

Molecular Imaging in the selection and evaluation of response in patients treated with Radium-223 in six different solid tumors: A single center experience

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Abstract

Objective: Evaluate impact after ^{223}Ra therapy and ^{18}F -NaF (sodium fluoride) PET/CT in the selection and evaluation of response in patients treated with ^{223}Ra in six different solid tumors.

Material and Methods: Twenty patients with metastatic castration-resistant prostate cancer (mCRPC), seven metastatic castration-sensitive prostate cancer (mCSPC), three osteosarcoma, two breast cancer, two non-small cell lung cancer (NSCLC), one chondrosarcoma, one chordoma and one patient lung neuroendocrine carcinoma. Three groups of study were defined according total skeletal tumor-burden obtained by ^{18}F -NaF PET/CT, group 1 $<1000\text{cm}^3$, group 2 $1001\text{--}2999\text{cm}^3$ and group 3 $>3000\text{cm}^3$ VOI's. A semi-quantitative comparison was performed measuring the SUVmax values of VOIs values in all bone metastases in each patient previous to receive the first cycle of ^{223}Ra , after 3 and 6 cycles.

Results: 30 patients non-progress disease was documented after 24 ± 4 weeks. 8 patients progress disease was presented after three cycles of ^{223}Ra , two patients with osteosarcoma, four patients with mCRPC, one patient with chondrosarcoma and one patient with NSCLC. Group 1 patients showed better response rates compared to group 3 ($p<0.05$). Group 2 patients who showed improvement clinical and radiological, had prostate malignancies compared to those in the same group, but non-prostatic malignancies ($p<0.05$). No significant difference in group 2 patients compared to group 3 ($p<0.67$). Symptomatic skeletal-related event was observed in 7 patients.

Conclusion: ^{18}F -NaF PET/CT allows to identify patients who show osteoblastic bone activity and discard or confirm progression in the interval PET/CT image, allowing change of treatment, reducing costs. High tumor-burden strongly suggests a poor response to treatment

Introduction

Radium-223 (^{223}Ra) was the first bone-targeting agent to demonstrate improved overall survival in patients with Castration Resistant Prostate Cancer and bone metastases (mCRPC), in addition to bone pain relief, improvement in quality of life (QoL), and prolonging time to skeletal-related events (SREs); in addition is the first therapeutic alpha-emitting radionuclide approved for treating metastatic skeletal disease in prostate cancer [1, 2].

Although there are currently multiple publications about the benefits of ^{223}Ra in patients with mCRPC; currently ^{223}Ra is being tested in 2 phase 3 trials in combination with novel antihormonal agents in the chemotherapy-naive setting of asymptomatic or mildly symptomatic mCRPC, the radiological response during ^{223}Ra therapy is at present poorly defined [3, 4].

Recently interest has grown to demonstrate its usefulness in other types of solid tumors, such as breast cancer (BC), osteosarcoma, lung cancer (LC) and metastatic castration-sensitive prostate cancer (mCSPC) [5–8]

For decades, the evaluation of metastatic bone disease in PC has been limited to the use of the bone scintigraphy, a method with high sensitivity but limited specificity. ^{18}F -Fluoride PET/CT (^{18}F -NaF) bone imaging is ideal for staging and restaging patients with PC because of greater sensitivity, specificity, and accuracy than conventional bone scintigraphy [9]. Moreover, the project named *Focus 1* to develop consensus statements in prostate cancer, recommend ^{68}Ga -prostate specific membrane antigen (PSMA), ^{18}F -Choline and recently ^{18}F -Fluciclovine, cancer-targeted PET at biochemical recurrence to replace conventional imaging methods (bone scintigraphy or CT), and the preferred imaging method was PET-CT with a PSMA-targeting tracer. [10]

In clinical practice, bone scintigraphy with $^{99\text{m}}\text{Tc}$ -MDP has been most commonly used to assess osteoblastic metastases after 6 cycles of ^{223}Ra and sometimes interim (after 3 cycles) to evaluate to response; in some centers in Europe, PET/CT with ^{18}F -Choline or ^{68}Ga -PSMA are the preferred radiotracers; however, these radiotracers are not yet approved for the evaluation of metastatic bone disease in other types of solid tumors; in addition, there are no criteria for response of bone metastases, but only criteria for disease progression, as evident by the emergence of new lesions [10–11]. Unfortunately, there are many limitations in evaluate response to metastatic osteoblastic lesions because is considerate non-measurable lesion, unless it is a lytic lesion associated with soft tissue component. In addition, there is a poor evidence in the role of ^{18}F -NaF PET/CT in staging, restaging or evaluate to response of another solid tumors such as osteosarcoma or lung cancer, for this reason we hypothesized that ^{18}F -NaF PET/CT is a better modality in selecting candidate, evaluate quantitative and qualitative response in the bone metastasis tumors treated with bone-targeted alpha particle therapy.

The objective of this study were to evaluate the impact after ^{223}Ra therapy and the potential use of ^{18}F -NaF PET/CT in the selection and evaluation of response in patients treated with ^{223}Ra in six different solid tumors.

Materials And Methods

The present retrospective clinical study was conducted at nuclear medicine and molecular Imaging department in Instituto Nacional de Cancerologia, Mexico, between February 2015 and January 2019. All PET and PET/CT examinations were performed in compliance with 1964 Declaration of Helsinki, and the responsible regulatory bodies in Mexico. All patients (except mCRPC) received ^{223}Ra under the "compassionate use" clause of the Mexico. Written informed consent was obtained from each subject

Patients

Thirty-seven patients with a mean age of 55 years (29 men and 3 women, age range 20–69 years) were included in this retrospective study. Twenty patients had mCRPC, seven had mCSPC, three patients had osteosarcoma, two patients had breast cancer, two patients had non-small cell lung cancer (NSCLC), one patient had chondrosarcoma, one patient with chordoma and one patient with lung neuroendocrine carcinoma. Inclusion criteria for ^{18}F -NaF PET/CT was diagnosis of metastatic bone disease and progression disease after conventional therapy, with previous ^{18}F -FDG-PET/CT imaging as usually imaging in the evaluation of different disease, and before to initiate therapy with ^{223}Ra . The most representative characteristics of the population study are summarized in Table 1. In addition, patients with non-prostatic malignances experienced progression under first or second-line chemotherapy (platinum agents, doxorubicin, ifosfamide, docetaxel and everolimus) or were not eligible for chemotherapy were included. In patients with mCRPC next-generation androgen-deprivation therapy (abiraterone or enzalutamide) or first- or second-line chemotherapy (docetaxel or cabazitaxel) were included. Patients with evidence of visceral metastases, lymph nodes metastases > 3 cm in long-axis diameter, confirmed by a CT scan, were excluded. Other exclusion criteria included recent or complicated nonhealing fracture and use of concomitant radiotherapy.

