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Platinum Opinion

More Accurate Imaging Is Not Stage Migration: Time To Move from "Hubble" to "Webb" in Hormone-sensitive Prostate Cancer

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1. Introduction

The Hubble space telescope enabled scientists to visualize an extrasolar planet, Fomalhaut b, for the first time. A few years later, astronomers found something fishy when the planet had seemingly disappeared. Reanalysis of the data confirmed that the planet was actually an expanding dust cloud [1]. Similarly, some osteoblastic lesions visualized on bone scans are initially considered to represent bone metastases, only to be redefined as benign pathologies on next-generation imaging. Prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/computed tomography (CT) produces strikingly superior images in comparison to conventional imaging, with higher sensitivity and specificity. Better images are compelling for both doctors and patients, but some clinicians are concerned that the resulting management changes might be detrimental to patient outcomes. We, however, are more alarmed at the continued guidance of patient management with less accurate imaging. A particular area of controversy, highlighted at the recent Advanced Prostate Cancer Consensus Conference (APCCC), focused on concerns regarding stage migration from low-volume to high-volume disease in patients with hormone-sensitive prostate cancer (HSPC) on next-generation imaging [2].

International guidelines recommend prostate radiotherapy for hormone-naïve prostate cancer with small-volume metastatic disease but not for high-volume disease [3]. This is based on high-level evidence from the STAMPEDE study [4] using a predefined definition of low- and high-volume metastatic disease based on the CHAARTED trial [5]. In both of these trials, the visceral metastatic burden was evaluated via CT, and the number and location of osseous metastases were evaluated via whole-body bone scans, raising the important question of whether conventional imaging is sufficiently accurate to guide patient management. In addition, if next-generation imaging is adopted, what happens if stage migration occurs because the modality can "see more", without truly contributing to improving clinical outcome?

2. Reducing false-positive results is not stage migration

A secondary analysis of the STAMPEDE trial showed that the survival benefit from prostate radiotherapy in metastatic disease decreased as the number of bone metastases, defined on two-dimensional planar scans, regardless of location. Significant survival benefit occurred when three bone or fewer bone metastases were identified [6]. However, there are two concerning issues raising the possibility of confounding factors interfering with the result achieved. First, it is important to note that many osteoblastic lesions seen on whole-body bone scans and subsequently reported as osseous metastases (as per the STAMPEDE criteria) are indeed benign lesions on single-photon emission CT (SPECT)/CT imaging (Fig. 1). There are data showing that when moving from planar two-dimensional scans to three-dimensional SPECT/CT, the diagnostic accuracy improves significantly [7]. This increase in accuracy and diagnostic confidence is not stage migration, which in this context refers to improved sensitivity rather than improved

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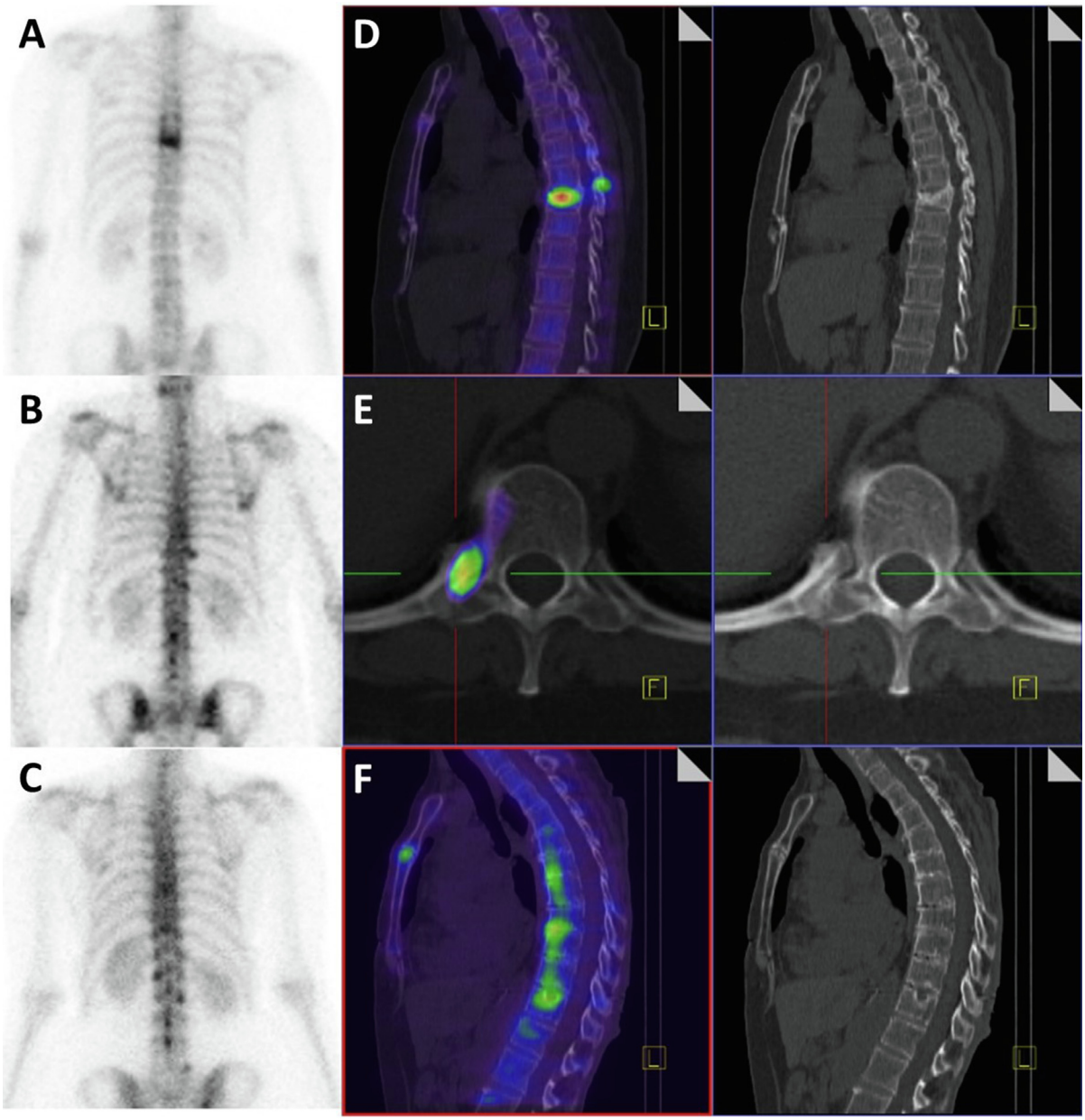

