REVIEW ARTICLE

IMAGING BONE METASTASIS OF PROSTATE CANCER: A MINI REVIEW

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Case History

Sixty four years old male presented with history of urinary symptoms and raised PSA level (123 ng/ml). Sextant biopsy of prostate revealed adenocarcioma with a Gleason's score of 8/10. Pelvic MRI revealed grossly enlarged prostate with a hypointense nodule over apex with evidence of right pelvic lymphadenopathy. A radionuclide bone scan (BS) was performed which revealed foci of abnormal tracer deposits over body of sternum with non-specific widespread degenerative arthritic changes (Fig.1). A follow up computerized tomogram (CT) scan (bone window) of chest was unremarkable (Fig.2). Subsequent magnetic resonance imaging (MRI) of sternum revealed two areas of abnormal signal intensity involving body of sternum with post-contrast enhancement consistent with bone metastases (Fig.3). In view of this interesting case, we will elucidate upon the imaging of bone metastasis in patients with prostate cancer (PC).

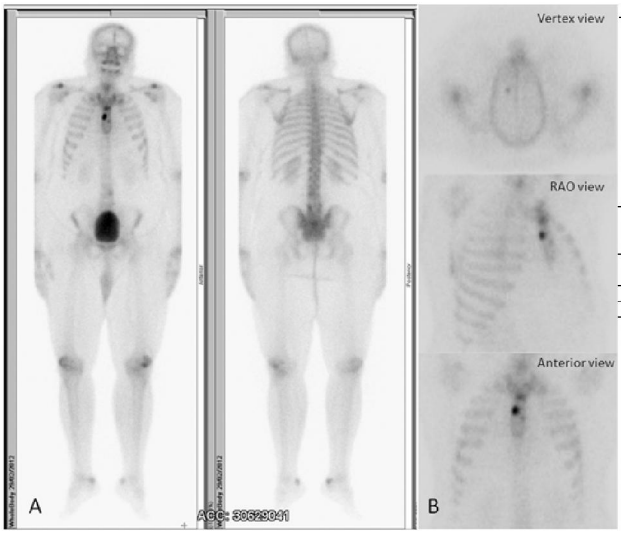

Figure 1: Radionuclide bone scan (A; whole body; B: static views) showing abnormal tracer deposits over body of sternum and left frontoparietal region with widespread arthritic changes as well.

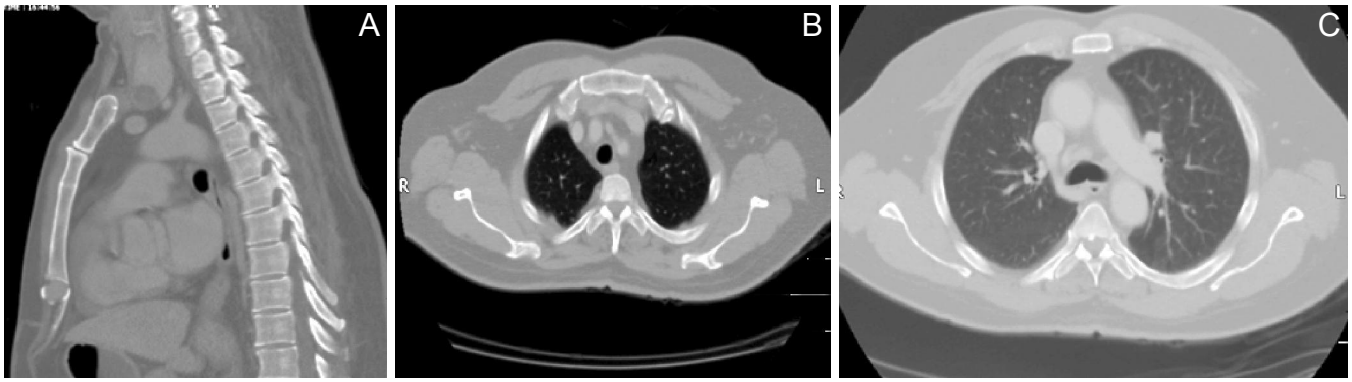

Figure 2: CT scan (bone window; A: Sagittal, B: Axial upper thorax, C: Mid thorax level) showing no bony abnormality in sternum.

