F-18 fluorocholine positron emission tomography–computed tomography in initial staging and recurrence evaluation of prostate carcinoma: A prospective comparative study with diffusion-weighted magnetic resonance imaging and whole-body skeletal scintigraphy

ABSTRACT
Prostate cancer (PCa) is one of the major causes of death due to cancer in men. Conventional imaging modalities such as magnetic resonance imaging (MRI) provide locoregional status, but fall short in identifying distant metastasis. C-11 choline F-18 fluorocholine (F-18 FCH) has been shown to be useful in imaging of PCa. The present prospective study evaluates and compares the role of F-18 FCH positron emission tomography–computed tomography (PET-CT) with locoregional MRI and whole-body bone scintigraphy in PCa patients for initial staging and recurrence evaluation. This study included a total of 50 patients. Tc-99m skeletal scintigraphy, F-18 FCH PET-CT, and diffusion-weighted MRI of the pelvic region were performed within a span of 2–3 weeks of each other, in random order. For the primary site, core biopsy findings of the lesion were considered as gold standard. The kappa test was used to measure agreement between bone scintigraphy, F-18 FCH, and MRI. For comparing Tc-99m bone scintigraphy, F-18 FCH, and MRI, McNemar's test was applied. F-18 FCH PET-CT and MRI were able to detect primary lesion in all initial staging patients. The sensitivity and specificity of F-18 FCH PET-CT versus MRI were found to be 92.8% versus 89.2% and 100 versus 80%, respectively, for the recurrence at the primary site. A total of 55 bony lesions at distant sites were detected on F-18 FCH PET-CT in comparison to 43 bone lesions on whole-body bone scintigraphy. F-18 FCH PET/CT also detected additional lung lesions in 2 patients and abdominal lymph nodes in 12 patients. F-18 FCH PET-CT could detect primary lesions, local metastasis, bone metastasis, and distant metastasis in a single study and is also a useful modality in recurrence evaluation in PCa patients.

Keywords: F-18 fluorocholine, magnetic resonance imaging, positron emission tomography–computed tomography, prostate cancer, prostate-specific antigen, Tc-99m MDP bone scans

INTRODUCTION
Prostate cancer (PCa) is one of the most common and the second leading causes of death due to cancer in men. The incidence is highest in North America, Australia, Northern, and Western Europe and is rising due to the increase in longevity imparted by better therapeutics and standard of care.[1] The age-adjusted incidence rate in the urban Indian population is about 6–8/100,000.[2] Genetics and environment, including a fatty diet, appears to play role in PCa incidence.[3] The risk doubles with a single affected relative and is even higher with multiple affected relatives.[4] Though generally slow growing in nature, aggressive variation of PCa
cases have also been reported. Bones and lymph nodes are the major sites of metastases from PCa.

Serum prostate-specific antigen (PSA) is an established biochemical marker for early diagnosis as well as follow-up of PCa. Bone scintigraphy, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, and prostate bed biopsy are regularly adopted for localizing the primary tumor and diagnosing the recurrent and metastatic disease. However, conventional imaging modalities such as MRI, giving locoregional anatomical detail, still have inherent limitations in differentiating the postsurgical or radiotherapy (RT) changes from recurrence and fall short in identifying distant metastatic lesions which are common in these patients.

Hybrid functional and structural imaging modalities such as positron emission tomography (PET) have been increasingly used in the diagnosis and follow-up of PCa. F-18 fluorodeoxyglucose (F-18 FDG), being a glucose metabolism marker, has a limited role in PCa due to the relatively low metabolic rate of well differentiated prostate tumors.\(^5\) Alternative radiopharmaceuticals such as C-11 choline (C-11 CCH) and F-18 fluorocholine (F-18 FCH) have also been shown to be useful. Choline is a substrate for the phosphatidylcholine synthesis and a major phospholipid in the cell membranes. Cell membrane biosynthesis is rapid in tumor tissues, and the upregulation of choline kinase activity induced by malignancy results in higher uptake of C-11/F-18 FCH by tumor cells. PET-CT imaging using radiolabeled choline has emerged as a promising method for disease localization in PCa patients with biochemical relapse after primary treatment. The greatest advantage of this method is its capability of assessing the disease recurrence in multiple anatomical sites with higher accuracy than conventional imaging and F-18 FDG PET-CT imaging.\(^5\)

