phosphorus-32

Phosphorus-32 is pure beta-emitting radionuclide with a physical half-life of 14.3 days. The average beta particle energy is 695 keV. The mean and maximum particle ranges in tissue of

phosphorus are 3 and 8 mm, respectively. P-32 is used orthophosphate compound as palliative treatment purposes. Approximately 85% of the total phosphate pool is located in the skeleton bound as inorganic phosphate to the hydroxyapatite matrix. From five to ten percentage of administered activity is excreted via the kidneys within the first 24 h. Total bone doses in the range 0.4–1.7 cGy/MBq have been reported [4, 15].

2.2.3. Strontium-89

Strontium-89 is a pure beta-emitter with a beta particle energy of 1.46 MeV and a physical half-life of 50.5 days [15]. It localizes in bone primarily in areas of osteoblastic activity. It is an mean particle range in tissue of 2.4 mm. The fix dose is 148 MBq (4 mCi). The radiation dose of metastatic foci is about 1000–5000 cGy. Bone marrow radiation dose is approximately ten percent of metastatic foci. 89Sr can be effective at relieve pain from bone metastases, particularly for metastatic prostate or breast cancer [4].

2.2.4. Rhenium-186

Rhenium-186 is a beta- and gamma-emitting radionuclide. The maximum beta particle energy is 1.07 MeV. Re-186 has a 137 keV, 9% abundance gamma-photon with a physical half-life of 89.3 h. It is forms a stable diphosphonate chelate with hydroxyethylidene diphosphonate (HEDP). Rhenium-186 HEDP has rapid urinary excretion. It is excreted about 70% of dose within 6 h in the urine [4].

2.2.5. Sn-117m

Sn-117m is gamma-emitting radionuclide with 159 keV. Physical half-life of Sn-117m is 13.6 days. It is decays by short-range conversion electrons. Bone marrow toxicity of this radionuclide is low because of its short range. Therefore, Sn-117m can be used to treat bone tumors and rheumatoid arthritis [16].

2.2.6. Samarium-153

Samarium-153 is a reactor which produced high radionuclidic purity by neutron bombardment of enriched 152Sm oxide [3]. Samarium-153 is a beta-emitter with a short half-life (46.7 h), which also emits gamma-photons suitable for imaging at 103 keV. Samarium-153 principal radiation emission data are shown in **Table 2**. The isotope is chelated to ethylene diamine tetramethylene phosphonate (EDTMP), which targets the bone matrix as a polyphosphonate (**Figures 1** and **2**). The therapeutic doses administered to patients about 50% settle in the bone excretion are through the kidneys. The proportion of skeletal uptake is the highest for the bone-seeking radiopharmaceuticals. The effective range of 153Sm is 2–3 mm in bone [1]. 153Sm-EDTMP is indicated for the relief of pain in patients with osteoblastic metastatic bone lesions at a standard dose of 37 MBq/kg to a maximum of 5550 MBq [1, 2]. Clinical benefit is reported by 60–80% of patients within 2 weeks of administration, frequently within 48 h, with a response duration of 4–40 weeks [4].

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Radiation	Energy (keV)	Abundance (%)
Beta	640	30
Beta	710	50
Beta	810	20
Gamma	103	29

*Maximum energies are listed for beta emissions, and the average beta particle energy is 233 keV

Table 2. Samarium-153 principal radiation emission data.

