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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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ABSTRACT

Background: 18-Fluoride labeled sodium fluoride (Na-18-F) positron emission tomography with computer tomography (PET/CT) has a better sensitivity and specificity than whole body bone scan (WBBS) in detecting osseous metastatic prostate cancer. We performed a pilot study of 20 men to examine what level of impact Na-18-F PET/CT has on management plans when used for staging newly diagnosed prostate cancer.

Materials and methods: Twenty men were prospectively enrolled into the study in South Australia. Men were eligible if they had newly diagnosed, untreated, and biopsy-confirmed intermediate- or high-risk prostate cancer (D'Amico classification). WBBS and Na-18-F PET/CT scans were performed within 1 week of each other. Following review of the WBBS, treatment type and intent was documented by the treating urologist. The Na-18-F PET/CT scan was then reviewed. The impact of the Na-18-F PET/CT was measured on whether treatment modality or intent was subsequently altered: high impact = treatment intent or modality was changed; medium impact = treatment modality was modified; low impact = no change in treatment.

Results: In 18 men (90%), the WBBS and Na-18-F PET/CT were negative for osseous metastases. In one man (5%), the WBBS demonstrated widespread osseous metastases which were similarly demonstrated on the Na-18-F PET/CT. One man (5%) had a normal WBBS; however, the Na-18-F PET/CT demonstrated widespread osseous metastases. 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 management. In one man (5%), the addition of the Na-18-F PET/CT had a high impact as treatment type and intent was altered.

Conclusions: Our pilot study is the first of its kind in Australia, and our findings suggest that Na-18-F PET/CT is a safe and feasible modality for staging prostate cancer. However, its true impact on prostate cancer management warrants further investigation.

1. Introduction

Aside from skin cancers, prostate cancer is the most commonly diagnosed cancer in Australia.[1] Since the era of prostate specific antigen (PSA) screening, there has been an increasing incidence of organ-confined disease.[2] Locally advanced and metastatic prostate cancer is still found in up to 22% of men at initial diagnosis[3], and bony metastases (BMs) are detected in 4% of all men with current staging modalities.[4] 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

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surgery or radiotherapy alone.[5] Metastatic disease impacts significantly on prognosis (median survival, 42 months[6]) and thus early diagnosis is crucial for prognostication and implementation of the appropriate management plans for disease and symptom control, as well as quality of life.

To date, 99mTc-bisphosphonate planar bone scintigraphy (whole body bone scan—WBBS) is the most frequently used imaging modality for detecting BM and remains the method of choice within the major international urological association guidelines.[7] Because not all prostate cancers pose the same risk for metastatic disease at diagnosis, most guidelines advise only performing WBBS in men with intermediate-risk to high-risk prostate cancer features.[7] In this group, however, WBBS has a sensitivity, specificity, positive predictive value, and negative predictive value of just 57%, 57%, 59%, and 55%, respectively.[8, 9]

Positron emission tomography with computer tomography (PET/CT) has become the gold-standard imaging modality for staging many cancers. The most common tracer, ^{18}F-fluorodeoxyglucose (^{18}F-FDG), however, has failed to afford the same benefits in staging prostate cancer as it has with other nonprostate malignancies.[4] The use of ^{68}Ga-prostate-specific membrane antigen (PSMA) PET/CT and related radiopharmaceuticals for the detection of metastatic prostatic cancer is increasing but access and cost remains a barrier in many parts of the world.[8, 10, 11]

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.[12–15] 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.[15] 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.[10, 15, 16] It is unclear whether Na-18-F PET/CT will detect more men with metastatic prostate cancer or whether it will just detect more lesions when compared with WBBS.

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 (cT2b, Gleason score of 7 or PSA >10 and ≤20 ng/ml) and high risk (cT2c—3a, Gleason score ≥8, or PSA level >20 ng/ml)[17]. 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 Phillips 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 of 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 tested as stated in the British Pharmacopoeia 2012: Fluoride (^{18}F) 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 deidentified 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.[15] (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.

Table 1
Description of impact on management.

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.

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	No. (%)
Gleason 7 (3 + 4)	10 (50%)
Gleason 7 (4 + 3)	5 (25%)
Gleason 8	5 (25%)
Men with high risk prostate cancer	$n = 8$
Age (mean, SD)	67.4 (6.9)
PSA (mean, SD)	9.04 (5.0)
Gleason score	No. (%)
Gleason 7 (3 + 4)	2 (25%)
Gleason 7 (4 + 3)	1 (12.5%)
Gleason 8	5 (62.5%)
Men with intermediate risk prostate cancer	$n = 12$
Age (mean, SD)	65.1 (2.7)
PSA (mean, SD)	6.47 (1.6)
Gleason score	No. (%)
Gleason 7 (3 + 4)	8 (66.7%)
Gleason 7 (4 + 3)	4 (33.3%)

PSA, prostate specific antigen; SD, standard deviation.