The short half-life of C-11 (20 min) generally precludes late imaging in which the tumor-to-blood ratio is considered optimal for detecting the recurrence. Due to the multifaceted chemistry and short half-life of C-11, the use of C-11 CCH is limited. On the other hand, F-18 FCH is more widely available with a stable biodistribution and a longer half-life (110 min). Moreover, delayed imaging can be performed in order to better differentiate physiological urinary excretion of radiotracer from recurrence. The in vitro uptake and phosphorylation of F-18 FCH are similar to those of C-11 CCH and superior to those of other radiopharmaceuticals.\(^10\) Though new Ga-68-based radiopharmaceuticals including Ga-68 PSMA-11, Ga-68 Bombesin, and Ga-68 RM2 have also been used for imaging of PCa, still F-18 FCH PET-CT is considered an important diagnostic modality according to the NCCN guideline due to its longer half-life.

This prospective study aimed to evaluate the role of F-18 FCH in initial staging and recurrence evaluation in patients with PCa and to compare it with diffusion-weighted (DW) MRI for locoregional involvement and with whole-body bone scan for bone involvement.

**MATERIALS AND METHODS**

A total of 50 male patients with histopathologically proven adenocarcinoma of the prostate, having Gleason score ≥6 and PSA level >4 ng/mL (>0.04 ng/mL in case of radical prostatectomy earlier), were prospectively included in the study, irrespective of the treatment received earlier. Patients having in situ implants (contraindication for MRI) were not included in the study. The study was duly approved by the institutional ethics committee (Ref No: NK/1611/MD/10199-200, dated 3.09.14). Written informed consent was obtained from all the patients included in the study.

**Imaging**

All the 50 patients underwent whole-body Tc-99m methylene-diphosphonate (Tc-99m MDP) bone scintigraphy, F-18 FCH PET-CT, and DW MRI of the pelvic region within a span of 2-3 week of each other, in random order. No special patient preparation was required prior to Tc-99m MDP bone scan and F-18 FCH PET-CT imaging. F-18 FCH PET-CT whole-body images were acquired from vertex to mid-thigh, 45 min postintravenous (IV) injection of approximately 370 MBq of F-18 FCH, using a hybrid PET-CT scanner (Discovery 710, GE Healthcare Milwaukee, USA). Diagnostic CT was acquired first with oral and IV contrast followed by PET imaging (2 min/bed position). Data obtained from F-18 FCH PET-CT were reconstructed using ordered subset expectation maximization iterative reconstruction algorithm with attenuation correction. Transaxial, sagittal, and coronal images were generated after reconstruction and evaluated qualitatively for positive findings. The images were interpreted for the primary lesion, local involvement, pelvic lymph nodes, abdominal lymph nodes, pelvic bone metastasis, and distant metastasis (distant skeletal and lung metastasis) by two experienced nuclear medicine physicians individually. Whole-body bone scan (head to toe) was acquired 3 h postinjection of approximately 740 MBq of Tc-99m MDP on a dedicated dual-headed gamma camera (Infinia Hawkeye, GE Healthcare, Milwaukee, USA). Within 2 weeks (before or after) of the Tc-99m MDP and F-18 FCH PET-CT scans, DW MRI was performed and T2-weighted (TR, 4030 msonds; TE, 100 msonds, FOV, 200
mm; slice thickness, 3 mm) sequences were acquired on a 3T MRI scanner (GE 750 WR) after IV administration of a low-molecular weight gadolinium contrast (0.1 mmol/kg). The MRI of the pelvis was interpreted by a radiologist blinded to clinical and Tc-99m MDP/F-18 FCH PET-CT findings. The data were interpreted for the primary lesion, recurrence, pelvic lymph nodes, and pelvic bones involvement.

Data analysis
The uptake of F-18 FCH was assessed from a circular region of interest over the entire lesion/lesions and expressed as the maximum standardized uptake value (SUVmax). The data thus obtained were compared with the MRI data in terms of the primary lesion and locoregional lymph nodes and pelvic bone involvement. The bone involvement was also compared with Tc-99m MDP bone scan. Involvement of any extra bony lesion was also ruled out. The data were assessed using the number of extra lesions found in either scan.

