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Impact of ^{18}F-fluoride PET-CT on implementing early treatment of painful bone metastases with Sm-153 EDTMP☆

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ABSTRACT

This study evaluated the diagnostic impact of using skeletal ^{18}F-fluoride PET/CT on patients with painful bone metastases to schedule an early palliative radionuclide treatment. *Methods*: The skeletal involvement from prostate cancer metastases was assessed by both ^{99m}Tc-diphosphonate bone scan (BS) and ^{18}F-fluoride PET/CT within four weeks in 24 patients (67.7 ± 5.1 years) suffering from a borderline degree of bone pain for which radionuclide palliation was not shortly planned for administration. The BS and ^{18}F-fluoride PET/CT results were compared, assessing the number and extension of the skeletal sites involved. Afterward, the patients were randomly assigned either to the study group (N = 12) receiving radionuclide therapy (Samarium-153 EDTMP) or to the control group (N = 12) not receiving radionuclide therapy. The short-term results from the radionuclide palliation group (evaluated with a visual analogue scale) were compared with the controls. *Results*: Overall, at BS, 7.6 ± 1.4 sites were considered metastatic, involving at least 5 ± 1 body regions. At ^{18}F-fluoride PET/CT, 116 ± 19 sites presented metastatic involvement with 12/12 body regions concerned. No differences were found in regards to either the number of metastatic sites or regions at both BS and ^{18}F-fluoride PET/CT between the study group and controls (p = ns). At CT, 88 blastic metastases were identified, whereas 110 were mainly lytic. Most of mainly lytic lesions were not detectable at BS. The reduction in total discomfort and bone pain in the study group was significantly greater than in the controls ($p < 0.0001$). *Conclusion*: Sm-153 EDTMP therapy should be considered for patients with early bone pain from prostate cancer even if their BS only indicates a few metastases before the initiation of a severe pain syndrome. ^{18}F-fluoride PET/CT may be helpful in deciding if the implementation of bone pain palliation using bone-seeking radionuclides at pain onset is necessary.

1. Introduction

Systemic radioisotope therapy with Samarium-153 (Sm-153) complexed with the chelator ethylenediaminetetramethylenephosphonate (EDTMP) has proven to be an effective tool for alleviating pain, improving quality of life and reducing the need for supportive analgesic therapies in patients suffering from painful bone metastases [1–4]. Systemic therapy with radionuclides may be used alone or in combination with a comprehensive therapeutic approach along with other analgesics or curative treatments such as chemotherapy, bisphosphonates, radiation and surgery [5–7]. There is no therapeutic constrain that hampers the early use of radionuclides in metastatic bone lesions before the initiation of structured pain syndromes or at an earlier stage in high-risk patients who are likely to develop bone metastases. In addition, this therapy could be implemented in asymptomatic patients with positive bone scans, thereby preventing pain initiation.

In this context, it is critical to identify reliable diagnostic modalities to detect both the blastic and lytic components of bone lesions and obtain an earlier, more complete and rigorous assessment of bone metastatic involvement.

After the introduction of readily available Tc-99m, bone scintigraphy quickly became one of the most common nuclear medicine procedures performed to detect bone metastatic involvement [8]. In particular, Tc-99m methylene diphosphonate, which demonstrated faster blood-pool clearance than most other Tc-99m-labeled diphosphonates, was adopted as the standard agent for skeletal scintigraphy [8,9].

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Based on the favorable skeletal kinetics of ^{18}F-fluoride, Phelps et al. [10] used ^{18}F-fluoride PET as a model for the evolution of skeletal whole-body PET [11]. PET/CT technology has exhibited higher spatial resolution and substantially greater sensitivity than conventional gamma cameras, resulting in higher image quality for skeletal PET than for planar bone scintigraphy or SPECT [12–14]. The increasing availability of PET/CT systems has renewed interest in using ^{18}F-labeled-NaF as a radiotracer for skeletal imaging because previous technical and logistical limitations to its routine usage for bone imaging are no longer present.

We aimed to evaluate the impact of skeletal PET/CT with ^{18}F-fluoride on managing patients with a low degree of pain due to bone metastases from prostate cancer to schedule an early palliative radionuclide treatment using Sm-153. The short-term results from radionuclide therapy were compared with those of patients who did not undergo pain palliation.