Table 1
Baseline characteristics of patients studied (n = 37)

| | Patients | |
|--|----------|------|
| | No. | % |
| Sex | 4 | 10.8 |
| Female | 33 | 89.2 |
| Male | | |
| Age | 20–70 | |
| Range | 55 | |
| Mean | | |
| Type cancer | 20 | 54.1 |
| <i>mCRPC</i> | 7 | 18.9 |
| <i>mCSPC</i> | 3 | 8.1 |
| <i>Osteosarcoma</i> | 2 | 5.4 |
| <i>Breast cancer</i> | 2 | 5.4 |
| <i>Lung cancer</i> | 1 | 2.7 |
| <i>Chordoma</i> | 1 | 2.7 |
| <i>Chondrosarcoma</i> | 1 | 2.7 |
| <i>Lung neuroendocrine carcinoma</i> | | |
| Previous treatment | 23 | 62.2 |
| QT | 2 | 5.4 |
| RT | 3 | 8.1 |
| QT + RT | 7 | 18.9 |
| Hormonal therapy* | 2 | 5.4 |
| Other** | | |
| Concomitant treatment | 19 | 51.4 |
| Zoledronic acid | 11 | 29.7 |
| Denosumab | 7 | 18.9 |
| LHRH + Bicalutamide | | |
| ECOG | 22 | 59.5 |
| 0–1 | 13 | 35.1 |
| 2 | 2 | 5.4 |
| 3 | | |
| mCRPC = metastatic castration-resistant prostate cancer. mCSPC = metastatic castration-sensitive prostate cancer. QT = chemotherapy. RT = radiotherapy. LHRH = luteinizing hormone-releasing hormone agonist. *Patients with mCSPC androgen deprivation therapy was initiated after diagnosis of mCSPC and before compassionate exemption of ^{223}Ra treatment, and was given continuously. **other treatments include antiproliferative therapy or surgery. | | |

Imaging protocol

Imaging was performed with a Biograph mCT 20 PET/CT (Siemens Medical Solutions, USA) at the at nuclear medicine and molecular Imaging department in Instituto Nacional de Cancerologia. After intravenous injection of ^{18}F -NaF a mean of 250 MBq (4 MBq per kg bodyweight, range 230–290 MBq) WB emission scans were acquired at 60 minutes post-injection. Low-dose CT (from the vertex of the skull to the feet) correction was performed for both attenuation correction and topographic localization. The CT parameters used for acquisition were 140 kV, 80 mA, and 0.5 s per rotation, with a pitch of 6:1 and a slice thickness of 5 mm. After completion of the CT scan, PET data were acquired for 3 min per bed position. Emission data were corrected for randoms, dead time, scatter, and attenuation and were reconstructed iteratively by an ordered-subsets expectation maximization algorithm (4 iterations, 8 subsets) followed by a post-reconstruction smoothing gaussian filter (5 mm in full width at one-half maximum).

Timing imaging

All patients had documented disease progression before the initiation of ^{223}Ra therapy. Before to begun therapy all patients underwent baseline $^{18}\text{F}\text{-NaF}$ PET/CT and after 3 and 6 cycles of ^{223}Ra . Same activity, biodistribution time and parameters of acquisition was applied in subsequent imaging in each patient.

Imaging analysis

PET/CT images in all standard planes were reviewed by use of the dedicated software (syngo by SIEMENS). Images were analyzed visually and quantitatively by two nuclear medicine physicians with more than 5 years of experience. Maximum standardized uptake values (SUVmax) were obtained by drawing circular regions of interest, which were automatically adapted (40% isocontour) to a 3D VOI using syngo software. Volumes of interest (VOIs) with edges around 1 to 3 cm were drawn on regions of interest, the uptake in the VOIs was classified as malignant on the basis of the radiopharmaceutical distribution pattern with match CT images (Fig. 1).

Three groups of study was defined according total skeletal burden obtained by VOIs and SUVmax values (TLSB), group 1 had less 1000 cm^3 , group 2 had 1001–2999 cm^3 and group 3 more than 3000 cm^3 , these classification was established by consensus between two nuclear medicine physicians ($\kappa = 0.85$). (Fig. 2).

Treatment

^{223}Ra (Xofigo; Bayer®) was administered to 37 patients. Patients were administered intravenous ^{223}Ra at 50 kBq/kg body weight (until June 2016, after this point the dose were calculated at 55 kBq/kg body weight) every 4 weeks for 6 cycles. Patients with mCSPC were maintained on androgen deprivation therapy (ADT) was initiated after diagnosis of mCSPC and before compassionate exemption of ^{223}Ra treatment, and was given continuously. ADT included bicalutamide + luteinizing hormone-releasing hormone agonist. One patient with lung cancer (EGFR mutation) gefitinib was given concomitant. One patient with breast cancer was Luminal A, letrozole and zoledronic acid was given concomitant.

Safety

Previous to each cycle, absolute blood count (hemoglobin, erythrocytes, leukocytes, platelets, neutrophils and lymphocytes) was evaluated. Treatment was continued as long as absolute blood count was ≥ 1.0 g/L for neutrophils and ≥ 50 g/L for platelets. Written informed consent was obtained from each patient before administration of ^{223}Ra . On the basis of blood levels, toxicity was categorized using the Common Toxicity Criteria for Adverse Events (CTCAE version 4.03).

Efficacy and Response

Patient follow-up consisted of assessment of pain (according to Visual Analog Scale for Pain), physical examinations and laboratory assessments including hematologic, alkaline phosphatase (ALP), dehydrogenase lactic (DHL) in all patients, plus prostate specific antigen (PSA) in mCRPC and mCSPC patients; in addition, carcinoembryonic antigen (CEA) in LC patient and CA 15 – 3 in BC patient, at baseline and after 3 and 6 cycles of ^{223}Ra . IN patients with prostatic malignances the tumor marker PSA was used for the response evaluation. The response was defined as any decline in the PSA level after after 3 and 6 cycles of ^{223}Ra compared with the baseline PSA, PSA decline of $> 30\%$ were determined as well; however, because small number of patients with non-prostatic malignances, another markers were used only for monitoring disease and correlated with PET/CT. Treatment response and diagnosis of progression were evaluated using CT $^{18}\text{F}\text{-NaF}$ PET/CT, according to RECIST 1.1 criteria; in addition or molecular evaluation of TLSB, the $^{18}\text{F}\text{-NaF}$ PET images were evaluated as follows: partial response, $> 30\%$ reduction in $^{18}\text{F}\text{-NaF}$ expression in the TLSB; progressive disease, $> 30\%$ increase in $^{18}\text{F}\text{-NaF}$ expression in the TLSB or developing new lesions; and stable disease, $< 30\%$ change in $^{18}\text{F}\text{-NaF}$ expression in the TLSB

Statistical Analyses

A semi-quantitative comparison was performed measuring the TLSB in each patient. The means of the lesions VOIs measurements in each patient were used as a quantitative measure of global metastatic activity previous to receive the first cycle of ^{223}Ra , after 3 and 6 cycles of ^{223}Ra . Univariate analysis was performed according to each subtype of neoplasm. A $p < 0.05$ was considered to be statistically significant. Statistical analyses were conducted with software SPSS (version 22).

