Bone-Targeted Imaging and Radionuclide Therapy in Prostate Cancer

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Although selective metabolic and receptor-based molecular agents will surely be included in the future of prostate cancer diagnosis and therapy, currently available inorganic compounds—such as ^{18}F-NaF for the diagnosis of bony disease and ^{223}RaCl$_2$ for the therapy of bone metastases—were recently shown to be superior to standard ^{99m}Tc-phosphonates for diagnosis and ^{153}Sm-ethylenediaminetetramethylene phosphonate or ^{89}SrCl$_2$ for therapy. The advantages of ^{18}F-NaF include improved lesion detection and, when used in combination with CT, improved diagnostic confidence and specificity. In addition to being the first approved α-emitter, ^{223}RaCl$_2$ is the first radiopharmaceutical to show an increase in overall survival, a decrease in skeletal events, palliation of bone pain, and a low profile of adverse reactions (which are mild and manageable). The management of metastatic bone disease with ^{223}RaCl$_2$ is uniquely satisfying, as patients can be monitored directly during their monthly treatment visits.

Key Words: PET/CT; PET; prostate; cancer; bone; radium

The American Cancer Society has estimated that there will be 180,890 new prostate cancer (PC) patients and 28,170 deaths in 2016 (1). Prostate cancer ranges from asymptomatic to a progressive systemic malignancy. Lymph nodes and bones are the most common sites of metastases. Serum prostate-specific antigen (PSA) levels, Gleason score, and clinical stage at presentation are used to assess pretreatment risk and the probability of recurrence or metastases. On the basis of these criteria, patients are characterized as having low risk (bone metastases unlikely) or high risk (bone metastases likely). Skeletal metastases correlate with a poor prognosis. ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) scintigraphy has been the imaging method of choice for the evaluation of predominantly sclerotic skeletal PC metastases. However, the growing availability of PET imaging systems, the establishment of commercial regional distribution centers for PET radiotracers, and the relatively recent concerns with shortages of ^{99m}Tc-labeled radiotracers have prompted much interest in the use of PET in this clinical setting (2).

^{18}F-NAF PET IN PC

^{18}F-NaF is a positron-emitting radiopharmaceutical that was used for skeletal scintigraphy in the 1970s. Clinical use was limited then because of logistic difficulties in delivering tracers with a half-life of 110 min and the absence of PET technology. ^{18}F-NaF was replaced in the late 1970s by ^{99m}Tc-labeled phosphonates, which had improved γ-camera compatibilities (3,4). As an analog of the hydroxyl group found in hydroxyapatite bone crystals, ^{18}F-NaF is an avid bone seeker. Ion exchange is its mechanism of uptake, and blood flow is the rate-limiting step in the transfer of fluoride ions from blood to bone (4,5). As with ^{99m}Tc-phosphonates, which adhere to bone by chemisorption, fluorine is directly incorporated into the bone matrix, converting hydroxyapatite to fluoroapatite (6). ^{18}F-NaF is rapidly cleared from plasma, with only 10% of ^{18}F-NaF remaining in plasma at 1 h (7,8). This desirable characteristic of rapid blood clearance in association with fast and high bone uptake leads to high-quality (high target-to-background uptake ratio) skeletal images in less than 1 h after intravenous ^{18}F-NaF administration (Fig. 1). Nonuniform uptake of ^{18}F-NaF in normal skeleton reflects differential regional blood flow and bone crystal surface nonuniformity. Regional high uptake in abnormal scans corresponds to processes that increase blood flow to the exposed bone crystal surface.

^{18}F-NAF PET/CT VS. ^{99m}TC-MDP BONE SCINTIGRAPHY

^{18}F-NaF PET/CT is currently under evaluation for the detection of malignant skeletal lesions. In December 2015, the Centers for Medicare & Medicaid Services issued a decision memorandum regarding the use of ^{18}F-NaF PET for the detection of bony metastasis, concluding that available outcome evidence was not sufficient to allow for ^{18}F-NaF PET reimbursement (9). The Centers for Medicare & Medicaid Services recommended continuation of coverage with evidence development for another 2 y, as before, through the National Oncologic PET Registry for ^{18}F-NaF (9). ^{99m}Tc-MDP bone scintigraphy has been the method of choice for the evaluation of osseous metastases, as it enables a relatively low-cost whole-skeleton survey. Applications of skeletal scintigraphy include initial staging, monitoring the response to therapy, and detection of areas at risk for pathologic fracture. Although ^{99m}Tc-MDP scintigraphy is sensitive for the detection of advanced skeletal metastatic lesions, early involvement may be missed because this technique relies on identification of the osteoblastic reaction of the involved bone rather than detection of the tumor
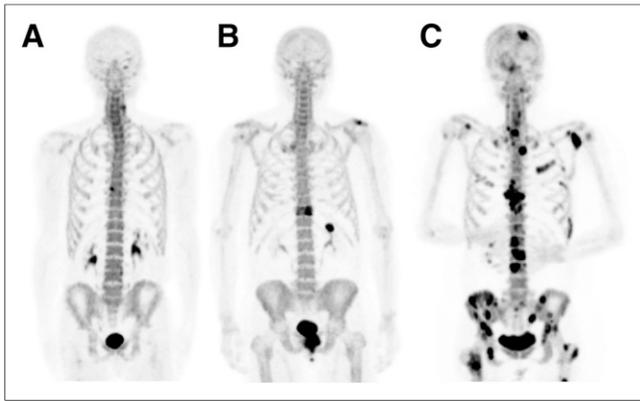
FIGURE 1. ^{18}F-NaF PET/CT maximum-intensity-projection images illustrating appearance of anterior osteophyte (A), solitary metastasis (B), and multiple metastases (C) in 3 different PC patients.