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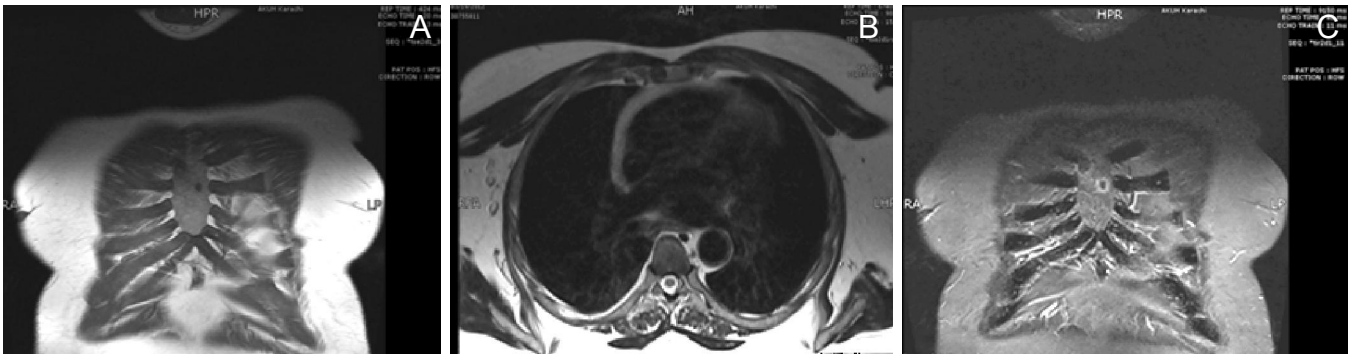

Figure 3: T1 coronal (3A), T2 axial (3B) and STIR coronal (3C) images of the sternum. The lesions are low signal both on T1 and T2 weighted images and have a halo of surrounding oedema which is most evident on the STIR image.

Bone Metastasis and Prostate Cancer

PC is currently the most common malignancy diagnosed in American and British males.[1] In European Union, PC constitutes about 13% of all malignancies diagnosed in male but unfortunately its magnitude in Pakistan is not clearly known.[2] However, according to Karachi Cancer Registry,[3] PC is the 6th commonest male cancer in Pakistan. Identification of bone metastases, which is present in up to 14% cases at presentation and about 80-85% in later phase,[4] is essential for staging, choice of therapy and prognosis. Currently prostate specific antigen (PSA) is used as a tumor marker to assess the therapeutic response and normalization of its titer predicts a prolong response in most of patients.[5] Imaging of bone metastasis in PC involves a wide spectrum of modalities ranging from plain X-ray, BS, CT, MRI to hybrid imaging like positron emission tomography and CT (PET/CT). In this review we will describe the pathophysiology of bone metastasis in PC and role of above mentioned imaging modalities.

Pathophysiology

In PC bones are involved by means of three routes

1. Direct or Local Invasion: it occurs in locally advanced PC in which periosteum and then cortical bone of surrounding skeleton is invaded by tumor cells.
2. Retrograde Venous Route: tumor emboli enter into Batson's venous plexus (valveless system) and considered as the major route in PC and preferential involvement of vertebrae and ribs.
3. Systemic Circulation: seeding with tumor emboli enter in systemic circulation following the seed-and-soil theory of Paget[6] and spread follows the distribution of adult red bone marrow in axial and appendicular skeletons.

As a metastatic lesion grows in the medullary cavity, surrounding cortical bone is remodeled by mean of an osteoblastic response in 71% and osteoclastic or mixed phenomenon in 29%.[7]

Imaging Modalities for Bone Metastasis in PC

Plain X-ray: It is the best method for characterizing the bone metastasis as osteoblastic, osteolytic or mixed lesions. Metastatic lesions of vertebra are hallmarked by pedicle destruction, associated soft tissue mass and deformity of vertebral endplates. Cost and easy availability are the major strength of plain X-ray but its sensitivity is limited as it requires >50% loss of mineral content in a lesion to be appreciable

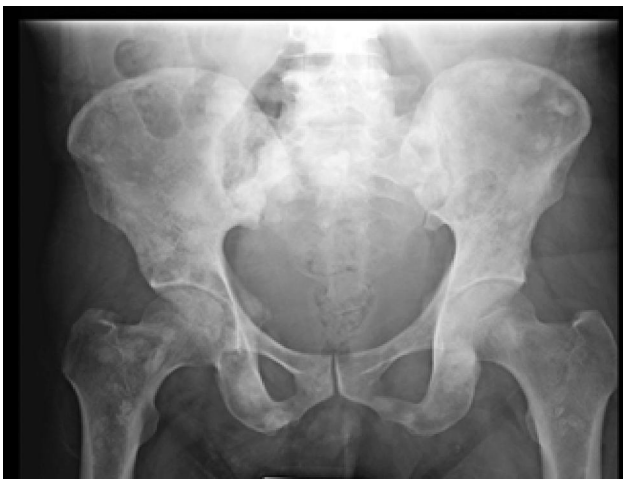

Figure 4: Plain radiograph of pelvis showing multiple sclerotic lesions in pelvic bones and proximal femori consistent with osteoblastic metastases in PC.