Statistical analysis
The statistical analysis was carried out using the Statistical Package for the Social Sciences, version 22.0 for Windows (SPSS Inc., Chicago, IL, USA). Descriptive statistics such as mean and range were used to describe demographics and clinical profile of all patients. For the primary site lesion core biopsy findings were considered as gold standard. Pelvic MRI was compared to the regional F-18 FCH PET-CT findings and Tc-99m MDP bone scan of the pelvic region. The whole-body F-18 FCH PET-CT scan was compared to the whole-body bone scan for any extra lesion found in any of them. Agreement between MRI, FCH, and bone scintigraphy was measured using the kappa test. McNemar’s test was applied for comparing MRI, FCH, and Tc-99m MDP bone scan. Involvement of any extra bony lesion was also ruled out. The data were assessed using the number of extra lesions found in either scan.

RESULTS
A total of 50 patients with mean age 66.8 ± 6.8 years were enrolled in the study, out of which 17 patients were for initial staging, and 33 patients were for recurrence evaluation (posttreatment with either of hormonal therapy/RT/chemotherapy/orchidectomy/prostatectomy alone or in combination). The mean value of PSA level was 43 ng/ml, ranging from 0.08 to 947 ng/ml. The demographic and clinical characteristics are shown in Table 1.

Comparison of regional fluorocholine positron emission tomography–computed tomography and pelvic magnetic resonance imaging for primary detection/recurrence at primary site evaluation
All the 17 patients studied for initial staging were observed to be positive for primary disease on both F-18 FCH PET-CT and pelvic MRI. The mean SUVmax of the primary lesion was found to be 5.8 (range 2.1–11.2). The sensitivity of 100% was observed on both F-18 FCH PET-CT and pelvic MRI to detect primary lesion. Since there was no negative patient on both modalities, specificity could not be determined. However, MRI showed a better anatomical assessment of the primary lesion in the prostate gland with respect to local extent of the lesion, capsular involvement, seminal vesicles, and neurovascular involvement in comparison to F-18 FCH PET-CT scan.

In patients with suspected local recurrence, 26/33 versus 25/33 were found to be positive on F-18 FCH and pelvic MRI, respectively [Table 2]. Of these 26 patients with local recurrence on F-18 FCH PET-CT, 10 patients had prostatectomy, 4 patients had taken RT, 3 patients had orchidectomy, 6 patients were on hormonal therapy, and 3 patients had combination therapy (hormonal, RT,

| Table 1: Demographics and clinical characteristics of all patients |
|---------------------------------------------------------------|
| **Characteristics**                                             | **Initial staging** | **Restaging** |
| Number of patients (n=50)                                      | 17                | 33            |
| Age (years)                                                   | 67.6              | 66.3          |
| Mean                                                          | 55-75             | 51-77         |
| PSA level at the time of MRI/PET/bone scan (ng/ml)            | 16.9              | 57            |
| Mean                                                          | 4.48-67.7, 0.08-947.64 |
| Gleason score at the time of MRI/PET/bone scan                | 8                 | 7             |
| Mean                                                          | 6-10              | 6-9           |
| SUVmax of primary lesion                                      | 5.8               | 6.3           |
| Range                                                         | 2.1-11.2          | 1.2-16.9      |

PSA: Prostate-specific antigen, MRI: Magnetic resonance imaging, PET: Positron emission tomography, SUVmax: Maximum standardized uptake value

| Table 2: Comparison of F-18 fluorocholine positron emission tomography–computed tomography and diffusion-weighted magnetic resonance imaging with histopathology in patients for initial staging and recurrent disease at primary site |
|---------------------------------------------------------------|
| **Test** | **Initial Staging (n=17)** | **Recurrence (n=33)** |
| PET/CT |   DW-MRI | PET/CT | DW-MRI |
| Positive | 17 | 17 | 26 | 26 |
| Negative | 0 | 0 | 07 | 7 |
| True positive | 17 | 17 | 26 | 25 |
| False positive | 0 | 0 | 0 | 1 |
| True negative | 0 | 0 | 05 | 4 |
| False negative | 0 | 0 | 02 | 3 |
| Sensitivity (%) | 100 | 100 | 92.85 | 89.28 |
| Specificity (%) | NA | NA | 100 | 80 |

