**International Journal of Studies in Natural and Medical Sciences**
Volume 02 Issue 05, May, 2023
ISSN (E): 2949-8848
Scholarsdigest.org

# Modern Approaches to Treating Multiple Osteogenic Metastases (Literature Review)

Rakhimov Nodir Makhmamatkulovich
Samarkand State Medical University, Samarkand, Uzbekistan

Shahanova, Shakhnoza Shavkatovna
Samarkand State Medical University, Samarkand, Uzbekistan

Davronov Eshboy Egamkulovich
Samarkand State Medical University, Samarkand, Uzbekistan

Mirzakulov Bunyod Gaybullayevich
2Samarkand branch of the Republican Specialized Scientific and Practical Medical Center of Oncology and Radiology

Murodov Shakhzod Tokhir ugli
Samarkand State Medical University, Samarkand, Uzbekistan

**Abstract**
Early detection of bone metastases is crucial in reducing morbidity and improving outcomes. However, current imaging methods, such as bone scintigraphy, have limitations in sensitivity, while whole-body MRI may be limited in accessibility and cost. Existing standards only recommend imaging when symptoms, such as bone pain or fractures, are present, thereby limiting the diagnosis of patients with debilitating or complicating metastases. In the absence of appropriate methods, adequate monitoring with clinical observation becomes essential in managing patients with multiple osteogenic metastases.

**Keywords**: multiple osteogenic metastases, X-rays, bone.

## Introduction

It is worth noting that current surveillance measures primarily involve standard imaging of the chest and abdomen, which do not include the extremities and neck. This should be taken into account when making clinical decisions. Adequate imaging should be initiated when clinical symptoms indicating bone disease are present and/or persist (11). In most cases, X-rays can only detect mineral loss in bones ≥50%, which limits their applicability for detecting osteogenic metastases of multiple primary cancers in bones.

**International Journal of Studies in Natural and Medical Sciences**
Volume 02 Issue 05, May, 2023
ISSN (E): 2949-8848
Scholarsdigest.org

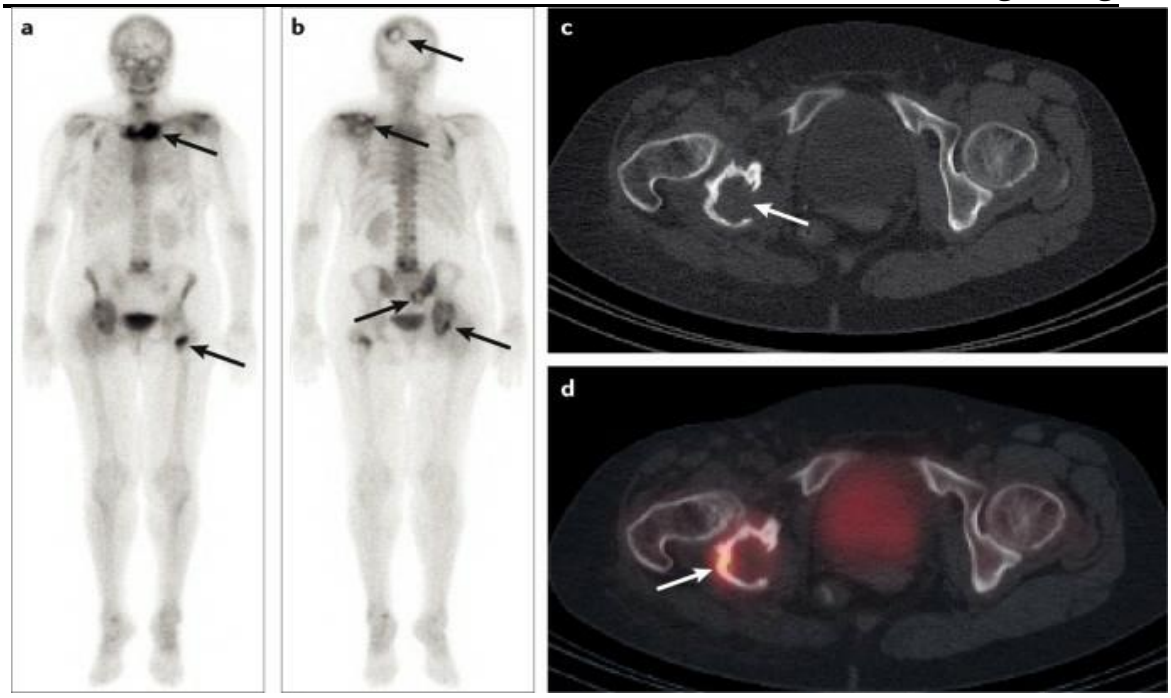


**Figure 1: Radionuclide image of bone metastases.**

The osteolytic nature of bone metastases from multiple primary cancers reduces bone scanning sensitivity to ≤50% since bone scanning only reflects the osteoblastic reaction of the bone tissue to metastatic cells, which is often absent in bone metastases from multiple primary cancers. The deposition of radiopharmaceuticals for bone scanning occurs through physicochemical adsorption (chemosorption) onto the hydroxyapatite structure of the bone tissue. These radiopharmaceuticals cannot purely visualize osteolytic lesions where the bone structure is replaced by tumor cells, thus false-negative results are common for osteolytic lesions (11).