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.[5] 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 ^{68}Ga-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".[18] This pilot study aimed to assess the feasibility of a larger study to examine whether a change to newer technology

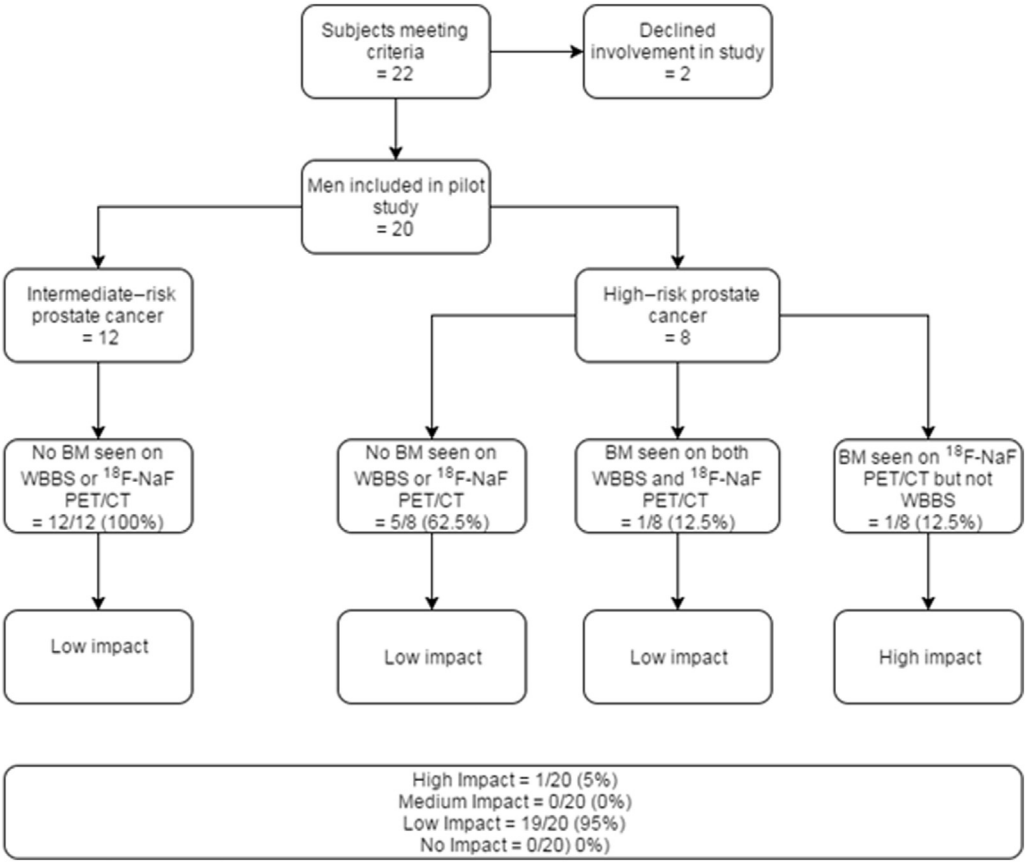

Fig. 1. Flow diagram demonstrating the level of impact that Na-18-F PET/CT had on the management of men with medium- and high-risk prostate cancer. BM, bony metastasis; PET/CT, positron emission tomography with computer tomography; WBBS, whole body bone scan.