radiologically. Healing of a metastatic lesion (osteoblastic response) is characterized by sclerosis and in PC as most of the lesions are sclerotic (osteoblastic) (Fig. 4), assessment of response to therapy becomes difficult to ascertain. Furthermore, sclerotic metastasis may be difficult to distinguish from other sclerotic lesions as bone islands, tuberous sclerosis, mastocytosis and osteopoikilosis.

Radionuclide Bone Scan (BS): BS using ^{99m}Tc-methylenediphosphonate (MDP) or hydroxymethylene diphosphonate (HMDP) is considered a very sensitive method for detecting skeletal metastases. BS can detect a 10% change in bone mineral turnover (compared to >50% demineralization before a lesion is detected by plain X-ray) and can also detect bone metastases up to 18 months before plain X-ray reveals them.[8] It is important to note that BS images secondary effect of tumor (i.e. remodeling / osteoblatic response of cortical bone induced by tumor invasion) and not tumor itself (direct). In cases of widespread metastases, scan shows abnormally high and non-homogenous tracer distribution over skeleton (mainly skull, ribs, spine and pelvis) with very low soft tissue uptake , i.e. enhanced bone to soft tissue tracer uptake ratio and this presentation is called superscan (Fig. 5). This reduces the specificity of BS significantly as false positive findings occur due to degenerative process, trauma, infection, inflammation and Paget's disease. Similarly the osteoblastic response that occurs as a result of bone healing can also lead to a false-positive diagnosis of disease progression (flare phenomenon). Flare response (healing process) has been reported in 6-25% of PC and is caused by increased vascularity or increased turnover of hydroxyapatite in a healing lesion. It is characterized by worsening of BS within 3 month of introduction of therapy usually in contrast to clinical improvement and a repeat scan after 6 months can resolve the query.[9] In addition BS has limitations of reduced spatial and contrast resolution.

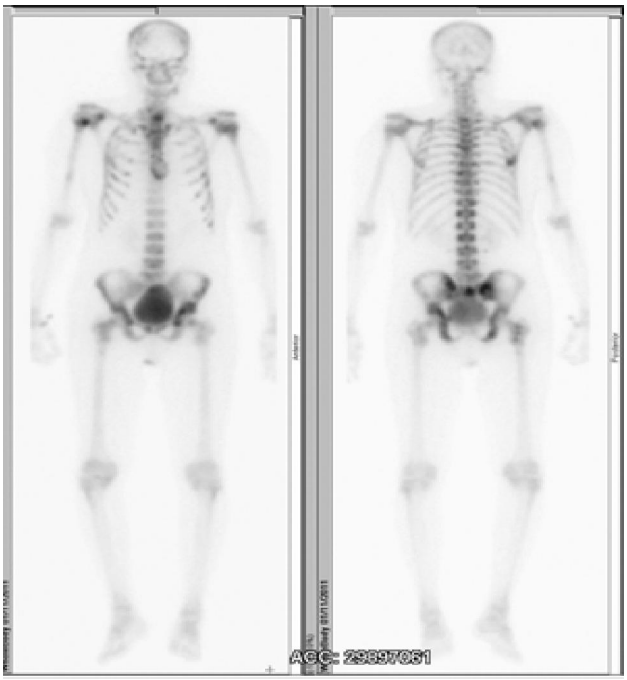

Figure 5: Whole body Tc-99m MDP bone scan showing abnormally enhanced and non-homogenous skeletal but reduced soft tissue uptake (faintly outlined kidneys) consistent with "Super scan" in PC with extensive bony metastases (same in Figure 4).