itself. The technique relies significantly on regional blood flow to bone. Spatial resolution limitations imposed by planar scintigraphy and SPECT also affect bone scintigraphy sensitivity for osseous metastases (10). In a study by Even-Sapir (11), patients with high-risk PC underwent ^{99m}Tc-MDP bone scintigraphy with SPECT and ^{18}F-NaF PET/CT. In a patient-based analysis, the sensitivities of ^{99m}Tc-MDP planar scintigraphy, SPECT, and ^{18}F-NaF PET/CT were 70%, 92%, and 100%, respectively. The specificities of ^{99m}Tc-MDP planar scintigraphy, SPECT, ^{18}F-NaF PET, and ^{18}F-NaF PET/CT were 57%, 82%, 62%, and 100%, respectively. Another study involving 42 PC patients demonstrated a sensitivity of 91%, a specificity of 89%, and an accuracy of 90% for ^{18}F-NaF PET/CT in the detection of bone metastases (12). Cook et al. compared qualitative bone scintigraphy with semiquantitative ^{18}F-NaF PET for evaluation of the response to bone metastasis treatment with [223]RaCl$_2$ (13) and concluded that ^{18}F-NaF PET was more accurate than ^{99m}Tc-MDP (Fig. 2).

A recent study comparing ^{18}F-NaF PET with ^{99m}Tc-MDP scintigraphy demonstrated that ^{18}F-NaF PET/CT was more accurate than conventional bone scintigraphy for localizing and characterizing malignant bone lesions (14). High-quality imaging, increased clinical accuracy, and greater patient and referring physician convenience support ^{18}F-NaF PET/CT in comparison with planar bone scintigraphy, SPECT, SPECT/CT, and whole-body MRI, including diffusion-weighted imaging, for the evaluation of skeletal malignancy (15,16). Despite the high performance of ^{18}F-NaF PET/CT, clinical use remains low because of limited access and nonuniform reimbursement. The exact PSA threshold for using ^{18}F-NaF PET/CT also remains to be established, although the threshold is probably lower than that for ^{99m}Tc-MDP scintigraphy (typically a serum PSA level of >20 ng/mL).
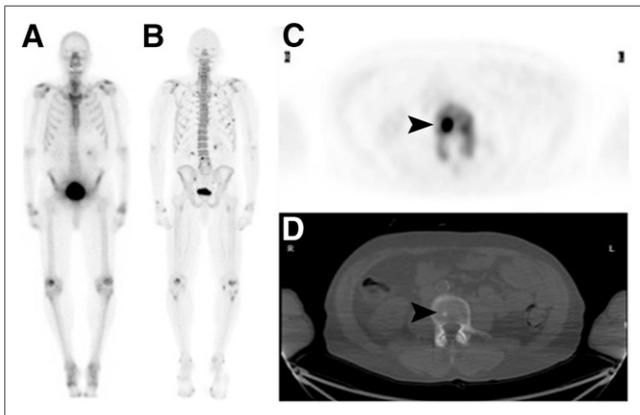
Our results indicated the feasibility and utility of the combined administration of ^{18}F-NaF and ^{18}F-FDG in a single PET/CT examination for the detection of malignancy, including PC (17–20).

TARGETED RADIONUCLIDE THERAPY FOR BONE METASTASES

Initial and subsequent treatment of PC is complex and may involve surgery, radiation therapy, hormonal therapy, chemotherapy, bisphosphonates, pain medication, or a combination of these. Typically, the initial phase of hormone dependence gives way to hormone independence or castration resistance, at which time the cancer tends to metastasize more readily, especially to bone. About 90% of patients with advanced castration-resistant PC (CRPC) will develop bone metastases (21). Bone lesions may cause pain, disability, deterioration of quality of life, and skeletal events (e.g., pathologic fractures or spinal cord compression) that may require treatment, with associated costs and potential complications. Metastatic CRPC (mCRPC) is associated with significant morbidity and mortality. Successful mCRPC treatment alleviates bone pain, reduces skeletal events, reduces disease biomarkers (such as alkaline phosphatase and PSA levels), and improves survival.

Prostate cancer cell proliferation generally induces an osteoblastic reaction in bone. One successful strategy for improving clinical outcomes in PC patients with bone metastases is the use of radiopharmaceutical agents that preferentially accumulate at sites of increased osteoblastic activity and provide a local antitumor effect (21,22). Targeted radionuclide therapy is used to deliver a specific amount of radioactivity to specific tissues in a certain area of the body to destroy cancer lesions (Table 1).