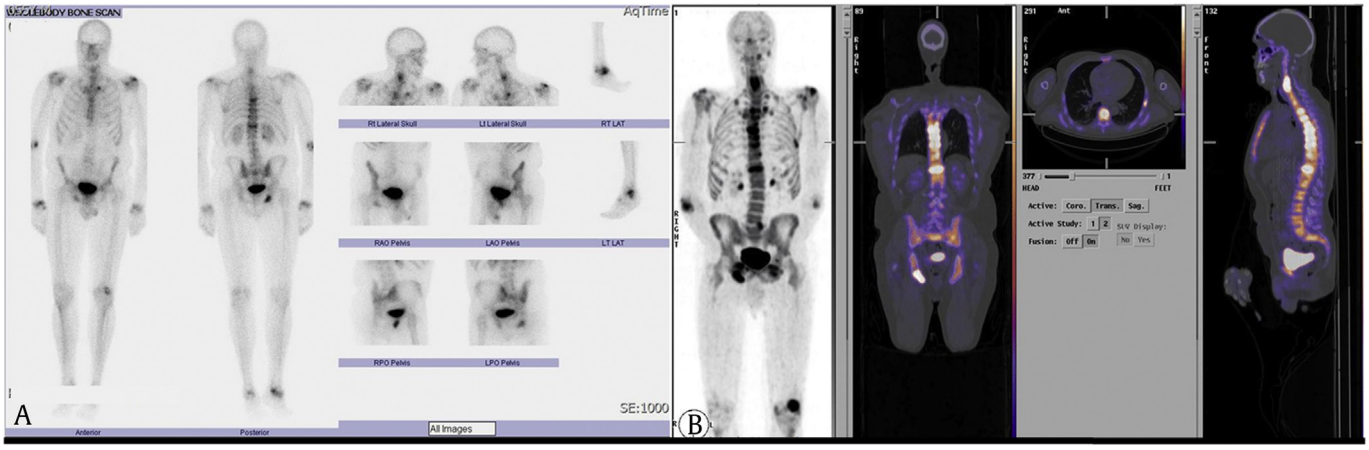

Fig. 2. (A) WBBS with widespread foci of increased uptake in the skeleton. Review of the low-dose CT showed corresponding degenerative changes favoring nonmetastatic uptake. (B) Na-18-F PET/CT showing extensive metastatic disease involving the axial skeleton. PET/CT, positron emission tomography with computer tomography; WBBS, whole body bone scan.

resulted 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 $\geq$ 20 or Gleason score $\geq$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.[8] 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%[8] although this number should be viewed with some skepticism. In a retrospective multicentre audit of 8328 Na-18-F PET/CT scans, 1024 of which were performed for initial staging of prostate cancer, a change in management occurred in 12—47% of cases (depending on definition).[16] Wondergem et al identified eight studies that examined the use of Na-18-F PET/CT in prostate cancer, and on a lesion basis, the pool weighted sensitivity and specificity was 88.6% and 90.7%, respectively—superior detection rates when compared to conventional WBBS. Variation in reference standards or markers of malignant lesions versus benign lesions on imaging confound the results. Despite this, a change in management occurred in up to 12% of patients.[4]

The treatment of all cancers has become more complex than when many conventional staging modalities were introduced. It is intuitive to think that the use of improved staging methods should help tailor better treatment regimens, and this has been demonstrated in other cancers.[15, 19, 20] The introduction of new technologies needs to be critically assessed, however, based on the potential benefits and harms to the patient as well as the cost to the society. While no formal analysis could be performed during this pilot study, the radiopharmaceutical for PET/CT used is currently more expensive and additional cost to the PET/CT scanners exceed those of a standard gamma camera.

This pilot study demonstrated that Na-18-F PET/CT imaging is safe and images obtained are of high quality with no additional training required to aid interpretation. Only one man (5%) had his management changed. Interestingly, upon review, there is a suspicion of a metastatic deposit in the ischial tuberosity on WBBS which had been reported as enthesitis (Fig. 2) and as such the change in management must be accepted. It does, however, illustrate the potential for interobserver variation and levels of confidence in reporting within radiology. Overall, our results show a slightly lower level of impact than previous studies[4, 8]. A larger prospective study would add certainty to the potential impact and advantages of Na-18-F PET/CT.

Apart from being a pilot study, several limitations exist within this study. Men enrolled represent a narrow population with relatively low PSA levels and similar demographics. Bone metastases are seen more frequently in men with higher PSA levels and it would be interesting to evaluate the change in management seen in men who were at a higher risk of metastatic disease. The diagnosis of BM on both WBBS and Na-18-F PET/CT was based on the experienced nuclear physicians' interpretation of the scan. It is neither ethically nor practically possible to confirm the diagnosis in every lesion seen.

There was no follow-up in this trial and therefore outcomes were not assessed.

5. Conclusion

In this pilot study, it has been demonstrated that Na-18-F PET/CT scans are well-tolerated by patients and deliver high-quality images for specialist interpretation. There is insufficient evidence in this pilot to suggest that Na-18-F PET/CT has a high impact on the management plan when compared to WBBS in the staging of new, untreated, intermediate- and high-risk prostate cancer.

We advocate for the adoption of multicentre collaborative approaches to assess new imaging technology as to ensure safety, efficacy, and critical review prior to widespread adoption.

Conflicts of interest

Neither authors nor the institution received any payment or services from a third party for any aspect of the submitted work and report no conflict of interest. There are no reported financial relationships with any entities by any of the authors. There are no patents pending based upon this publication. There are no relationships or activities that readers could perceive to have influenced, or give the appearance of influencing, the submitted work.

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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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