Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study

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Summary

Background Conventional imaging using CT and bone scan has insufficient sensitivity when staging men with high-risk localised prostate cancer. We aimed to investigate whether novel imaging using prostate-specific membrane antigen (PSMA) PET-CT might improve accuracy and affect management.

Methods In this multicentre, two-arm, randomised study, we recruited men with biopsy-proven prostate cancer and high-risk features at ten hospitals in Australia. Patients were randomly assigned to conventional imaging with CT and bone scanning or gallium-68 PSMA-11 PET-CT. First-line imaging was done within 21 days following randomisation. Patients crossed over unless three or more distant metastases were identified. The primary outcome was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease defined by the receiver-operating curve using a predefined reference-standard including histopathology, imaging, and biochemistry at 6-month follow-up. This trial is registered with the Australian New Zealand Clinical Trials Registry, ANZCTR12617000005358.

Findings From March 22, 2017, to Nov 2, 2018, 339 men were assessed for eligibility and 302 men were randomly assigned. 152 (50%) men were randomly assigned to conventional imaging and 150 (50%) to PSMA PET-CT. Of 295 (98%) men with follow-up, 87 (30%) had pelvic nodal or distant metastatic disease. PSMA PET-CT had a 27% (95% CI 23–31) greater accuracy than that of conventional imaging (92% [88–95] *vs* 65% [60–69]; p<0·0001). We found a lower sensitivity (38% [24–52] *vs* 85% [74–96]) and specificity (91% [85–97] *vs* 98% [95–100]) for conventional imaging compared with PSMA PET-CT. Subgroup analyses also showed the superiority of PSMA PET-CT (area under the curve of the receiver operating characteristic curve 91% *vs* 59% [32% absolute difference; 28–35] for patients with pelvic nodal metastases, and 95% vs 74% [22% absolute difference; 18–26] for patients with distant metastases). First-line conventional imaging conferred management change less frequently (23 [15%] men [10–22] *vs* 41 [28%] men [21–36]; p=0·008) and had more equivocal findings (23% [17–31] *vs* 7% [4–13]) than PSMA PET-CT did. Radiation exposure was 10·9 mSv (95% CI 9·8–12·0) higher for conventional imaging than for PSMA PET-CT (19·2 mSv *vs* 8·4 mSv; p<0·001). We found high reporter agreement for PSMA PET-CT (κ=0·87 for nodal and κ=0·88 for distant metastases). In patients who underwent second-line image, management change occurred in seven (5%) of 136 patients following conventional imaging, and in 39 (27%) of 146 following PSMA PET-CT.

Interpretation PSMA PET-CT is a suitable replacement for conventional imaging, providing superior accuracy, to the combined findings of CT and bone scanning.

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Introduction

Defining the extent of prostate cancer spread with imaging is important for therapeutic decision-making in patients with high-risk localised prostate cancer. Despite careful selection of patients before surgery or radiotherapy, relapse following treatment with curative intent is common[1,2], partly because existing standard-of-care conventional imaging[3,4] with CT and bone scan has insufficient sensitivity and specificity to detect non-localised disease.[5,6] Novel imaging might improve outcomes by more accurately defining disease extent at the outset, enabling a more tailored multimodal treatment plan to be proposed.

Prostate-specific membrane antigen (PSMA) is a cell-surface glycoprotein overexpressed on prostate cancer cells. Radiolabelled small molecules that bind with affinity to PSMA enable whole-body tumour-specific imaging with PET-CT. Emerging data suggest that PSMA PET-CT is an important advance for imaging prostate cancer, particularly

Research in context

Evidence before this study

We searched PubMed and MEDLINE for peer-reviewed, original studies published in English until Feb 22, 2017, using the search terms "PSMA", "Prostate Specific Membrane Antigen", "positron emission tomography", and "PET". We also reviewed key journals and congress abstracts in the fields of nuclear medicine and urologic oncology. We found data suggesting that prostate-specific membrane antigen (PSMA) PET-CT is an important advance for imaging prostate cancer, particularly in the setting of recurrent cancer. Data were limited by retrospective or single-centre design, without comparison with a reference standard or conventional imaging. No prospective or randomised data for primary staging were available. Therefore, we designed a phase 3 imaging trial to investigate the utility of this novel modality. Several studies have been published after the proPSMA study commenced, but high-quality, prospectively collected data comparing PSMA PET-CT with conventional imaging do not exist to date.

Added value of this study

This randomised phase 3 study provides compelling evidence that PSMA PET-CT has better accuracy, with consequent management change, fewer equivocal results, and lower radiation exposure compared with current standard-of-care imaging with CT and bone scanning in men with newly-diagnosed prostate cancer.