Results

All patients had bone metastases without soft-tissue lesions or visceral metastases; they all had baseline $^{18}\text{F}\text{-NaF}$ PET/CT. None of the patients were pretreated with ^{223}Ra or another bone seeking radiopharmaceutical. Five patients had a history of localized radiotherapy (3–4 months before starting treatment with ^{223}Ra) to bone, due to intense pain. All patients had pain at least Visual Analog Scale for Pain (VAS) 7, despite to receive painkillers such as NAIDS and opioids. Baseline characteristics before starting treatment with ^{223}Ra are presented in Table 2–4.

Table 2
Baseline characteristics only patients with mCSPC before starting treatment with Ra-223

| Patient | Skeletal burden group | TLSB (Range) | PSA (ng/ml) | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ /μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) | Previous RT |
|--|-----------------------|-------------------|-------------|------------|------------|-----|-----------|-----------------------------|-------------------------------------|------------------------------------|-------------|
| 1 | 3 | 91.6 (79.1–144.1) | 3.2 | 270 | 181 | 8 | 13.3 | 286 | 4.5 | 7.2 | NO |
| 2 | 2 | 66.8 (26.9–84.2) | 34 | 196 | 189 | 8 | 12.9 | 190 | 4.1 | 5.5 | YES |
| 3 | 1 | 58.7 (22.5–76.4) | 26 | 348 | 207 | 8 | 14.8 | 323 | 5.4 | 5.1 | NO |
| 4 | 1 | 81.7 (33.1–91.9) | 36.4 | 160 | 291 | 8 | 14.2 | 263 | 3.8 | 7.3 | NO |
| 5 | 2 | 69.1 (36.9–101.2) | 18.3 | 455 | 299 | 7 | 11.1 | 328 | 3.2 | 4.2 | NO |
| 6 | 3 | 89.7 (53.1–101.6) | 6.7 | 211 | 189 | 7 | 13.1 | 401 | 3.7 | 4.5 | NO |
| 7 | 3 | 96.6 (84.7–155.0) | 71 | 901 | 604 | 7 | 12.1 | 388 | 2.9 | 3.1 | YES |
| mCSPC = metastatic castration-sensitive prostate cancer; RT = Radiotherapy; Hb = Hemoglobin; Plt = platelets TLSB = total skeletal burden | | | | | | | | | | | |

Table 3
Baseline characteristics only patients with mCRPC before starting treatment with Ra-223

| Patient | Skeletal burden group | TLSB (Range) | PSA (ng/ml) | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ /μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) | Previous RT |
|--|-----------------------|--------------------|-------------|------------|------------|-----|-----------|-----------------------------|-------------------------------------|------------------------------------|-------------|
| 1 | 3 | 99.6 (89.1–164.8) | 21.2 | 499 | 685 | 8 | 11.9 | 277 | 4.0 | 8.1 | NO |
| 2 | 2 | 70.1 (46.9–88.2) | 44 | 802 | 377 | 9 | 10.9 | 289 | 3.9 | 4.8 | NO |
| 3 | 2 | 68.0 (32.9–96.7) | 29.5 | 398 | 299 | 7 | 13.0 | 303 | 5.5 | 4.7 | NO |
| 4 | 1 | 34.7 (13.0–67.2) | 22.9 | 170 | 287 | 8 | 13.2 | 290 | 3.9 | 6.6 | NO |
| 5 | 1 | 49.1 (26.0–86.8) | 58.1 | 495 | 248 | 8 | 13.2 | 328 | 4.2 | 5.0 | YES |
| 6 | 1 | 55.3 (23.1–99.6) | 46.1 | 491 | 309 | 8 | 12.1 | 387 | 4.0 | 5.0 | YES |
| 7 | 3 | 92.8 (81.7–135.0) | 49 | 401 | 504 | 9 | 11.0 | 348 | 3.9 | 3.1 | YES |
| 8 | 2 | 77.8 (49.0–100.8) | 71.2 | 569 | 700 | 9 | 10.8 | 199 | 3.9 | 5.0 | NO |
| 9 | 1 | 49.1 (26.9–89.9) | 59 | 708 | 487 | 8 | 14.0 | 248 | 4.3 | 3.9 | YES |
| 10 | 2 | 60.7 (36.9–80.9) | 36.7 | 590 | 449 | 8 | 11.4 | 278 | 5.2 | 3.9 | YES |
| 11 | 1 | 39.9 (19.0–64.2) | 44.3 | 450 | 397 | 7 | 12.2 | 302 | 3.6 | 4.6 | NO |
| 12 | 1 | 40.7 (30.0–79.8) | 40.2 | 790 | 448 | 8 | 10.9 | 128 | 4.1 | 4.1 | NO |
| 13 | 1 | 53.9 (29.7–77.6) | 88.1 | 571 | 609 | 9 | 13.4 | 307 | 3.7 | 4.3 | NO |
| 14 | 3 | 102.3 (66.7–155.1) | 59.1 | 780 | 569 | 9 | 11.9 | 149 | 4.3 | 5.1 | NO |
| 15 | 3 | 90.1 (76.3–128.5) | 64 | 662 | 607 | 9 | 14.2 | 209 | 4.5 | 4.1 | NO |
| 16 | 3 | 88.0 (62.9–116.5) | 79.0 | 798 | 669 | 9 | 10.4 | 153 | 3.5 | 3.7 | YES |
| 17 | 1 | 44.1 (14.6–87.8) | 19.9 | 370 | 245 | 7 | 12.9 | 280 | 4.3 | 4.6 | NO |
| 18 | 3 | 109.1 (66.0–156.8) | 78.4 | 590 | 688 | 9 | 10.4 | 131 | 3.2 | 3.0 | YES |
| 19 | 1 | 57.0 (19.1–84.3) | 33.2 | 391 | 299 | 7 | 12.1 | 400 | 3.9 | 5.4 | YES |
| 20 | 3 | 91.9 (74.9–137.3) | 89.2 | 587 | 504 | 9 | 11.9 | 148 | 4.1 | 3.7 | NO |
| mCRPC = metastatic castration-resistant prostate cancer; RT = Radiotherapy; Hb = Hemoglobin; Plt = platelets TLSB = total skeletal burden | | | | | | | | | | | |

