REVIEW

Sodium fluoride (Na^{18}F) PET Response Criteria in Solid Tumors (NAFCIST): a framework for response assessment in bone tumors

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The current Response Evaluation Criteria in Solid Tumors for measuring tumor response in osteosarcoma may be sub-optimal, as even responsive bone tumors may show limited change in tumor diameters. This limits the use of traditional imaging assessment tools. Therefore, discerning osteosarcoma response to therapy on magnetic resonance imaging before surgery is often difficult, and it is typically evaluated after surgery by assessing the amount of necrosis in resected surgical specimens. To address these challenges, sodium fluoride (Na^{18}F) positron emission tomography/ computed tomography (PET/CT) scans can be utilized to better image bone response to therapy, as, fluoride is avidly taken up by bone. Na^{18}F Response Criteria in Solid Tumors (NAFCIST) has been developed as a novel method to evaluate treatment response using Na^{18}F PET/CT. Current evidence supporting NAFCIST comes from a pilot study that evaluated alpha particle radium-223 in patients with osteosarcoma. In this review, practical guidance for utilizing NAFCIST in the context of bone tumors is illustrated to aid future studies.
Key words: osteosarcoma, PET/CT, precision oncology, sodium fluoride, bone tumors

INTRODUCTION

Osteosarcoma is an aggressive bone tumor with poor clinical outcomes in the relapsed/recurrent setting.[1] Although relatively rare, it is the most frequent malignant type of bone tumors.[2-4] Osteosarcoma commonly occurs at a bimodal age distribution in the distal femur, proximal tibia, or proximal humerus.[2,3,5,6] Treatment for localized disease classically includes surgery, pre-operative, and possibly post-operative chemotherapy. Recurrence, however, occurs in many patients and dramatically compromises the overall survival.[5] The disseminated disease commonly presents with lung metastases and in itself confers a feature of poor prognosis.[7,8] Treatment options in the recurrent and metastatic settings are limited although many potential therapies are being explored in early-phase clinical trials.[5,9,10] In this concept paper, we elaborate on a novel method that uses sodium fluoride scans to evaluate treatment response and activity of bone-targeted therapies specifically in the context of alpha particle radiopharmaceuticals in osteosarcoma.