Implications of all the available evidence

Collective data from this prospective imaging study and other series provides data that PSMA PET-CT is better than and can replace conventional imaging with CT and bone scan for staging men with high-risk prostate cancer before surgery or radiotherapy with curative intent. Existing guidelines should be reviewed in light of these findings. Further health-economic analyses are required to support potential reimbursement to enable widespread access to PSMA PET-CT for men.

in the setting of recurrent cancer.[7–11] For primary staging, evidence is limited by retrospective or single-centre study design, without comparison with conventional imaging.[12–15] Furthermore, a paucity of data exists with follow-up or comparison with a reference standard.

The proPSMA trial aimed to investigate whether PSMA PET-CT had improved accuracy when compared with the combination of CT and bone scan. We explored the diagnostic utility of PSMA PET-CT as a replacement for conventional imaging.

A video abstract is available online.

Methods

Study design and participants

We did a multicentre, two-arm, randomised trial at ten centres in Australia (appendix p 4). We recruited men, aged at least 18 years. Patients were eligible if they had histopathologically-confirmed prostate cancer and were being considered for radical prostatectomy or radiotherapy with curative intent. All patients had high-risk features including at least one of either a prostate-specific antigen (PSA) concentration of 20 ng/mL or more within 12 weeks before randomisation, International Society of Uropathology (ISUP) grade group 3–5, or clinical stage T3 or worse. Exclusion criteria included any imaging done for staging within 8 weeks before randomisation, with the exception of MRI of the prostate before biopsy (appendix p 10).

The study protocol was carried out in accordance with the Declaration of Helsinki and Good Clinical Practice, and all patients gave written informed consent before study entry.

The trial was approved by the institutional ethics board at each participating site. The protocol was reviewed by the scientific committees of the Australasian Radiopharmaceutical Trials Network and the Australian and New Zealand Urogenital and Prostate Cancer Trials Group. The trial protocol has been previously published (appendix p 32).[16]

Randomisation and masking

Men were randomly assigned (1:1) ratio to either conventional imaging or PSMA PET-CT. Block randomisation was stratified by centre and occurred only after eligibility was confirmed. Enrolment was competitive and each site enrolled patients until the total targeted number was reached. Participants were recruited by urologists and radiation oncologists, most of whom were further involved with the trial. We used a web-based system for data collection and randomisation.

Procedures

Patients who were randomised to the control group underwent first-line imaging consisting of abdomen and pelvis CT with intravenous contrast, and technetium-99m bone whole-body planar imaging with single-photon-emission CT (SPECT) CT of the chest to pelvis. Conventional imaging was defined by the combined findings of CT and bone scanning. Patients randomised to the experimental group underwent gallium-68 (^{68}Ga) PSMA-11 PET-CT using a standardised protocol defining minimum specifications for radiopharmaceutical production, quality control, and PET-CT acquisition (appendix p 10). First-line imaging was done within 21 days following randomisation. Men further underwent second-line cross-over imaging within 14 days unless three or more unequivocal distant metastases were identified on first-line imaging. This selective cross-over was chosen to minimise futile imaging because the identification of additional sites of disease in patients with widespread

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See Online for appendix

See Online for video

metastatic disease is not likely to provide patient benefit. Imaging was interpreted by experienced radiologists and nuclear medicine specialists, some of whom were further involved with the trial. Results of first-line imaging were available when reporting second-line imaging.

Following second-line imaging, additional confirmatory studies done at the discretion of the treating doctor were recorded. For patients with distant metastases, when feasible, biopsy confirmation of disease was strongly encouraged in the clinical protocol. Patients who had surgery underwent pelvic lymph node dissection at the discretion of the treating urologist. At 6 months (plus or minus 30 days) men underwent repeat imaging as per randomised group with cross-over if imaging evidence of N1 or M1 disease at baseline was found, or if we found biochemical or clinical suspicion of residual or recurrent disease.