2. Materials and methods

2.1. Patients

Patients had a definite Rx diagnosis of metastatic painful bone lesions (blastic and/or mixed lytic/blastic) from prostate cancer. The skeletal involvement from prostate cancer metastases was assessed by both ^{99m}Tc-diphosphonate bone scan (BS) and ^{18}F-fluoride PET/CT within a four-week period in 24 patients (67.7 ± 5.1 years) who suffered from a borderline degree of bone pain, such as pain during daily activity, for whom radionuclide palliation was not otherwise shortly planned to be implemented. The BS and ^{18}F-fluoride PET/CT results were compared.

Patients presenting pain at one or more sites with increased tracer uptake were eligible for the study.

Nine patients had undergone prostatectomy, eight had undergone radiation therapy, five had undergone brachytherapy and two had undergone expectant therapy. Eighteen patients had received previous hormone therapy, and one patient had received chemotherapy. Nineteen patients had recently started (within the 7 months preceding the study) bisphosphonate therapy in the form of intravenous (i.v.) zoledronic acid every three weeks. The patient serum prostate specific antigen levels at the time of enrollment ranged from 9.8 to 974 ng/ml.

Patients were randomly assigned either to the study group (N = 12) receiving radionuclide therapy (Samarium-153 EDTMP) or to the control group (N = 12) not receiving radionuclide therapy. They were required to have a Karnofsky performance status of 40 or greater and an estimated survival of at least 6 months. No enrolled patients had received previous skeletal external radiation therapy.

The exclusion criteria were as follows: leucocytes count below 2.5×10^9/L, evidence of global and rapid reduction of blood counts, platelet count below 140×10^9/L and serum creatinine above 176.8 μmol/L. Patients who received chemotherapy or hormone therapy within the preceding eight weeks prior to enrollment or previous administration of radiopharmaceuticals were excluded.

Our institutional review board provided approval for the procedures included in the study. All patients who underwent radionuclide therapy signed an informed consent form in accordance with the Declaration of Helsinki.

2.2. Imaging modalities

In all patients, ^{99m}Tc-diphosphonate BS was performed 3 h after the i.v. injection of 666 ± 74 MBq of tracer using a dual-head large-field gamma camera (Philips SKYLight, Philips Medical Systems, Milpitas, CA, USA) equipped with low-energy high-resolution collimators (speed 8 cm/min, matrix 256 × 1024, averaged collected counts: 1500 Kcnts). The BS was acquired with the patient in the supine position, removing attenuating articles and with an instruction to the patients to remain motionless.

All patients underwent ^{18}F-fluoride PET/CT. The patients were well-hydrated before receiving ^{18}F-fluoride intravenously (555 ± 74 MBq). Forty-five minutes after the tracer injection, PET and CT were carried out with a commercial PET/CT scanner (Discovery LS; GE Milwaukee, WI, USA) that combined an Advance NXi PET scanner and a Light Speed Plus Four Rows MDCT system. Helical CT (pitch 1.5, 120 mA, 120 kVp) was performed without the use of an intravenous contrast medium. The PET scan was subsequently performed, acquiring four minutes per bed position and seven to eight bed positions per patient (up to 28 total min), depending on patient height. The raw computed tomography (CT) data were reconstructed into transverse images with a 4.25-mm section thickness. Sagittal and coronal CT images were generated by reconstruction of the transverse data.

Raw PET data were reconstructed with and without attenuation correction into transverse, sagittal, and coronal images. Attenuation correction was based on CT attenuation coefficients, which were determined by iterative reconstruction. All images were reviewed at a workstation by using PET/CT fusion software (Volumetrix for PET, GE).

2.3. Imaging evaluation

Three observers with fifteen years of expertise separately interpreted each BS and PET/CT study (two of them were also radiologists). They were blinded to the patient histories and symptoms. Any disagreements in the evaluations were resolved by consensus. The examiners first evaluated the CT images alone. Bone lesions were visually estimated (i.e., lytic, predominantly lytic, blastic) and their attenuation coefficient computed. Destructive changes of the trabecular architecture and/or the cortex or increased bone density with loss of definition of trabecular pattern, associated with multiplicity, suggested lytic or blastic malignancy, respectively. In addition, the most significant lesions were measured for minimum and maximum diameter by using vendor-provided software. A significant lesion in the CT study was defined as an identifiable area in the skeleton larger than 1.0 cm in minimum diameter and presenting altered density using bony window settings.