CHALLENGES IN RADIOLOGICAL DIAGNOSIS

Response assessment has been historically challenging in osteosarcoma given the nature of the disease in the bone. For example, responsive tumors may show necrosis but still a limited change in tumor diameters is observed. This usually limits the use of traditional imaging assessment tools e.g. Response Evaluation Criteria in Solid Tumors (RECIST) that relies on dynamic changes in measurements.[11,12] Traditionally, the response to therapy in patients with osteosarcoma has been evaluated with pathological analysis following surgical excision, which might not be feasible in metastatic or recurrent patients with multiple lesions.[13] Functional qualitative imaging including [^{18}F]2-fluoro-2-deoxy-D-glucose positron emission tomography/ computed tomography (FDG—PET/CT), therefore, offers an opportunity for tracking tumor activity in lieu of a diameter-based assessment. Incorporating anatomical size changes and functional activity has the potential to enable better assessment of response to therapeutic options.[14,15] FDG—PET/CT-based response criteria have been developed for use in solid tumors, namely PET Response Criteria in Solid tumors (PERCIST).[16,17] PERCIST has been suggested in
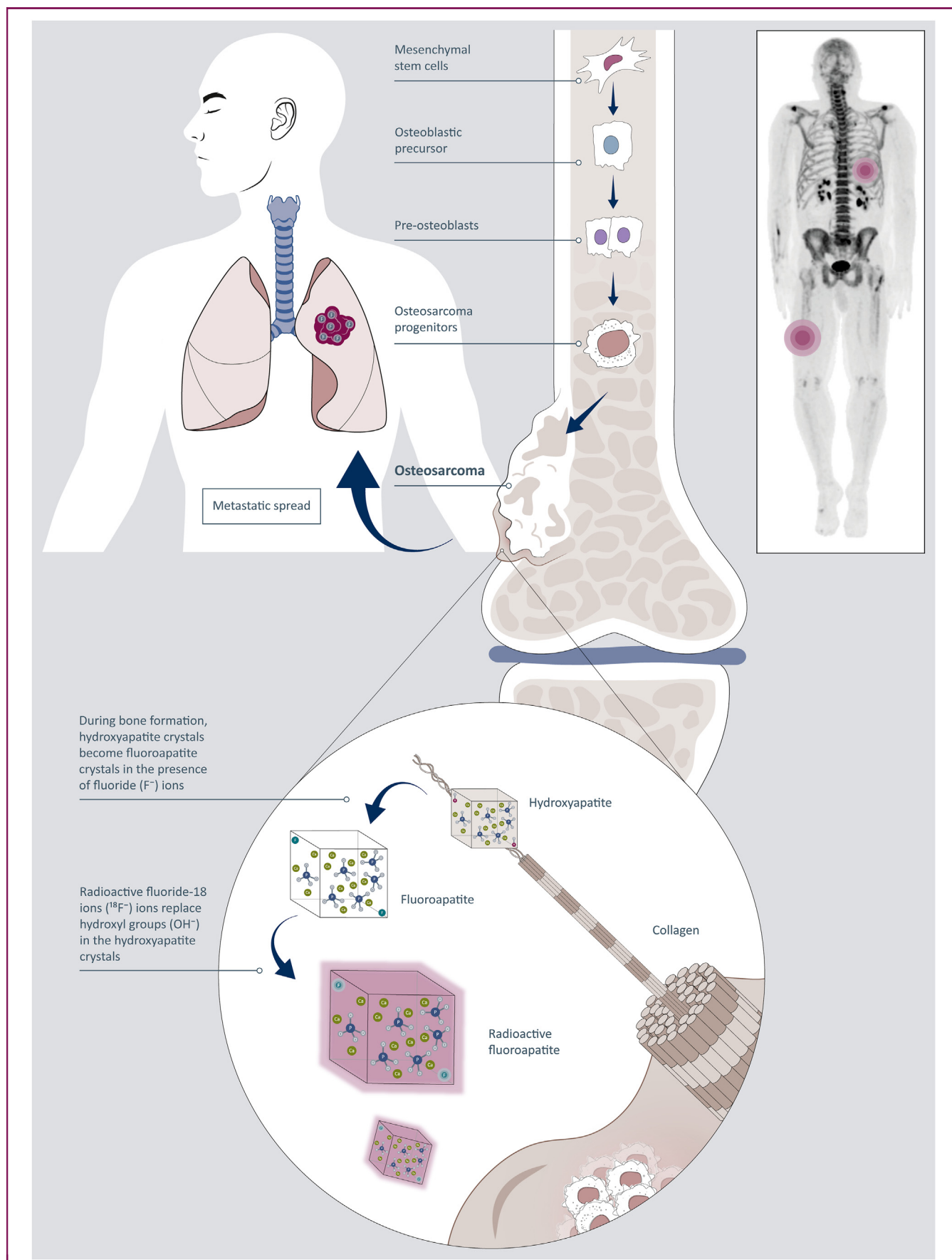
https://doi.org/10.1016/j.esmoop.2023.101575   **1**