[89]SRCL$_2$ AND [153]SM-ETHYLENEDIAMINETETRAMETHYLENE PHOSPHONATE ([153]SM-EDTMP)

Historically, the most common radiopharmaceuticals for bone pain palliation in the United States were the β-emitting radiopharmaceuticals [89]SrCl$_2$ and [153]Sm-EDTMP. [89]SrCl$_2$ was approved by the U.S. Food and Drug Administration (FDA) in 1993 and has a physical half-life of 50.5 d, a maximum β-energy of 1.463 MeV (100%), and a tissue range of 8 mm. The typical dose is 148 MBq (4 mCi) through a slow intravenous push. Doses can be repeated at 3-mo intervals. Pain relief usually begins in 10–20 d and lasts up to 6 mo, resulting in reduced management expenditures (23). Although the tumor-to-marrow absorbed dose is approximately 10:1, to avoid complications from marrow suppression, a pretreatment platelet count of greater than 60,000/mm^3 and a white blood cell count of greater than 2,400/mm^3 are suggested. With specific instructions, effective doses to bystanders are acceptable (24). Kurosaka et al. showed that [89]SrCl$_2$ was effective in reducing pain, including a subset of patients who became pain-free, with resultant improvement in quality of life (25).

FIGURE 2. 73-y-old man with PC. (A and B) ^{99m}Tc-MDP bone scan was negative (A), whereas ^{18}F-NaF PET/CT revealed single L4 metastasis (B). (C and D) Axial PET (C) and CT (D) revealed focal uptake in small sclerotic lesion (arrowhead).

TABLE 1
Bone-Targeted Radiopharmaceuticals

Radiopharmaceutical	Physical half-life (d)	Particle type	Usual administered activity	Typical response time (d)	Typical response duration	Retreatment interval
^{89}SrCl$_2$ (Metastron; GE Healthcare Ltd.)	50.5	β	148 MBq	14–28	12–26 wk	>3 mo
^{153}Sm-EDTMP (Quadramet; IBA-Molecular)	1.9	β	37 MBq/kg	2–7	8 wk	>2 mo
^{223}RaCl$_2$ (Xofigo; Bayer Healthcare)	11.4	α	50 kBq/kg × 6 every 4 wk	<10	Unknown	Unknown

^{89}SrCl$_2$ may also be effective in combination with other drugs. In a study by Tu et al., 36 patients who had CRPC and were randomly assigned to receive ^{89}SrCl$_2$ and doxorubicin had a median survival time of 27.7 mo; in contrast, for 36 patients who received doxorubicin alone, the median survival time was 16.8 mo ($P = 0.0014$) (26). However, such an outcome benefit with combined therapy was not demonstrated in patients with advanced castration-sensitive prostate cancer (27).

^{153}Sm-EDTMP was approved by the FDA in 1997, emits both medium-energy β-particles and a γ-photon (which allows for imaging), and has a physical half-life of 46.3 h (Fig. 3). The recommended dose of ^{153}Sm-EDTMP is 37 MBq/kg (1.0 mCi/kg), administered intravenously. The patient should ingest or receive fluids and should void often to minimize bladder radiation. ^{153}Sm-EDTMP has a desirable combination of high bone uptake, low nonosseous uptake, and rapid blood clearance, making it useful in treating bone metastases. The highest doses are present in bone and the urinary bladder wall (28). ^{99m}Tc-MDP and ^{153}Sm-EDTMP concentrate in metastatic skeletal lesions through the same mechanisms (29). In a phase 1 study of patients with skeletal metastases, prospective radiation dosimetry calculation permitted an accurate ^{153}Sm-EDTMP dosage on the basis of total red marrow exposure, starting at 100 cGy and escalating to 280 cGy, to define dose-limiting myelotoxicity (30). Pain was relieved in 22 of 34 patients (65%) for periods ranging from 4 to 35 wk (30). Other, larger studies confirmed similar response rates in both breast cancer and prostate cancer (31–33). Transient myelosuppression with delayed thrombocytopenia was noted in some patients (30). Bayouth et al. reported that radiation estimates permitted the identification of at-risk patients before myelotoxicity was reached (34).

In 55 patients with painful bone metastases, Sartor et al. reported that repeat dosing with ^{153}Sm-EDTMP at 37 MBq/kg (1.0 mCi/kg) was safe and effective, and Heron et al. found that multiple treatments with ^{153}Sm-EDTMP had no effect on the severity of myelotoxicity (35,36). This treatment option is reasonable in patients who have adequate hematologic function and bone pain that recurs after an initial successful dose.

Baczyk et al. compared ^{89}SrCl$_2$ and ^{153}Sm-EDTMP in 60 patients with PC and 40 patients with breast cancer (37). Complete pain relief was found in 40% of women and men treated with ^{153}Sm-EDTMP and in 25% of women and 33% of men treated with ^{89}SrCl$_2$. No relief occurred in 20% of patients. Greater pain reduction occurred with osteoblastic metastases than with mixed metastases. Statistically significant pain reduction, pain drug requirements, and Karnofsky scale improvement were found with both radionuclides (37). Montesano et al. reported on 27 patients who had bone metastases (16 prostate, 5 breast, and 6 lung cancers) and received ^{89}SrCl$_2$ (17 patients) or ^{153}Sm-EDTMP (10 patients) (38). After therapy, there was no significant tumor marker or bone scan changes. ^{89}SrCl$_2$ and ^{153}Sm-EDTMP enabled partial or total pain relief and improvement in quality of life. No tumoricidal effect was found. Hematologic toxicity was limited and reversible. Patients with PC seemed to have a higher response rate (38).