CT is an important tool for assessing bone stability and structure (13) (Fig. 3). Given the propensity of metastatic spread to the proximal axial skeleton, which is covered by chest, abdomen, and pelvic CT, most lesions causing significant loss of bone mass are captured by CT. Therefore, subsequent monitoring can rely on routine CT, which includes proximal extremities and sagittal reconstructions of the spine using bone windows and bone-specific reconstruction techniques. CT is a powerful tool for assessing bone structure, providing higher sensitivity than bone scintigraphy for detecting bone metastases. MRI has a high sensitivity and specificity for detecting bone metastases.

The true value of PET-CT with 18F-sodium fluoride (18F-NaF) or 18F-fluorodeoxyglucose (18F-FDG) in staging multiple primary cancers is yet to be determined. 18F-NaF PET-CT appears to have higher sensitivity and accuracy than

bone scanning or CT in detecting bone metastases from multiple primary cancers, but data are limited due to small patient groups and a limited number of comparative studies (24). 18F-FDG-PET without CT has shown high specificity but limited sensitivity in detecting distant bone metastases in earlier studies before hybrid PET-CT was introduced, providing overall specificity and sensitivity of 100% and 63.6%, respectively (11). Hybrid 18F-FDG-PET-CT combines the advantages of both PET and CT, demonstrating high sensitivity in detecting disease recurrence or metastases during postoperative follow-up of patients with advanced multiple primary cancers (sensitivity 89.5% and specificity 83.3%) (17). 18F-NaF PET-CT has shown even higher sensitivity, although in small patient groups (15). However, PET-CT is generally not used due to its high cost and limited accessibility. This method can be employed as a complement when conventional imaging fails to yield definitive results, as early diagnosis of metastatic disease can profoundly impact treatment strategies. PET offers high specificity of MRI depends on the radioactive tracer used, and its sensitivity is typically >93% for detecting skeletal metastases (13) (Figure 3). However, MRI is not commonly used for follow-up due to high associated costs and limited availability. In patients with apparent solitary or oligometastatic bone involvement before extensive surgical resection, a whole-body MRI should be performed to ensure that the patient indeed has a limited number of surgically treatable bone lesions.

Current state of treatment for bone metastases: In a meta-analysis of 9 studies involving 2,189 patients with advanced cancer and bone metastases, bisphosphonates reduced the risk of developing bone complications by 17% (relative risk [RR], 0.83; 95% CI, 0.78-0.89; $P < 0.001$). This effect was more modest but still significant when episodes of hypercalcemia were excluded (10 studies, 2,656 patients; RR 0.85; 95% CI 0.79-0.91; $P = 0.0001$). Overall, intravenous bisphosphonates reduced the risk of developing bone complications by 17% (95% CI, 0.78-0.89) compared to oral bisphosphonates, which reduced the risk by 16% (95% CI, 0.76-0.93) (11).