Outcomes

The primary outcome of the trial was accuracy of first-line imaging for identifying either pelvic nodal or distant-metastatic disease. The accuracy of both diagnostic instruments was assessed by the area under the curve (AUC) of the receiver operating characteristic curve. The AUC was calculated as the mean of the estimated sensitivity and specificity. The reference standard regarding the presence of pelvic nodal or distant metastases was determined by each site's principal investigator at 6 months (plus or minus 30 days) after randomisation using a predefined composite panel encompassing histopathologic, imaging, clinical, and biochemical findings. Cases were considered positive if one of the following hard criteria were met: histopathology showing prostate adenocarcinoma, or change of a bone lesion to sclerotic or blastic on follow-up imaging. Cases were also considered positive if at least three soft criteria were met (appendix p 11). These included (1) typical appearance of multi-focal metastatic disease; (2) a metastatic lesion on an imaging modality other than the one done as the index scan; (3) increase in size or number of lesions from one imaging exam to the next; (4) decrease in size or number of lesions from one imaging exam to the next, following appropriate treatment; (5) lesion associated with clinical symptoms suggesting malignancy; (6) patient received localised treatment for imaging finding; (7) increase in PSA in keeping with clinical scenario of progression, or decrease in response to treatment; and (8) unequivocal persistence of positive finding on repeating imaging at 6 months in patients with a PSA concentration of more than 0·2 ng/mL at least 3 weeks following prostatectomy. The reference-standard was defined separately for pelvic nodal and distant metastases.[17] All available imaging and follow-up including second-line imaging, if done, was used to define hard and soft criteria.

The protocol did not specify treatment for patients, although any change in patient management as a result of the imaging results was recorded prospectively using a referrer-reported questionnaire. Management decisions were considered in the setting of support from multi-disciplinary genitourinary oncology teams in participating academic centres. At baseline, this management questionnaire result was obtained before randomisation and knowledge of the assigned diagnostic group. The questionnaire was repeated following first-line and second-line imaging. Management change was defined by a change in treatment intent (eg, curative to palliative), addition or removal of a treatment modality, or change in surgery or radiotherapy technique (appendix p 12). Change was classified as high (change in management intent or modality), medium (change in modality delivery), low (management plan was not altered), or potential effect ignored (management plan not altered despite findings showing distant metastatic disease).

Incremental accuracy of second-line imaging was defined by the ability to change stage of regional nodal or distant metastatic disease. Incremental management effect of second-line imaging was also recorded using the same definitions as first-line imaging.

The effective radiation exposure in millisieverts (mSv) from first-line imaging was calculated for each imaging study from the dose-length product for CT and administered radioactivity of radioisotopes.

Any adverse events of ^{68}Ga-PSMA-11 administration were recorded. Data related to service delivery and use were also recorded to assess the costs associated with PSMA PET-CT, which will be reported separately.

All sites were certified by an independent review before site activation involving PET scanner validation[18] and radiopharmaceutical production (appendix p 10).

During the study, PSMA PET-CT images were reviewed by a central imaging laboratory of expert readers. Reporter agreement between local and central review was recorded according to the American Joint Committee on Cancer staging system for nodal (N0, N? [equivocal] or N1) and distant metastases (M0, M? [equivocal], M1a, M1b or M1c). In the event of disagreement, the final result was at the discretion of the local reviewer.

De-identified source documentation of the first five patients from each site and a random selection of 10% thereafter were reviewed for accuracy 77 (25%) of 302 of patients were reviewed. 5% of patients had recorded protocol deviations which were mostly minor without influence on the analyses (appendix p 14).

Statistical analysis

We calculated that a sample size of 300 patients (150 per group) would achieve a power of 0·85 using the following pragmatic assumptions: (1) conventional imaging has a true underlying AUC of 0·65, consisting of a sensitivity of 0·65 and a specificity of 0·65; (2) PSMA PET-CT has a true underlying AUC of 0·9, consisting of a sensitivity of 0·9 and a specificity of 0·9; (3) the proportion of patients

with pelvic nodal or distant metastatic disease is 25%; (4) a margin of 10% improvement (absolute) in AUC is required to declare PSMA PET-CT superior; (5) a two-sided type I error of 10%; and (6) allow for a 10% patient dropout. The initial sample of 200 patients was based on an estimated proportion of cases of 40%. This proportion was subsequently revised to 25% after study commencement on the basis of trial management committee discussions without review of study data and availability of funding enabling study expansion. No interim analysis was done. The statistical analysis plan was prespecified and approved by the trial management committee. All statistical analyses were done in SAS (version 9.4). Data preparation was completed in R (version 3.6.0). The main analysis was done by the study biostatistician and the report was reviewed by a second independent biostatistician.

For the primary endpoint, all participants who underwent the first-line imaging to which they were assigned were included in the analysis. If the reference standard could not be determined because of incomplete follow-up data, the patient was deemed an incomplete patient and excluded from the primary endpoint analysis. For the purpose of estimating sensitivity and specificity, lesions rated as equivocal were considered negative for metastatic disease. The primary analysis was a patient-level analysis, with the presence of any pelvic nodal or distant metastasis in a patient considered positive for metastatic disease. The AUC was calculated as the mean of the estimated sensitivity and specificity. We reported the difference in AUC between the groups and the p-value for the null hypothesis that the AUC for PSMA PET-CT is 10% greater (absolutely) than the AUC in the conventional imaging group.