^{223}RACL$_2$

^{223}RaCl$_2$ (Xofigo; previously Alpharadin; Bayer Healthcare) is the newest radiopharmaceutical approved by the FDA (on May 15, 2013) for the treatment of painful osseous lesions from mCRPC (39). Compared with ^{89}SrCl$_2$ and ^{153}Sm-EDTMP, ^{223}RaCl$_2$ represents a significant departure for 2 important reasons. First, ^{223}RaCl$_2$ is primarily an α-emitter rather than a β-emitter (decay scheme: 93.5% as α-particles, <3.6% as β-particles, and <1.1% as γ-radiation). Second, ^{223}RaCl$_2$ is the first radiopharmaceutical to show an increase in overall survival (OS), a decrease in skeletal events, palliation of bone pain, and low toxicity.

Until 2010, docetaxel was the only chemotherapeutic agent able to prolong survival after development of CRPC, and ^{89}SrCl$_2$ and
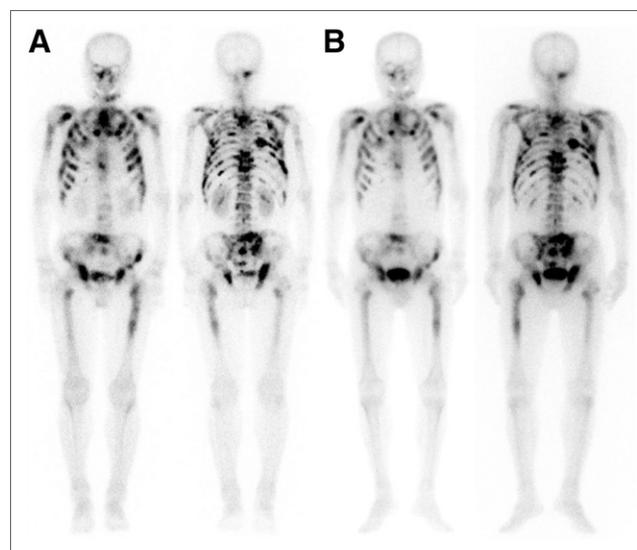
FIGURE 3. 72-y-old man who had PC and was referred for ^{153}Sm-EDTMP treatment of painful bone metastases. ^{99m}Tc-MDP bone scan (A) and ^{153}Sm-EDTMP (B) revealed extensive metastases.

^{153}Sm-EDTMP were used for bone pain palliation, along with pain medications (40). Since then, 5 new drugs have been proven to be efficacious in prolonging survival: sipuleucel-T, cabazitaxel, abiraterone, enzalutamide, and ^{223}RaCl$_2$ (41–44).

Because of their short range, α-particles deliver a large amount of radiation to target tissue while relatively sparing normal surrounding tissue. ^{223}RaCl$_2$ has a much higher energy and a shorter tissue range than either ^{89}SrCl$_2$ or ^{153}Sm-EDTMP (45). The range of α-particles in human tissue is approximately 0.1 mm. The administration of ^{223}RaCl$_2$ is similar to that of ^{89}SrCl$_2$ and ^{153}Sm-EDTMP (a slow intravenous push). Dosimetry was studied during a phase 1 study of ^{223}RaCl$_2$ for 3 cohorts, at 50, 100, and 200 kBq/kg. Dose rates were usually less than 2 μSv/h/MBq on contact and averaged 0.02 μSv/h/MBq at 1 m immediately after administration. Fecal excretion was the primary method of clearance, with resulting whole-body effective half-lives of 2.5–11.4 d (Fig. 4) (45–47).

α-particles require relatively minimal radiation safety precautions (48). For example, in the average patient receiving 3.5 MBq (95 μCi) of ^{223}RaCl$_2$, the dose measures 0.35 μSv/h (0.035 mrem/h) at 1 m. Thus, no contact precautions are associated with ^{223}RaCl$_2$. Similar to recommendations for ^{131}I therapy, bathroom precautions are recommended for 1 wk to minimize radiation exposure to others; these precautions include multiple flushing, area cleanup, and hand washing.

An early phase 2 study (49) was done to investigate the dose–response relationship and pain-relieving effect of ^{223}RaCl$_2$. In that study, 100 mCRPC patients were randomized to receive a single ^{223}RaCl$_2$ dose of 5, 25, 50, or 100 kBq/kg. The pain index 2 wk after ^{223}Ra administration was significantly related to the dose ($P = 0.035$). At week 8, there were 40%, 63%, 56%, and 71% pain responders in the groups receiving 5, 25, 50, and 100 kBq/kg, respectively. All doses were considered safe, and a decrease in the bone alkaline phosphatase level in the group receiving the highest dose was noted ($P = 0.0067$).

