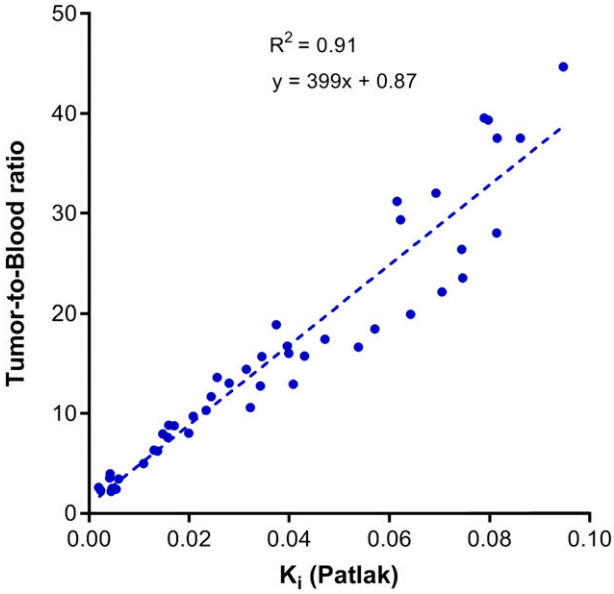

FIGURE 1. Correlation of image-based tumor-to-blood ratios and K_i derived from Patlak's graphical analysis.

robust and valid simplified method for ^{18}F-DCFPyL uptake quantification—despite its widespread (often unvalidated) use. The main reason for the invalidity of SUV is that the input function, that is, the bioavailability of the tracer in plasma to tissue, is not comparable between subjects. Normalizing tracer uptake by injected activity over body weight (or lean body mass) assumes that the input function of individual patients is simply a scaled version of a population curve. When this assumption is violated, quantitative kinetic approaches that include an individually measured input function, such as Patlak analysis, are required. A simplification to the Patlak approach could be to normalize the tumor uptake to blood activity concentrations, as was shown in our paper. The use of TBR, at least partly, compensates for changes in the input functions that are not explained by variation in injected activity and weight alone. In our specific case, the overall mass of the disease affected the shape and amplitude of the input function, and thus normalizing tumor uptake by injected activity over weight, that is, SUV, should not be used for the quantification of ^{18}F-DCFPyL uptake.

Lastly, we agree with Laffon et al. that not only the repeatability of tumor uptake (SUV) should be evaluated, but also the repeatability of the TBR (and the blood–activity concentration itself) must be understood. The same differences in tracer bioavailability that were observed between patients can develop within patients over time, in the case of disease progression or treatment response. Results on our repeatability study are expected shortly.

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Off-Target Report on ^{18}F-Sodium Fluoride PET/CT for Detection of Skeletal Metastases in Prostate Cancer

TO THE EDITOR: In a recent report in the *Journal of Nuclear Medicine*, cited by AuntMinnie, Zacho et al. found, according to the title of their communication, "No added value of ^{18}F-sodium fluoride (^{18}F-NaF) PET/CT for the detection of bone metastases in patients with newly diagnosed prostate cancer with normal bone scintigraphy" (*1*). In 81 intermediate- or high-risk prostate cancer patients with negative bone scintigraphy scheduled for prostatectomy, ^{18}F-NaF PET/CT "indicated bone metastasis" in 1 and was equivocal in 7 patients. None of these patients exhibited biochemical failure (prostate-specific antigen level $\geq$ 2 ng/mL 6 wk/6 mo after radical prostatectomy), whereas all 6 patients with biochemical failure had negative ^{18}F-NaF PET/CT (and negative bone scintigraphy)—findings making the authors conclude as stated in their title.

Their report is off-target because (1) skeletal metastases are bone *marrow* and not bone metastases and (2) neither ^{18}F-NaF PET/CT nor bone scintigraphy mirror bone marrow metastases, but late-occurring bone changes that may or may not be due to active cancerous processes (*2,3*). As in other recent communications (*4,5*), the authors disregarded the true nature of skeletal metastases, which home and grow in the bone marrow long before they give rise to structural changes in the osseous bone substance that can be detected by bone scintigraphy, ^{18}F-NaF PET/CT, or other imaging modalities. This was highlighted more than 10 y ago by Basu et al. (*6,7*) and has recently given rise to comments in both the *Journal of Nuclear Medicine* and the *European Journal of Nuclear Medicine and Molecular Imaging* (*2,3*), the latter calling for a much needed paradigm shift, since we cannot go on using methods unable to fulfil their stated purpose and that, therefore unfortunately, may lead to inappropriate patient management.