The analyses of the primary objective were repeated to define sensitivity, specificity, and accuracy for nodal and distant metastatic groups separately. A sensitivity analysis was also done in which lesions that were rated as equivocal were considered positive for metastatic disease.

For secondary outcomes, the proportion of patients with management effect and equivocal findings were compared using Fisher's exact test. Radiation exposure was compared using Student's unpaired t-test. Reporter agreement between local and central readers were assessed using Cohen's weighted κ. To assess the incremental accuracy of second-line imaging, the proportion of patients who were upstaged by identification of nodal or distant metastases was calculated; the number of patients who were accurately or inaccurately upstaged using the 6-month reference standard was also calculated.

This trial was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12617000005358.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

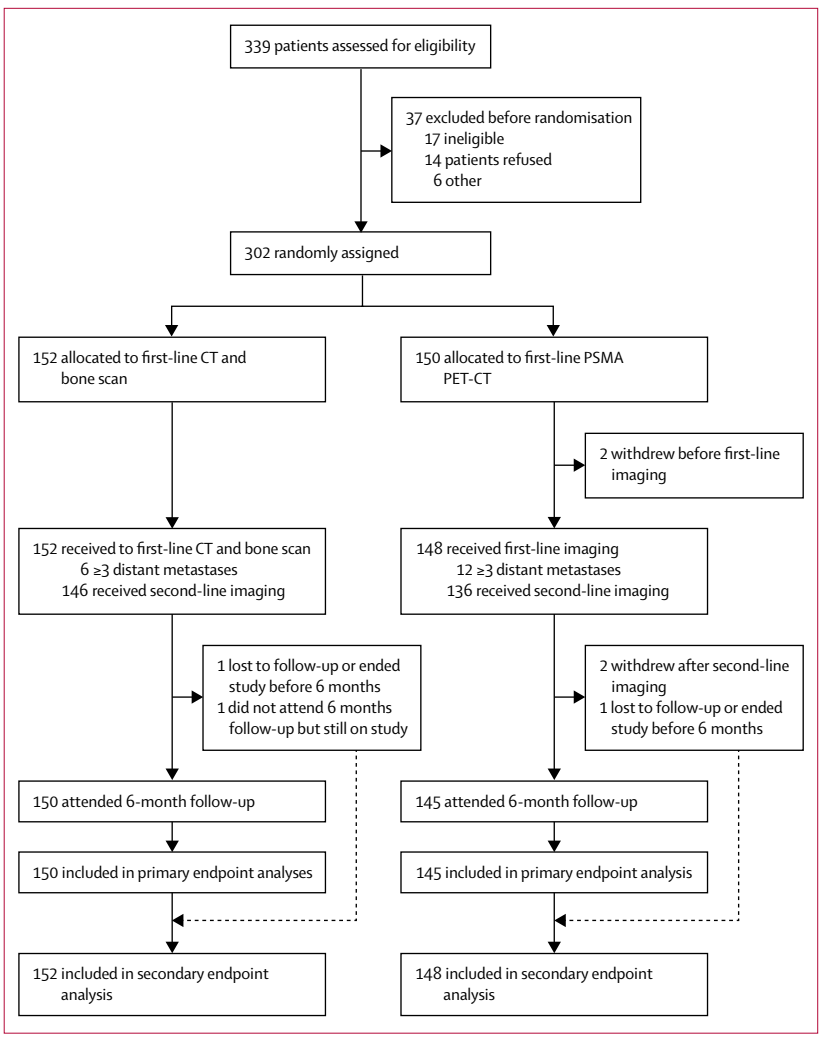

Figure 1: **Trial profile**
PSMA=prostate-specific membrane antigen.

Results

From March 22, 2017, to Nov 2, 2018, 302 participants were randomly assigned at ten sites (figure 1; appendix pp 7, 16). Two patients withdrew before first-line imaging and were replaced. 300 patients received first-line imaging according to their randomly assigned group. Baseline characteristics were similar in the two groups (table; appendix p 16). The median age of participants was 68·1 years (IQR 63·0–73·5). 293 (98%) men fulfilled eligibility on the basis of having a tumour of ISUP grade group 3 or more, 65 (22%) with PSA concentration of 20 ng/mL or more, and 82 (27%) men with clinical stage T3–4. 146 (96%) men randomly assigned to conventional imaging underwent second-line PSMA PET-CT imaging,