Table 4
Baseline characteristics rest of patients (none prostatic malignancies) before starting treatment with Ra-223

| Tumor | Skeletal burden group | TLSB (Range) | ACE (ng/ml) | CA 15-3 | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ /μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) | Previous RT |
|--|-----------------------|--------------------|-------------|---------|------------|------------|-----|-----------|-----------------------------|-------------------------------------|------------------------------------|-------------|
| Osteosarcoma | 3 | 93.3 (89.7–137.1) | - | - | 670 | 481 | 8 | 15.7 | 315 | 4.3 | 6.1 | NO |
| Osteosarcoma | 2 | 71.7 (46.9–82.9) | - | - | 490 | 580 | 8 | 14.1 | 291 | 4.3 | 5.0 | YES |
| Osteosarcoma | 1 | 49.9 (21.0–72.9) | - | - | 348 | 501 | 8 | 12.8 | 313 | 5.9 | 7.4 | NO |
| Breast cancer | 2 | 85.1 (41.1–92.5) | - | 85 | 369 | 331 | 8 | 13.2 | 253 | 4.2 | 5.5 | NO |
| Breast cancer | 1 | 59.8 (34.2–88.9) | - | 44 | 465 | 399 | 7 | 11.7 | 267 | 5.5 | 7.7 | NO |
| Lung cancer | 2 | 88.5 (54.1–102.5) | 23 | - | 311 | 409 | 8 | 12.1 | 201 | 3.3 | 5.3 | NO |
| Lung cancer | 3 | 106.7 (88.5–175.3) | 44 | - | 802 | 523 | 9 | 11.1 | 270 | 2.8 | 4.0 | YES |
| Chordoma | 2 | 81.4 (52.0–101.7) | - | - | 440 | 679 | 9 | 12.0 | 402 | 3.1 | 3.9 | YES |
| Chondrosarcoma | 3 | 93.4 (79.9–159.8) | - | - | 489 | 590 | 9 | 11.6 | 300 | 4.4 | 5.9 | YES |
| Lung neuroendocrine carcinoma | 3 | 91.9 (80.8–149.9) | - | - | 403 | 501 | 7 | 12.1 | 287 | 5.2 | 8.8 | NO |
| RT = Radiotherapy; Hb: = Hemoglobin; Plt = platelets; TLSB = total skeletal burden | | | | | | | | | | | | |

Thirteen patients corresponded to group 1; ten patients corresponded to group 2 and fourteen patients corresponded to group 3 according to TLSB. The mostly patients with group 2 and all patients with group 1 showed a reduction of levels serum markers such as APE, LDH and AP; none patient with NSCLC and BC showed significant changes of tumor markers. All patients with mCSPC showed reduction of PSA values of interim and after 6 cycles of ²²³Ra. Moreover half patients with mCRPC showed reduction of PSA values (Table 5–7)

Table 5
Characteristics only patients with mCSPC after 6 cycles with Ra-223

| Patient | TLSB (Range) | TLSB (Range) [% of baseline] After 3 cycles* | TLSB (Range) [% of baseline] After 6 cycles** | PSA (ng/ml) | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ /μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) |
|--|-------------------|--|---|-------------|------------|------------|-----|-----------|-----------------------------|-------------------------------------|------------------------------------|
| 1 | 91.6 (79.1–144.1) | 63.3 (45.4–99.1) [69.1%] | 58.1 (40.7–70.3) [63.4%] | 0.6 | 70 | 145 | 4 | 12.5 | 216 | 3.7 | 4.9 |
| 2 | 66.8 (26.9–84.2) | 49.3 (18.9–69.7) [73.8%] | 19.9 (14.4–49.0) [30%] | 5.7 | 129 | 148 | 2 | 13.1 | 202 | 4 | 5.5 |
| 3 | 58.7 (22.5–76.4) | 40.2 (17.2–54) [68.5%] | 17.3 (4.1–28.8) [29.5%] | 0.13 | 49 | 120 | 1 | 13.1 | 300 | 3.3 | 4.7 |
| 4 | 81.7 (33.1–91.9) | 73.0 (28.6–80.1) [89.3%] | 38.7 (14.8–66.2) [47.4%] | 1.3 | 53 | 230 | 1 | 13.1 | 277 | 3.9 | 6.3 |
| 5 | 69.1 (36.9–101.2) | 52.9 (31.0–89.7) [76.5%] | 27.3 (14.4–49.9) [39.5%] | 1.2 | 119 | 85 | 2 | 9.7 | 188 | 2.5 | 4.1 |
| 6 | 89.7 (53.1–101.6) | 70.5 (42.1–88.8) [78.6%] | 66.9 (38.7–80.9) [74.6%] | 0.9 | 101 | 113 | 2 | 9.9 | 283 | 3.4 | 3.9 |
| 7 | 96.6 (84.7–155.0) | 95.3 (88.3–141.1) [98.6%] | 90.9 (80.7–131.7) [94.1%] | 2.4 | 120 | 134 | 4 | 8.8 | 209 | 2.9 | 2.9 |
| *Percentage of declined Mean SUVmax after 3 cycles of Ra-223 ** Percentage of declined Mean SUVmax after 6 cycles of Ra-223 | | | | | | | | | | | |

Table 6
Characteristics only patients with mCRPC after 6 cycles with Ra-223

| Patient | TLSB (Range) | TLSB (Range) [% of baseline] After 3 cycles* | TLSB (Range) [% of baseline] After 6 cycles** | PSA (ng/ml) | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ /μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) |
|---------|--------------------|--|---|-------------|------------|------------|-----|-----------|-----------------------------|-------------------------------------|------------------------------------|
| 1 | 99.6 (89.1–164.8) | 88.1 (70.3–152.2) [88%] | 80.9 (65.2–123.6) [81.2%] | 18.3 | 377 | 381 | 4 | 8.1 | 114 | 2.7 | 4.1 |
| 2 | 70.1 (46.9–88.2) | 66.2 (40.2–84.2) [94.4%] | 60.6 (37.3–77.2) [86.4%] | 21.9 | 709 | 316 | 4 | 10.5 | 195 | 3.3 | 2.5 |
| 3 | 68.0 (32.9–96.7) | 65.2 (29.9–94.0) [95.8%] | 59.9 (25.5–88.2) [88%] | 14.7 | 323 | 291 | 2 | 10.8 | 244 | 3.6 | 5.1 |
| 4 | 34.7 (13.0–67.2) | 19.9 (8.8–40.1) [57.3%] | 13.8 (6.6–30.8) [39.7%] | 10.2 | 185 | 253 | 1 | 12.4 | 290 | 4.2 | 4.3 |
| 5 | 49.1 (26.0–86.8) | 30.8 (18.8–62.9) [62.7%] | 19.9 (15.4–50.8) [40.5%] | 33.4 | 437 | 233 | 1 | 9.9 | 208 | 2.9 | 3.6 |
| 6 | 55.3 (23.1–99.6) | 39.3 (18.8–79.3) [71%] | 29.4 (17.9–61.1) [53.1%] | 40.1 | 399 | 331 | 2 | 8.1 | 283 | 3.4 | 3.9 |
| 7 | 92.8 (81.7–135.0) | 102 (92.2–178.6) [109.9%] | Not completed | 62.3 | 495 | 683 | 6 | 8.3 | 209 | 2.9 | 2.9 |
| 8 | 77.8 (49.0–100.8) | 70.2 (43.3–92.1) [90.2%] | 66.2 (38.5–82.7) [85%] | 68.4 | 483 | 516 | 6 | 9.4 | 248 | 3.1 | 4.0 |
| 9 | 49.1 (26.9–89.9) | 31.4 (21.2–68.8) [63.9%] | 23.1 (16.5–44.8) [47%] | 55.4 | 518 | 401 | 4 | 10.9 | 233 | 4.0 | 4.2 |
| 10 | 60.7 (36.9–80.9) | 55.4 (31.9–75.3) [91.2%] | 50.2 (25.9–70.2) [82.7%] | 33.1 | 498 | 356 | 4 | 10.3 | 183 | 3.6 | 4.4 |
| 11 | 39.9 (19.0–64.2) | 28.8 (16.2–56.7) [72.1%] | 20.7 (13.1–42.2) [51.8%] | 22.8 | 393 | 302 | 1 | 11.0 | 113 | 2.9 | 3.9 |
| 12 | 40.7 (30.0–79.8) | 34.7 (22.9–65.5) [85.2%] | 21.3 (12.8–40.6) [52.3%] | 41.4 | 683 | 397 | 4 | 11.7 | 121 | 3.2 | 3.3 |
| 13 | 53.9 (29.7–77.6) | 49.3 (26.4–70.7) [91.4%] | 35.5 (18.3–58.9) [65.8%] | 73.2 | 416 | 412 | 2 | 10.1 | 113 | 3.9 | 4.0 |
| 14 | 102.3 (66.7–155.1) | 156.5 (89.4–196.6) [152%] | Not completed | 66.3 | 777 | 551 | 10 | 7.2 | 101 | 2.2 | 3.2 |
| 15 | 90.1 (76.3–128.5) | 137.8 (88.9–157.4) [152.9%] | Not completed | 77.4 | 794 | 650 | 10 | 7.0 | 95 | 2.6 | 3.0 |
| 16 | 88.0 (62.9–116.5) | 99.4 (79.3–132.8) [112.9%] | Not completed | 85.4 | 795 | 701 | 10 | 8.2 | 66 | 2.5 | 2.9 |
| 17 | 44.1 (14.6–87.8) | 39.4 (11.7–70.1) [89.3%] | 23.9 (8.9–51.2) [54.1%] | 11.2 | 318 | 227 | 1 | 8.9 | 129 | 4.0 | 3.8 |
| 18 | 109.1 (66.0–156.8) | 119.4 (71.3–171.2) [109.4%] | 92.1 (59.8–137.3) [84.4%] | 55.3 | 392 | 471 | 2 | 8.1 | 78 | 2.9 | 2.7 |

