

Out with the Old, in with the New: Can We Bridge the Gap Between Clinical Trial Results Based on Bone Scans and the Era of Modern Prostate Cancer Imaging?

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Prostate cancer is a significant contributor to overall cancer-related morbidity and mortality (1). Accurate disease staging is a critical component in making informed therapeutic decisions (2). Prostate cancer imaging has witnessed noteworthy advancements in recent years, with a noticeable shift from traditional imaging techniques such as ^{99m}Tc bone scans and CT to PET/CT modalities, most notably using various tracers targeting prostate-specific membrane antigen (PSMA). The Food and Drug Administration has granted approval for 5 PET/CT tracers since 2012, namely, ¹¹C-choline (2012), ¹⁸F-fluciclovine (2016), ⁶⁸Ga-PSMA-11 (2020), ¹⁸F-piflufolastat (2021), and ¹⁸F-flotufolastat (2023). The Food and Drug Administration–approved indications for these agents include biochemical recurrence (BCR) in prostate cancer, with the latter 3 agents also approved for initial staging.

Extensive research has been performed to ascertain the diagnostic accuracy of PET/CT tracers as well as their performance in relation to conventional imaging. In a prospective trial that compared the diagnostic efficacy of ⁶⁸Ga-PSMA-11 with that of ¹⁸F-fluciclovine, the former demonstrated significantly higher detection rates (3). Moreover, the multicenter, randomized pro-PSMA trial evaluated CT and bone scanning versus ⁶⁸Ga-PSMA-11 PET in staging men with high-risk prostate cancer, with PSMA PET demonstrating a 27% greater accuracy (4). Furthermore, in comparison to conventional bone scanning or PET/CT with bone-seeking tracers, whole-body PSMA PET/CT offers the advantage of detecting additional sites of disease beyond skeletal metastases, providing the added benefit of a 1-stop shop in its staging. Indeed, the mounting body of evidence on the diagnostic accuracy of PSMA PET agents has led to their inclusion in the National Comprehensive Cancer Network prostate cancer guidelines. Specifically, the guidelines recommend that ¹⁸F-piflufolastat or ⁶⁸Ga-PSMA-11 PET/CT or PET/MRI be considered as alternatives to conventional imaging at initial staging, BCR, and workup for progressive disease (<https://www.nccn.org>).

Appropriate-use criteria for PSMA PET/CT, published in this journal in 2022 (5), also suggest that PSMA PET/CT is appropriate for staging newly diagnosed unfavorable intermediate- to high-risk

prostate cancer, staging BCR after radical prostatectomy or definitive radiotherapy, and assessing nonmetastatic castration-resistant prostate cancer based on conventional imaging. However, in the context of evaluating therapy response and restaging in castration-resistant disease, there are limitations in the available data for PSMA PET and a lack of validated standardized criteria for assessing response using this modality. As a result, conventional imaging remains the gold standard modality, as recognized by the Prostate Cancer Clinical Trials Working Group 3 (6).

The study published by Hope et al. (7) in this issue of *The Journal of Nuclear Medicine* is a great attempt at translating clinical trial findings derived from bone scans to PSMA PET/CT. This international multicenter retrospective study was conducted to evaluate the diagnostic efficacy of bone scans in detecting osseous metastases using PSMA PET/CT as a reference standard. The study enrolled 167 patients with prostate cancer (77 at initial staging, 60 at BCR, and 30 in the setting of castration resistance) who underwent bone scanning and PSMA PET/CT within 100 d. Three independent masked readers evaluated each scan without access to clinical information or other imaging results. Overall, the bone scans had a positive predictive value, negative predictive value, and specificity of 0.73, 0.82, and 0.82, respectively. However, when only the initial staging cohort was considered, the positive predictive value, negative predictive value, and specificity were 0.43, 0.94, and 0.8, respectively. In total, 27% of patients with bone metastases detected on bone scanning were found to be negative on PSMA PET/CT. This (false-positive) percentage increased to 57% in the initial staging group. In the separate analysis for BCR and castration-resistant patients, the positive predictive value was 0.77 and 1, respectively. This suggests that the rate of false-positive bone scans decreased as the pretest probability for metastatic disease increased (positive and negative predictive values are directly related to disease prevalence).

Hope et al. further discussed their findings in relation to the secondary analysis of the STAMPEDE M1 radiation therapy trial (8), which demonstrated the effectiveness of prostate irradiation in combination with androgen-deprivation therapy and docetaxel for patients with low-volume disease on bone scans (fewer than 4 bone metastases). Discovering the disease overestimation by bone scanning compared with PSMA PET/CT, Hope et al. then extrapolated that it was highly likely that many patients classified as having low-volume metastatic disease at initial staging in the STAMPEDE

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M1 radiation therapy trial based on bone scanning ($\leq 57\%$) would have had localized disease had they been staged by PSMA PET/CT. Therefore, the additional survival benefit derived from the trial intervention would realistically be attributed to treating only localized disease. However, it is not possible to totally dismiss the added benefit of the trial intervention in the subset of patients who truly had low-volume M1 metastatic disease on bone scans. Despite Hope et al. and other groups' best efforts, it remains unknown how low-volume disease on the bone scan translates to PSMA PET/CT and whether there still is a survival benefit from irradiation of the primary in the presence of a (yet undefined) low burden of PSMA PET-detected metastatic disease.

It is noteworthy that Hope et al. screened 10,807 patients who had a PSMA PET/CT scan, only to find 973 patients (9%) who also had a bone scan. After excluding studies with scans performed more than 100 d apart and patients who had treatment between the 2 imaging modalities, they included 167 patients (1.5% of the screened population) in their final cohort, 70% (117 patients) of whom underwent PSMA PET/CT before bone scanning. Although this observation is a true reflection of a real-world scenario where bone scanning has been replaced by PSMA PET/CT, this would unintentionally introduce a selection bias in this study population.

Hope et al. were also masked to clinical and correlative imaging information when interpreting bone scans and used planar imaging only, with no category for equivocal scan interpretation, which is far from the reality of modern imaging reporting. The retrospective nature of the study, inclusion of metastatic castration-resistant prostate cancer patients, and known higher accuracy of PSMA PET/CT than of bone scanning could have also potentially introduced an unconscious bias into this study and the way bone scans were interpreted compared with what was undertaken in the original STAMPEDE trial (8). Finally, it is not clear how comfortable the readers in this study were at interpreting planar bone scans without SPECT/CT.

The dynamic landscape of prostate cancer imaging is witnessing novel PSMA PET/CT agents replacing CT and bone scanning. Although the accuracy of PSMA PET/CT findings is now accepted, integrating these findings in clinical situations where the body of evidence for treatment decision-making is based on conventional imaging remains an ongoing challenge. Further research is warranted to elucidate these nuances and to ensure a seamless transition. Incorporation of PSMA PET/CT (or in broader terms, novel molecular

imaging techniques and tracers) in future clinical trials should become mandatory. Additionally, efforts should be directed toward standardization of PSMA PET/CT reporting, establishing it as the new modern benchmark in future clinical trials and practice.

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