In another phase 2 study, the efficacy and safety of ^{223}RaCl$_2$ at 3 different doses were evaluated in mCRPC patients (50). In this phase 2 double-blind multicenter study, 122 patients were randomized to receive 3 injections of ^{223}Ra at 6-wk intervals: 25 kBq/kg ($n = 41$), 50 kBq/kg ($n = 39$), and 80 kBq/kg ($n = 42$). The primary endpoint was reached, with a statistically significant dose–response relationship, for no patients (0%) in the group receiving 25 kBq/kg, for 2 patients (5%) in the group receiving 50 kBq/kg, and for 5 patients (12%) in the group receiving 80 kBq/kg ($P = 0.0297$). A decrease in the bone alkaline phosphatase level of greater than or equal to 50% was identified in 6 patients (16%), 24 patients (67%), and 25 patients (66%) in the groups receiving 25, 50, and 80 kBq/kg, respectively ($P < 0.0001$). The most common treatment-related adverse events occurring up to wk 24 across all dose groups were diarrhea (21%), nausea (16%), and anemia (14%). No difference in the incidences of hematologic events was seen among the dose groups. ^{223}RaCl$_2$ was well tolerated at all doses and had a dose-dependent effect on serum CRPC activity markers.

Final approval of ^{223}RaCl$_2$ followed the phase 3 ALSYMPCA (Alpharadin in Symptomatic PC) trial (51). In this randomized, double-blind, placebo-controlled study, 921 patients who had received, were not eligible to receive, or declined docetaxel (in a 2:1 ratio) were randomized to receive six injections of ^{223}RaCl$_2$ (50 kBq/kg) or matching placebo every 4 wk. The primary endpoint was OS. The main secondary efficacy endpoints included time to the first symptomatic skeletal event and various biochemical endpoints. A prespecified interim analysis conducted when 314 deaths had occurred assessed the effect of ^{223}RaCl$_2$ versus placebo on survival. An updated analysis conducted when 528 deaths had occurred was performed before the crossover from placebo to ^{223}RaCl$_2$.

At an interim analysis of 809 patients, compared with placebo, ^{223}RaCl$_2$ significantly improved OS (median, 14.0 vs. 11.2 mo; hazard ratio, 0.70; 95% confidence interval, 0.55–0.88; 2-sided $P = 0.002$). An updated analysis of 921 patients confirmed the ^{223}RaCl$_2$ survival benefit (median, 14.9 vs. 11.3 mo; hazard ratio, 0.70; 95% confidence interval, 0.58–0.83; $P < 0.001$). Assessments of efficacy endpoints also revealed a benefit of ^{223}RaCl$_2$ compared with placebo. ^{223}RaCl$_2$ was associated with low myelosuppression rates and fewer adverse events. The study was terminated for efficacy, as ^{223}RaCl$_2$ improved OS (51–53). The encouraging outcome of the ALSYMPCA clinical trial not only resulted in FDA approval but also led to the recent incorporation of ^{223}RaCl$_2$ into the updated National Comprehensive Cancer Network guideline (version 3.2013).

Although there may be a decrease in the PSA or alkaline phosphatase level similar to that seen with ^{89}SrCl$_2$ or ^{153}Sm-EDTMP, some patients either did not have a decrease in PSA or had an increase in PSA after ^{223}RaCl$_2$ therapy. Thus, PSA can fail to accurately indicate the response of mCRPC to a variety of therapies (54). Both patients and physicians should be aware of this potential unlinking of OS and PSA in mCRPC so that therapy is not unnecessarily stopped prematurely.
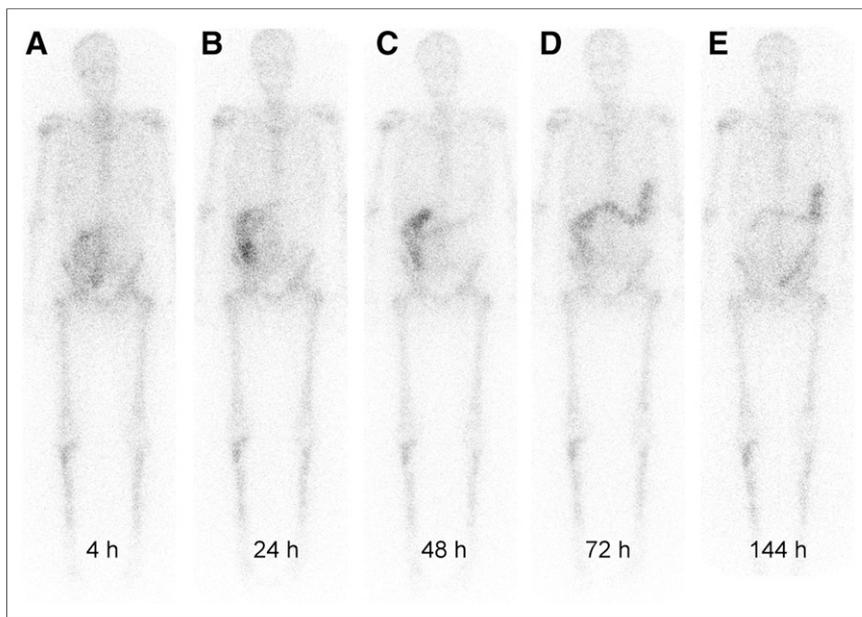
FIGURE 4. Biodistribution of ^{223}RaCl$_2$. (Adapted with permission of (47).)