FCH: Fluorocholine, DW-MRI: Diffusion-weighted magnetic resonance imaging, PET/CT: Positron emission tomography–computed tomography, NA: Not available
chemotherapy). The mean SUVmax of the suspected lesion was found to be 6.3 (range 1.2–16.9). The sensitivity and specificity were 92.8% versus 89.2% and 100 versus 80% for F-18 FCH PET/CT and MRI, respectively. The positive predictive value (PPV) for recurrent disease in the F-18 FCH PET-CT was found to be 100%, while in pelvic MRI PPV was 96%.

Comparison of pelvic magnetic resonance imaging and regional fluorocholine positron emission tomography–computed tomography for pelvic lymph node metastasis

MRI and F-18 FCH PET-CT were able to detect metastatic pelvic LN in 17 versus 25 patients, respectively. Of these patients, 2 versus 7 patients were for initial staging and 15 versus 18 were with recurrent disease, on MRI and F-18 FCH PET-CT, respectively. The subcentimetric lymph nodes which were not detected on MRI showed increased tracer uptake in F-18 FCH PET-CT scan [Figures 1 and 2]. Good agreement was noticed between these two modalities with kappa value being 0.680. The mean SUVmax of the pelvic LN positive on MRI scan was 5.9 ± 2.5 (range 2.0–9.5), while the mean SUVmax of the LN negative on pelvic MRI was 5.1 ± 2.4 (range 2.2–10). Significant statistical difference ($P = 0.008$) was observed on McNemar’s comparison test in the detection of pelvic LN on F-18 FCH PET-CT and MRI.

In addition, abdominal lymph node metastasis was observed in 12/50 (24%) patients on the whole-body F-18 FCH PET-CT scan. Lung nodules suggesting metastasis were also found in 2/50 (4%) patients. The histopathological examination of these lung nodules came out to be adenocarcinoma metastasis. Table 3 shows the comparative findings and results between three imaging modalities.

Table 3: Comparative evaluation of various lesions in magnetic resonance imaging, F-18 fluorocholine positron emission tomography–computed tomography, and Tc-99m methylene-diphosphonate bone scan

| Site of involvement          | Number of patients (number of lesions) |
|------------------------------|----------------------------------------|
|                              | Initial staging                         |
| Pelvic lymph nodes           |                                        |
| MRI                          | 2                                      |
| F-18 FCH PET/CT              | 7                                      |
| Pelvic bone metastasis       |                                        |
| MRI                          | 1                                      |
| Tc-99m MDP                   | 1                                      |
| F-18 FCH PET/CT              | 2                                      |
| Other sites of bone metastasis|                                        |
| Tc-99m MDP                   | 2 (8)                                  |
| F-18 FCH PET/CT              | 2 (9)                                  |
| Additional sites on F-18 FCH |                                        |
| Abdominal lymph node         | 2                                      |
| Lung lesion                  | 0                                      |

FCH: Fluorocholine, MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography–computed tomography, MDP: Methylene-diphosphonate

Figure 1: Whole-body F-18 fluorocholine positron emission tomography–computed tomography (a-d), regional magnetic resonance imaging (e and f), and bone scan (g) for initial staging of a 64-year-old man with prostate-specific antigen of 8.16 ng/ml. Maximum intensity projection image (a) shows foci of abnormal uptake in thoracic and pelvic regions. The corresponding fused transaxial positron emission tomography–computed tomography image (b) shows intense radiotracer uptake (maximum standardized uptake value 11.2) in the nodular lesion in right peripheral zone of prostate gland. Moderate F-18 fluorocholine is also noted in right internal iliac and hilar lymph nodes (c and d respectively). CE-magnetic resonance imaging image (e) shows early enhancement focus in the right peripheral zone and diffusion restriction in the same region on DWI-magnetic resonance imaging image (f). Tc-99m methylene-diphosphonate whole-body bone scan (g) does not show any metastasis. The mild focal uptake on MIP image on the right side of the head near midline corresponded to choroid plexus in transaxial images and is physiological uptake. Radical prostatectomy specimen on histologic evaluation showed adenocarcinoma in the right lobe while left lobe was free of tumor.
Comparison of pelvic magnetic resonance imaging and pelvic fluorocholine positron emission tomography–computed tomography for bone involvement