	All patients (n=300)	Conventional imaging (n=152)	PSMA PET-CT imaging (n=148)
Age, years			
Median (IQR)	69·0 (63·0–73·5)	68·0 (62·5–72·0)	70·0 (64·0–74·0)
PSA, ng/mL			
Mean (SD)	17·3 (36·6)	16·3 (17·7)	18·3 (49·0)
Median (IQR)	10·2 (6·6, 17·1)	10·5 (6·5, 20·0)	10·0 (6·9, 14·1)
≥20	65 (21·7%)	39 (25·7%)	26 (17·6%)
Clinical stage			
≥T3	82 (27%)	39 (26%)	43 (29%)
ISUP grade group			
1	1 (<1%)	1 (<1%)	0
2	6 (2%)	2 (1%)	4 (3%)
3	101 (34%)	47 (31%)	54 (36%)
4	61 (20%)	33 (22%)	28 (19%)
5	131 (44%)	69 (45%)	62 (42%)
ISUP grade group ≥3			
No	7 (2%)	3 (2%)	4 (3%)
Yes	293 (98%)	149 (98%)	144 (97%)

Data are n (%), unless otherwise specified. PSMA=prostate-specific membrane antigen. PSA=prostate-specific antigen. ISUP=International Society of Uropathology.

Table: **Baseline characteristics**

and 136 (92%) patients randomly assigned to PSMA PET-CT underwent second-line conventional imaging (appendix pp 17–24). Reference standard was assessable in 295 (98%) men (appendix p 26), with 87 (30%) positive for nodal or distant metastases. Repeat imaging that enabled assessment of temporal change at 6 months was done in 124 (41%) men. Pelvic lymph-node sampling was done in 83 (66%) of 126 men who underwent prostatectomy. The reference standard was defined by hard criteria in 20 (23%) of 87 men with nodal or distant metastases.

PSMA PET-CT had a 27% (95% CI 23–31, p<0·0001) absolute greater AUC for accuracy than conventional imaging did (92% [88–95] *vs* 65% [60–69]; figure 2; appendix p 27). This finding reflected a lower sensitivity (38% [24–52] *vs* 85% [74–96]) and specificity (91% [85–97] *vs* 98% [95–100]) for conventional imaging compared with that of PSMA PET-CT. A sensitivity analysis was done, in which lesions rated as equivocal were considered positive rather than negative, also showed the superiority of PSMA PET-CT (28% absolute greater AUC [23–33]; AUC 89% [85–92] *vs* 61% [55–66]; appendix p 28). Results for subgroups of patients with pelvic nodal (AUC 91% *vs* 59% [32% absolute difference; 28–35]) and distant (95% *vs* 74% [22% absolute difference; 18–26]) metastases also showed superiority of PSMA PET-CT (appendix p 30). First-line PSMA PET-CT detected pelvic nodal disease in 30 (20%) of 148 men, abdominal nodal metastases in 13 (9%), bone metastases in 15 (10%), and visceral metastases in one (1%; appendix p 8). In a further post-hoc analysis, the AUCs for the analyses of subgroups of men with Gleason grade group 4 disease or higher were 25% (20–30) greater, 37% (31–42) greater for those with grade group 3 or lower, and 36% (28–44) greater for those with a PSA concentration of 20 ng/mL or more; all of which were superior for PSMA PET-CT with (appendix p 39).

More equivocal findings for identifying any metastatic disease were seen with conventional imaging compared with PSMA PET-CT (35 men [23%; 95% CI 17–31] *vs* 11 men [7%; 4–13]; p<0·001). Findings were similar for men with pelvic nodal (nine men [6%; 3–11] *vs* one [1%; 0–5%]) and distant metastases (32 men [21%; 15–28] *vs* 10 men [7%; 3–12]; figure 3, appendix p 30).

Conventional imaging conferred management change with a high or medium effect (change in management intent or modality, or change in modality delivery) in 23 men (15%; 95% CI 10–22), compared with 41 men (28%; 21–36) who underwent first-line PSMA PET-CT (p=0·008; figure 3; appendix pp 30, 31). Following first-line PSMA PET-CT, 20 (14%) of 148 patients were directed from curative to palliative-intent treatment, 11 (7%) had a change in radiotherapy technique, and 11 (7%) in surgical technique.

Radiation exposure from first line diagnostic imaging was 10·9 mSv (95% CI 9·8–12·0; p<0·001) higher with conventional imaging compared with PSMA PET-CT (19·2 mSv [18·2–20·3] *vs* 8·4 mSv [8·1–8·7]; figure 3; appendix pp 9, 32, 33).