On the basis of phase 2 and 3 trials, the most common (>10%) adverse reactions in patients receiving ^{223}RaCl$_2$ were nausea, diarrhea, vomiting, and peripheral edema. The most common hematologic abnormalities were anemia, lymphocytopenia, leukopenia, thrombocytopenia, and neutropenia (52). One study reviewed the 1-y clinical experience with ^{223}RaCl$_2$ in 25 mCRPC patients (55). About one-quarter of the cohort completed the entire 6-dose treatment cycle. Advancing soft-tissue disease was the primary reason for the cessation of therapy. Adverse events were mild and manageable. A decline in the serum alkaline phosphatase level was more common than a decline in the PSA level. Another retrospective investigation reviewed the clinical experience after 532 cycles of ^{223}RaCl$_2$ administration in 110 patients (56). That study showed that there were significant reductions in the serum alkaline phosphatase level and pain score and that progression risk was associated with a decrease in the serum PSA doubling time. Simultaneous external-beam radiation therapy was associated with an increased risk of bone marrow failure.

The effectiveness of ^{223}RaCl$_2$ therapy was recently evaluated in relation to skeletal tumor burden on whole-body ^{18}F-NaF PET/CT (57). In 42 patients, skeletal tumor burden indices derived from PET/CT at baseline were highly correlated and were significant independent predictors of OS. In an earlier study, an SUV$_{max}$ threshold of 10 was shown to exclude nearly all normal bone activity from volumetric calculations (58).

CONCLUSION

^{18}F-NaF PET provides superior diagnostic performance compared with ^{99m}Tc-MDP bone scintigraphy for the evaluation of patients with PC. Radionuclide therapy for painful bone metastases is undergoing a significant resurgence because of the introduction of ^{223}Ra and the use of radiopharmaceuticals in combination with standard chemotherapy. These developments will contribute significantly to the care of patients with PC in the era of personalized and precision medicine (59).

DISCLOSURE

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66:7–30.
2. Picchio M, Giovannini E, Messa C. The role of PET/computed tomography scan in the management of prostate cancer. *Curr Opin Urol.* 2011;21:230–236.
3. Jadvar H, Desai B, Conti PS. Sodium ^{18}F-fluoride PET/CT of bone, joint, and other disorders. *Semin Nucl Med.* 2015;45:58–65.
4. Czernin J, Satyamurthy N, Schiepers C. Molecular mechanisms of bone ^{18}F-NaF deposition. *J Nucl Med.* 2010;51:1826–1829.
5. Grant FD, Fahey FH, Packard AB, Davis RT, Alavi A, Treves ST. Skeletal PET with ^{18}F-fluoride: applying new technology to an old tracer. *J Nucl Med.* 2008;49:68–78.
6. Blau M, Ganatra R, Bender MA. ^{18}F-fluoride for bone imaging. *Semin Nucl Med.* 1972;2:31–37.
7. Bridges RL, Wiley CR, Christian JC, Strohm AP. An introduction to Na^{18}F bone scintigraphy: basic principles, advanced imaging concepts, and case examples. *J Nucl Med Technol.* 2007;35:64–76.
8. Cook GJR. PET and PET/CT imaging of skeletal metastases. *Cancer Imaging.* 2010;10:1–8.
9. Centers for Medicare & Medicaid Services. Decision memo for positron emission tomography (NaF-18) to identify bone metastasis of cancer (CAG-00065R2).