A total of 9/50 patients (8 patients with recurrent disease) were found to have pelvic bone metastases on MRI, while F-18 FCH PET-CT was positive for pelvic bone metastases in 11/50 patients (9 with recurrent disease); good agreement was found between these two modalities (kappa value 0.875). The mean SUVmax of the bony lesions which were positive on MRI scan was 9.9 ± 3.7 (range 5.2–15.2). The mean SUVmax of the skeletal lesions which were negative on pelvic MRI was 6.4 ± 2.1 (range 3.4–9.3). Comparison of pelvic skeletal metastasis on MRI and F-18 FCH PET-CT using McNemar’s test showed no statistical difference ($P = 0.5$, nonsignificant) between the two modalities for pelvic bone involvement.

Both, Tc-99m MDP bone scan and regional MRI showed concordant lesions for pelvic bone metastasis in 1/17 patients for initial staging versus 8/33 patients in recurrent disease, respectively.

Comparison whole-body Tc-99 m methylene-diphosphonate bone scan and F-18 fluorocholine positron emission tomography–computed tomography for skeletal involvement

Pelvic bone lesions were identified in 10/50 (9 with recurrent disease) versus 11/50 (9 with recurrent disease) patients in Tc-99m MDP bone scan and F-18 FCH PET-CT, respectively. A representative image is depicted in Figure 3.

Metastasis at other bone sites was detected in 2/17 patients with primary disease on both bone scan and FCH PET-CT. However, 12/33 versus 13/33 patients with recurrence were found to be positive on Tc-99m MDP and F-18 FCH imaging, respectively. Good agreement was observed between these two modalities (kappa value 0.947). The mean SUVmax of the skeletal lesions was 8.4 ± 4.01 (range, 3.2–15.2). A total of 8 concordant lesions were detected in initial staging patients in both modalities. However, one additional lesion was detected on F-18 FCH PET-CT. In case of patients with recurrent disease, 34 concordant lesions were observed in both modalities. F-18 FCH PET-CT was able to detect 12 additional metastatic lesions as compared to bone scan. Furthermore, in 3/33 patients, widespread skeletal metastasis was observed in both imaging modalities. McNemar’s test showed no statistical significance difference between two modalities for distant skeletal metastasis ($P = 1.00$, nonsignificant).

DISCUSSION

PCa is the second most common malignancy affecting men in old age. Serum PSA is a screening method for early diagnosis as well as follow-up. Pelvic MRI is the standard
of care to look for the local extent of the primary tumor, seminal vesicle involvement, neurovascular involvement, and local lymph node metastasis. Tc-99 m MDP whole-body bone scan is also performed to detect bony metastases in advanced PCa. Tumor recurrence is usually evaluated by PSA as its elevation precedes the detectable clinical recurrence. LN staging is crucial for optimal management in patients with PCa. Multiparametric MRI has been described in many studies to be superior to both the modalities in the exact localization of the primary lesion within the prostate gland. Turkbey et al. showed that multiparametric MRI improves the performance for detection of primary, local infiltration, and seminal vesicle involvement.\textsuperscript{11}

The diagnosis of a malignant focus in prostate gland is usually done with TRUS-guided biopsy in patients with elevated PSA level. Falsenegative biopsies are common, leading to multiple sittings. Hence, a noninvasive modality which localizes the primary site for taking biopsy is very helpful in limiting the need for multiple biopsies and reducing the false-negative results. The proximity of the urinary bladder and low metabolic activity of PCa makes F-18 FDG PET-CT a disparaging imaging modality for staging or recurrence evaluation of PCa.\textsuperscript{12} The excreted radiotracer in the urinary bladder may mask the primary lesion and local extent of the lesion. Due to these drawbacks of F-18 FDG PET-CT for imaging PCa, other tracers such as C-11 CCH, F-18 FCH, Ga-68 PSMA, and many more are being used.