Computerized Tomography (CT): CT has been used to monitor bone metastases, but bone scanning and MR imaging are superior to CT in the diagnosis of bone metastases.[8,10] CT scans may be false negative in cases of metastatic disease detected at radionuclide BS (as in this case report), but CT allows more accurate distinction of malignant from benign causes of increased radioisotope uptake at bone scanning.[11] Individual osseous metastases are more accurately defined as individual lesions on a CT scan than on a BS (Fig. 6) and, therefore, clear changes in osseous lesions seen at CT can be used to monitor responses to systemic therapy. Caution should be exercised in interpreting all osteoblastic lesions as metastases, as CT typically depicts the effects of tumor cells on normal osteoblasts rather than directly reflecting metastases, and bone changes in response to therapy may lag behind therapeutic effects.

Magnetic Resonance Imaging (MRI): MRIs is currently the most sensitive modality for diagnosis of bone metastasis because it can detect early changes in bone marrow that precede the osteoblastic response in cortical matrix. Marrow infiltration by tumor cell results in prolongation of T1 relaxation time and reduced signal intensity and high signal intensity on T2 weighted fat suppression sequences as short tau inversion recovery (STIR). In a recently published prospective study, the sensitivity and specificity of MRI was 100% and 88% for detecting bone metastasis.[12] BS is less sensitive tool than MRI as it images the osteoblastic response in bony matrix in response to tumor invasion.8 Conventional MRI has limitation of whole body coverage but newer scanners with whole body coil have been introduced although prolong imaging time and difficulty in interpretation of certain areas like ribs are known

limitations. Diffusion weighted imaging (DWI) based on differences in water diffusion between tissues has great potential for detecting bone metastasis and monitoring the treatment response using apparent diffusion coefficient (ADC) maps.[13] Preliminary data suggest that DWI may surpass conventional T1W and STIR imaging for lesion detection and is as effective as ^{11}C-Choline PET/CT.[14] (Fig. 7)

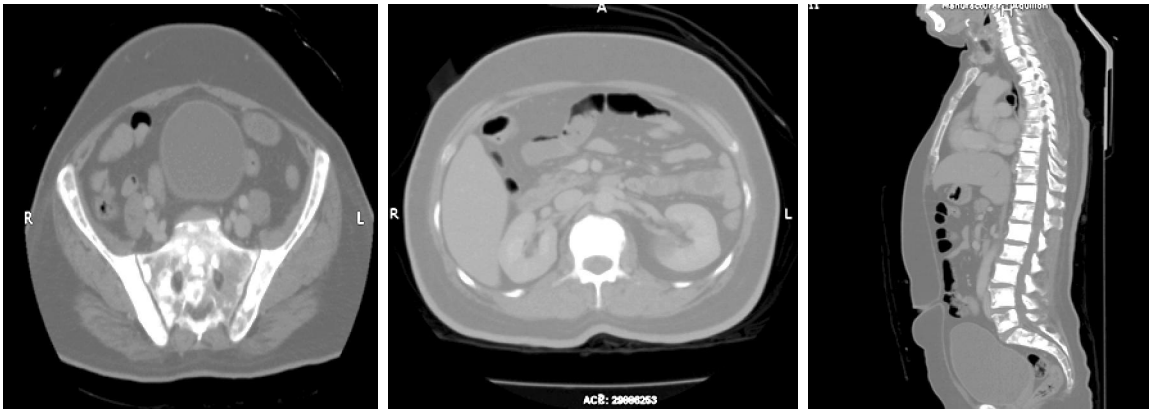

Figure 6: CT scan bone windows (A: axial pelvis; B: axial L1 level; C: Sagittal) showing widespread sclerotic bone metastases in PC (same patient as in Figure 4).

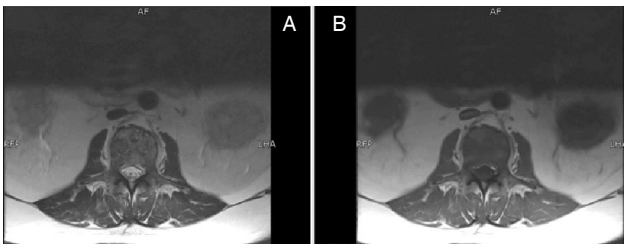

Figure 7A and 7B: T1 (B) and T2 (A) Axial images of the lumbar spine at L1 showing patchy low signal on T1 and a mixed hetrogenous signal on T2 weighted images. Metastases from Prostatic carcinoma a usually low signal on both T1 and T2 weighted images. In these images the T1 low signal represents replacement of marrow by tumour cells. The mixed signal of T2 represents a combination of tumour infiltration and oedema due to trabecular microfractures