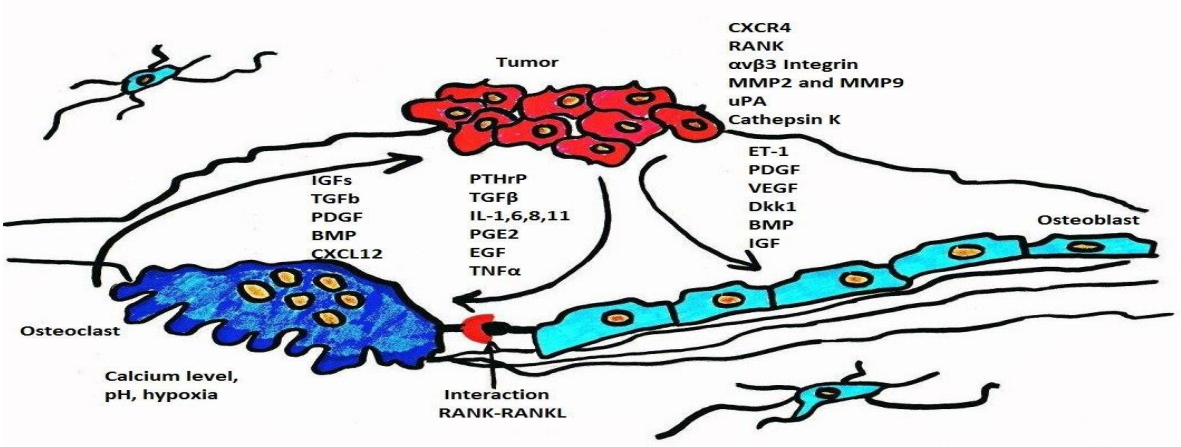


**Figure 2. Molecular mechanism of bone metastasis development.**

Other currently available anti-resorptive treatments include RANKL inhibitors and systemic radiation methods: samarium oxabifore or strontium ranelate. The formation, functioning, and survival of osteoclasts require RANKL activity (26). Experts suggest that tumor cells induce osteoclast activation through RANKL, which then leads to bone resorption and release of growth factors, resulting in a cycle of bone destruction and tumor proliferation. Denosumab is an investigational treatment in this regard monoclonal antibody directed against RANKL binds to RANKL and blocks ligand stimulation of osteoclast formation (16). Preliminary studies of denosumab in patients have shown a significant reduction in urinary NTx that is sustained for six months with a single subcutaneous dose. Additional clinical trials are currently being conducted to evaluate denosumab for the prevention and treatment of bone metastases in kidney cancer (27). Clinical trials assessing denosumab for use in osteoporosis and bone metastases are also ongoing. Fizazi et al. recently reported that among patients with elevated NTx levels, denosumab normalized NTx levels more frequently than continued intravenous bisphosphonate therapy (22).

Renal toxicity is a major concern with intravenous administration of nitrogen-containing bisphosphonates. An increase in creatinine levels is observed in 10% of patients and varies depending on the drug, dosage regimen, duration of administration, and concomitant therapy. Reducing the dose according to recommendations and extending the infusion time may help address this issue. Jaw osteonecrosis occurs in 1.3% of patients receiving zoledronic acid. Risk factors for jaw osteonecrosis include poor oral hygiene, gum disease, use of glucocorticoids and antiangiogenic drugs, and oral surgical procedures. Whenever possible, all oral manipulations are best completed prior to initiating bisphosphonate therapy.

Renal toxicity and flu-like syndrome are less frequently observed with denosumab administration. Unlike bisphosphonates, denosumab is not excreted by the kidneys but is eliminated through intracellular catabolism in phagocytes, similar to the mechanism of elimination for other therapeutic monoclonal antibodies. Therefore, it can be used in patients with chronic kidney insufficiency. In registration studies, hypocalcemia of any grade was observed twice as often in the denosumab group compared to the zoledronic acid group, and severe hypocalcemia (<1.75 mmol/L) was reported in 3.1% versus 1.3% of cases, respectively. In the most severe cases, hypocalcemia was prolonged.

In a meta-analysis comparing denosumab and zoledronic acid, jaw osteonecrosis was more frequently observed in the zoledronic acid group; however, the differences were not statistically significant (1.8% versus 1.3%, $p < 0.13$) (13). Dental procedures are safer to perform 26 days after denosumab administration compared to 6 months with bisphosphonates, as the half-life of denosumab is shorter.

**International Journal of Studies in Natural and Medical Sciences**
Volume 02 Issue 05, May, 2023
ISSN (E): 2949-8848
Scholarsdigest.org

