Optimization of Radiation Exposure in ^{18}F-Sodium Fluoride Positron Emission Tomography-Computed Tomography in Bone Imaging: Quo Vadis

Sir,

^{99m}Tc-methylene diphosphonate (MDP) bone scan has been the standard method for nuclear medicine imaging of the skeleton for decades, providing information about the presence, extent, location, and response to treatment in patients with osseous metastasis. For better resolution and characterization, up to 20 mCi or more of tracer is required and still higher doses are required for obese population, leading to higher radiation burden and secondary increased risk of cancer.[1] Currently, bone imaging is a part of oncology workup as a pretreatment staging; however, an interim and end-of-therapy scan is also advised for response evaluation in metastatic bone disease, leading to a cumulative absorbed doses of approximately 18–19 mSv for a given line of treatment.

It is well known that cancer risk is induced from radiation.[1,2] Lifetime attributable risk of cancer incidence, according to the principles of the National Academies' Biological Effects of Ionizing Radiation Report VII, was calculated to be between 0.231% and 0.514% for 20-year-old females and between 0.163% and 0.323% for 20-year-old males.[3]

Rediscovered ^{18}F-sodium fluoride (NaF) positron emission tomography-computed tomography (PET-CT) has revolutionized the bone imaging in the recent past and has shown to be a promising agent for the management of bone disorders.[4] Distinguished properties of this tracer include rapid clearance from plasma in a biexponential manner, with most of the tracer retained by the bone after a single pass (chemisorption with the exchange of $^{18}F^-$ion for OH^-ion on the surface of the hydroxyapatite matrix of the bone forming fluorapatite and migration of $18F^-$ion into the crystalline matrix of the bone). There is minimal binding to serum protein that contributes to the high quality of images with high bone-to-background ratio in a shorter time (60 min and less) than for standard ^{99m}Tc-based tracers (2–3 h).[4,5]

Segall *et al*. suggested a fixed-dose method of imaging dose of ^{18}F-NaF, that is, 185–370 MBq (5–10 mCi) in 2010 in procedure guideline of SNMMI.[6] The fixed-dose method varied from physician to physician, leading to a lack of standardized formula for NaF imaging till date. The effective absorbed doses by this fixed method came out to be even higher than the ^{99m}Tc MDP bone scan, that is, 0.024 mSv/MBq (0.089 mrem/mCi) or 4.44 mSv–8.88 mSv, for an average 70-kg man for the above-mentioned dose range [Table 1], leading to approximately 17% higher exposure than the exposure reported for ^{99m}Tc-MDP, that is, 4.21 mSv–6.32 mSv for a typical activity of 740–1110 MBq (20–30 mCi).

Keeping in view the same issue, Ohnona *et al*. imaged 40 patients according to EANM and SNM guidelines and reported in 2013 that the dose of ^{18}F-NaF may be lowered without major untoward effect on image quality by reducing the injected activity (e.g., by about half) such that the effective dose would then be comparable to that for ^{99m}Tc-MDP.[9]

Further refinement of the idea was done by Lim *et al*. who reported that the radiation dosimetry for ^{18}F-NaF PET is similar to that with ^{99m}Tc-MDP imaging, and good-quality ^{18}F-NaF imaging can be effectively performed using a smaller administered dosage than is typically employed for MDP, resulting in an actual radiation absorbed dose that is equivalent to that received from standard single-photon imaging.[10]

Chilton *et al*.[11] reported that the total uptake of ^{18}F-fluoride by the bone is similar to that of ^{99m}Tc-MDP, at approximately 50% of the injected dose.[11] Considering the imaging point of view, the soft-tissue half-value layers for the 511- and 140-keV photons are 7.3 and 4.6 cm, respectively; it means that 511-keV photons can deliver their energy to organs distant from the source organ, making imaging better, whereas the 140-keV photons will deliver more of their energy to organs near the source organ.

Keeping in view the inference of Ohnona *et* al., Lim *et al*., and Chilton *et al*., we performed prospective ^{18}F-NaF imaging in 6000 patients from January 2012 to December 2016. 1062/6000 were included in evaluation of low-dose NaF study standardizing the imaging dose as 0.06 mCi/kg[7] followed by a prospective study of 212/6000 morbidly obese patients for evaluation of the effect of body mass index (BMI) in ^{18}F-NaF imaging.[12]

Prospective imaging data of a large cohort of 1062 patients by Marafi *et al*.[7] showed significant dose reduction keeping the imaging quality at acceptable levels, which is in accordance with the already published results of Ohnona *et al*. Good-quality ^{18}F-NaF imaging was seen at the lowest dose standards of 0.06 mCi/kg for all age groups excluding the pediatric population [Figure 1].

Recently published data of Usmani *et al*. have given an excellent imaged-based crispy outlook in morbidly obese patients (up to 66 kg/m^2 BMI) where they showed that ^{18}F-NaF imaging can be done in all age groups without

Table 1: Comparison of international standards of ^{18}F-NaF imaging with Kuwait Cancer Control Center standard

