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Is PSMA PET-CT Better than Bone Scan? When and Why

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Abstract

Prostate cancer (PCa) has a unique tropism to bone. Indeed, bone is the most frequent site of distant metastasis and cause of morbidity due to skeletal complications. 99mTc-Methylene diphosphonate (MDP) bone scintigraphy/scan (BS) is the current standard imaging due to increase adsorption of the tracer at osteoblastic sites. However, it has limited specificity due to false positives in degenerative changes, benign causes and false negatives in bone marrow metastasis and lytic lesions. Another drawback of BS is flare response. Prostate Specific Membrane Antigen (PSMA) has been the most studies target in prostate cancer imaging in recent time due to 100-1000 time over-expression in cancer cells. 68Ga-PSMA-11, a small molecule with PSMA enzyme inhibition activity has been found promising in recurrence and lymph-node staging. In our experience of 97 staging prostate cancer patients, PSMA PET-CT showed 57.41% with pure sclerotic metastasis. Mixed (33.33%), marrow (7.14%) and lytic (2.3%) types of lesions constitute the rest and thus BS alone in these patients may leads to underestimation of bony disease burden. PSMA has not been found positive in degenerative changes however its role in response to anti-androgen needs caution due to know synergistic effect on PSMA expression. We concluded, PSMA PET-CT would have better sensitivity and specificity due to unique distinction for detecting non-sclerotic metastases. We presumed if PSMA has been performed for staging workup then there is limited role of BS except in clinical trial patient. Overall PSMA PET may become one-stop-shop for PCa workup.

Keywords: PSMA PET-CT; Bone scan; Marrow metastasis; Lytic metastasis; One-stop-shop

Introduction

Prostate cancer (PCa) is the second most common cancer and sixth leading cause of cancer death in man worldwide [1]. In India though the incidence is less than the western world, it is showing a rising trend now. Indeed in many metro-cities like Delhi it has become the runners up with age-adjusted incidence of $10.9/10^5$ person-years [2]. A large number of patients diagnosed with early stage PCa got cured with definitive local therapy i.e. Radical prostatectomy or Radiotherapy, however many will develop metastatic disease. PCa has a unique exquisite tropism to spread in bone [3]. Haematogenous spread in red bone marrow of axial and proximal appendicular skeleton leads to development of bone metastases (BMs). BMs are the most frequent and main distant metastatic site in about 80% of PCs patients and is therefore one of the most important determinants of treatment and outcome [4,5]. Skeletal complications known as 'skeletal-related events (SREs)' accounts for most of the PCa's morbidity and mortality [6]. Bone marrow replacement by PCa cells leads to anaemia while involvement of cortical bone can lead to pain, fractures, and spinal cord compression. Once bone metastasis is diagnosed, local definitive treatment goes out of the picture and the intent of treatment become palliative. Hence timely diagnosis of bone metastasis is important for correct treatment planning and prevention of SREs.

Bone scintigraphy/scan (BS) with 99mTc-Methylene diphosphonate (MDP) is the most favoured investigation for detecting BMs. This is due to physiological adsorption of this radiopharmaceutical at the site of osteoblastic activity. In PCa BMs there is predominant upregulation of osteoblasts lead to formation of characteristic sclerotic lesions. Hence this method has high sensitivity (range 62-89%) for BMs in PCa [7]. Briganti has showed risk on BMs in low (Gleason ≤ 7, T2-T3 and PSA<10 ng/ml), intermediate (Gleason ≤ 7, T2-T3 and PSA>10 ng/ml) and high risk (Gleason>7) PCa of 1.8%, 8.5% and 16.4% respectively [8]. Therefore, most guidelines suggest BS to be performed in patients with high risk PCa or those presenting with bone symptoms [9-11].

BS has been associated with number of limitations as well. It is a well-known fact that BM begins in bone marrow, hence it is predicted that BS will not able to detect bone marrow lesions or early lesion with insufficient osteoblastic activity. In addition it is a non-specific tracer and many a times it is hard to differentiate between degenerative bone disease and BMs hence frequently requiring additional imaging modality for characterization [12]. With modern hybrid imaging SPECT-CT (Single Photon Emission Computed Tomography-Computed Tomography), MDP BS has largely addressed this issue of low specificity and able to correctly characterized planner imaging equivocal lesions. It has been reported that the number of equivocal lesions dropped from 61 to 8% with addition of SPECT-CT [13]. Flare response is another known fact in BS [14]. Post treatment increase in tracer activity or new lesion is tricky in interpretation. Whether this is due to reparative response or due to disease progression is a matter of concern. Nonetheless this phenomenon has been assumed as response by most physicians and presumed to have better outcome.

Despite these limitations, bone scan has been recommended as standard for BMs in clinical trials by prostate cancer working group. Reason being it is widely available, low cost, time tested and whole body imaging. In addition it has been reported superior to X-Ray and CT [15], roughly equivalent to 11C-Choline-positron emission tomography (PET) [16] as well. Though it is inferior to whole body MRI [17] and 18F-Fluoride PET [18] but these imaging has still not able to find their way in clinical practice and associated with few limitations as well.