On the PET scans, all lesions with increased uptake were evaluated. Maximum standardized uptake values and body weight corrected (SUVmax) were determined by using vendor-provided software. An SUVmax level greater than 2.5 was considered abnormal. Briefly, focal or diffuse (surrounding lytic lesions) ^{18}F-fluoride uptake above normal bone tissue absorption into a destructive location matched with abnormal bone density was interpreted as abnormal and was considered to be indicative of a target lesion (bone metastasis).

Increased articular uptake at BS, as well as areas of enhanced ^{18}F-fluoride uptake at PET/CT matching with traumatic/post-traumatic alterations or with arthrosis, osteophytes, hyperostosis and spinal enthesopathy, was excluded from this analysis.

A Sm-153 EDTMP BS, as a part of the therapeutic procedure (gamma emission), was performed 3 h after the i.v. tracer injection using the same dual-head large field gamma camera and the same parameters employed for the ^{99m}Tc-diphosphonate BS.

The BS and ^{18}F-fluoride PET/CT results were compared by assessing the number and extension of skeletal sites involved in each of 12 skeletal body regions (head and neck, scapulas and clavicles, left arm, left ribs, right arm, right ribs, thoracic spine, lumbar spine with pelvic bone, left femur, right femur, left lower leg, and right lower leg).

2.4. Treatment procedures

The study group received 2285 ± 335 MBq of Sm-153 EDTMP. Radioactive treatment (37 MBq/Kg) was administered in a room with appropriate protection. Each patient received 750 mL of saline solution intravenously before the administration of the radioisotope

and 500 mL in the subsequent half hour period. The radioactive solution was administered using an i.v. catheter over 60 s and then slowly flushed with saline solution.

2.5. Pain and performance status assessment

Pain level, postural conditions, as well as the overall performance status were documented in a record worksheet that each patient filled out once a day starting from the week before radionuclide administration (baseline assessment) until week 8 post-treatment. In the diary, the patients specified the level and extent of pain in the 12 aforementioned body regions according to a visual analogue scale (VAS) [15], with ratings from 0 (no pain–no discomfort) to 10 (worst pain–worst discomfort). The general discomfort was evaluated considering the following postural conditions: no pain, pain during daily activity, and pain at rest with routine activities strongly limited. Due to the uncertainty related to patient pain self-assessment and to the unstructured subjective description of pain sites, a hyperbolic transformation of the visual analogue scale was applied when required [16]. Pain medication intake and dose were recorded daily.

A physician global evaluation was performed at enrollment. Clinical examination was carried out thereafter, at months 1 and 2 following the treatment, to assess the pain level, general discomfort and impact of pain and discomfort on daily routine. In addition, the patients' diaries were reviewed at a two-month follow-up. Patients undergoing Sm-153 EDTMP were evaluated for related toxicity.

3. Statistical analysis

Continuous data are expressed as the mean ± SD. Comparisons between the mean values were performed with a paired Student's t test. Categorical data are expressed as percentages. Chi-square analysis was applied when appropriate. To compare the data, a linear generalized model (LGM) for repeated measurements (two-way ANOVA) was used. With this method, we assessed, for each patient, if a reduction of the effect during the follow-up period occurred. In addition, we also investigated the statistical relevance of changes within the follow-up period between the two groups (study and control groups). A p value < 0.05 was considered statistically significant.

4. Results

At ^{99m}Tc-diphosphonate BS, overall, 7.6 ± 1.4 sites were considered metastatic, involving at least 5 ± 1 body regions, whereas at ^{18}F-fluoride PET, metastatic involvement was found in 116 ± 19 sites, with 12/12 body regions concerned. On a patient basis, the number of sites indicating bone metastases at PET was significantly higher compared with the ^{99m}Tc-diphosphonate BS results ($p < 0.0001$) (Fig. 1).

BS indicated 8.0 ± 1.7 sites in the study group and 7.2 ± 1.2 sites in the control group ($p = 0.20$). The number of involved body regions at BS was 4.8 ± 0.7 in the study group and 5.0 ± 0.7 in the control group ($p = 0.58$).