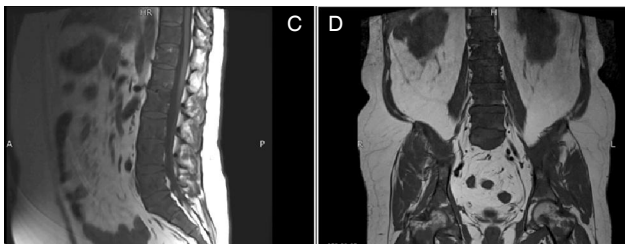

Figure 7C and 7D: Diffuse skeletal infiltration by metastatic disease. All lesions are low signal on T1 weighted images (C and D). Note the lesions in the proximal femora bilaterally on the coronal T1 image (D)

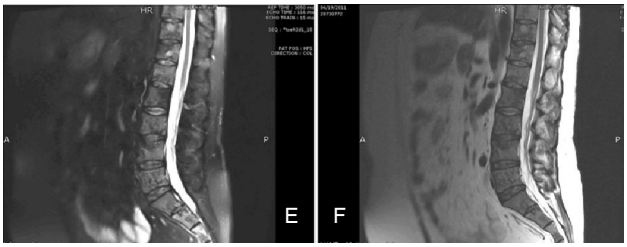

Figure 7E and 7F: T2 Saggital images, with (E) and without (F) fat suppression. Diffuse patchy signal abnormality from all the vertebrae which is better defined on the fat suppression sequences.

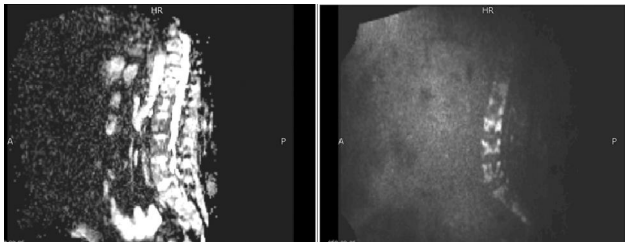

Figure 7G and 7H: Diffusion Weighted Images: The lesions show high signal on b1000 images (H), with low Apparent Diffusion Coefficient values depicted as dark areas on the ADC map (G). The diffusion restriction reflects the high cell density leading to loss of diffusibility of the extracellular water.

PET/CT Imaging: PET/CT is the most potent hybrid imaging and considered as standard of care in management of various malignancies. In carcinoma prostate various PET radiotracers are used.

a. **^{18}Fluorodeoxyglucose (^{18}FDG) PET/CT:** ^{18}FDG is a glucose analogue and is transported by Glut-1 (expressed in various malignant tumor) into tumor cell where it is pohosphorylated by FDG-6-phosphate by hexokinase and does not undergo further metabolism and retained in malignant cell. Tumor hypoxia is one of factors which enhances ^{18}FDG uptake through glycolysis. The basic limitation of ^{18}FDG is non-specificity as uptake

has also been noted in inflammatory and infective processes. Furthermore, in slow growing tumors like PC with modest enhancement of glycolysis, either relatively low FDG uptake or no visible uptake is noted in primary tumor, nodal and bony metastases.[15] Sclerotic metastases show little ^{18}FDG uptake compared with lytic lesions[16] and ^{18}FDG PET is less sensitive than BS with a reported sensitivity of 16% -18%.[17,18] Addition of CT on hybrid PET/CT scanners offers the advantage of fusing anatomical and functional data and improves specificity. (Fig. 8) The concordant lesions found on both PET and CT are highly likely to represent bone metastases; however, this likelihood falls if only the PET is positive and is reduced even further if the lesion is solitary. Solitary lesions positive on PET but not on CT should be interpreted with caution. Lesions seen on CT but not on 18FDG PET have an even lower positive predictive value.[19]