Figure 1. Schematic illustration of the role of sodium-^{18}-fluoride (Na^{18}F)-PET imaging in metastatic osteosarcoma. The fluoride ion (^{18}F$^-$) of Na^{18}F is replacing one hydroxyl group (OH-) in the bone hydroxyapatite forming radioactive fluorapatite which can be imaged with a PET camera. Bone formation is present in soft-tissue
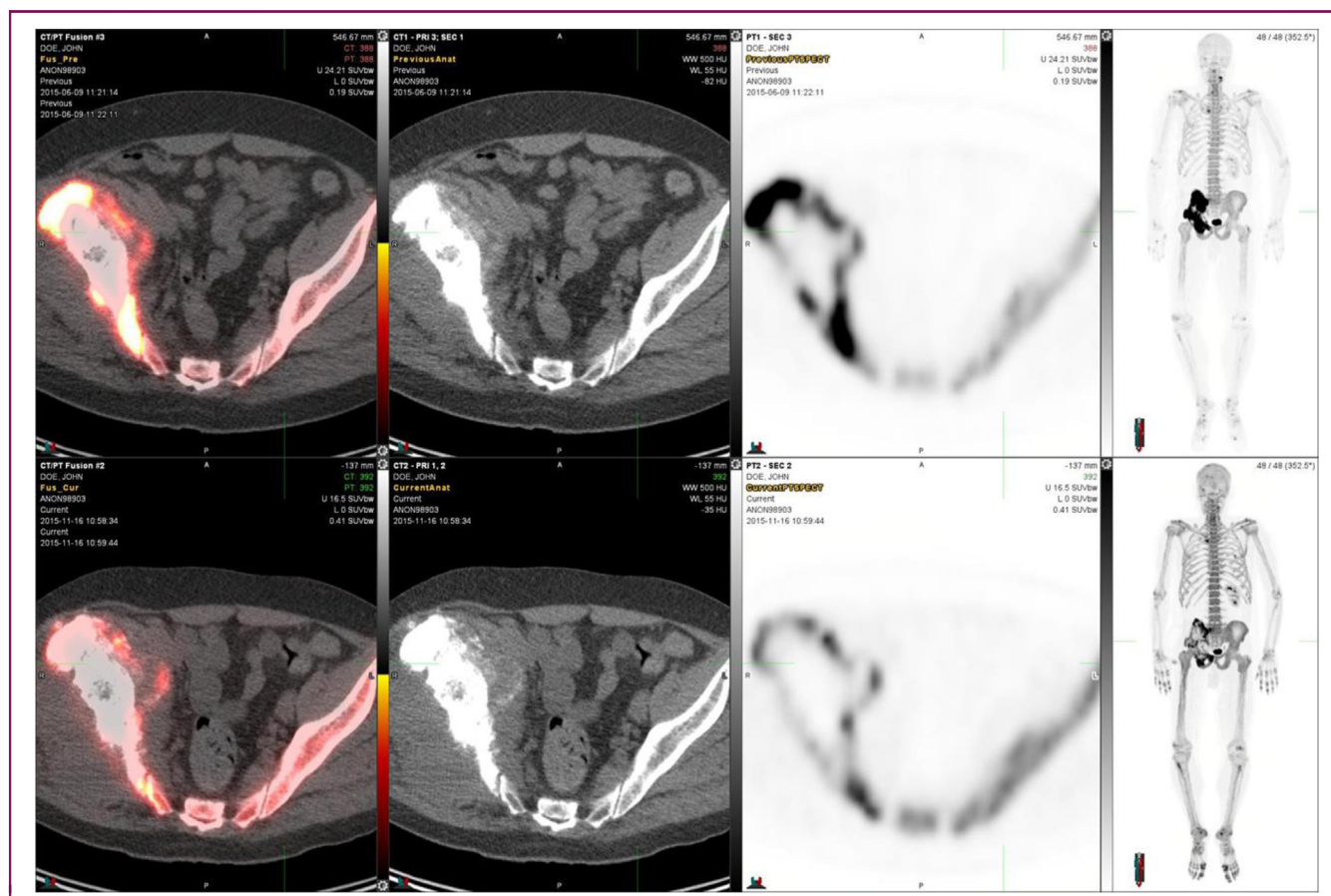
Figure 2. A 63-year-old male diagnosed with metastatic fibroblastic osteosarcoma in the right pelvis with soft-tissue expansion. Quantitatively, NaF-PET-images demonstrated an SUV decrease ($96.3 \rightarrow 37.1 \rightarrow 26.7$) after three and six cycles of ^{223}RaCl$_2$, respectively. A cumulative activity of 50.3 MBq of ^{223}Ra was administered. The upper row shows the left pelvic transaxially PET/CT-fusion image, CT image, PET image, and whole-body maximal intensity projection (MIP) image before any treatment, and the lower-row corresponding images after six cycles of ^{223}RaCl$_2$.

