Original Article

18-Fluoride labeled sodium fluoride positron emission tomography with computer tomography: the impact of pretreatment staging in intermediate- and high-risk prostate cancer

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1. Introduction

Aside from skin cancers, prostate cancer is the most commonly diagnosed cancer in Australia. Since the era of prostate specific antigen (PSA) screening, there has been an increasing incidence of organ-confined disease. Locally advanced and metastatic prostate cancer is still found in up to 22% of men at initial diagnosis, and bony metastases (BM) are detected in 4% of all men with current staging modalities. For patients with metastatic disease, treatment is focused on systemic therapies such as androgen-deprivation therapy, androgen blockage, and chemotherapy. This contrasts significantly to organ-confined disease which may be treated with...
Positron emission tomography with computer tomography (PET/CT) has become the gold-standard imaging modality for staging many cancers. The most common tracer, fluorodeoxyglucose ($^{18}$F-FDG), has, however, failed to afford the same benefits in staging prostate cancer as it has with other nonprostate malignancies. The use of $^{68}$Ga-prostate-specific membrane antigen (PSMA) PET/CT and related radiopharmaceuticals for the detection of metastatic prostate cancer is increasing but access and cost remains a barrier in many parts of the world.

$^{18}$-Fluoride labeled sodium fluoride (Na-$^{18}$-F) is a bone-seeking tracer with similar biological properties to Tc-bisphosphonates used in WBBS. It is the greater accumulation of Na-$^{18}$-F around rapidly metabolizing bone (such as metastatic deposits) that forms the basis for the detection of metastatic disease. Na-$^{18}$-F is more readily available than other tracers and has been used in PET imaging for metastatic cancers such as sarcoma, breast, and non–small-cell lung cancer and in these malignancies; it has been shown to be highly sensitive and specific. The improved image quality and intrinsic 3D information that PET imaging provides along with the anatomical localization of the simultaneous CT scan may be expected to provide superior diagnostic information to WBBS in prostate cancer.

The value that a new imaging modality provides needs to be weighed against the potential risks and cost to the patient. Hicks et al examined the use of Na-$^{18}$-F PET/CT in restaging non–small-cell lung cancer. In this seminal study, they described “levels of impact” that the modality had on the patient’s care and found a significant difference in subsequent management and survival. It remains unclear whether Na-$^{18}$-F PET/CT could play an added role in prostate cancer staging. While improved sensitivity and specificity has been demonstrated in other cancers, these favorable characteristics have not been shown to translate into changes in management and improved patient outcomes in prostate cancer.

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We conducted a pilot study directly comparing the impact that Na-$^{18}$-F PET/CT had on the management plans of men with newly diagnosed intermediate- and high-risk prostate cancer.

### 2. Materials and Methods

Men aged 18 years and above with newly diagnosed, untreated, biopsy-confirmed intermediate- and high-risk prostate cancer were eligible for this study. Risk stratification was based on D’Amico’s classification of prostate cancer: intermediate risk (Gleason score $\geq 6$, PSA $<10$, and $<20$ ng/ml) and high risk ($\geq 3$, Gleason score $\geq 8$, or PSA level $>20$ ng/ml). Men were ineligible if they had a history of other cancers (except for non–melanoma skin cancer), had undergone previous treatment for prostate cancer, or were unable to provide informed consent.

Subjects were recruited prospectively from a single private institution in Adelaide, South Australia. Men who met the inclusion criteria were identified by the treating urologist and recruitment was performed in a sequential manner. Funding for this pilot study was provided for 20 Na-$^{18}$-F PET/CT scans and this defined our subject number. Ethics approval was provided by the local hospital Human Research Ethics Committee.

All subjects were assessed with a medical history, physical examination including digital rectal exam, PSA level, and transrectal ultrasound guided prostate biopsy. Subjects underwent Na-$^{18}$-F PET/CT (Siemens Biograph or Philips Gemini PET/CT scanner), 99mTc-MDP WBBS, and a serum PSA concentration test within one week of each other. All men received a standard 200MBq intravenous dose of Na-$^{18}$-F and underwent a predetermined, standardized field of view analysis from cranium to feet PET/CT. Participants were observed for any medical or procedural complications of the Na-$^{18}$-F injection. The bone scan followed standardized local protocols already in existence with whole body sweeps and multiple localized views.

The Na-$^{18}$-F generated from the study was manufactured under Good manufacturing practice (GMP) at the South Australian Health and Medical Research Institute and sold as Na-$^{18}$-F Fluoride (18F) Solution for radiolabelling (Ph Eur monograph 2309). Equipment used was validated and tested in adherence to regulations stated in Pharmaceutical Inspection Co-operation Scheme (PIC/S) guide.

Images from both the PET/CT and WBBS were interpreted by two experienced nuclear medicine specialists. Scans were de-identified and reported in real time to avoid delay in management decisions by the treating urologists. At no stage the PET/CT and WBBS from the same patient was reported by the same physician. Criteria for malignancy were of the opinion of the reporting doctor. A final opinion was designated as: definite metastatic disease, probably metastatic disease, probably not metastatic disease, and normal.

After reviewing the subject’s history and WBBS, urologists documented the TNM stage and detailed their proposed management plan and intent. This was recorded as the pre-PET management plan. Following this, the results of the PET/CT were reviewed, and a final TNM stage and management decision was documented. This was recorded as the post-PET management plan.

The level of impact that the Na-$^{18}$-F PET/CT had on the patient’s management was measured by a validated scoring system. (see Table 1).