In 291 selected patients with fewer than three distant metastases who crossed over to second-line imaging, conventional imaging had a high or medium effect in 5% (95% CI 2–10) compared with 27% (20–35) with PSMA PET-CT (figure 3; appendix pp 33, 34). After second-line imaging, conventional imaging findings resulted in a change of stage for nodal or distant metastases in 20 men (14% [95% CI 9–22), compared with 33 men (22% [16–30]) for PSMA PET-CT findings. Compared with the reference standard, the change in stage was correct in three men (2% [0–6]) for conventional imaging, compared with 26 men (18% [12–25]) for PSMA PET-CT (appendix p 35). In a post-hoc analysis of the second-line imaging subpopulations, the AUC of accuracy was 17% (13–22) higher for second-line PSMA PET-CT compared with that of second-line conventional imaging (84% [80–88] *vs* 67% [62–71]; appendix p 36).

Final implemented management included surgery in 126 (42%), radiotherapy in 122 (41%), androgen deprivation therapy alone in 26 (9%), and androgen deprivation therapy combined with chemotherapy in 19 (6%) men (appendix p 36).

Reporter agreement was high with PSMA PET-CT for nodal (κ=0·87 [95% CI 0·81–0·94]) and distant disease (0·88 [0·84–0·92]; appendix p 37). No adverse events to ^{68}Ga-PSMA-11 were reported.

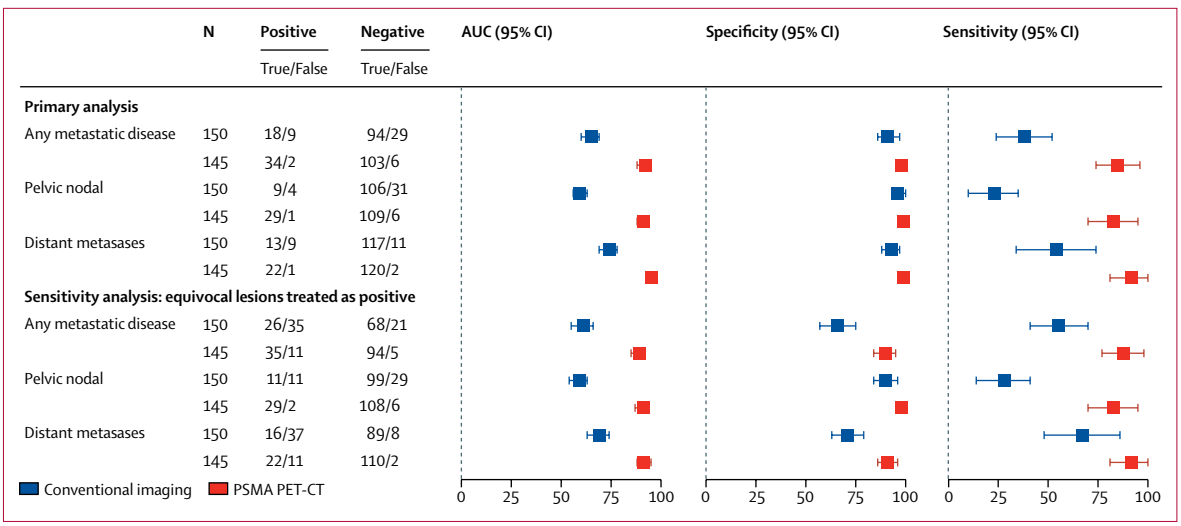

Figure 2: **Accuracy, sensitivity, and specificity of conventional imaging compared with PSMA PET-CT**
PSMA=prostate-specific membrane antigen. AUC=area under the curve.