Standard	Age (Effective dose factor)	Recommended IV dose mCi/kg (MBq/kg)	Average patient group (MBq)	Effective dose (mSv) NaF only	Remarks evidence based studies
^{18}F-NaF (KCCC)	Adult 0.024 mSv/MBq	2.22 MBq/kg (0.06 mCi/kg)	For 70 kg 155.4 MBq=3.73 mSv	1.37 mSv-5.7 mSv)[7] Minimum-maximum	Weight-based standard
	Pediatric 0.086 mSv/MBq	2.22 MBq/kg (0.06 mCi/kg)	For 20 kg (5 years) 44.4 MBq=3.81 mSv	0.38 mSv-8.29 mSv[6]	Fixed-dose method by SNM guidelines
^{18}F-NaF (SNMMI)	Adult 0.024 mSv/MBq	185-370 MBq (5-10 mCi)	For 70 kg 185 MBq-370 MBq=4.44 mSv-8.88 mSv	4.44 mSv-8.88 mSv	
	Pediatric 0.086 mSv/MBq	2.22 MBq/kg (0.06 mCi/kg)	For 20 kg (5 years) 44.4 MBq=3.81	0.38 mSv-8.29 mSv[6]	
^{99m}Tc-MDP (SNMMI)	Adult 0.0057 mSv/MBq	740-1110 MBq (20-30 mCi)	For 70 kg 740 MBq=4.21 mSv	4.21 mSv-6.32 mSv[6]	
	Pediatric 0.025 mSv/MBq	9-11 MBq/kg	For 20 kg (5 years) 200 MBq=5.0 mSv	0.045 mSv-12.10 mSv[6]	
^{18}F-NaF EANM	Adult 0.024 mSv/MBq	1.5-3.7 MBq/kg	For 70 kg 2.52 mSv-6.216 mSv	2.52 mSV-6.216 mSv	EANM guidelines
	Pediatric 00.086 mSv/MBq	2.2 MBq/kg (18.5 MBq-185 MBq)	For 20 kg (5 years) 44.4 MBq=3.81	0.38 mSv-8.29 mSv[8]	

KCCC: Kuwait Cancer Control Center, Kuwait, SNMMI: Society of Nuclear Medicine and Molecular Imaging,[6] EANM: European Society of Nuclear Medicine and Molecular Imaging[8]

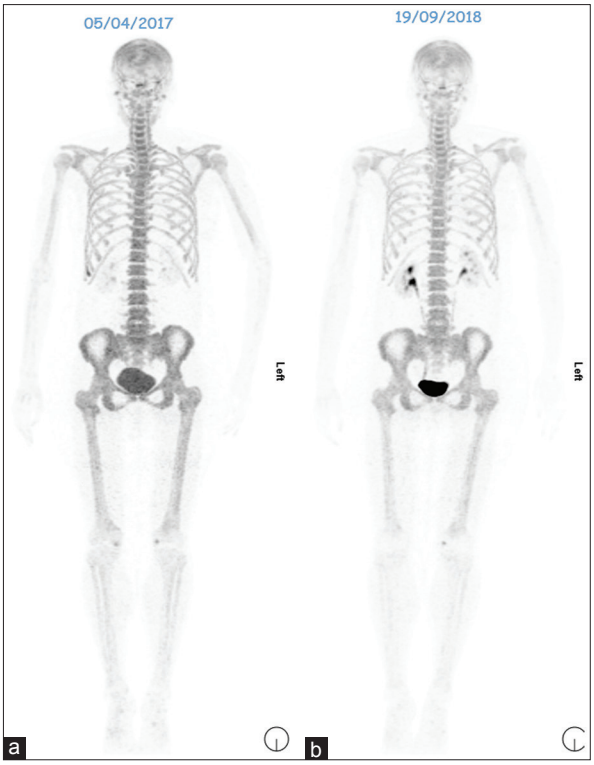

Figure 1: ^{18}F-sodium fluoride whole-body images of a known case of breast cancer. (a) ^{18}F-sodium fluoride positron emission tomography-computed tomography images acquired using EANM dose protocols of 185 MBq (5 mCi) of injected dose in 2017. (b) ^{18}F-sodium fluoride positron emission tomography-computed tomography images of the same patient acquired in 2018 using local Kuwait Cancer Control Center protocol of 2.22 MBq/kg (0.06 mCi/kg), that is, for 50 kg (3 mCi) showing the same quality of images

altering the diagnostic accuracy of bone images. These results are also in concordance to results published by Chilton *et al*. where they suggested that NaF uptake is similar with MDP bone uptake as low as 50% of injected dose. This is not possible with MDP where image deteriorates as there is an increase in BMI.

It is obvious from Table 1, that the absorbed doses for maximum I.D. are 5.7 mSv for Kuwait Cancer Control Center (KCCC) protocol. When compared to the exposure imparted by SNM guidelines for maximum I.D., the exposure by KCCC guidelines is 69.14% and 67.45 % lower than then the exposure imparted by the 18F-NaF and 99mTc MDP, respectively.[12]

Similarly, by following KCCC protocols, the dose exposure is 12% and 14 % lower than the EANM recommended injected dose range of minimum and maximum, respectively i.e. (1.5–3.7 MBq/kg).[8]

This work is also supported by SKELETA clinical trial conducted by Jambor *et al*. who report that ^{18}F-NaF PET-CT is more sensitive, accurate, and has less equivocal findings than ^{99m}Tc hydroxymethylene-diphosphonate planar (^{99m}Tc-HDP) bone scintigraphy, ^{99m}Tc-HDP single-photon emission tomography (SPECT), and ^{99m}Tc-HDP SPECT-CT for the detection of bone metastases in high-risk breast and prostate cancer patients.[13]

Conclusion/Suggestions

^{18}F-NaF, a lost and found molecule, has time-proven potential for evaluation of bone diseases. In the light of the above data, we infer that through proper tailoring of injected doses of NaF, high-quality imaging can be achieved keeping the injected doses at minimum levels.

Here, we suggest a new standard for adult bone imaging dose of 0.06 mCi/kg for ^{18}F-NaF based on the recently published data. Keeping in view the potential of ^{18}F-NaF, due to its unique *in vivo* chemistry, we suggest to update the current available guidelines of ^{18}F-NaF adult bone imaging in nuclear medicine.

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Conflicts of interest

There are no conflicts of interest.

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