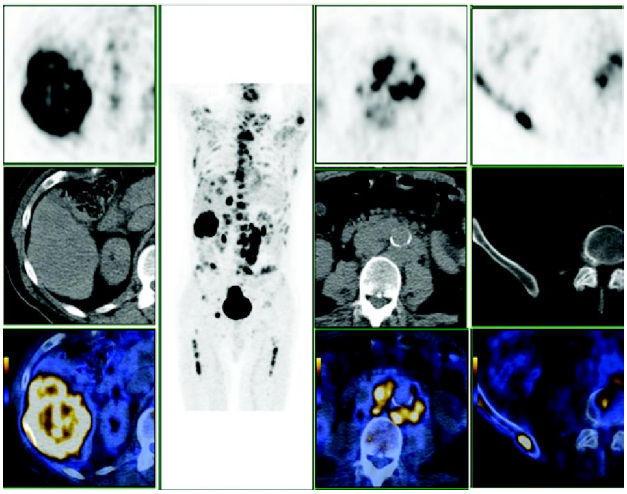

Figure 8: ^{18}F-Flouro Deoxy Glucose (FDG) PET/CT in a 71 year old male with PC showing uptake in liver nodal and bone metastasis (A: Metastasis in right liver lobe; B: MIP image; C: nodal metastasis; D: metastasis in right iliac bone, upper row: PET, mid row: CT, Lower row: fused PET/CT) (image courtesy to Dr. Mohsen Beheshti, Dr. Werner Langsteger and Dr. Martin Steinmair, PET - Center LINZ, St. Vincent's Hospital, Linz, Austria).

b. **^{18}F-flouride:** Like ^{99m}Tc- MDP, ^{18}F-flouride is a non-specific PET tracer with a half life of 110 minute and does not require an on-site cyclotron as for ^{18}FDG. It forms fluoroapatite complexes at site of increased bone turn-over. Although non-specific as conventional BS, ^{18}F-flouride PET has higher contrast and resolution which ensure better sensitivity than BS for osteoblastic and osteolytic metastases.[20] Furthermore, combination of CT (PET/CT) also ensures better specificity than conventional BS. (Fig.9)

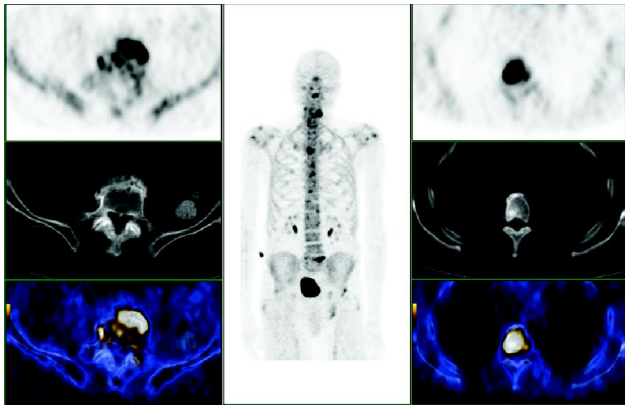

Figure 9: ^{18}F-Flouride PET/CT in a 71 year old male with PC (same in Figure 8) showing tracer uptake in bone metastasis and also over site of degenerative arthritis over L5 (A: arthritic change over L5; B: MIP image; C: metastatic lesion in T4; upper row: PET, mid row: CT, Lower row: fused PET/CT) (image courtesy to Dr. Mohsen Beheshti, Dr. Werner Langsteger and Dr. Martin Steinmair, PET - Center LINZ, St. Vincent's Hospital, Linz, Austria).

c. **^{11}C-choline/^{18}F-choline:** Because tumor cells are also characterized by their ability to actively incorporate choline to produce phosphatidylcholine (a membrane constituent) to facilitate tumor cell duplication, ^{11}C-choline and ^{18}F-choline have been used for diagnosis and staging for PC. ^{11}C-choline (half life of 20 min) imaging in prostate cancer have shows promising results for assessing localized or nodal disease and also bone metastasis.[21] It has minimal urinary excretion which makes easier to detect pelvic disease. However, its short half life (requiring an on-site cyclotron), longer positron range (impairing the image resolution) and uptake in liver, spleen, pancreas and kidneys (difficulty inn assessment of disease over these sites) are major limitations. This has prompted the development of ^{18}F-choline with a half life of 110 minute (not requiring an on-site cyclotron) and shorter positron range which ensures better resolution. However, its excretion into urine interferes with pelvic imaging but routinely performed dynamic pelvic acquisition overcomes this drawback as pathologic uptake begins 1 minute postinjection, before urinary excretion and bladder filling. (Fig. 10) In patients treated with antiandrogen, uptake of ^{11}C-choline/^{18}F-choline is reported to be decreased.[22]