| Patient | TLSB (Range) | TLSB (Range) [% of baseline] After 3 cycles* | TLSB (Range) [% of baseline] After 6 cycles** | PSA (ng/ml) | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ / μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) |
|--|--------------------------|--|---|----------------|---------------|---------------|-----|--------------|---------------------------------------|--|---------------------------------------|
| 19 | 57.0 (19.1– 84.3) | 45.8 (15.3–77.8) [80.3%] | 40.1 (12.8–70.3) [70.3%] | 21.7 | 316 | 251 | 1 | 11.5 | 155 | 4.1 | 3.7 |
| 20 | 91.9 (74.9– 137.3) | 88.3 (77.4–121.3) [96%] | 85.4 (72.1–116.9) [92.9%] | 91.3 | 518 | 366 | 2 | 8.4 | 99 | 3.2 | 3.6 |
| *Percentage of declined Mean SUVmax after 3 cycles of Ra-223 ** Percentage of declined Mean SUVmax after 6 cycles of Ra-223 | | | | | | | | | | | |

Table 7
Characteristics rest of patients (none prostatic malignances) after 6 cycles with Ra-223

| Tumor | TLSB (Range) | TLSB (Range) [% of baseline] After 3 cycles* | TLSB (Range) [% of baseline] After 6 cycles** | ACE (ng/ml) | CA 15 – 3 | ALP (UI/L) | LDH (UI/L) | VAS | Hb (g/dl) | Plt (x 10 ³ / μL) | Neutrophils (x 10 ³ /μL) | Leukocytes (x 10 ³ /μL) |
|--|---------------------------|---|--|----------------|-----------------|---------------|---------------|-----|--------------|---------------------------------------|--|---------------------------------------|
| Osteosarcoma | 93.3 (89.7– 137.1) | 99.5 (92.1– 149.3) [106.6%] | Not completed | - | - | 771 | 668 | 8 | 8.5 | 106 | 3.2 | 5.8 |
| Osteosarcoma | 71.7 (46.9– 82.9) | 84.3 (52.9– 95.8) [117.5%] | Not completed | - | - | 516 | 691 | 10 | 10.3 | 122 | 4.1 | 4.1 |
| Osteosarcoma | 49.9 (21.0– 72.9) | 44.1 (18.8– 66.9) [88.3%] | 40.2 (15.5– 60.8) [80.5%] | - | - | 316 | 397 | 4 | 10.6 | 201 | 3.0 | 3.7 |
| Breast cancer | 95.1(41.1– 92.5) | 71.2 (34.1– 88.3) [74.8%] | 66.1 (30.5– 79.2) [69.5%] | - | 80 | 354 | 301 | 2 | 11.4 | 157 | 4.2 | 4.7 |
| Breast cancer | 59.8 (34.2– 88.9) | 55.1 (31.2– 81.8) [92.1%] | 50.8 (28.8– 76.7) [84.9%] | - | 41 | 408 | 309 | 1 | 9.2 | 108 | 4.0 | 3.8 |
| Lung cancer | 88.5 (54.1– 102.5) | 93.4 (69.8– 122.4) [105.5%] | 85.2 (50.1– 97.8) [96.2%] | 19 | - | 301 | 391 | 6 | 9.1 | 102 | 3.1 | 4.4 |
| Lung cancer | 106.7 (88.5– 175.3) | 112.9 (94.3– 193.3) [105.8%] | Not completed | 56 | - | 901 | 663 | 10 | 7.8 | 101 | 2.5 | 2.9 |
| Chordoma | 81.4 (52.0– 101.7) | 70.3 (40.3– 93.6) [86.3%] | 59.8 (31.2– 76.4) [73.4%] | - | - | 319 | 331 | 2 | 10.9 | 288 | 3.7 | 4.2 |
| Chondrosarcoma | 93.4 (79.9– 159.8) | 142.3 (99.2– 193.2) [152.3%] | Not completed | - | - | 685 | 703 | 8 | 7.6 | 96 | 2.3 | 3.3 |
| Lung neuroendocrine carcinoma | 91.9 (80.8– 149.9) | 88.2 (75.6– 130.2) [95.9%] | 83.4 (71.2– 124.6) [90.7%] | - | - | 385 | 419 | 4 | 10.4 | 211 | 2.9 | 4.2 |
| *Percentage of declined Mean SUVmax after 3 cycles of Ra-223 ** Percentage of declined Mean SUVmax after 6 cycles of Ra-223 | | | | | | | | | | | | |

Improvement of bone pain was observed in 32 patients at the end of treatment compared to baseline. In three patients a significant decrease in pain was observed after the first two cycles of Ra-223; in two patients after four cycles.