The reason why Zacho et al. did not observe an association between biochemical failure and abnormal ^{18}F-NaF PET/CT findings is a simple one: there should not be an association—at least not a very close one. An increase in prostate-specific antigen, however unspecific, is usually a reaction to cancer cells that are still present and growing after prostatectomy. However, this may have little to do with what is seen by ^{18}F-NaF PET/CT or bone scintigraphy, since both methods depict unspecific structural changes in osseous tissue that occur late in the development of skeletal metastasis and remain unchanged for a long time after the cancer may have disappeared, for instance, due to effective chemo- or radiation therapy (*2,3*). Thus, it is time to realize that all imaging modalities demonstrating structural bone changes are not reliable harbingers of skeletal metastases and should be abandoned in favor of ^{18}F-FDG PET/CT and, when it comes to prostate cancer, perhaps PSMA PET/CT. Time will show which of the latter 2 approaches are preferable for showing bone marrow metastases in prostate cancer.

However, in most other cancers, ^{18}F-FDG PET/CT will probably prevail for this purpose for reasons stated in detail elsewhere (*2,3*). Experts in nuclear medicine and molecular imaging should understand and communicate this, because otherwise how do we make cooperating surgeons and oncologists understand and act accordingly?

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Reply: Off-Target Report on ^{18}F-Sodium Fluoride PET/CT for Detection of Skeletal Metastases in Prostate Cancer

REPLY: We thank the authors for the insightful comments on our study (*1*). We very much agree with the authors that bone metastases are preceded by bone marrow metastases and that both bone scintigraphy and ^{18}F-NaF PET/CT indirectly visualize skeletal metastases via the osteoblastic reaction to metastatic deposits in the bone. However, we do not think an evaluation of the added value of ^{18}F-NaF PET/CT in patients without bone metastases on bone scintigraphy is off-target. First, bone scintigraphy is the recommended method for assessment of bone metastases in prostate cancer across urologic and oncologic guidelines (*2,3*). This recommendation comes from decades of research showing the ability of bone scans to identify patients for curative and palliative treatments. Second, ^{18}F-NaF PET/CT has replaced bone scintigraphy in many centers around the world for the evaluation of bone metastases in prostate cancer, probably mostly due to superior diagnostic accuracy and capacity. Thus, these methods are well-validated clinically.

Even though cancer cell targeting agents may, in theory, possess advantages over indirect imaging methods, there is a lack of clinical data in the literature showing the superiority of direct over indirect methods in prostate cancer. Radiolabeled PSMA, choline, and ^{18}F-FDG possess the inherent advantage of depicting the tumor cells directly. However, ^{18}F-FDG is obsolete in the staging of prostate cancer, and it is beyond the scope of this correspondence to discuss imaging in nonprostate cancer.

In comparison with choline PET/CT, ^{18}F-NaF PET/CT has been shown to have premium diagnostic accuracy in prostate cancer (*4,5*). Moreover, every comparison of PSMA PET/CT and ^{18}F-NaF PET/CT has consistently shown that ^{18}F-NaF PET/CT is noninferior to PSMA PET/CT in terms of diagnostic accuracy for the detection of bone metastases in prostate cancer (*5–9*).

Our recent study showed that a bone scan is indeed a robust tool for evaluation of the skeletal system in patients with newly diagnosed, predominantly intermediate-risk prostate cancer undergoing radical prostatectomy; ^{18}F-NaF-PET/CT did not identify any bone metastases missed by bone scintigraphy. Two years of follow-up among the 6 patients with biochemical failure after radical prostatectomy confirmed these findings; no bone metastases developed. Five of these patients underwent PSMA PET/CT, which was negative for bone marrow metastases.

While awaiting further clinical evidence for imaging methods of the bone marrow, bone scintigraphy, and ^{18}F-NaF PET/CT remain potent tools in the diagnostic armamentarium in prostate cancer. The low cost, availability, and diagnostic performance of bone scan in prostate cancer emphasizes the guideline recommendation.

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