Fig. 1 – "All that glitters is not gold!" Representative example of three patients with back pain and newly diagnosed with metastatic hormone-sensitive prostate cancer who underwent bone scintigraphy. (A–C) On planar two-dimensional whole-body bone scans, osteoblastic osseous lesions throughout the thoracolumbar spine are presumed to be metastases. Using STAMPEDE data, planar scans are sufficient for skeletal metastatic assessment and management guidance. (D–F) On single-photon emission computed tomography/computed tomography (CT) images, however, the osteoblastic lesions are redefined as benign degenerative changes. This highlights the limited specificity of planar bone scanning, which images bone reaction, in contrast to tumor-specific imaging such as prostate-specific membrane antigen positron emission tomography/CT.

specificity or reporter agreement. Logically, the chance of false-positive results is much higher when there are only a few osteoblastic lesions. In patients with high-burden disease having more than three osteoblastic lesions on bone scans, the lesions can be confidently reported as osseous metastatic disease, whereas when there are only few osteoblastic lesions (as was categorized in the low-burden disease group in the STAMPEDE trial), the chance of false-positive results is relatively higher. Accordingly, we are concerned that a number of patients categorized as having low-burden metastatic disease and showing a survival benefit from prostate radiotherapy in fact had nonmetastatic disease with non-malignant osteoblastic lesions on planar bone scan incorrectly considered as osseous metastases (Fig. 2).

3. How frequent are false-positive results with conventional imaging? How much more accurate is PSMA PET?

Data from the multicenter randomized ProPSMA clinical trial showed 27% greater accuracy from PSMA PET/CT compared to the combined findings from contrast-enhanced CT and a bone scan with SPECT/CT (92% vs 65%)