CT, computed tomography; NaF, sodium fluoride; PET, positron emission tomography; SUV, standardized uptake values.

different studies to provide a potentially better assessment of the tumor response status.[18-21]

Na^{18}F PET/CT AS A POTENTIAL MODALITY FOR OSTEOSARCOMA

Another analog of FDG-based PET/CT is sodium fluoride (^{18}F-NaF) PET/CT which uses sodium fluoride (^{18}F-NaF) as the radioactive material.[12,22] Na^{18}F is an old radiopharmaceutical that was used in gamma camera—based scintigraphy before the introduction of technetium (Tc)-based compounds. It can be used for the assessment of bone metabolism, primarily in the evaluation of malignancy and metastatic disease of the bony skeleton. Na^{18}F uptake is both a reflection of blood flow to the bones and of bone remodeling. A renewed interest in NaF-based PET imaging has evolved over the past few years given its high bone specificity.[23] The radiotracer is injected intravenously and once diffused through capillaries feeding the bones where turnover is highest, the ^{18}F is exchanged for a hydroxyl group in the bone mineral hydroxyapatite crystal form $Ca_{10}(PO_4)_6(OH)_2$, leading to the formation of the ^{18}F-fluoroapatite crystal form $Ca_{10}(PO_4)_6F_2$ (Figure 1). The same phenomenon occurs in bone formation in soft tissues. This means that soft-tissue metastases of osteosarcoma become fluoride-ion (^{18}F$^-$) avid and can be detected and evaluated using NaF PET/CT. Comparative studies have suggested a better image and higher sensitivity of detection of bony lesions with NaF PET/CT compared to ^{99m}Tc-MDP whole-body scan, conventional CT and magnetic resonance imaging images, and FDG—PET/CT.[23]

DEVELOPMENT OF NaF PET/CT RESPONSE CRITERIA

The first NaF PET/CT Response Criteria in Solid Tumors (NAFCIST) were proposed in 2019 to accommodate the need for a newer response assessment tool in osteosarcoma.[24] The tool was developed as part of a phase I study of alpha particle therapy (radium-223) in advanced osteosarcoma that included 18 patients.[24] In this study, NaF PET/

metastases of osteosarcoma, and ^{18}F-fluoroapatite in osteoblastic cells will be visualized using a PET camera. Thus Na^{18}F-PET can be used for staging metastatic osteosarcoma because soft-tissue metastases become visible.