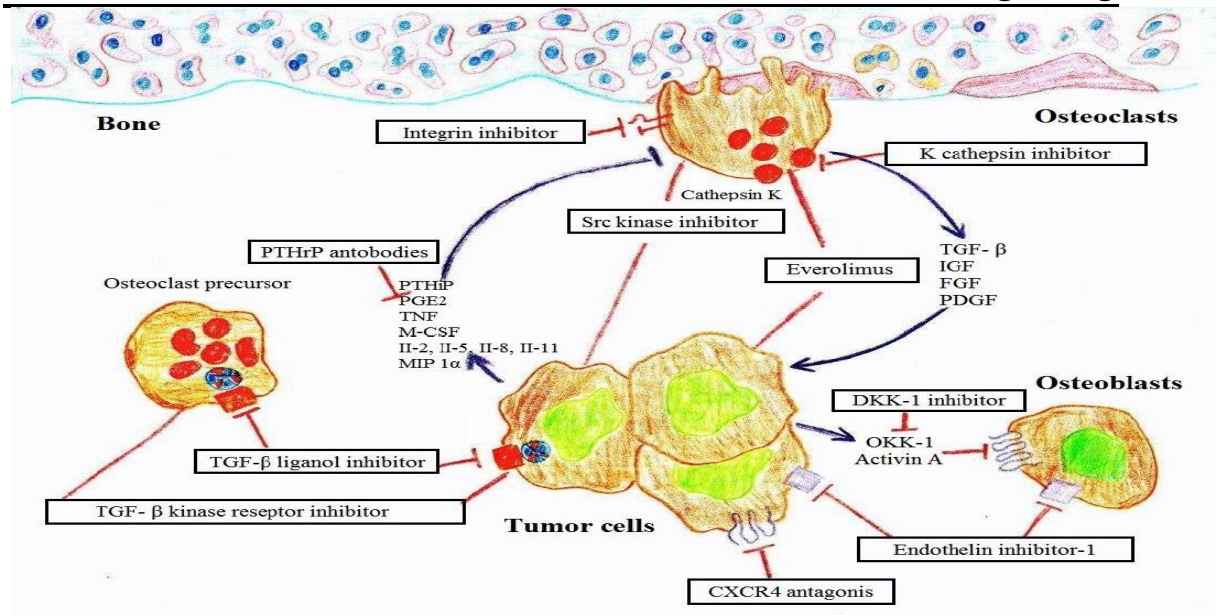


**Figure 3. Investigational targeted therapies for the treatment of bone metastases**

Targeted therapies that work through Src kinases (dasatinib, saracatinib, bosutinib, and others) have demonstrated effectiveness in preclinical and early clinical stages. Recently, the results of a Phase II study of dasatinib in combination with letrozole for bone metastases in breast cancer were published. A significant increase in progression-free survival was demonstrated in the combination treatment group compared to the group receiving letrozole alone. Phase II studies are underway with bosutinib, which blocks Src/Abl tyrosine kinases and other groups of kinase enzymes. It also shows high antitumor potential in monotherapy but does not affect bone marker levels. Odanacatib, an inhibitor of cathepsin K, reduces the level of urinary N-terminal telopeptide (uNTx) similar to zoledronic acid after four weeks of treatment for bone metastases in breast cancer.

A wide range of radiopharmaceuticals have been successfully used for the therapy of bone metastases worldwide. These radiopharmaceuticals are based on various radionuclides with β-emission as their common radiotherapeutic effect. They are administered intravenously (oral administration is possible only for 32P) rather than locally into the metastases, leading some authors to refer to this treatment as "systemic radiation therapy" or "systemic radionuclide therapy." Radiopharmaceuticals are delivered to pathological sites through various transport compounds (EDTMP, HEDP, DTPA, etc.) or, in the case of 89Sr-chloride, are fixed in the bone matrix instead of calcium.

In global practice, radiopharmaceuticals based on 153Sm, 89Sr, 32P, 33P, 186Re, 188Re, 117mSn, 177Lu, 90Y, 131I, and others are actively used for palliative therapy of bone metastases. In Russia, this list is currently limited to two drugs: samarium

oxabifor - 153Sm and strontium-89Sr chloride. By their chemical nature, 153Sm EDTMP (EDTMP), samarium oxabifor, and 153Sm are phosphonate compounds that transport the radionuclide 153Sm to sites requiring enhanced mineralization (metastases). The highest concentration of the drug is found in the interface between the bone and metastases and in peripheral areas of bone metastases.

In these zones, high doses of β-radiation are locally generated, affecting tumor tissue, areas of perifocal infiltration and inflammation, as well as osteoclasts that degrade bone tissue. These mechanisms inhibit tumor progression and reduce the intensity of pain. 153Sm-based drugs are widely used in clinical practice worldwide and are manufactured by various companies in different countries, including France, the Czech Republic, Russia, and Uzbekistan.

A positive property of 153Sm-based drugs is the presence of gamma radiation in their spectrum, allowing scintigraphic imaging on a gamma camera to accurately monitor the accumulation of the drug in affected areas after administration. Repeat scintigraphy with 153Sm can provide insights into the dynamics and success of treatment. However, this property also has a negative aspect, as the presence of gamma radiation requires the hospitalization of patients who have been administered samarium oxabifor, 153Sm, according to current radiation safety standards. Typically, analgesic effects begin to manifest within 5-10 days, although the onset of clinical effects may vary. The duration of pain suppression, like other drugs, is variable, but authors often indicate 4-6 months or longer.

The effectiveness of palliative treatment, as noted by various authors, ranges from 70% to 80% on average. Similar to other medications, myelosuppression is the practically sole side effect requiring attention. 153Sm-based drugs are estimated to be cheaper than 89Sr chloride.

Thus, bone-targeted therapy is an important part of the multidisciplinary approach to treating bone metastases in prostate and kidney cancer. Treatment should begin with nitrogen-containing bisphosphonates (zoledronic acid) or denosumab in all patients regardless of clinical manifestations of the disease. The choice between these two groups of drugs remains open. According to ASCO recommendations, there is insufficient data indicating the superiority of one drug over another. Greater effectiveness in terms of initial and subsequent skeletal complications was observed in Phase III studies favoring denosumab. Ease of administration and the absence of the need to monitor creatinine levels are additional advantages. In metastatic renal cell carcinoma (mRCC), bone is the second most common site of metastasis. The majority of bone metastases are found in the pelvis, sacrum, spine, and proximal extremities. Furthermore, most cases of bone metastases exhibit an osteolytic nature with elements of destruction, and mixed-type metastases are also encountered.This predisposes patients to skeletal-related events (SREs) such as pathological fractures and spinal cord compression, necessitating radiation therapy or surgical interventions in the bone.