Treatment-related adverse events were observed in 10 patients (6 patients with superscan); such as fatigue, diarrhea and nausea; meanwhile did not affect continuation of therapy. We found slight to moderate decreases in neutrophils and hemoglobin in 14 (38%) patients at the end of entire therapy. During treatment and at term, 8 patients required transfusion. Four patients (two with superscan) required prior to the last cycle administration of colony stimulating factor. None patient presented severe adverse event's Grade III or IV according to CTCAE.

in 30 patients no progress disease was documented after 24 ± 4 weeks. In 8 patients progress disease was presented after three cycles of ^{223}Ra (two presented visceral metastases), two patients with osteosarcoma, four patients with mCRPC, one patient with chondrosarcoma and one patient with NSCLC (Figs. 3 and 4)

Symptomatic skeletal-related event (SSE) was observed in 7 patients, 3 patients with mCRPC (two development pathologic fracture, and one patient required radiation therapy for worsening pain), one patient with NSCLC (pathologic fracture), one patient with osteosarcoma, one patient with chondrosarcoma and one patient with chordoma (the three patients for worsening pain)

Those patients in group 1 showed better response rates compared to those in group 3 ($p < 0.05$). Patients in group 2 who showed improvement clinical and radiological, had prostate malignancies compared to those in the same group, but non-prostatic malignancies ($p < 0.05$). While there was no significant difference in the group of patients in group 2 compared to group 3 ($p < 0.67$). Response rates were established according to the percentage of decreasing TLSB values, biochemical markers and improvement in pain (Fig. 5)

Nine patients progressed, five patients with mCRPC, two patients with osteosarcoma, one patient with chondrosarcoma and one patient with NSCLC. All patients had high tumor burden because corresponding to group 2 and 3, but only 7 patients developed SSE as previously mentioned. In addition, the mean TLSB doesn't improve after three cycles of ^{223}Ra .

Discussion

^{223}Ra is a bone-seeking radiopharmaceutical that emits α -particles that deposit high linear energy within a short penetration range to areas of increased bone turnover, as radioactive decay occurs, near osseous metastatic sites, it selectively kills cancer cells. ^{223}Ra has a complex decay scheme in which 4 alpha particles resulting in high energy deposition (28.2 MeV), the high linear energy transfer of radiation results in generation of double-strand DNA breaks, and gives rise to cytotoxicity that is independent of dose rate, cell cycle growth phase, and oxygen concentration. The range of the α particles ($< 100 \mu\text{m}$) results in less hematologic toxicity than expected from β emitters [12, 13]. Currently ^{223}Ra is recommended as a first-line treatment in mCRPC symptomatic or mildly symptomatic without visceral metastases [14]

Maybe one of the doubts that does not end with clearing the ALSYMPCA trial is the poor evaluation of response with bone scan or another molecular imaging method, only was performed a baseline bone scan [1]. In recent years several studies have been published as a result of research conducted with different radiotracers, due to the need to assess the response and toxicity associated with this therapy [15, 16].

However, the current recommendations of the Prostate Cancer Working Group 3 (PCWG3), European Association of Urology (EAU), NCCN, and many another guidelines, are unclear in defining the evaluation of response to any treatment of a non-measurable disease such as bone disease of the blastic type; for these reason numerous investigations have suggested the use of nuclear medicine techniques for patient selection and response evaluation, in addition similar to other therapies for mPC, a flare phenomenon with increase of bone metastases-related pain, or "increase" in apparent number of bone metastases on bone scan, may be noted during the first treatment cycles, and should not be interpreted as disease progression [14–19]

The present study showed that besides that ^{223}Ra do not approved in another neoplasm such as BC, LC, mCSPC, and bone tumors the osteoblastic activity of the bone metastases may represent a therapeutic target due to calcium-mimetic characteristic of ^{223}Ra .

Skeletal evaluation with ^{18}F -NaF PET/CT is better to bone scintigraphy in mPC patients because of greater sensitivity, specificity, and accuracy; also, in another neoplasm such as breast cancer or lung cancer when the osteoblastic component predominates, for this reason molecular imaging always should precede therapy with ^{223}Ra to determine active osteoblastic lesions, because the focal uptake with ^{18}F -NaF PET/CT or MDP-bone scan correlates with the intensity of bone metabolism and eventually the uptake of ^{223}Ra [20–22].

Because the work done by Subbiah V, et al [23], the ^{223}Ra was considerate as second-line therapy in metastatic osteosarcoma according to most recently National Comprehensive Cancer Network (NCCN) practical guidelines for osteosarcoma, they showed in 18 patients treated with higher doses of ^{223}Ra (100 kBq/kg) a mixed responses rates, one patient had partial responses in metastatic site (brain), and another patient in liver metastases [24].

To our knowledge, at the time of writing this article, we are the first to report the value of ^{18}F -NaF PET/CT in the selection and evaluation of patients treated with ^{223}Ra in non-prostatic neoplasms such as chondrosarcoma and chondroma. Where we found that ^{18}F -NaF PET/CT plays an important role in the selection of patients who are candidates for treatment with ^{223}Ra since it allows visualizing and quantifying the osteoblastic tumor burden, which is the therapeutic target of ^{223}Ra , in addition to monitored response. Unfortunately, the aggressiveness of tumors such as osteosarcoma and

chondrosarcoma did not allow the completion of the 6 cycles of ^{223}Ra ; for which the PET/CT allowed to easily identify the visceral and bone progression in these patients.

In patients with both types of lung cancer, the 6 cycles were allowed to conclude; however, in one of them, the progression occurred 8 weeks after the end of the treatment. Taber AM, et al, showed that 5 patients with NSCLC who have received front-line chemotherapy, the progression free survival (PFS) at 6 months was 80.0% and 40.0% at 12 months in patients treated with 6 cycles of ^{223}Ra ; in addition, only one patient developed SSE after 219 days, and the four remaining patients did not experience a SSE during follow-up [25]

Tahara RK, et al, carried out a single-center phase II study to determine the efficacy and safety of ^{223}Ra in combination with hormonal therapy and denosumab, a total of 22 patients were studied the security of this combination, observed that most common hematological AEs were grade 1 or 2 neutropenia (23%), anemia (14%), and thrombocytopenia (18%) in median follow-up time was 4 months; in addition, there were no grade 3 or 4 AEs [26]; however, no PET/CT with any radiotracer was performed baseline or in the follow-up. Our results in two patients showed a good tolerability and no progression was observed in $^{18}\text{F-NaF}$ PET/CT.

One of the most important limitations of the present study is the wide variety of tumors which determines that the results are not uniform; to counteract such a limitation, we chose to categorize them into three study groups according to the bone tumor burden to highlight the value of PET/CT. Unfortunately, the small subgroup of patients with bone neoplasms prevents conclusions with an impact on survival.

More studies dedicated to each subgroup of patients are needed to obtain important data such as progression-free survival and overall survival.

Conclusion

The molecular imaging with $^{18}\text{F-NaF}$ allows identify patients who show osteoblastic bone activity and discard or confirm progression in the interval PET/CT image, allowing an opportune change of the treatment reducing the costs for the patient and the institution. In addition, a high tumor burden strongly suggests a poor response to treatment, which in all cases is not synonymous with progression. ^{223}Ra is an agent with good tolerability with low SSEs rate and good pain response after completing 6 treatment cycles.