Recently prostate-specific membrane antigen (PSMA) has been acclaimed as a distinct target in PCa. Its expression is 100-1000 times more in PCa cells [19] and level of expression is directly proportional to gleason score, androgen independence, metastasis and progression [20]. Many monoclonal antibodies and small molecule inhibitors have been developed to target PSMA. Out of these, a small molecule inhibitor Glu-NH-CO-NH-Lys-(Axe)-[68Ga(HBED-CC)] (68Ga-PSMA-11) is being most investigated. It has shown to be of high clinical value for lymph node staging [21] and detection of local recurrence [22,23]. For BMs PSMA PET has unique distinction of being positive in bone marrow metastasis and not being positive in degenerative bone disease. In a direct comparison, PSMA PET outperformed planner BS for detection of affected bone regions as well as overall bone disease volume [24,25]. Overall 17.6% of affected bone regions were exclusively recognized only by PSMA PET while only 1.2% of bony regions exclusively detected by BS. PSMA-PET showed significantly higher sensitivity and accuracy than BS (90.5% *vs.* 73.68%, and 97.0% *vs.* 86%) for BMs [26]. In our experience of 97 staging PSMA PET studies, we found only 57.41% of patients with BMs had pure sclerotic lesions. Mixed (33.33%), marrow (7.14%) and lytic (2.3%) types of lesions constitute the rest and thus BS alone in these patients may leads to underestimation of bony disease burden. We found that overall the PSMA PET allows envisioning an all-in-one metastatic work up (both visceral and bone) in high risk prostate cancer (Figures 1 and 2). In addition, we believe PSMA PET will have upper hand in response evaluation of BMs then BS however, data is deficient in the literature.

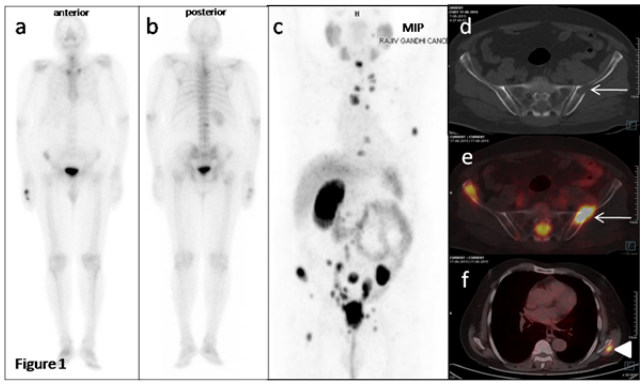

Figure 1: 68 Years male with adenocarcinoma prostate, gleason score 4+5, PSA 121.5 ng/ml underwent MDP bone scan (image a and b) and 68GaPSMA PET-CT (image c, d, e, f). MDP bone scan shows doubtful lesions in right iliac crest, D3 and L2 vertebrae. PSMA PET-CT showed locally infiltrating prostate lesion with pelvic lymphnodes, multiple osteolytic bony lesions (arrow) and a left infraspinatus muscle deposit (arrow head).

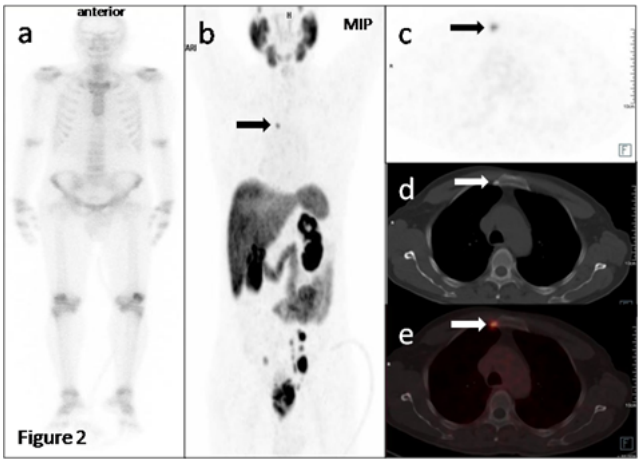

Figure 2: 62 Years male with adenocarcinoma prostate, gleason score 5+4, PSA 17.5 ng/ml underwent MDP bone scan (image a) and 68GaPSMA PET-CT (image b, c, d, e). MDP bone scan was reported normal while PSMA PET-CT showed locally infiltrating prostate lesion with pelvic lymphnodes and a solitary bony lesion in sternum (block arrows).

Nevertheless we need to understand that PSMA PET is still in infancy stage and no prospective data is available for its role in BMs. Availability limited to few tertiary care cancer institutes is a big challenge for PSMA PET to come in main stream. Cost and reimbursement are other critical points here for PSMA PET as BS is often covered in health insurance. With growing availability of SPECT-CT makes BS specific and a strong contender to PSMA PET in BMs especially in advanced diseases. It has been noticed that PSMA expression is inversely related to androgens level hence, its expression will increase in androgen deprivation state [27]. This influence of anti androgens on PSMA expression is requiring attention in interpretation of response as initial flare up to 3 months can be expected [28,29]. Further studies might be interested in order to disentangle this treatment dependency of PSMA in response assessment of BMs.

Conclusion

We concluded PSMA PET has better sensitivity and specificity then BS and a unique distinction for detecting non-sclerotic metastases. Its role in response evaluation to anti-androgens needs caution and further studies. We presumed if PSMA has been performed for staging workup then there is limited role of BS except in clinical trial patient. Overall PSMA PET may become one-stop-shop for PCa workup.

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