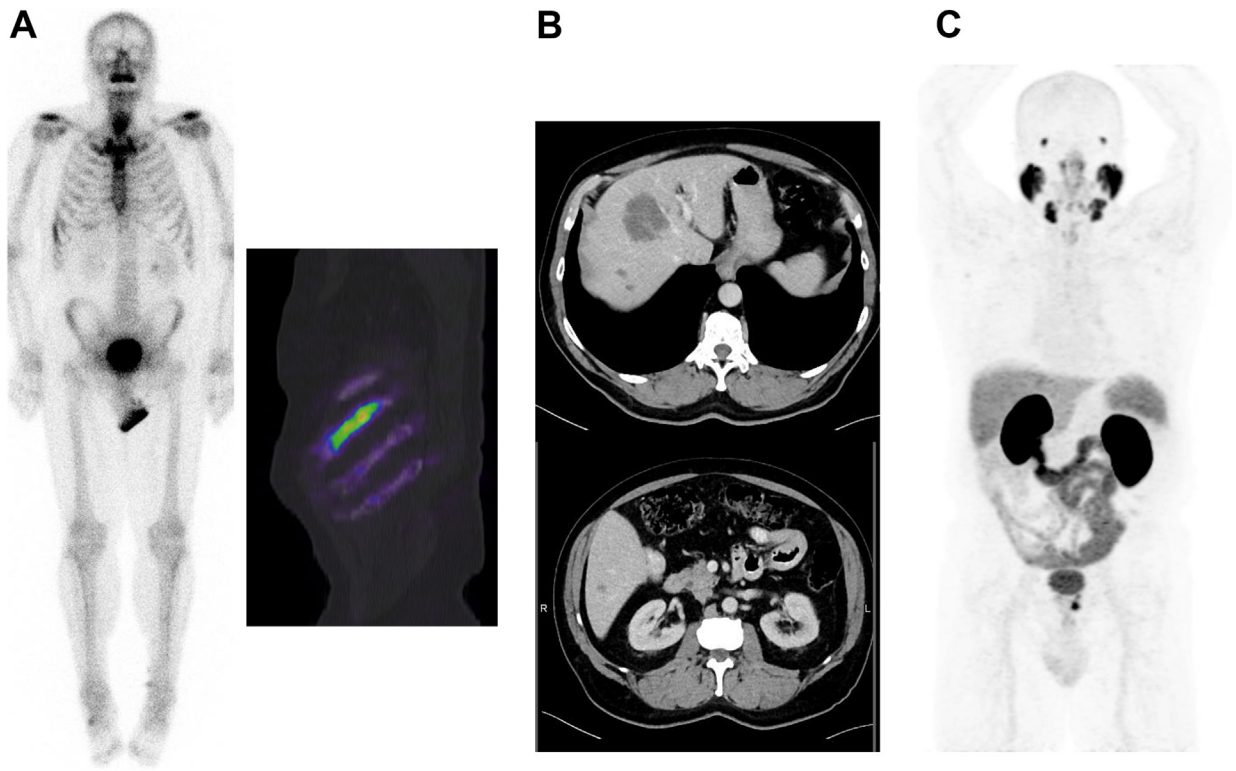

Fig. 2 – A 63-yr-old man newly diagnosed with Gleason score 4 + 5 = 9 (grade group 5) prostate cancer presented for initial staging as part of the ProPSMA study. (A) A bone scan shows an unequivocal osteoblastic lesion in the lateral aspect of the right tenth rib. (B) Computed tomography (CT) shows a hypoattenuating, irregularly shaped hepatic lesion, reported as visceral metastasis. (C) The next day, prostate-specific membrane antigen (PSMA) positron emission tomography/CT was performed, demonstrating a PSMA-avid primary prostate lesion with no evidence of regional nodal or distant metastatic disease. The patient underwent radical prostatectomy. At 6-mo follow-up, prostate-specific antigen remained undetectable, in keeping with nonmetastatic disease.

For the primary endpoint, equivocal finding on imaging were considered not to represent metastases, resulting in a frequency of false-positive results of 6% for conventional imaging compared to 1% for PSMA PET. However, in a prespecified sensitivity analysis, if equivocal findings were considered positive—which may be more reflective of community clinical practice, where there is a desire to avoid missing metastatic lesions—the rate of false-positive results was 23% for conventional imaging (SPECT/CT bone scan plus contrast-enhanced CT) versus 7% for PSMA PET/CT [8] We think a 1-in-4 false-positive rate, which may even more frequent on planar bone scintigraphy [7], should alarm clinicians and patients.

The results of the phase 3 STAMPEDE study cannot be ignored, as it is biologically plausible that radiotherapy to the primary site in the setting of low-volume metastatic disease improves survival. This might be because of abscopal effects or eradication of primary disease as a seeding source for further metastases. However, even if we accept the premise of benefit in small-volume disease, lesion counting on conventional imaging is too simplistic. Metastases can vary in size enormously. True three-dimensional tumor volumetric measurement is now feasible with PET/CT. Barbato et al. [9] showed that volume quantification with PSMA PET/CT (using a 40-ml cutoff) translates to a low versus high burden on conventional imaging in metastatic HSPC, with additional subclassification of disease extent critical for guiding targeted or systemic therapy. More evidence is certainly required to determine the optimal PSMA quantitative thresholds, and the best way to obtain these data is to incorporate PSMA PET/CT into all our prospective clinical trials. In a different setting of castration-resistant metastatic diseae, we recently showed that PET quantitative parameters are predictive biomarkers for response to PSMA radioligand therapy [10]. Currently, specialised software is needed but we hope this research will spur single click software solutions for determination of quantitative PET biomarker parameters.

Medical imaging can be viewed as an extension of physical examination, with the extent of abnormalities used to define the most appropriate patient management to ensure well-being. When a new, more accurate, less time-consuming modality with lower radiation dose and cost efficiency [11] provides better information with a strong impact on patient management, it deserves to be incorporated into clinical practice, trials, and guidelines. Nowadays, we are requiring every new procedure (from imaging to therapy) to have a positive impact on overall survival and/or quality of life; however, such an impact has never been demonstrated for old approaches, such as bone scanning. Essentially, we moved from an era before evidence-based medicine (EBM), in which imaging was adopted too rapidly, to a post-EBM era, in which new imaging is becoming very hard to incorporate into guidelines. Is the use of planar

two-dimensional bone scans, as in the STAMPEDE trial, really sufficiently accurate for bone staging and subsequent patient management?

Scientists believe that the transition from the "Hubble" to the "Webb" telescopes has remarkably helped them in discovering the universe. Each human being is a universe of their own and deserves to be managed accurately. Next-generation imaging including PSMA PET is needed and can be a successor to conventional imaging in the staging of metastatic HSPC. It is time for this transition.

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