^{18}F-fluoride PET indicated metastatic involvement in 114 ± 17 bone sites in the study group and 117 ± 21 in the control group ($p = 0.67$). Both groups had 12/12 body regions involved.

At CT, as a part of PET/CT study, 88 significant blastic metastases were identified, whereas 110 were mainly lytic and fifty-five were classified as mixed. Overall, the mean lesion diameter was 2.7 ± 1.4 cm (2.7 ± 1.5 and 2.6 ± 1.3; $p = 0.76$, in the study and control group, respectively). A large number of the mainly lytic lesions (78/110, 71%) were not detectable at BS (Table 1).

At PET scan, the overall mean SUVmax of the bone metastases was 13 ± 9 (range 2.7–39.3). As expected, according to the density of bone matrix, the SUVmax in the lytic lesions was slightly but significantly lower than that of blastic lesions (12 ± 3 vs 18 ± 9, respectively; $p < 0.001$).

The results from the Sm-153 EDTMP bone BS in the study group were comparable with those obtained from the ^{99m}Tc-diphosphonate BS (10 ± 1 sites involved; $p = 0.09$).

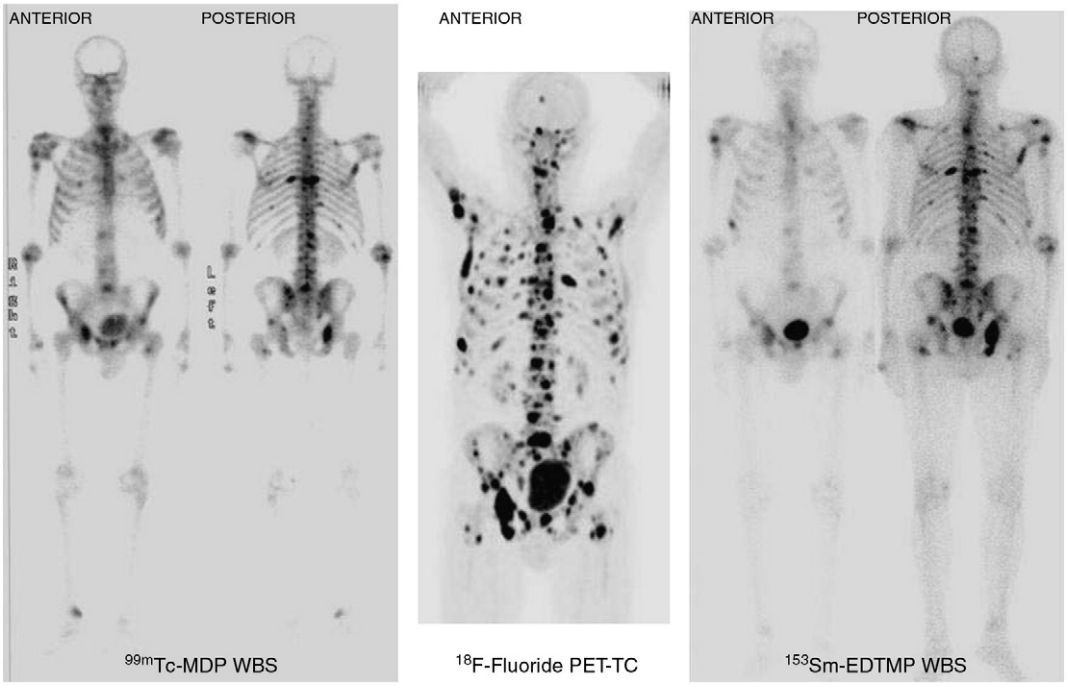

Fig. 1. Patient with low-grade pain syndrome due to bone metastases from prostate cancer. Initially, 2516 MBq of Sm-153 EDTMP was administered early, on the basis of ^{18}F-fluoride PET results, as well. Note the differences between the bone scans (Tc-99m MDP, Sm-153 EDTMP) and the ^{18}F-fluoride PET, all performed within three weeks. In Bone Metastases; A translational and clinical approach, Springer Netherlands, Volume 12, 2009, Radionuclide Therapy by Storto G.; Figure 16.1; With kind permission of Springer Science and Business Media.