Declarations

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

INFORMED CONSENT

The institutional review board of our institute approved this retrospective study, and the requirement to obtain informed consent was waived.

AVAILABILITY OF SUPPORTING DATA

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

COMPETING INTERESTS

All authors declare that they have no conflict of interest.

FUNDING

Not applicable

AUTHOR CONTRIBUTION STATEMENT

All authors have read this final version of the manuscript and have agreed with its present form. S. Medina-Ornelas and F. García-Pérez contributed equally to this work in conceptualization and design and methodology. All co-authors provided critical revisions of the manuscript for important intellectual content and formal analysis and investigation. The authors read and approved the final manuscript.

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CONSENT FOR PUBLICATION

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Figures

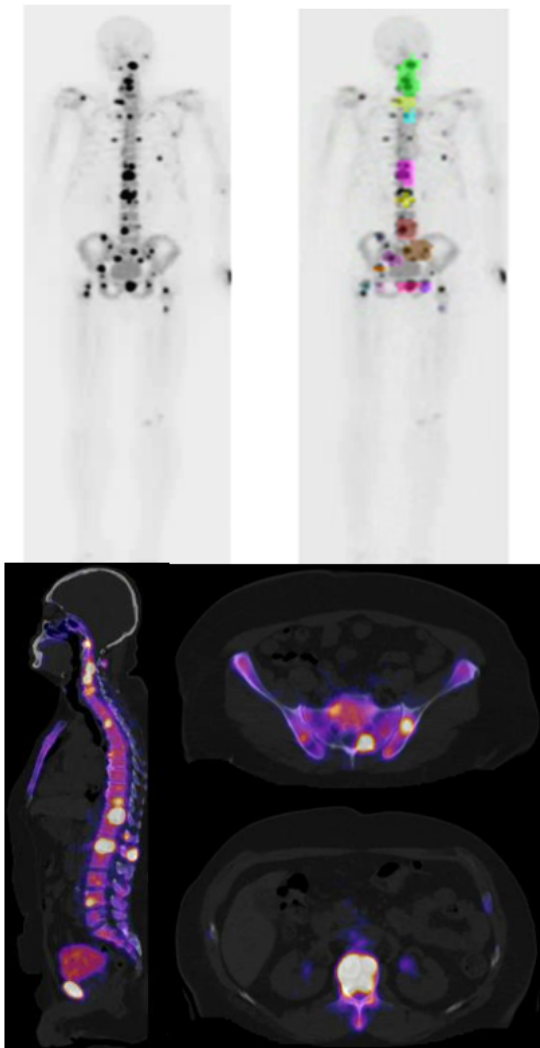


Figure 1

Top left. Multiple sites of focal increased uptake that result in metastatic bone disease predominantly blastic type axial skeleton in the MIP 18F-NaF PET. Top right. Volumes of interest (VOIs) with edges around 1 to 3 cm were drawn on regions of interest, the uptake in the VOIs was classified as malignant on the basis of the radiopharmaceutical distribution pattern with match CT images. Lower. Fused sagittal and axial slices showed intense focal uptake in multiple vertebral bodies and pelvis.

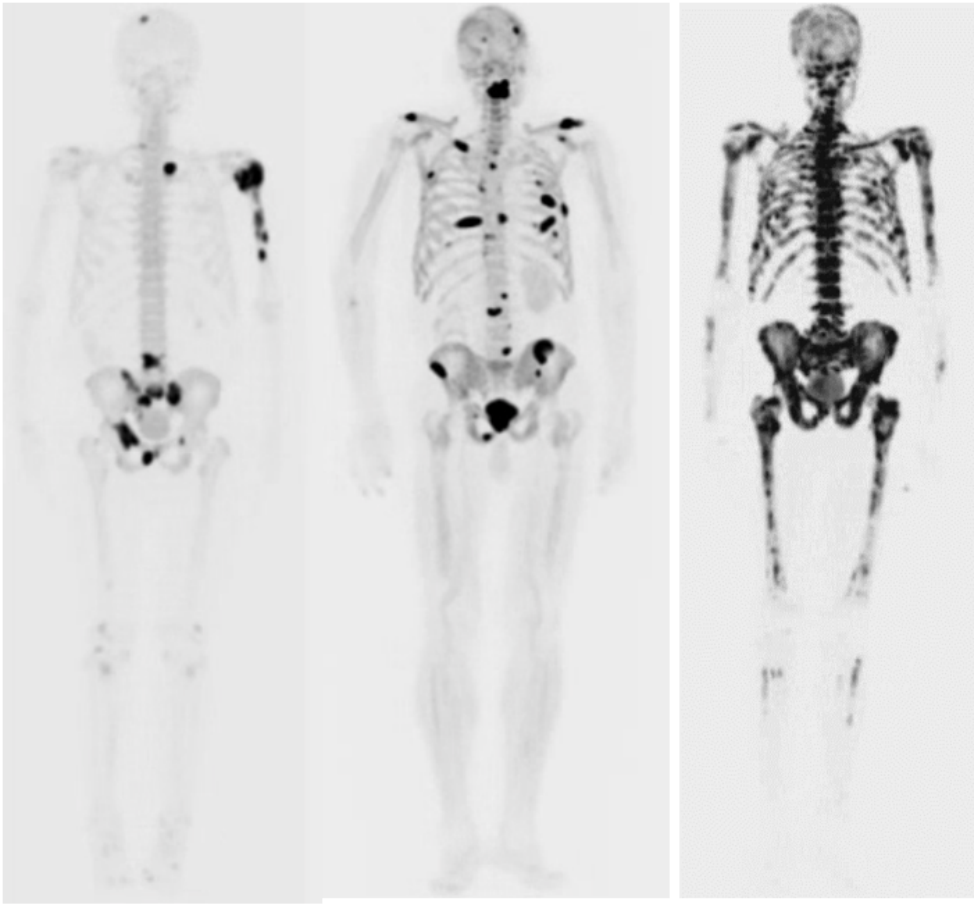


Figure 2

Left. MIP 18F-NaF PET showed multiple sites of focal increased uptake that result in metastatic bone disease blastic type axial skeleton, VOI's and SUVmax values according group 1 (less 1000 cm³). Middle. MIP 18F-NaF PET showed multiple sites of focal increased uptake that result in metastatic bone disease blastic type axial skeleton, VOI's and SUVmax values according group 2 (1001 to 2999 cm³). Right. MIP 18F-NaF PET showed multiple sites of focal increased uptake that result in metastatic bone disease blastic type axial skeleton, VOI's and SUVmax values according group 3 (more than 3000 cm³), note the intense metastatic burden disease compared with group 1 and 2.