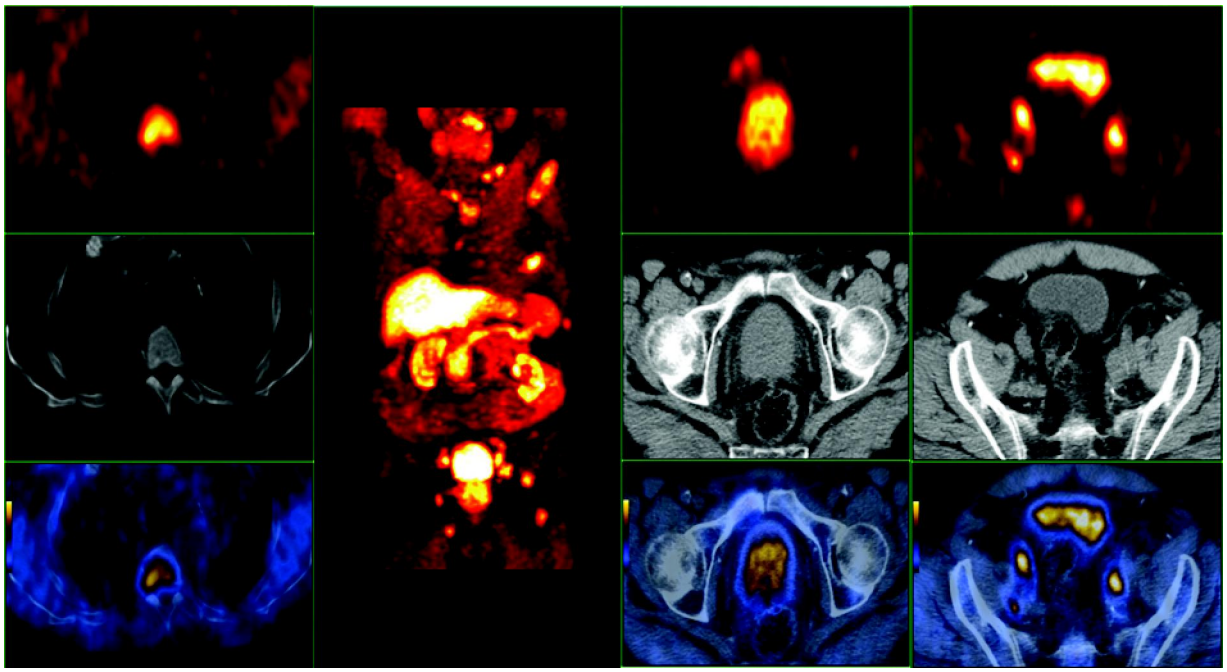

Figure 10: ^{18}F-Flourocholine (FCH) PET/CT in a 71 year old male with PC (same in figure 8) showing uptake in bone metastasis, primary tumor and nodal metastases (A: Bony metastasis; B: MIP image; C: Uptake in malignant prostate lesion; D: Nodal metastasis, upper row: PET, mid row: CT, Lower row: fused PET/CT) (image courtesy to Dr. Mohsen Beheshti, Dr. Werner Langsteger and Dr. Martin Steinmair, PET - Center LINZ, St. Vincent's Hospital, Linz, Austria).

^{111}Indium labeled Capromab (ProstaScint®): it is a murine monoclonal antibody that reacts with prostate membrane specific antigen (PMSA, a membrane glycoprotein different from PSA), which is highly expressed in prostate cancer. Immunoscintigraphy is accomplished by labeling the antibody with ^{111}Indium having a half life of 67 hours. Technique is approved for imaging soft-tissue metastases from prostate cancer in patients with clinically-localized disease who are at high risk for metastases and patients with high clinical suspicion for occult recurrent or residual prostate cancer. However, it is not approved for imaging bone metastases of PC.

In PC bone metastasis is seen in more 80% patients in later phase of disease and has an impact on staging, choice of therapy and prognosis. Bone metastases of PC are osteoblastic in majority while lytic or mixed lesions are seen in minority. Plain radiograph is the cost effective modality but has limited sensitivity. BS is the most commonly used tool for metastatic work in PC due to its sensitivity and availability despite of relatively low specificity which may be enhanced by combining the anatomical information provided by plain radiograph and CT. MRIs is currently the most sensitive modality for diagnosis of bone metastasis because it can detect early changes in bone marrow that precede the osteoblastic response in cortical matrix. PET/CT (hybrid imaging) using various radiopharmaceuticals are very robust options for imaging PC bony and soft tissue metastases and would become standard of care in future. ^{111}Indium labeled monoclonal antibody (Capromab, ProstaScint®, Cytogen) has recently been approved for imaging primary PC and nodal metastasis but not for bone metastasis.

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