Table 1
Number of bone metastases detected at Bone Scintigraphy and ^{18}F-fluoride Positron Emission Tomography versus CT characteristics of the most significant lesions.[a]

	Bone Metastases at CT		
	Blastic (N = 88)	Mainly lytic (N = 110)	Mixed (N = 55)
^{99m}Tc-diphosphonate Bone Scintigraphy Nr of positive finding (%)	68 (77%)	32 (29%)	35 (63%)
^{18}F-fluoride Positron Emission Tomography Nr of positive finding (%)	85 (96%)	97 (88%)	53 (94%)

[a] Identifiable area in the skeleton larger than 1.0 cm in minimum diameter and presenting altered density; Chi square = 12.1, $p < 0.01$.

4.1. Bone pain assessment

There were no significant differences in the baseline characteristics between the study and control groups (Table 2).

Baseline VAS was 2.8 ± 0.8 and 2.8 ± 0.8 in the study and control groups, respectively ($p = 0.6$). The reduction of total discomfort and bone pain in the group receiving radionuclide therapy was significantly greater than in the controls, who presented no improvement (0.3 ± 0.4 vs 4.1 ± 1.6, respectively, at the two-month follow-up; $p < 0.0001$) (Fig. 2, Table 2). Based on the fact that an improvement of 2 points on the VAS, at a low pain level, is considered a reasonable cut-off in identifying significant pain relief, 83% of patients treated with Sm-153 EDTMP and none of those untreated patients presented significant pain relief (Table 3). Consistent improvement of clinical conditions during daily activities was observed by physicians in the study group during the monitored period compared with the control group.

In the group receiving radionuclide therapy, 10 of 12 (83%) patients on analgesic therapy (non-opioid, non-steroidal anti-inflammatory drugs; NSAIDs) were able to cease use of the medication during the follow-up period, whereas 1 of 12 (0.8%) untreated patients discontinued the use of analgesic therapy ($p < 0.0001$).

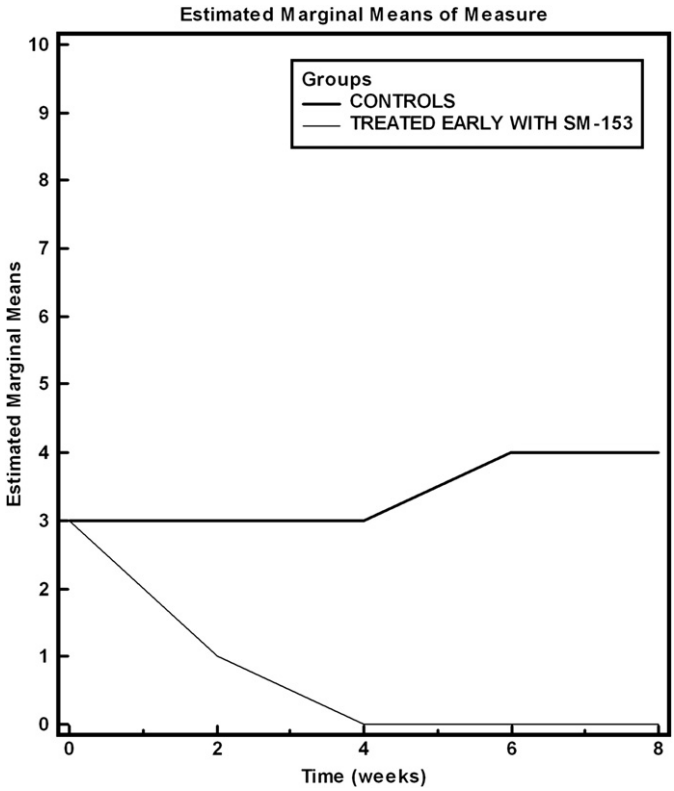

Fig. 2. Improvement in reported pain scores according to the diary data of patients treated with Sm-153 and controls. VAS = Visual Analogue Scale.

Conversely, most of the controls (66%) indicated the increased use of analgesics and worsening pain status (Tables 2 and 3).

Patients who underwent Sm-153 EDTMP therapy exhibited a mild, transient myelosuppression. Their mean platelet and white cell counts were reduced by 30% and 20% from baseline, respectively. The nadirs

Table 2
Individual data from study and control group patients.