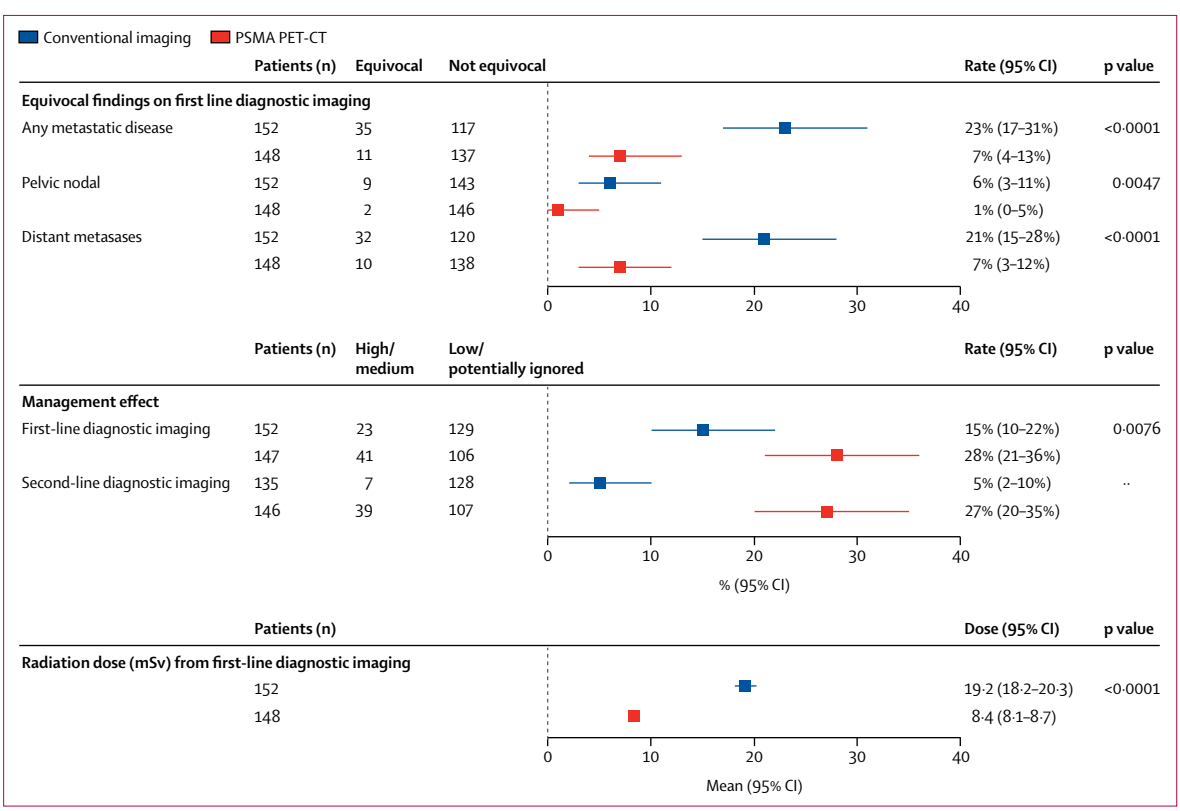

Figure 3: **Equivocal findings, management effect, and radiation exposure of conventional imaging compared with PSMA PET-CT**
PSMA=prostate-specific membrane antigen.

Discussion

We found that PSMA PET-CT had a superior diagnostic accuracy than conventional imaging did in men with high-risk prostate cancer. This finding is supported by results from retrospective single-centre studies that have suggested that PSMA PET-CT might have a higher accuracy than that of CT or MRI in the staging of pelvic lymph nodes before prostatectomy, using histopathology as the standard-of-reference.[12,20] In one study involving 130 patients with intermediate-to-high-risk prostate cancer, PSMA PET-CT outperformed CT or MRI, with a diagnostic accuracy of 0·83 (95% CI 0·76-0·91) versus