F-18 FCH PET-CT is very helpful in determining the extent of the primary lesion and the multiplicity of the lesion inside the prostate gland.\textsuperscript{13} The reported sensitivity and specificity for detecting the primary lesion ranges from 64\% to 100\% and 47\%-90\%, respectively.\textsuperscript{14-16} In the present study, the sensitivity and specificity for detecting the lesion at primary site in recurrent disease using F-18 FCH PET-CT have been found to be 92.8\% and 100\%, respectively, which is in good agreement with the literature. A study by Treglia et al. revealed superiority of Ga-68 PSMA over F-18 FCH in patients with biochemical recurrent PCa lesions with PSA levels ≤1 ng/ml. However, same trend was not observed in patients with PSA levels >1 ng/ml.\textsuperscript{17}

For lymph node metastasis, the sensitivity of MRI has been reported to be 80\%-90\%.\textsuperscript{18} However, MRI is not very useful in detecting the subcentimetric lymph nodes having metastatic activity. The reported sensitivity and specificity of F-18 FCH PET-CT imaging is more than 90\%.\textsuperscript{19,20} Similar results were observed in our study, F-18 FCH detected 16\% more pelvic LN compared to MRI.

Whole-body bone scan with Tc-99 m MDP is still the most common examination for evaluating bone metastases in patients with very high risk, high risk, and unfavorable intermediate risk if lesion is T2 and PSA >1 ng/ml.\textsuperscript{21} F-18 FCH PET-CT has better sensitivity and specificity because of high spatial resolution and higher target-to-background ratios.
of the PET-CT. However, a recent meta-analysis by Zhou et al. suggested overall superiority of Ga-68 PSMA over F-18 FCH and Tc-99 m bone scan in the detection of bone lesions in PCa. In the present study, F-18 FCH PET-CT was observed to detect 16 additional metastatic lesions at distant sites (other than pelvic bone) as compared to Tc-99 m MDP bone scan indicating its superiority over conventional bone scan. Beauregard et al. in a similar study of 16 patients reported a higher sensitivity for F-18 FCH PET-CT than conventional imaging modalities (100 vs. 67%) for the detection of bone metastases.

F-18 FCH PET-CT has been also employed to assess for local recurrence or metastases in PCa in the setting of biochemical recurrence with sensitivities from 42 to 96%. Conventional imaging such as CT, MRI, and the bone scan have different limitations and a low-to-moderate sensitivity. A recent multicenter comparison study suggested high detection rates of extra prostate fossa lesions with both F-18 FCH and Ga-68 PSMA in patients with rising PSA post radical prostatectomy with negative/equivocal MRI. In this study, additional abdominal lymph nodes and lung lesions were detected in 24% and 4% of patients, respectively, in F-18 FCH PET-CT. However, no additional improvement in lesion/LN detection was observed in patients with biochemical recurrent PCa, when whole-body MRI was performed along with F-18 FCH/Ga-68 PSMA. Chondrogiannis et al. reported a higher positive detection rate for F-18 FCH PET-CT for restaging. A meta-analysis by Evangelista et al. (study including 19 studies with a total of 1555 patients) for the role of F-18 FCH PET-CT for restaging in PCa recurrence reported a sensitivity of 85.6% and specificity of 92.6%. Vees et al. showed the usefulness of F-18 FCH PET-CT in the evaluation of recurrence in a small population (n = 22) of PCa patients who were referred for adjuvant therapy with PSA levels <1 ng/ml with a rate of 55%. Our result data also showed the supremacy of F-18 FCH PET-CT scan over MRI and Tc-99 m bone scan in detecting pelvic lymph nodes, pelvic bone, and distant metastasis.

CONCLUSION

F-18 FCH PET-CT is a useful modality in recurrence evaluation and initial staging of PCa patients. Another advantage of PET-CT is that in a single study, we can detect primary lesions for TRUS guided biopsy, local metastasis, bone metastasis, and distant metastasis like lung and brain. Although Ga-68 PSMA PET/CT has become the favored modality for imaging PCa, F-18 FCH may be useful at places with in-house cyclotron facility but nonavailability of Ge-68/Ga-68 generators.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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