	Patients undergoing radionuclide therapy		Controls	
Patients	12		12	
Mean age (SD)	69	(3.1)	67	(7.1)
Performance status (Karnofsky)		%		%
0–40	0	(0)	0	(0)
41–80	10	(83)	9	(75)
81–100	2	(17)	3	(25)
Previous therapy[a]				
Hormone-therapy	8	(67)	10	(83)
Chemo-therapy	1	(8)	0	(0)
None	3	(25)	2	(17)
Current therapy				
Bisphosphonate therapy	9	(75)	10	(83)
Non-opioid/NSAIDs[b]	12	(100)	12	(100)
Bone involvement[c] (mean ± SD)				
^{99m}Tc-diphosphonate bone scan	8.0 ± 1.7		7.2 ± 1.2	
^{18}F-fluoride PET/CT	114 ± 17		117 ± 21	
Pain degree (VAS[d])				
Baseline	2.8		2.8	
On month 1	0.4		3.1	
On month 2	0.3		4.1	
Final pain status (n)				
Decreased	12		0	
Unchanged	0		4	
Increased	0		8	

Karnofsky index no less than 40.
[a] Previous therapy at least 12 weeks before enrollment.
[b] NSAIDs: non-steroidal anti-inflammatory drugs.
[c] Number of involved sites at bone scintigraphies; PET/CT: positron emission tomography/computed tomography.
[d] VAS: visual analogue scale.

Table 3
Number of patients with different bone pain response and controls.

Treatment	Degree of pain relief[a]			Duration[b] (weeks)
	Very good	Noticeable	None	
Study Group Sm-153 (EDTMP)	10	2	0	7 (6–8)
Controls Conventional therapy (non-opioid/NSAIDs)	0	0	12	-

NSAIDs = non-steroidal anti-inflammatory drugs.
[a] Pain response according to visual analogue scale: very good = ≥2 points; noticeable = 1 point; none = no pain reliefs.
[b] Mean (range).

occurred at the end of week 3 and recovery at week 6 after therapy. One patient experienced a slight flare response (within 48 h) after receiving Sm-153-EDTMP.

5. Discussion

The main finding of the present study is that bone pain palliation using Sm-153-EDTMP may be implemented in patients with initial bone pain from metastatic prostate cancer even if conventional bone scans indicate only limited disease. ^{18}F-fluoride PET/CT allows the identification and characterization of a huge number of bone metastatic lesions compared with ^{99m}Tc-diphosphonate scintigraphy and thereby supports the use of bone-seeking radionuclides therapy in advance of severe pain onset. Such treatment has beneficial implications for patient quality of life. The detection of a higher number of bone metastatic sites earlier justifies palliative therapy, as a more disseminated skeletal involvement is associated with a major risk of increased pain.

Patients with advanced prostate cancer are frequently affected by bone metastasis, [17,18], which is an untreatable progression of the disease and burdening cancer-related morbidity. Even if therapeutic strategies to prevent the disease evolution and its complications are being persistently implemented [19,20], bone pain may also be present in the early stage, reducing the performance status of the patients and decreasing their quality of life.

Radiopharmaceutical Sm-153 (EDTMP) has become an excellent means, in terms of both efficacy and tolerability, among the various, mostly palliative, therapies used to treat bone metastases [16,21,22]. However, to our knowledge, only a few studies have addressed the early use of radionuclide therapy [23,24], especially during pain onset or when a patient suffers from a low–moderate degree of bone pain, as the treatment is normally reserved only for advanced disease stages. Such an approach has been commonly adopted because of legal constraints, the precise indications for using radionuclides and, sometimes, as a consequence of the lack of pre-therapeutic diagnostic evidence for widespread bony disease. In this context, the question of whether a palliative treatment by Sm-153 (EDTMP) can be implemented early-on in the management of bone pain, despite some toxicity, arises. In fact, radionuclide bone pain palliation is usually performed in patients who suffer from unresponsive pain due to disseminated pluri-ostotic metastases. Nevertheless, when a patient suffers from a pain syndrome, even at a low level, palliative therapies should be readily employed to improve the patient's quality of life. There is a strong argument for early intervention because the treatment delays the development of new pain in preexisting silent sites [25,26].

