# Theranostic approach in lung cancer bone metastases.

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## Abstract

**Bone is the most common site of neoplastic metastasis and Non-Small Cell Lung Carcinoma (NSCLC) frequently metastasizes at the bone level, frequently in a osteolytic form.**

**By means of bone scintigraphy, information on osteoblastic activity and skeletal perfusion is obtained. For detection of malignant bone involvement the most sensitive imaging modality is represented by $^{18}$F-fluoride PET and $^{18}$F-fluoride can be considered as a biomarker for calcium metabolism. Considering that pain is the most observed symptom, once bone metastases have been diagnosed, a therapeutic approach must be provided. After taking in account various forms of therapy (drugs based and radiotherapy), the paper considers bone seeking radionuclides as a good approach for bone metastases therapy, and taking into account the similar biological behavior between $^{99mTc}$-MDP and $^{18}$F-Fluoride PET with respect to $^{153}$Sm-ESTMP and $^{223}$Ra-dichloride, it configures a theranostic approach to this type of treatment of bone metastases.**

**Keywords**: Lung cancer, Non-Small Cell Lung Carcinoma (NSCLC)

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## Introduction

Bone is the most common site of neoplastic metastasis and bone metastases are a major cause of pain reported in cancer patients.

The presence of bone metastases may also be responsible for complications that may in some cases become disabling, such as pathologic bone fractures, hypercalcemia, spinal cord compression and skeletal events that require a surgical treatment or the use of radiotherapy, sometimes in emergency conditions [1].

Non-small cell lung carcinoma (NSCLC) frequently metastasizes at the bone level [2]. Autopsy studies have shown bone metastases in 30-55% of patients died from this disease [3]. Some peculiar characteristics of NSCLC are recognized:

- pain, an important pain accompanies patients with lung carcinoma, very often and probably much more frequently than patients with breast and prostate cancer [4]
- the high frequency of hypercalcemia
- the poor prognosis, the median survival is around 6-7 months [5]

The classification of bone metastases depends from the main mechanism of interference with the normal bone remodeling, according to which are classified as osteolytic, osteoblastic or mixed. Lung carcinoma frequently causes osteolytic bone metastases (74.3% [6]), characterized by destruction of normal bone [7].

## Diagnosis

When bone metastases are clinically suspected, bone imaging is required. Bone scans and positron emission tomography (PET), ideally coupled with CT scans, are helpful for the systemic screening for bone metastasis [8].

Bone scintigraphy usually has a low specificity [9,10] even if it is highly sensitive. The false-positive rate of bone scintigraphy with $^{99m}$Tc-MDP is 40% and the sensitivity is reported between 62 and 89%. Compared to simple films and computerized tomography (CT) scans, $^{99m}$Tc-MDP bone scan is more sensitive and more specific, while magnetic resonance imaging (MRI) better visualizes vertebral metastases [11].

By means of bone scintigraphy, information on osteoblastic activity and skeletal perfusion is obtained. Sites of active bone formation preferentially uptake the radiopharmaceutical as a consequence of the metabolic reaction of the bone to the pathological process, be it neoplastic, traumatic or inflammatory [12].

For detection of malignant bone involvement the most sensitive imaging modality is represented by $^{18}$F-fluoride PET [13-16]. In several reports the superiority of $^{18}$F-fluoride–PET for the detection of metastatic skeletal involvement compared with $^{99m}$Tc-MDP bone scintigraphy have shown by Schirrmeister et al. [17-19]. However, $^{18}$F-fluoride being not tumor-specific also accumulates excessively in benign bone abnormalities. $^{18}$F-luoride spreads through the bone capillaries in the extracellular fluid, after intravenous administration. Because of its smaller molecular weight and the fact that its protein binding is negligible, the efficiency of single-pass $^{18}$F-fluoride extraction is higher than that of $^{99m}$Tc-MDP and its plasma clearance is faster. In the hydroxyapatite, at the surface of bone crystals, $^{18}$F-fluoride ions exchange with hydroxyl groups from the bone ECF, so forming fluoroapatite, with high turnover, at sites of bone remodeling [20,21]. Blood flow and osteoblastic activity are, therefore, reflected by uptake of $^{18}$F-fluoride. Bone uptake of $^{99m}$Tc-MDP is two time less than that of Fluoride [21,22]. Significant correlations between the regional plasma clearance of $^{18}$F-fluoride and bone formation rate [23] and mineral apposition rate [24,25] have recently shown by some Authors,

so $^{18}$F-fluoride can be considered as a biomarker for calcium metabolism. The changes occurring at sites of particular interest can be distinguished by $^{18}$F-fluoride PET, as well as the difference in response between trabecular and cortical bone [26].

## Therapy

Once bone metastases have been diagnosed, a therapeutic approach must be provided, considering that pain is the most observed symptom, but also hypercalcemia, spinal cord compression, pathological fractures, neurological deficits and severe psychological trauma and all of them significantly impact the quality of life of the patients. Over time various therapeutic approaches have been used, both radiant and pharmacological (Figure 1).