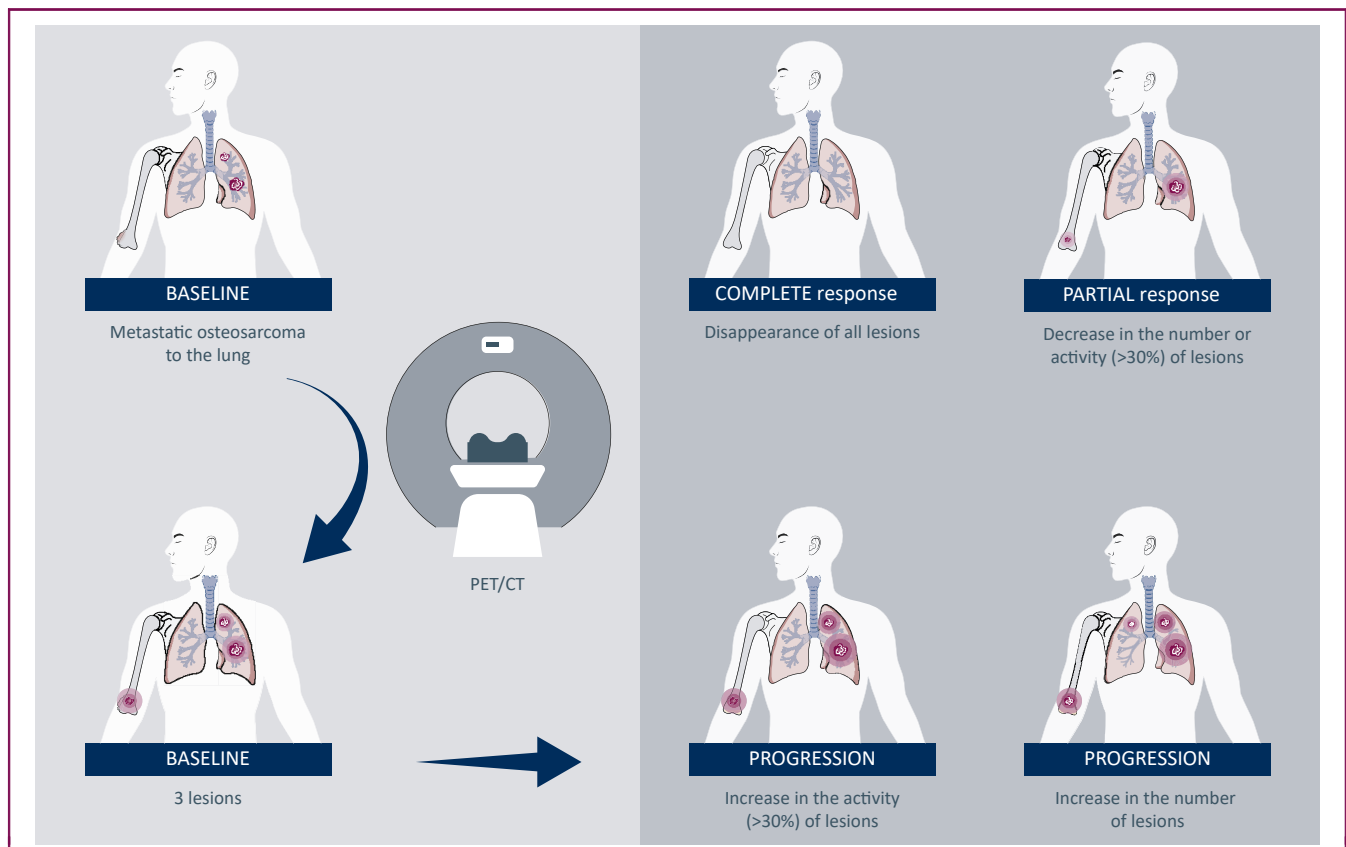PET, positron emission tomography.

Figure 3. A proposal for NAFCIST for future studies.
New lesions or >30% increase in NAFCIST (sum of five lesions) is a progression. For a response >30%, decrease in NAFCIST is required. NAFCIST, Na^{18}F Response Criteria in Solid Tumors.

CT identified osteosarcoma lesions in many sites that were not avid on FDG—PET/CT, indicating a potential role for NaF PET/CT in osteosarcoma's baseline evaluation of lesions and response to therapy. Moreover, NaF PET/CT could detect skeletal metastases of osteosarcoma better than other imaging methods.[24] Post-treatment pathologic response was evaluated in a patient whose tumor showed extensive tumor necrosis after two doses. More importantly, the NaF PET/CT and FDG—PET/CT scans depicted the lesions more accurately than conventional scans. In fact, the two were often complementary, with NaF PET/CT showing more bony lesions than other modalities. Therefore, a preliminary NAFCIST has been developed similar to PERCIST based on data from patients with osteosarcoma treated in this phase I trial.[12] An example is shown in Figure 2 which

demonstrates a 63-year-old male patient who had metastatic fibroblastic osteosarcoma and received six cycles of ^{223}RaCl$_2$. The patient demonstrated a metabolic response visible on FDG—PET/CT. This patient had three target lesions measurable on bone scintigraphy and more than five indicator lesions visible on NaF PET/CT. Visual inspection of the bone scintigraphy revealed a reduction in the number and size of lesions in this patient. Quantitatively, this patient had a reduction in standardized uptake values (SUV) per NaF PET/CT (from 96.3 to 37.1 and 26.7) as measured after three cycles and six cycles of ^{223}RaCl$_2$. It is important to highlight that the fluoride ion and radium cation do not form a theragnostic pair similar to that of gallium-68 and lutenium-177 in another setting.[25] However, calcium and radium could form a pair and therefore the fluoride ion here can act as a surrogate marker.