https://www.cms.gov/medicare-coverage-database/details/nca-decision-memo.aspx?NCAId=279. Accessed July 22, 2016.
10. Savelli G, Maffioli L, Maccauro M, De Deckere E, Bombardieri E. Bone scintigraphy and the added value of SPECT (single photon emission tomography) in detecting skeletal lesions. *Q J Nucl Med.* 2001;45:27–37.
11. Even-Sapir E. Imaging of malignant bone involvement by morphologic, scintigraphic, and hybrid modalities. *J Nucl Med.* 2005;46:1356–1367.
12. Even-Sapir E, Metser U, Mishani E, Lievshitz G, Lerman H, Leibovitch I. The detection of bone metastases in patients with high-risk prostate cancer: ^{99m}Tc-MDP planar bone scintigraphy, single- and multi-field-of-view SPECT, ^{18}F-fluoride PET, and ^{18}F-fluoride PET/CT. *J Nucl Med.* 2006;47:287–297.
13. Cook G Jr, Parker C, Chua S, Johnson B, Aksnes AK, Lewington VJ. ^{18}F-fluoride PET: changes in uptake as a method to assess response in bone metastases from castrate-resistant prostate cancer patients treated with ^{223}Ra-chloride (Alpharadin). *EJNMMI Res.* 2011;1:4.
14. Shen CT, Qiu ZL, Han TT, Luo QY. Performance of ^{18}F-fluoride PET or PET/CT for the detection of bone metastases: a meta-analysis. *Clin Nucl Med.* 2015;40:103–110.
15. Schirrmeister H, Guhlmann A, Elsner K, et al. Sensitivity in detecting osseous lesions depends on anatomic localization: planar bone scintigraphy versus ^{18}F PET. *J Nucl Med.* 1999;40:1623–1629.
16. Jambor I, Kuisma A, Ramadan S, et al. Prospective evaluation of planar bone scintigraphy, SPECT, SPECT/CT, ^{18}F-NaF PET/CT and whole body 1.5T MRI, including DWI, for the detection of bone metastases in high risk breast and prostate cancer patients: SKELETA clinical trial. *Acta Oncol.* 2016;55:59–67.
17. Iagaru A, Mittra E, Yaghoubi SS, et al. Novel strategy for a cocktail ^{18}F-fluoride and ^{18}F-FDG PET/CT scan for evaluation of malignancy: results of the pilot-phase study. *J Nucl Med.* 2009;50:501–505.
18. Iagaru A, Mittra E, Mosci C, et al. Combined ^{18}F-fluoride and ^{18}F-FDG PET/CT scanning for evaluation of malignancy: results of an international multicenter trial. *J Nucl Med.* 2013;54:176–183.
19. Minamimoto R, Mosci C, Jamali M, et al. Semiquantitative analysis of the biodistribution of the combined ^{18}F-NaF and ^{18}F-FDG administration for PET/CT imaging. *J Nucl Med.* 2015;56:688–694.
20. Minamimoto R, Loening A, Jamali M, et al. Prospective comparison of ^{99m}Tc-MDP scintigraphy, combined ^{18}F-NaF and ^{18}F-FDG PET/CT, and whole-body MRI in patients with breast and prostate cancer. *J Nucl Med.* 2015;56:1862–1868.
21. Rajpar S, Fizazi K. Bone targeted therapies in metastatic castration-resistant prostate cancer. *Cancer J.* 2013;19:66–70.
22. Fischer M, Kampen WU. Radionuclide therapy of bone metastases. *Breast Care (Basel).* 2012;7:100–107.
23. Choudhury AD, Kantoff PW. New agents in metastatic prostate cancer. *J Natl Compr Canc Netw.* 2012;10:1403–1409.
24. Lam MG, Hoekstra A, de Klerk JM, van Rijk PP, Zonnenberg BA. Radiation safety considerations for the bone seeking radiopharmaceuticals ^{89}SrCl$_2$, ^{186}Re-HEDP and ^{153}Sm-EDTMP. *Nuklearmedizin.* 2009;48:37–43.
25. Kurosaka S, Satoh T, Chow E, et al. EORTC QLQ-BM22 and QLQ-C30 quality of life scores in patients with painful bone metastases of prostate cancer treated with strontium-89 radionuclide therapy. *Ann Nucl Med.* 2012;26:485–491.
26. Tu SM, Millikan RE, Mengistu B, et al. Bone-targeted therapy for advanced androgen-independent carcinoma of the prostate: a randomised phase II trial. *Lancet.* 2001;357:336–341.
27. Bilen MA, Johnson MM, Mathew P, et al. Randomized phase 2 study of bone-targeted therapy containing strontium-89 in advanced castrate-sensitive prostate cancer. *Cancer.* 2015;121:69–76.
28. Logan KW, Volkert WA, Holmes RA. Radiation dose calculations in persons receiving injection of samarium-153 EDTMP. *J Nucl Med.* 1987;28:505–509.
29. Singh A, Holmes RA, Farhangi M, et al. Human pharmacokinetics of samarium-153 EDTMP in metastatic cancer. *J Nucl Med.* 1989;30:1814–1818.
30. Turner JH, Claringbold PG, Hetherington EL, et al. A phase I study of samarium-153 ethylenediaminetetramethylene phosphonate therapy for disseminated skeletal metastases. *J Clin Oncol.* 1989;7:1926–1931.
31. Turner JH, Claringbold PG. A phase II study of treatment of painful multifocal skeletal metastases with single and repeated dose samarium-153 ethylenediaminetetramethylene phosphonate. *Eur J Cancer.* 1991;27:1084–1086.
32. Tripathi M, Singhal T, Chandrasekhar N, et al. Samarium-153 ethylenediamine tetramethylene phosphonate therapy for bone pain palliation in skeletal metastases. *Indian J Cancer.* 2006;43:86–92.
33. Coronado M, Redondo A, Coya J, et al. Clinical role of Sm-153 EDTMP in the treatment of painful bone metastatic disease. *Clin Nucl Med.* 2006;31:605–610.
34. Bayouth JE, Macey DJ, Kasi LP, Fossella FV. Dosimetry and toxicity of samarium-153-EDTMP administered for bone pain due to skeletal metastases. *J Nucl Med.* 1994;35:63–69.

35. Sartor O, Reid RH, Bushnell DL, Quick DP, Ell PJ. Safety and efficacy of repeat administration of samarium Sm-153 lexidronam to patients with metastatic bone pain. *Cancer.* 2007;109:637–643.

36. Heron DE, Brufsky A, Beriwal S, Kurman M. Myelotoxicity of samarium Sm 153 lexidronam in patients receiving prior treatment with chemotherapy or radiotherapy. *Ann Oncol.* 2008;19:1639–1643.