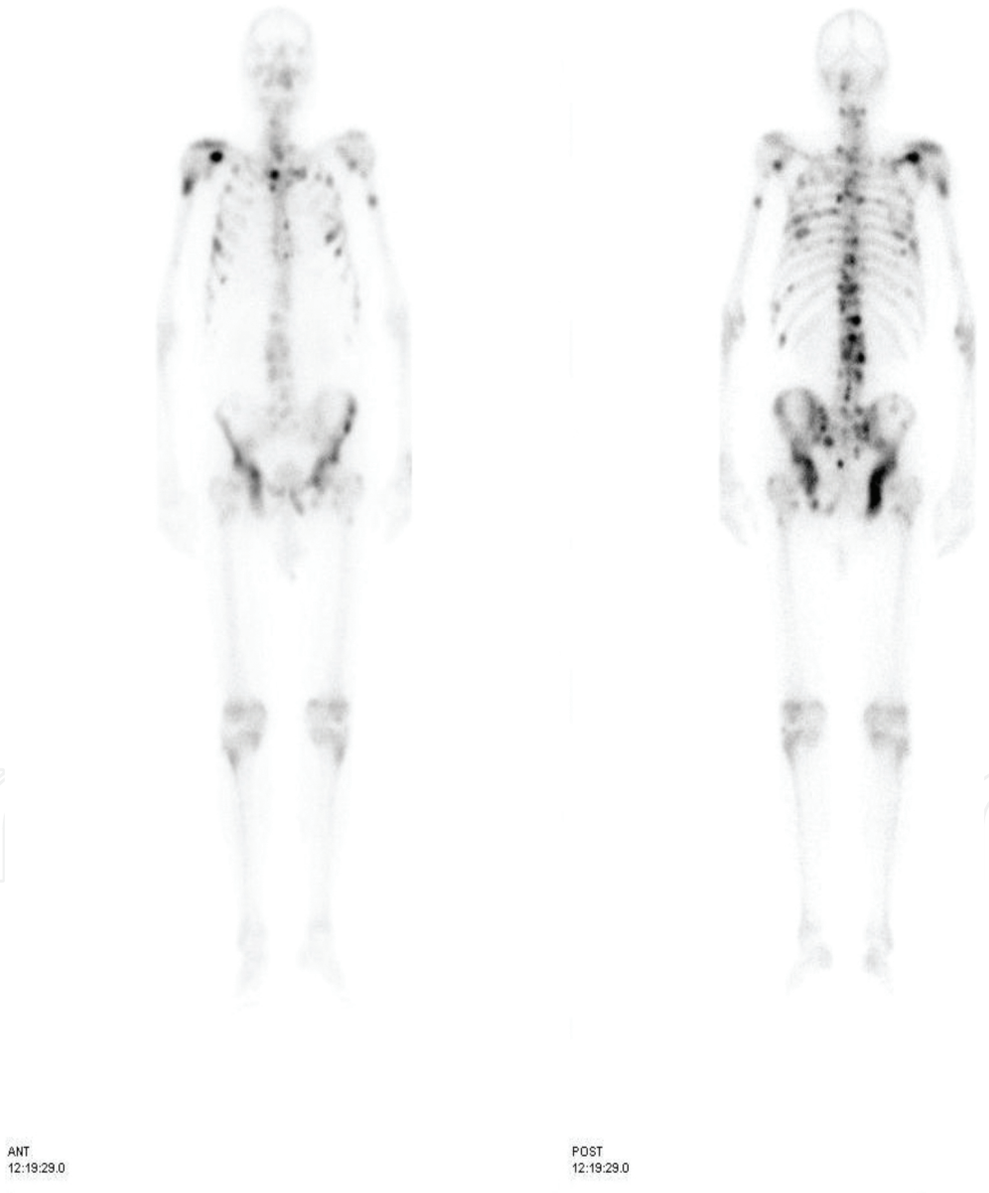


Figure 1. A bone scintigraphy that was obtained before the 153Sm-EDTMP treatment.



Figure 2. A bone scintigraphy that was obtained after the 153Sm-EDTMP treatment.

This treatment can be repeated several times to the patients. Repeat dosing with 153Sm is both safe and effective. The studied reports showed that the patients with symptomatic bone metastases receiving multiple doses of 153Sm have no significant differences in pain reduction or in myelosuppression after a second or third treatment [17].

Pregnancy, lactation, acute spinal cord compression, single metastatic lesion, renal failure, the long bone that holds more than 50% of the affected bone metastases, risk of fracture and in the presence of disseminated intravascular coagulation are the contraindications of pain palliation with 153Sm therapy.

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2.2.7. Radiation dose

The diagnostic and therapeutic procedures have been continuously increasing in most of the nuclear medicine facilities. The risk of radiation exposure of staff is of importance due to increasing procedures. The radiation sources of nuclear medicine Departments are preparing and administering of the radiopharmaceuticals. The workers may receive significant radiation dose to their whole body, especially to the hands.

Therapeutic nuclear medicine requires special consideration due to the high doses of radiation. Therapeutic radionuclides have usually beta electrons. Owing to 153Sm-EDTMP's intermediate beta-energy and low tissue penetration, the bone marrow, for the most part, is spared throughout the skeleton. For protection, two radiation safety consideration needs to be paid attention. One of them, external radiation dose of 153Sm, the interaction of high-energy beta particles with high atomic number materials (e.g., lead) will lead to the production of high-energy X-rays (Bremsstrahlung). Parlak et al. reported that external radiation dose of 153Sm is high for the first 8 h (**Figure 3**). They suggest that hospitalizing the patients treated with Sm-153 therapy in an isolated room for 8 h would be helpful for radiation protection of the public. On the other hand, radiation safety consideration is the contamination by excretion of the 153Sm. The variability of isolation times indicates a strong dependency of effective half-life on biological excretion and shows no relationship with administered activity. Certainly, this variability reveals the need to determine these parameters for each patient [1].

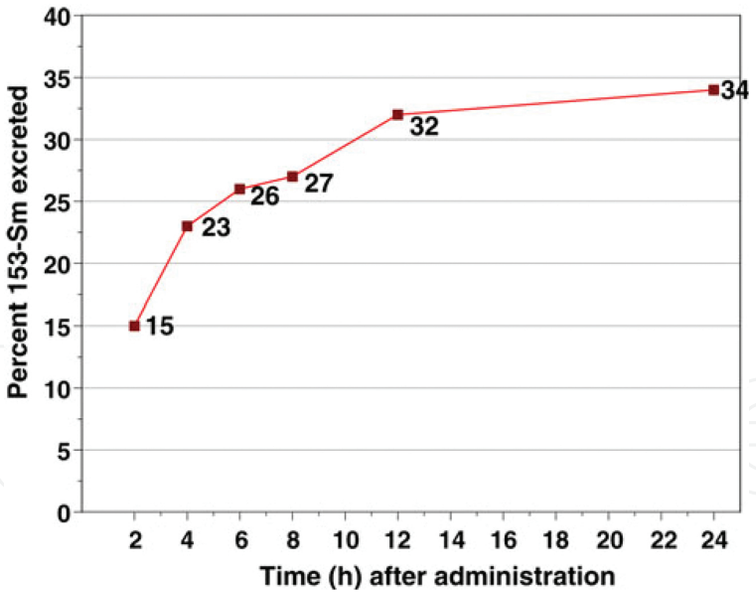


Figure 3. Excretion of 153Sm-EDTMP through the urinary tract in the first 24 h.

Developments in nuclear medicine show that applications involving beta-emitters will probably increase further. Data on the beta-radiation dose equivalents for the staff performing such treatments are limited. For this reason, additional measures should be provided for the training and continuing education of the staff in order to avoid any further increase in extremity doses.

Author details

Yasemin Parlak*, Gul Gumuser and Elvan Sayit

*Address all correspondence to: yasemin.gultekin@hotmail.com

Department of Nuclear Medicine, Medical School, Celal Bayar University, Manisa, Turkey

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