Among the numerous diagnostic tools available for bone assessment, PET/CT has been recognized as a useful resource. It offers the advantage of characterizing tissue functionally, which is mostly independent from lone morphologic criteria when assessing the extent of the disease [27]. In addition, ^{18}F-fluoride PET/CT has been used to identify skeletal metastases in patients with a range of primary tumors [28–30]. The technique has higher sensitivity compared to traditional anatomical and/or functional imaging modalities. Thus, the technique could redirect patient's therapeutic management [12,13,28,31].

^{18}F-fluoride PET allows high-quality skeletal imaging because of both highly specific bone uptake/rapid clearance of the tracer from the blood pool and the increased performance of PET imaging. In addition, ^{18}F-fluoride hybrid PET/CT has been reported to be more accurate in identifying skeletal metastases than separate PET and CT studies [32]. As a result, some studies have compared ^{18}F-fluoride PET to ^{99m}Tc-diphosphonate scintigraphy and found that ^{18}F-fluoride PET is more accurate than planar imaging or SPECT with ^{99m}Tc-diphosphonate for localizing and characterizing malignant bone lesions [12,13,31,33].

In our study, we found, like others [12], a significant difference in the number of bone metastases detected by PET compared with conventional bone scintigraphy. Moreover, the ^{18}F-fluoride PET/CT methodology allowed for the simultaneous characterizing of the alterations of metastatic bone density and the tracer uptake, which both are well-established markers of lesion severity and may be essential in judging the necessity of early implementation radionuclide therapies for pain palliation. For instance, most lytic lesions were not detectable at BS.

It has been reported that in cancer patients with multiple skeletal metastases an increased ^{18}F-fluoride uptake is detected both in lesions with sclerotic characteristics on CT and in lytic metastases [33]. Indeed, even if the osteoblastic lesions represent the main target of intravenous bone-seeking agents and of radionuclides for palliation, these agents reach both lesions, the mixed and the osteolytic, because they are surrounded by metabolically active bone.

In some applications, PET/CT permits a quantitative assessment that may add value to an image. The capability of reporting the absolute uptake of ^{18}F-fluoride PET has been described [34,35] and is useful for the clinical interpretation. In our patients, the uptake index (SUVmax) was significant in lytic lesions although slightly lower than that of blastic lesions. These findings are similar to those reported by Kawaguchi et al. in patients with various cancers [36] but discordant from those of other authors [37] who assessed ^{18}F-fluoride uptake in bone metastases from prostate cancer. In contrast to our results, this latter study described a different number and density pattern of bony lesions.

We found ^{18}F-fluoride PET/CT a valuable diagnostic tool to aid in the implementation of palliation with radionuclides earlier than scheduled in patients having undisclosed widespread bone disease. Such patients receiving the treatment and suffering from bone pain had their therapeutic management redirected, avoiding, for example, the repeated or expanded usage of analgesic drugs. It is conceivable that such patients would have otherwise suffered increased pain after a brief delay. The fact that the patients experienced pain relief and the findings from the short-term follow-up in untreated control patients, who did not present relief, support this idea. In selected clinical settings, it could be postulated that earlier treatment provides a better output/outcome.

However, to further delineate the role of ^{18}F-fluoride PET/CT in discriminating patients who may or may not benefit from early

treatment, a group of patients with early pain and limited disease on both ^{99m}Tc-diphosphonate BS and PET who did not receive radionuclide palliation is currently being studied.

6. Limitations

It could be suggested that the number of involved sites at post-therapy Sm-153 BS was not large enough compared to the number of PET/CT sites to substantiate the use of radionuclide palliation. However, apart from the significant differences in spatial resolution already discussed, we consider radionuclide action to occur mostly at the cell/tissue level [38], which is not always so clustered that it is detectable.

Most of our patients had started bisphosphonates, which are an irreplaceable supportive treatment in such a clinical setting. However, because the pain was still present, aggregate radiopharmaceutical therapy was warranted.

7. Conclusion

Sm-153 EDTMP therapy should be considered in patients with early bone pain from prostate cancer even if the ^{99m}Tc-diphosphonate bone scan only indicates a limited number of metastases to prevent the occurrence of a severe pain syndrome. ^{18}F-fluoride PET/CT may facilitate the recognition of a large number of bone metastatic lesions compared with conventional bone scintigraphies and is helpful in the implementation of bone pain palliation using bone-seeking radionuclides at pain onset.

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