SREs are associated with increased morbidity and have a significant negative impact on patients' quality of life. Specifically, bone pain is the most common type of cancer-related pain, which may require opioid analgesics and palliative radiation therapy for pain control. Therefore, preventing SREs is of paramount importance in this patient population. Prior to the implementation of targeted therapies, these complications occurred in 74-85% of cases .

Several studies have reported that the median overall survival (OS) after the diagnosis of bone metastases in prostate cancer ranges from 12 to 28 months. Patients with 1, 2-5, or >5 bone metastases had median OS of 28 months, 18 months, or 9 months, respectively. Patients with a solitary synchronous bone metastasis had the longest survival (40 months). Retrospective analysis of data allowed the identification of five risk factors for predicting prognosis in patients with prostate cancer and bone metastases: sarcomatoid differentiation of the primary tumor (P = 0.001), spinal involvement (P = 0.003), extracranial metastases (P = 0.021), elevated alkaline phosphatase level (>1.5 times the upper limit of normal; P = 0.0003), and elevated C-reactive protein level (>0.3 mg/dL; P = 0.018), as well as differentiation of the primary tumor.

The mechanism of pain relief remains controversial. The proposed mechanism involves reducing tumor mass, subsequently decreasing intracompartmental pressure, and relaxing the endosteum. Another possible mechanism is the reduction of cytokine and other mediator secretions at tumor invasion sites.

The radioisotope 153Sm emits three beta particles with average energies of 810 KeV (20%), 710 KeV (50%), and 640 KeV (30%), with a maximum bone range of up to 3.1 mm, which is sufficient for irradiating bone tissue. Additionally, radioactive samarium emits gamma rays with a photon energy of 103 (29%) KeV. This energy can be used for different purposes in the stages of diagnosis and treatment, such as using it as a radioactive tracer for bone scanning before or after targeted therapy and for dosimetry assessment. Due to its short half-life (43.6 hours), high radiation doses can be administered.The shorter half-life and higher administered dose of 153Sm allow for delivering a high dose rate over a shorter period of time. The recommended dose is 37-55 MBq/kg of patient body weight.

153Sm is bound in a 1:1 ratio with ethylenediaminetetramethylenephosphonic acid (EDTMP), which is an analog of pyrophosphate. The 153Sm-EDTMP complex has an affinity for skeletal tissue and concentrates via chemisorption in areas of increased osteoblastic and osteolytic activity, where it associates with hydroxyapatite crystals, similar to other phosphonates. The biodistribution of 153Sm-EDTMP and technetium-99m-methylenediphosphonate (MDP) (medronate) is very similar in metastatic and normal bone, allowing both samarium and technetium to be used for bone scanning. The clearance of 153Sm-EDTMP from the blood after infusion is rapid, with two phases at 5.5 and 65 minutes, respectively. In the first phase, the drug is quickly taken

up by bone tissue, and in the second phase, it is excreted in the urine (which is the most effective time for performing radionuclide bone scanning). Urinary excretion practically ceases after 6 hours post-infusion. Skeletal uptake ranges from 55% to 75% of the administered dose, depending on the quantity and extent of metastasis. The initial application of the radiopharmaceutical strontium-89 chloride (89Sr) for bone imaging was described by Pecher in 1940/41, followed by the first report of pain relief in a patient with bone metastases from breast cancer using phosphoric acid-32 (32P) by Friedell. In Europe, strontium-89 chloride is approved for pain relief in bone metastases from prostate cancer, while samarium-153 ethylenediaminetetramethylenephosphonate (EDTMP) is approved for treating pain from all osteoblastic bone metastases. The uptake of radionuclide tracers used in radionuclide therapy of bone metastases depends on osteoblastic activity and tumor tissue calcification. In the past, bone metastasis morphology in primary prostate cancer was typically characterized as osteoblastic, whereas plasmacytoma and renal cell carcinoma were primarily associated with osteolytic bone lesions. Selective uptake depends on the degree of metabolic (i.e., osteoblastic) response elicited in normal bone by the presence of metastatic tissue. Increased bone turnover leads to enhanced uptake of bone-seeking radiopharmaceuticals in metastatic sites compared to normal bone, thus providing a high target dose of localized radiation. Skeletal uptake of the radiolabeled bisphosphonate 153Sm-EDTMP is approximately 48% of the administered activity. Estimates of absorbed radiation doses to osteoblastic bone metastases vary widely: from 6 to 61 cGy/MBq for 89Sr, from 1000 to 14,000 cGy for standard therapeutic activity of 1295 MBq 186Re-HEDP (this radiopharmaceutical has recently been withdrawn from the market), and an average dose of 87 Gy from 2590 MBq 153Sm-EDTMP. A dose of 54 mGy/MBq has been reported using 117mSn-DTPA, with bone uptake ranging from 34% to 83% of the administered activity. The mechanism and radiobiology of pain reduction through therapy from open sources are not fully understood. Direct radiation effects on neural tissue appear unlikely due to the well-known high radiation resistance of peripheral neurons. It is more likely that radiation to cells and tissues surrounding the metastasis contributes to changes in cellular signal transmission, leading to modulation of both pain reception and transmission.