The use of biological drugs in this setting of patients is preferred, considering the better survival rates compared with those treated with only chemotherapy. Denosumab is a fully human monoclonal antibody that binds and neutralizes the mechanism of maturation and function of osteoclasts, so inhibiting the development and progression of bone metastasis [27]. Another drug used for bone metastases from lung cancer is an inhibitor of epidermal growth factor (EGF) which is considered an important mediator of bone metastasis in many cancers [28].

Another form of treatment of bone metastases is represented using bisphosphonate drugs, an important class of therapeutic agents. They induce osteoclast apoptosis, thereby preventing the development of cancer induced bone lesions [29]. In the treatment of bone metastases from all types of solid tumors, including lung, it has been demonstrated broad efficacy only of zoledronic acid [27].

Radiotherapy is an effective treatment in cases of painful bone metastases, with a pain response rate of more than 60% [30], with mild side effects depending from the dose, field size, and the anatomic area being irradiated [31-33]. The major problem of this therapeutic approach is represented by the fact that almost always, bone metastases, therefore also those from lung carcinoma are multiple, and it is impossible to hit them all with external beam radiotherapy.

## Nuclear Medicine and Theranostics

Treatment with radioactive isotopes has been the first clinical application of Nuclear Medicine, when, in the early '40s, the Phosphorus-32 was used for polycythemia and some forms of leukemia [34,35] and subsequently the administration of iodine-131 was adopted for the therapy of thyroid disease [35,36]. For the above mentioned multiple metastatic bone lesions (Figure 1), the most performing therapeutic agent seems to be the use of bone seeking radio-pharmaceuticals [37,38], moreover well-tolerated by patients [39].

In presence of bone metastases the use of bone-seeking radiopharmaceuticals started for bone pain palliation [40] and many radiopharmaceuticals have over time been used for this purpose [38].

The most frequent application of the palliative treatment of bone metastases from lung cancer is represented by EDTMP marked with $^{153}$Sm [41,42]. The complex $^{153}$Sm-EDTMP, an analogue of pyrophosphate similar to bone scanning agents and bisphosphonates, concentrates in osteoblastic activity sites around bone metastatic lesions and provides high doses of localized radiation because of its β-particle emissions.

Its biological behavior is similar to that of $^{99m}$Tc-MDP, the radiopharmaceutical used, as mentioned before, for the execution of bone scans. This fact was used by us for the prognostic evaluation of the therapeutic effects of 153Sm-EDTMP, basing on the amount of samarium deposited in the lesions, calculated in advance by a diagnostic scan after administration of 99mTc-MDP (Figure 2) [42,43]. This also allowed to perform a dosimetric evaluation of the administered radioactivity, allowing also to increase the administered dose