37. Baczyk M, Czepczynski R, Milecki P, Pisarek M, Oleksa R, Sowinski J. [89]Sr versus [153]Sm-EDTMP: comparison of treatment efficacy of painful bone metastases in prostate and breast carcinoma. *Nucl Med Commun.* 2007;28:245–250.

38. Montesano T, Giacomobono S, Acqualagna G, et al. Our experience on pain palliation of bone metastasis with Sr-89 or Sm-153 in cancer patients resistant to a conventional analgesic therapy: a retrospective study. *Clin Ter.* 2009;160:193–199.

39. Pinto A, Cruz P. Radium-223 chloride: a new treatment option for metastatic castration-resistant prostate carcinoma. *Drugs R D.* 2012;12:227–233.

40. Drake CG, Sharma P, Gerritsen W. Metastatic castration-resistant prostate cancer: new therapies, novel combination strategies and implications for immunotherapy. *Oncogene.* 2014;33:5053–5064.

41. Bishr M, Saad F. Overview of the latest treatments for castration-resistant prostate cancer. *Nat Rev Urol.* 2013;10:522–528.

42. Hafeez S, Parker C. Radium-223 for the treatment of prostate cancer. *Expert Opin Investig Drugs.* 2013;22:379–387.

43. Malik Z, Payne H, Ansari J, et al. Evolution of the treatment paradigm for patients with metastatic castration-resistant prostate cancer. *Adv Ther.* 2013;30:1041–1066.

44. Mukherji D, Omlin A, Pezaro C, Shamseddine A, de Bono J. Metastatic castration-resistant prostate cancer (CRPC): preclinical and clinical evidence for the sequential use of novel therapeutics. *Cancer Metastasis Rev.* 2014;33:555–566.

45. Harrison MR, Wong TZ, Armstrong AJ, George DJ. Radium-223 chloride: a potential new treatment for castration-resistant prostate cancer patients with metastatic bone disease. *Cancer Manag Res.* 2013;5:1–14.

46. Pacilio M, Ventroni G, De Vincentis G, et al. Dosimetry of bone metastases in targeted radionuclide therapy with alpha-emitting [223]Ra-dichloride. *Eur J Nucl Med Mol Imaging.* 2016;43:21–33.

47. Chittenden SJ, Hindorf C, Parker CC, et al. A phase 1, open-label study of the biodistribution, pharmacokinetics, and dosimetry of [223]Ra-dichloride in patients with hormone-refractory prostate cancer and skeletal metastases. *J Nucl Med.* 2015;56:1304–1309.

48. Dauer LT, Williamson MJ, Humm J, et al. Radiation safety considerations for the use of [223]RaCl$_2$ DE in men with castration-resistant prostate cancer. *Health Phys.* 2014;106:494–504.

49. Nilsson S, Strang P, Aksnes AK, et al. A randomized, dose-response, multicenter phase II study of radium-223 chloride for the palliation of painful bone metastases in patients with castration-resistant prostate cancer. *Eur J Cancer.* 2012;48:678–686.

50. Parker CC, Pascoe S, Chodacki A, et al. A randomized, double-blind, dose-finding, multicenter, phase 2 study of radium chloride (Ra 223) in patients with bone metastases and castration-resistant prostate cancer. *Eur Urol.* 2013;63:189–197.

51. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med.* 2013;369:213–223.

52. Kluetz PG, Pierce W, Maher VE, et al. Radium Ra 223 dichloride injection: U.S. Food and Drug Administration drug approval summary. *Clin Cancer Res.* 2014;20:9–14.

53. Wissing MD, van Leeuwen FW, van der Pluijm G, Gelderblom H. Radium-223 chloride: extending life in prostate cancer patients by treating bone metastases. *Clin Cancer Res.* 2013;19:5822–5827.

54. Romero Otero J, Garcia Gomez B, Campos Juanatey F, Touijer KA. Prostate cancer biomarkers: an update. *Urol Oncol.* 2014;32:252–260.

55. Jadvar H, Quinn DI, Conti PS. One-year postapproval clinical experience with radium-223 dichloride in patients with metastatic castrate-resistant prostate cancer. *Cancer Biother Radiopharm.* 2015;30:195–199.

56. Etchebehere EC, Milton DR, Araujo JC, Swanston NM, Macapinlac HA, Rohren EM. Factors affecting [223]Ra therapy: clinical experience after 532 cycles from a single institution. *Eur J Nucl Med Mol Imaging.* 2016;43:8–20.

57. Etchebehere EC, Araujo JC, Fox PS, Swanston NM, Macapinlac HA, Rohren EM. Prognostic factors in patients treated with [223]Ra: the role of skeletal tumor burden on baseline ^{18}F-fluoride PET/CT in predicting overall survival. *J Nucl Med.* 2015;56:1177–1184.

58. Rohren EM, Etchebehere EC, Araujo JC, et al. Determination of skeletal tumor burden on ^{18}F-fluoride PET/CT. *J Nucl Med.* 2015;56:1507–1512.

59. Fahey F, Zukotynski K, Jadvar H, et al. Proceedings of the Second NCI–SNMMI Workshop on Targeted Radionuclide Therapy. *J Nucl Med.* 2015;56:1119–1129.