Possible target cells likely include macrophages, mast cells, platelets, lymphocytes, and endothelial cells, which influence the secretion of pain mediators such as ATP, histamine, prostaglandin E (PGE), interleukin (IL)-1 and -2, leukotrienes.

A prerequisite for radionuclide therapy of metastatic bone pain is the demonstration of multifocal abnormal skeletal uptake on conventional 99m Tc phosphate bone scintigraphy corresponding to known pain sites. Patients should have reasonable bone marrow reserves, as indicated by (near) normal blood counts. Sm-153 gamma radiation is useful for early post-therapy visualization to confirm selective tracer uptake and targeting. 70-80% of patients with metastatic prostate or breast cancer report symptom

improvement after treatment with bone-seeking radiopharmaceuticals. Pain relief typically occurs within 1 week after intravenous administration of 153 Sm-EDTMP and usually lasts for about 8-12 weeks, although prolonged responses of up to 12 months have been reported (8).

Currently, radium-223 chloride therapy is an effective treatment method for patients with castration-resistant prostate cancer with bone metastases and without visceral metastases, both before and after chemotherapy. This therapy has been shown to increase overall survival and time to bone complications and is characterized by good tolerability, including an acceptable frequency of hematological and non-hematological adverse events. A full course of therapy, consisting of 6 injections of radium-223 chloride, improves overall survival and leads to a reduction in bone pain in this patient population. Currently, there is no consensus on the optimal placement of radium-223 chloride in the sequence of various treatments for castration-resistant prostate cancer with bone metastases. Therefore, the need for further randomized studies to determine the sequence of radium-223 chloride use in the treatment of castration-resistant prostate cancer with bone metastases is unquestionable.

There is a growing interest in expanding the role of radiopharmaceuticals for bone targeting beyond pain relief towards tumor-directed therapy. The potential benefit of early treatment of patients with asymptomatic metastases to achieve long-term disease control is well recognized.

Patients who receive treatment in the early stages of the natural course of the disease have longer response durations compared to patients with advanced metastases. This observation may be attributed to the action of long-range beta radiation on micro-metastases in the bone marrow. Such micro-metastases have been detected using polymerase chain reaction (PCR) in the bone marrow of prostate cancer patients staged N0 by clinical studies and imaging procedures.

Other anti-tumor options include escalating activity, re-administering radiopharmaceuticals, and combined regimens designed to exploit potential synergism between radionuclide therapy and external beam radiation therapy or chemotherapy. Preliminary range-of-activity studies using 153 Sm-EDTMP have shown improved response rates, better response quality, and longer survival in patients receiving high activity dose treatments.

The limitation of further activity escalation has been dose-limiting myelosuppression. Subsequent phase I studies have demonstrated PSA level reduction in CRPC patients receiving high-activity 186 Re-HEDP and support for peripheral stem cells.

Approximately 20% of patients become pain-free after radionuclide therapy. Most patients can reduce or discontinue opioid analgesics, but many continue to take nonsteroidal anti-inflammatory drugs. Economic analysis shows that targeted radionuclide therapy is a cost-effective alternative to multiple external beam irradiations for patients with multifocal skeletal metastases. Compelling data exist for

beta and alpha emitters that, in addition to their analgesic effect, clearly show an increase in median survival. The therapeutic potential of novel radiopharmaceuticals for pain relief in the bones is under investigation.

**Therapeutic Embolization**

Transarterial embolization is commonly used for primary or metastatic bone tumors to reduce surgical hemorrhagic risks or facilitate or enable more radical surgical interventions or in the context of palliative therapy. Clinical response to embolization has been reported in PCa patients. A small series involving 21 patients and 39 bone metastatic lesions reported a clinical response in 36 lesions with a median response duration of 5.5 months, highlighting the role of embolization in select patients.

In the mid-1970s, superselective and selective embolization were used to reduce perioperative bleeding during surgery. Since then, selective arterial embolization has become a standalone procedure or part of a broader therapeutic arsenal, providing benefits such as pain relief (decompression of periosteum and reduction of neurological symptoms) and improved quality of life for these patients. Therefore, considering the excellent pain control outcomes, some authors consider it a first-line palliative therapy.