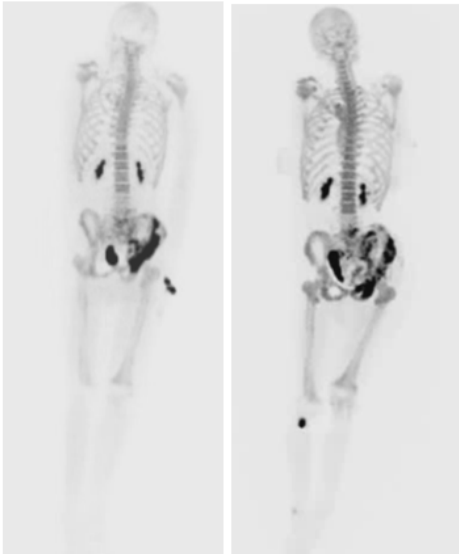


Figure 3.

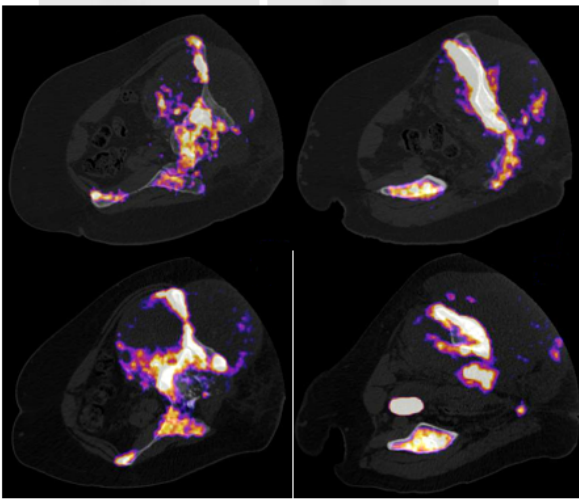


Figure 3

Top left. MIP 18F-NaF PET showed focal uptake in pelvis corresponding to patient with chondrosarcoma. Top right. MIP 18F-NaF PET (after 3 cycles of 223Ra) showed incremental osteoblastic lesion in pelvis and new lesions. Middle. Fused sagittal slices showed osteoblastic lesion in pelvis in addition tumoration soft tissue in left side of pelvis. Lower. Fused sagittal slices (after 3 cycles of 223Ra) showed incremental osteoblastic lesion in pelvis and size of tumoration soft tissue in left side of pelvis, more structures in pelvis was affected. Progression disease was documented and 223Ra was stopped, these patient was corresponding to group 2.

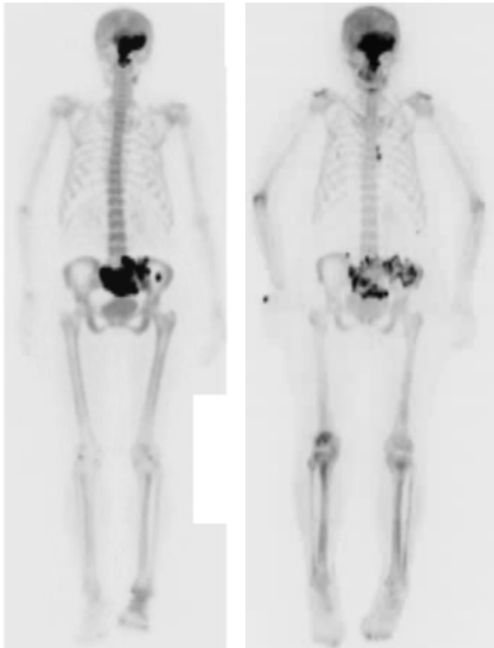


Figure 4.

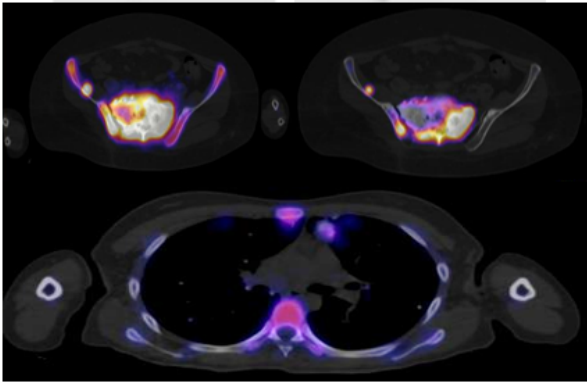


Figure 4

Top left. MIP 18F-NaF PET showed focal uptake in skull and pelvis corresponding to patient with osteosarcoma. Top right. MIP 18F-NaF PET (after 3 cycles of 223Ra) showed decrease osteoblastic lesion in sacrum, no changes in skull and new lesions in lung. Middle left. Fused sagittal slices showed osteoblastic lesion in sacrum and pelvis with intense uptake. Middle right. Fused sagittal slices (after 3 cycles of 223Ra) showed osteoblastic lesion in sacrum and pelvis with sclerotic changes and decrease uptake. Lower. Fused sagittal slices (after 3 cycles of 223Ra) showed new metastatic lesion in left lung with calcification. Progression disease was documented and 223Ra was stopped, these patient was corresponding to group 3.

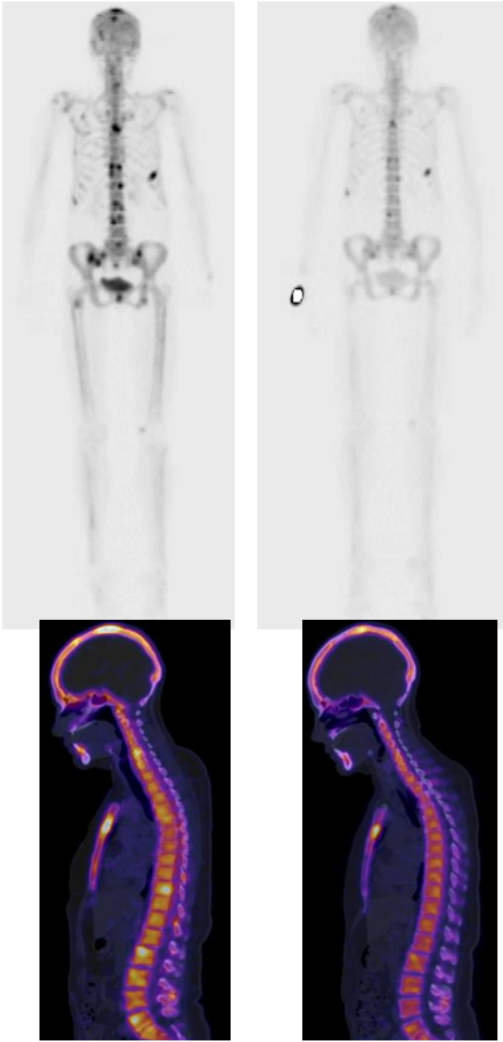


Figure 5

Top left. Baseline MIP 18F-NaF PET showed focal uptake in skull, multiple vertebral bodies and pelvis corresponding to patient with breast cancer, according to group 1. Top right. MIP 18F-NaF PET (after 6 cycles of 223Ra) showed decrease osteoblastic lesion in all lesions. Lower left. Fused sagittal slices showed multiple osteoblastic lesion in skull and vertebral bodies with intense uptake. Lower right. Fused sagittal slices (after 6 cycles of 223Ra) showed decrease osteoblastic lesion in all lesions. Partial response was documented. (interval PET no showed important changes respect to baseline)