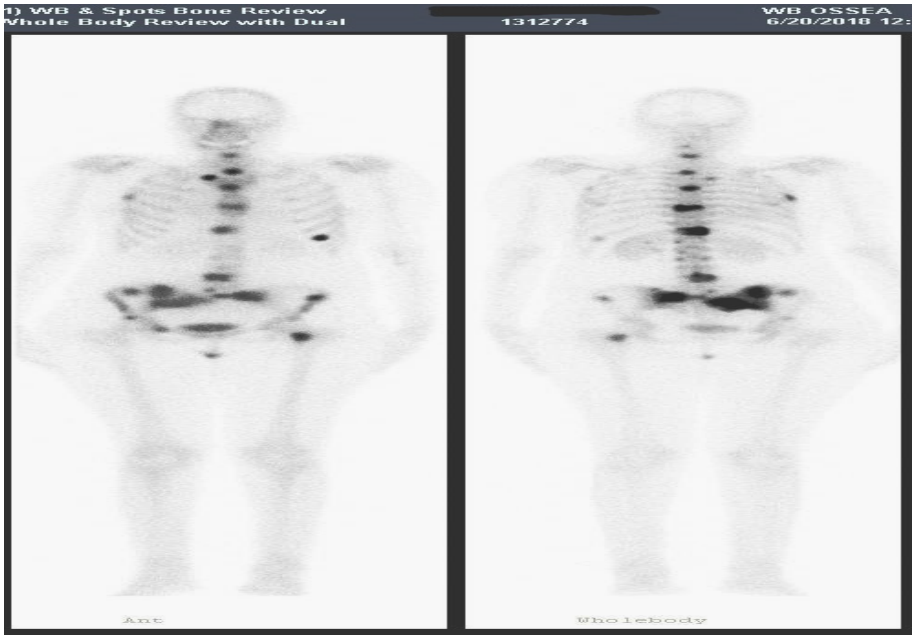


***Figure 1.*** *Bone 99mTc-MDP scintigrapgy in a lung cancer patient, showing multiple metastases.*

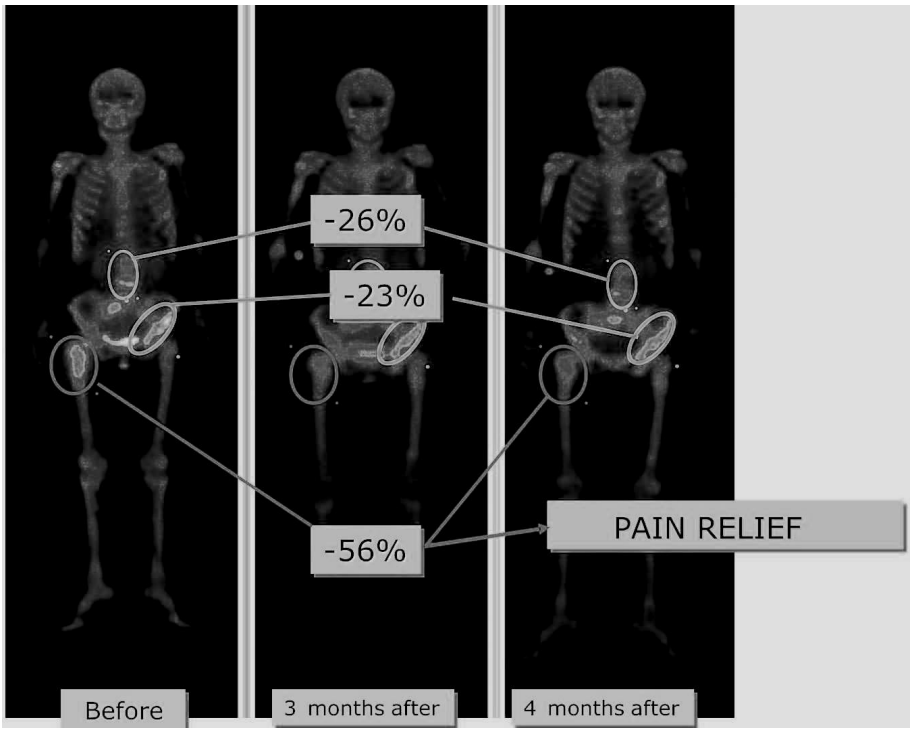


***Figure 2.*** *Bone scan 99mTc.MDP before and after 153Sm.EDTMP therapeutic administration (personal data).*

twice as much as recommended, without increasing negative side effects [44].

As theranostics (therapy-diagnostics) consists in a combination between administration of a biomolecule labelled by a radionuclide useful for diagnostic scintigraphic purpose and subsequent administration of the same molecule labelled by a radionuclide good for therapeutic purposes [45,46], the abovementioned practice can be considered as a *theranostic* approach to painfully bone metastases.

Quite recently a clinical interest towards alpha emitters in Nuclear Medicine therapy has arisen, coming from the fact that with these radionuclides is possible to easily delete individual tumor cells, while this is generally not possible with beta emitters, while maintaining an acceptable toxicity profile, in fact alpha particles emitting drugs have a higher BED of the most energetic beta particles, thus allowing more targeted treatments [47]. So alpha-emitting radionucleotides, such as Radium-223, have been developed to treat osteoblastic bone metastases from prostate cancer.

Radium-223 dichloride is a calcium mimetic tracer and therefore localizes to bone metastases where the slower speed of the alpha radiation results in a much shorter route than that of the electrons (beta particles) in the middle traversed, thus resulting in a Linear Energy Transfer (LET) much higher. In this manner the therapeutic effect is higher and side effects are minimized due to the very short route of alpha particles that few cell diameters, typically 5, are crossed by each particle [47]. Now 223Ra-dichloride is registered for therapy of prostatic bone metastases, typically osteoblastic, but a preclinical study indicate that such therapy may also be effective in treating osteolytic bone metastases [48], present in over 70% in lung cancer.

It must be also considered that the use of 223Ra-dichloride has shown not only palliative effects on bone pain, but also a significant effect on overall survival [49,50]. Still the advantages offered by this therapy can be increased by the application of precise dosimetric evaluations that can allow an increase in the dose administered to the lesions, without significantly affecting the side effects, local and systemic [51-53].

The method we used for dosimetric evaluation over bone lesions was based on lesions delineation on $^{99mTc}$-MDP whole-body images, and the ROIs superimposed on the $^{223}$Ra images after image coregistration using two of the three gamma peaks emitted from 223Ra, as the lesion uptake of $^{223}$Ra-dichloride was significantly correlated with that of $^{99m}$Tc-MDP [51].

The described method is nothing but a further form of theranostics applied to bone metastases. This approach can also be improved using the other diagnostic method for bone lesions. As we said before, the best diagnostic agent for bone metastases is represented by 18F-fluoride PET and if it is the best for diagnostics, it can also be used to control the effects of 223Ra therapy, in at least two of the 6 stages of therapy administration, given the high affinity of the two radiopharmaceuticals for bone lesions [54].

## Conclusion

In conclusion the system of identifying subgroups of patients who can benefit from a treatment based on image evidence obtained using the expression of an expected biological target, is at the basis of the theranostics. It refers to agents with identical or similar structure targeted to a specific biological entity for imaging and treatment, as 18F-fluoride, or even 99mTc-MDP, and 223Ra-dichloride for bone metastases.

The finding that the radium can also influence osteolytic bone lesions, as is often observed in lung carcinoma, opens important possibilities not only in the palliation of these lesions, but also on the overall survival of these patients. Through the adoption of dosimetric evaluation that allow the administration of the highest possible dose with minimal side effects [55].

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