According to Pazionis et al., failure to perform preoperative embolization can lead to massive bleeding with increased patient morbidity risk. Additionally, in patients with high cardiac risk, severe bleeding can also increase mortality, necessitating embolization.

For patients indicated for tumor resection, one of the important factors for surgical success after embolization is the period between the two procedures, considering that progressive neovascularization occurs within a few days, leading to a return of bleeding risk. Modern literature recommends performing open surgery within a maximum of three days after embolization. After this period, neoangiogenesis occurs, posing a new cumulative bleeding risk. In this clinical case report, the patient successfully underwent open resection of the left femur with prosthetic replacement 48 hours after embolization. Although rare, embolization is associated with certain procedure-related risks, focusing on artery dissection, accidental embolization of adjacent vessels, muscle necrosis, transient lower limb paresthesia (most commonly), and contrast nephropathy. However, the frequency of serious complications such as acute ischemia is less than 1%. Thus, the procedure is considered sufficiently safe with a low morbidity rate when performed by an experienced team.

Currently, there is only one case series available in the literature demonstrating the experience of using bone tumor embolization technique. Therefore, prospective studies are needed to evaluate not only short-term outcomes but also the late postoperative period and the impact on the long-term survival of these patients.

Selective and superselective preoperative embolization of renal cell carcinoma metastases plays an important role among the treatment options for oncological

diseases. It offers patients greater autonomy, better pain control, independence, and improved quality of life.

In summary, considering the above, the therapeutic strategy has undergone changes. The emergence of targeted drugs and the enrichment of radio pharmaceuticals have enriched the arsenal in the treatment of multiple osteogenic metastases. At the same time, there are individual results in the literature of combined therapy using bisphosphonates, monoclonal antibodies, and radio pharmaceuticals, which have been used in a combined form. This has prompted us to explore a new concept of combined and comprehensive treatment for multiple osteogenic metastases of kidney and prostate cancer.

**LITERATURE**

1. Alexeev B. Ya., Kalpinskiy A. S. The effectiveness of targeted therapy in a heterogeneous population of patients with metastatic kidney cancer. OU. 2012. No. 3. pp. 37-42.
2. Aliyev M. D., Teplyakov V. V., Sokolovsky V. A., Musayev E. R., Karpenko V. Yu. Organ-preserving methods of surgical treatment of kidney cancer metastases involving long tubular bones. OU. 2006. No. 1. pp. 12-16.
3. Ganov D. I., Varlamov S. A. Experience of octreotide use in patients with castration-resistant prostate cancer. OU. 2011. No. 4. pp. 71-73.
4. Gafur-Akhunov M. A., Polatova D. Sh., Sultonov B. B., Ziyavidinova S. Surgical treatment of metastatic spinal lesions. Sarcomas of bones, soft tissues, and skin. No. 2, Pages 57-571.
5. Zaborovsky N. S., Kostritsky S. V. Spinal metastasis in the background of renal cell cancer: treatment outcomes and survival after tumor removal. Spine surgery. 2017. No. 4. pp. 110-115.
6. Moiseenko F. V. The future of systemic therapy in oncourology: targeted therapy and/or immunotherapy. Practical Oncology. 2019. No. 2. pp. 137-143.
7. Rakhimov N. M., Shakanova Sh. Sh., Hakimov A. A., Kalyuta T. Yu., Velikanova M. G., Korolev A. Yu. Effectiveness of radiotherapy treatment in patients with bone metastases from prostate and renal cell cancer. Journal of Biomedicine and Practice. Volume 7, Issue 4. September 7, 2022.
8. Shakanova Sh. Sh., Rakhimov N. M., Esankulova B. S., Koraboev F. T., Hakimov A. A. Complications of targeted therapy in the treatment of bone and lymph node metastases from renal cell cancer. Journal of the Doctor. 2021, Volume 1, Issue 2 (99), pp. 116-120.
9. Shakanova Sh. Sh., Rakhimov N. M. Multimodal approach to the treatment of multiple bone metastases from kidney and prostate cancer. Clinical and Experimental Oncology. 2020, No. 4, pp. 50-56.