NAFCIST CRITERIA

Based on the preliminary data presented in the previous study, NAFCIST criteria (Figure 3) were proposed for the evaluation of osteosarcoma using a 30% cut-off level to demonstrate response or progression which was based on changes in other parameters including biomarkers (Table 1).[12] For example, NAFCIST correlated with changes in bone alkaline phosphatase level, a tumor marker in osteosarcoma.

Interestingly, the study reported that NAFCIST but not PERCIST correlates with overall survival (Supplementary

Table 1. NAFCIST criteria	
Response category	**Criteria**
Complete metabolic response	Normalization of all lesions (target and non-target) to SUV less than the mean skeletal SUV and equal to the normal surrounding tissue SUV
Partial metabolic response	>30% decrease in SUV peak
Progressive metabolic disease	>30% decrease in SUV peak, >75% increase in total Na 18F uptake, or new lesions
Stable metabolic disease	Does not meet other criteria

Adapted from Kairemo et al.[12]
NAFCIST, Na^{18}F Response Criteria in Solid Tumors; SUV, standardized uptake values.

Table 2. The new NAFCIST criteria versus RECIST and PERCIST in primary bone tumors

	RECIST	PERCIST	NAFCIST
Characteristics	Anatomic response criteria for soft-tissue disease	Functional response criteria reflecting tumor glucose metabolism	Metabolic response criteria for bone-forming disease
Advantages	Commonly used	Response determination is possible regardless of the location	Response determination is possible regardless of the organ
Disadvantages	Limited to 'measurable' soft-tissue disease	Limited to FDG avid disease	Limited to NaF avid disease

FDG, [^{18}F]2-fluoro-2-deoxy-D-glucose; NaF, sodium fluoride; NAFCIST, Na^{18}F Response Criteria in Solid Tumors; PERCIST, Positron Emission Tomography Response Criteria in Solid Tumors.

Figure S1, available at https://doi.org/10.1016/j.esmoop.2023.101575). Moreover, the NAFCIST change correlated inversely with the cumulated activity, indicating that probably the administered activity should be higher to obtain a response. There was no correlation between the administrated activity and PERCIST changes.

NAFCIST is maximally an SUV peak sum of five lesions. SUV peak is the average SUV value in 1 cm^3 of the most active lesion. Only two lesions per organ are accepted. A typical example is two bone lesions, two lung lesions, and one soft-tissue lesion. During the follow-up, all these lesions may change, but in our practice so far this has not happened. The idea is to pick the five most active lesions and remember to limit the maximum to two lesions per organ.

NAFCIST criteria compare favorably with RECIST and PERCIST criteria in primary bone tumors (Table 2). In fact, NAFCIST could supplant PET/CT functional response by adding metabolic response criteria for bone-forming diseases. Therefore, NAFCIST may represent a more accurate method of categorizing osteosarcoma than RECIST, which mainly relies on unidimensional measurements of tumor lesions and the sum of diameters. At least currently, NAFCIST and PERCIST should be considered complementary to each other.

LIMITATIONS

There are several limitations to the current use of NAFCIST. First, data on NAFCIST originate from a single study that needs to be prospectively validated by a larger cooperative group study. Prospective studies with the aim of confirming preliminary data previously presented and comparing NAFCIST to other methods of assessment may be helpful. Second, Na^{18}F scans can have a lot of false positives due to benign diseases which can be substantial in adult patients. Therefore, they may not be used in staging; but rather they may be used as baseline and follow up evaluation for radiopharmaceutical therapy to assess response.

CONCLUSIONS

In summary, Na^{18}F PET could become an essential part of osteosarcoma management where Na^{18}F PET and ^{18}F-FDG—PET are complementary. NAFCIST outcomes were consistent with disease characteristics indicated by alkaline phosphatase levels and bone destruction. However, these are preliminary findings that are hypothesis generating. A large-scale, prospective analysis through a cooperative group trial is warranted for the validation of NAFCIST in osteosarcoma. Herein, we provide a framework for using NAFCIST to evaluate the activity of bone-targeted therapy for future studies.

DISCLOSURE

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