We examined the level of impact that the additional imaging modality had on the subsequent management plan and treatment intent of the treating urologist. Results are described in narrative and table form, and for continuous data, mean and standard deviation were calculated.

| Impact level | Example |
|--------------|---------|
| High impact  | When the treatment intent or modality was changed (e.g., from curative to palliative treatment or from surgery to radiotherapy or from treatment to no treatment). |
| Medium impact| When the method of treatment delivery was changed (e.g., a change in radiation treatment volume, radiation modality, radiation field). |
| Low impact   | When the PET results did not indicate a need for change |
| No impact    | When the management chosen conflicted with post-PET disease extent and was believed to be inappropriate on the basis of a synthesis of all available information. |

PET, positron emission tomography.
3. Results

Twenty men were recruited for this pilot study. Twelve men had intermediate-risk prostate cancer and eight men had high-risk prostate cancer. The mean age of men was 66.5 years (range: 55–73). The mean PSA was 7.5 (range: 3.1–19). The majority of men with intermediate-risk disease had Gleason 3 + 4 prostate cancer, whilst the majority of men with high-risk disease had Gleason 4 + 4 prostate cancer. Subset analysis by risk category is found in Table 2.

There were no medical or technical complications associated with the additional Na-18-F PET/CT, and all images were deemed of high quality by those reporting.

In 18 men (90%), the WBBS and Na-18-F PET/CT were both reported as normal. In one man (5%), the WBBS demonstrated definite metastatic disease which was similarly reported on the Na-18-F PET/CT. One man (5%) had a normal WBBS reported; however, the Na-18-F PET/CT was reported as definite metastatic disease. Subsequently, in 19 men (95%), the results of the two scans were congruent and the addition of the Na-18-F PET/CT scan demonstrated a low impact on their management. In one man (5%), the addition of the Na-18-F PET/CT had a high impact as treatment type changed from surgery to systemic therapy and intent was altered from potentially curative to potentially palliative (Fig. 1).

4. Discussion

The importance of staging prostate cancer is well established, and the current use of WBBS is accepted as category A level of evidence. However, with its wide range of reported sensitivities and specificities and the development of newer technologies it is unclear whether this remains the most appropriate staging modality. It is likely that WBBS will be superseded by seemingly superior imaging modality such as Na-18-F or 68Ga-PSMA PET/CT, but too often newer technologies are accepted as the new orthodox without the supporting evidence for change. Buxton's Law states “it is always too early (for rigorous evaluation) until, unfortunately, it is too late”. This pilot study aimed to assess the feasibility of a larger study to examine whether a change to newer technology

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Table 2

| Age, PSA, and Gleason score of men enrolled. |
|--------------------------------------------|
| **All men** | n = 20 |
| Age (mean, SD) | 66.5 (4.7) |
| PSA (mean, SD) | 7.5 (3.5) |
| Gleason score | |
| Gleason 7 (3 + 4) | 10 (50%) |
| Gleason 7 (4 + 3) | 5 (25%) |
| Gleason 8 | 5 (25%) |

| Age, PSA, and Gleason score of men with high risk prostate cancer |
|---------------------------------------------------------------|
| n = 8 |
| Age (mean, SD) | 67.4 (6.9) |
| PSA (mean, SD) | 9.04 (5.0) |
| Gleason score | |
| Gleason 7 (3 + 4) | 2 (25%) |
| Gleason 7 (4 + 3) | 1 (12.5%) |
| Gleason 8 | 5 (62.5%) |

| Age, PSA, and Gleason score of men with intermediate risk prostate cancer |
|---------------------------------------------------------------|
| n = 12 |
| Age (mean, SD) | 65.1 (2.7) |
| PSA (mean, SD) | 6.47 (1.6) |
| Gleason score | |
| Gleason 7 (3 + 4) | 8 (66.7%) |
| Gleason 7 (4 + 3) | 4 (33.8%) |

PSA, prostate specific antigen; SD, standard deviation.

Fig. 1. Flow diagram demonstrating the level of impact that Na-18-F PET/CT had on the management of men with medium- and high-risk prostate cancer. BM, bony metastasis; PET/CT, positron emission tomography with computer tomography; WBBS, whole body bone scan.
results in a significant change of management in men being staged for prostate cancer.

To the best of our knowledge, this is the first study that has prospectively enrolled men with both intermediate- and high-risk prostate cancer to undergo Na-18-F PET/CT and WBBS imaging during their initial staging. Even Sapir et al assessed the detection of bone metastases in patients with high-risk prostate cancer (PSA > 20 or Gleason score ≥8 or nonspecific sclerotic lesions on CT) against 99mTc-MDP planar bone scintigraphy, single and multi field-of-view Single-photon emission computed tomography (SPECT), Na-18-F PET, and Na-18-F PET/CT. Of 44 men recruited, 25 were newly diagnosed cases. Eleven men were found to have BM on staging; 5 (45.4%) of them did not have BM detected on 99mTc-MDP planar bone scintigraphy. This resulted in a change of management in 20% of men suggesting the additional imaging modality added value and may beneficially impact the management of men with high-risk prostate cancer.

The sensitivity, specificity, positive, and negative predictive value of Na-18-F PET/CT has been reported as up to 100% although this number should be viewed with some skepticism. In a retrospective multicentre audit of 8328 Na-18-F PET/CT scans, 1024 of this number should be viewed with some skepticism. In a retrospective multicentre audit of 8328 Na-18-F PET/CT scans, 1024 of this number should be viewed with some skepticism. In a retrospective multicentre audit of 8328 Na-18-F PET/CT scans, 1024 of this number should be viewed with some skepticism. In a retrospective multicentre audit of 8328 Na-18-F PET/CT...
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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2017.12.002

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