10. Bensalah K. et al. French recommendations from the AFU Cancer Committee: Update 2018-2020: Management of kidney cancer. Progress in Urology. 2018. Vol. 28. No. 12. pp. S3-S31.
11. Dai J, Hall CL, Escara-Wilke J, et al. Prostate cancer induces bone metastasis through Wnt-induced morphogenetic protein-dependent and independent mechanisms. Cancer Research. 2018;68. pp. 5785-5794.
12. Denis-Bacelar A. M. et al. Bone lesion absorbed dose profiles in patients with metastatic prostate cancer treated with molecular radiotherapy. The British Journal of Radiology. 2018. Vol. 91. No. 1084. pp. 20170795.
13. Fallon M. et al. Management of cancer pain in adult patients: ESMO Clinical Practice Guidelines. Annals of Oncology. 2018. Vol. 29. pp. iv166-iv191.
14. Gong A. et al. The lncRNA MEG3 mediates renal cell cancer progression by regulating ST3Gal1 transcription and EGFR sialylation. Journal of Cell Science. 2020. Vol. 133. No. 16. pp. jcs244020.
15. Guo Q. et al. Incidence of bone metastasis and factors contributing to its development and prognosis in newly diagnosed renal cell carcinoma: a population-based study. Cancer Management and Research. 2018. Vol. 10. pp. 2935.
16. Hiley C.T., Swanton C. Spatial and temporal cancer evolution: causes and consequences of tumor diversity. Clinical Medicine (London). 2014. Vol. 14, Suppl 6. pp. 33–37.
17. Huang, Q., & Ouyang, X. (2013). Bone markers for monitoring efficacy in patients with bone metastases receiving zoledronic acid: a review of published data. The International Journal of Biological Markers. 2013. Vol. 28. No. 3. pp. 242-248.
18. Joyce JA, Pollard JW. Microenvironmental regulation of metastasis. Nature Reviews Cancer. 2017. Vol. 9. pp. 239–252.
19. Langer CJ. Early detection, management, and evidence-based clinical guidelines for bone metastases: a 2006 update. Johns Hopkins Advanced Studies in Medicine. 2016. Vol. 6. pp. 1057.
20. Ozu C, Nakashima J, Horiguchi Y, et al. Prediction of bone metastases by combination of tartrate-resistant acid phosphatase, alkaline phosphatase, and prostate-specific antigen in patients with prostate cancer. International Journal of Urology. 2015. Vol. 15. pp. 419–422.
21. Pazionis TJC, Papanastassiou ID, Maybody M, Healey JH. Embolization of hypervascular bone metastases reduces intraoperative blood loss: a case-control study. Clinical Orthopaedics and Related Research. 2014. Vol. 472. No. 10. pp. 3179-3187.

22. Pirasteh A., Lovrec P., Pedrosa I. Imaging and its Impact on Defining the Oligometastatic State. Seminars in Radiation Oncology. 2021. Vol. 31. No. 3. pp. 186-199.
23. Psutka S. P., Master V. A. Role of metastasis-directed treatment in kidney cancer. Cancer. 2018. Vol. 124. No. 18. pp. 3641-3655.
24. Radbruch L. et al. Redefining palliative care: A new consensus-based definition. Journal of Pain and Symptom Management. 2020. Vol. 60. No. 4. pp. 754-764.
25. Roodman GD. Biology of osteoclast activation in cancer. Journal of Clinical Oncology. 2001. Vol. 19. pp. 3562–3571.
26. Roodman GD. Mechanisms of bone metastasis. New England Journal of Medicine. 2014. Vol. 350. pp. 1655–1664.
27. Saha G. B. Diagnostic uses of radiopharmaceuticals in nuclear medicine. Fundamentals of Nuclear Pharmacy. Springer, Cham, 2018. pp. 269-354.
28. Shavkatovna, S. S., & Rakhimov, N. M. Morphological Verification of Malignant Neoplasm of the Urinary System With Multiple Bone Metastases. The American Journal of Medical Sciences and Pharmaceutical Research. 2021. Vol. 3. No. 6. pp. 145-149.
29. Taheri M. et al. 153Sm-EDTMP and 177Lu-EDTMP are equally safe and effective in pain palliation from skeletal metastases. Nuklearmedizin. 2018. Vol. 57. No. 5. pp. 174-180.
30. Tillashaykov Mirza, Yusupov Sherali, Temirov Orif, Khojitoev Sanjar, Tursunova Matluba. Intermitting hormonal therapy in patients with common prostate cancer. European Science Review. Austria, Vienna, 2017. No. 3-4. pp. 9–11.
31. Venkitaraman R, Cook GJ, Dearnaley DP, et al. Does magnetic resonance imaging of the spine have a role in the staging of prostate cancer? Clinical Oncology (Royal College of Radiologists). 2009. Vol. 21. pp. 39–42.
32. Weitzman R., Sauter N., Eriksen E.F., et al. Critical review: updated recommendations for the prevention, diagnosis and treatment of osteonecrosis of the jaw in cancer patients – May 2006. Critical Reviews in Oncology/Hematology. 2017. Vol. 62. pp. 148-152.
33. Young, R.H. From Krukenberg to today: The ever-present problems posed by metastatic tumors in the ovary. Part II. Advances in Anatomic Pathology. 2007. Vol. 14. No. 3. pp. 149-177.