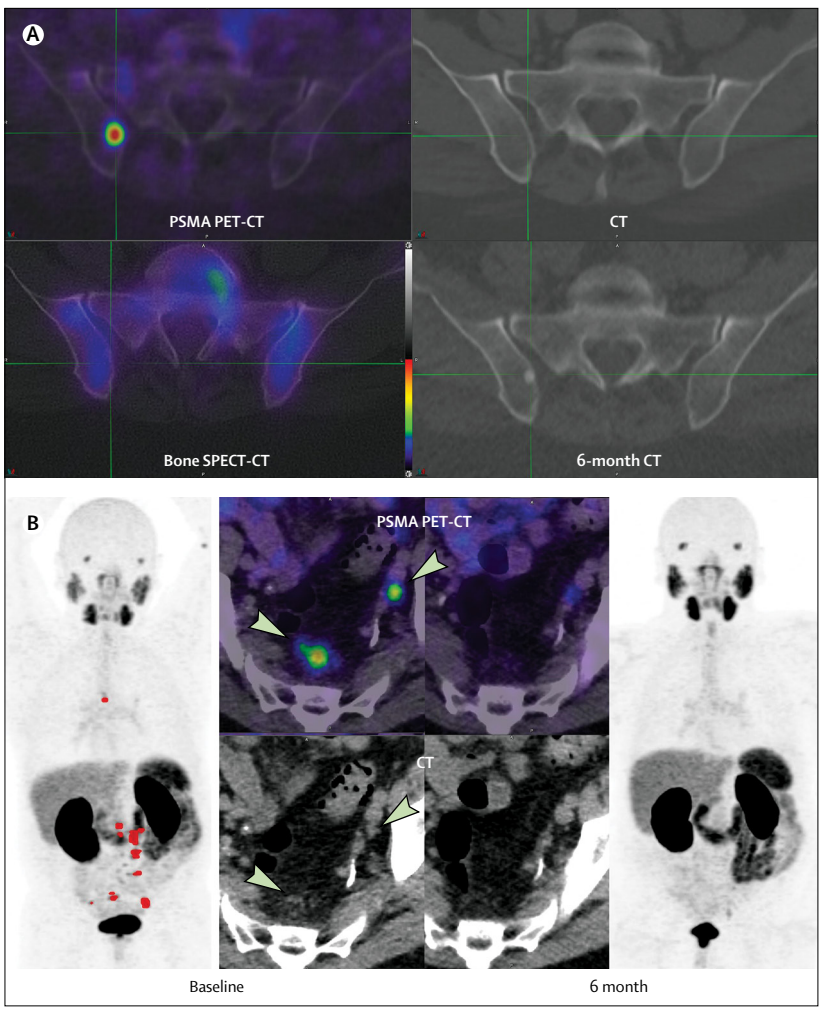

Figure 4: **Images of two men with normal results from baseline conventional imaging**
(A) PSMA PET-CT showed a right iliac bone metastasis in the first patient and 6-month follow-up imaging following systemic treatment showed regression of PSMA PET-CT findings with progressive sclerosis on CT. (B) PSMA PET-CT showed multiple sub-cm pelvic and distant nodal metastases in the second patient and 6-month follow-up imaging following systemic treatment showed regression of PSMA PET-CT findings with a decrease in the size of nodal changes on CT. Furthermore, prostate-specific antigen was undetectable in both patients at 6 months' follow-up. PSMA=prostate-specific membrane antigen.

0·69 (0·59–0·79).[12,20] Consistent with previous retrospective reports, the proPSMA study showed the diagnostic superiority of PSMA PET-CT compared with CT. By contrast with previous studies, the superiority was found not only for CT but also for bone scan with SPECT-CT, enabling comparison of regional nodal and distant metastases.

A cohort of men exists with apparently localised prostate cancer, who are at high risk of developing recurrence despite receiving timely and effective primary therapy. Regardless of whether or not these men undergo surgery or radiotherapy as primary treatment, up to 50% have biochemical recurrence, with a subsequently increased risk of metastases and 15-year prostate cancer-specific mortality rates of up to 35%.[11,19] A key reason for these high failure rates is that conventional imaging does not detect metastatic disease ab initio and local treatment is therefore destined to be ineffective. Accordingly, improved staging might enable better tailored treatments and improve outcomes in these high-risk men.

The primary role of any diagnostic imaging test is to provide accurate results.[21] Accordingly, we selected accuracy as the primary endpoint and showed unequivocal superiority of PSMA PET-CT compared with conventional imaging. This finding is attributed to the high tumour-to-background contrast and specificity of the radiotracer and consequent ability to identify small-volume nodal or visceral disease and early bone metastases before lytic or osteoblastic change (figure 4), which led to fewer equivocal findings compared with conventional imaging and high reporter agreement.

Key strengths of our study include the multi-centre design, with the assessment of first-line and second-line utility of PSMA PET-CT. Many imaging studies have assessed the additional value of a new modality after standard-of-care imaging has been done. Our key findings indicate that PSMA PET-CT is a suitable replacement for conventional imaging and that conventional imaging is not required following PSMA PET-CT. Although patients underwent selective cross-over to assess utility for second-line imaging, the primary endpoint was head-to-head comparison of first-line imaging before cross-over. Limitations of our second-line imaging analysis include the fact that the analysis was of a subset of patients and was not a randomised comparison. The trial included robust quality-control measures and recruited ahead of schedule. Although many potential confounders were managed through randomisation, the inability to blind imaging modality introduced potential bias.

Discovering the ground truth in a diagnostic imaging study is always subject to bias. Reflecting real-world practice, histopathologic assessment was not feasible in all participants, especially those with pelvic nodal metastases who underwent radiotherapy. Moreover, relying on histopathology alone is subject to sampling error and, arguably, our reference standard incorporating 6-month follow-up with repeat imaging is a more robust method in many patients. Our method enabled robust assessment of temporal changes with progression or regression of findings contributing to the reference standard. Nevertheless, some caution is warranted because our soft criteria were not conventional and might be subject to investigator bias.

Although we report that PSMA PET-CT led to changes in intended management, the cross-over design limited our ability to identify specific improvements in downstream patient outcomes between the groups. Our study design focused on the comparative accuracy of PSMA PET-CT compared with conventional imaging and we cannot ascertain whether the information provided by PSMA PET-CT and any consequent management effects translate to improved patient survival. Nevertheless, we contend that assessing survival or other

long-term outcomes are challenging for imaging studies. Improving accuracy is desirable because the detection of metastatic disease can prevent futile attempts at cure or better direct locoregional therapies. Furthermore, earlier detection of systemic metastases could also benefit patients because the efficacy of therapies is greater when the burden of disease is low.[22] Additionally, the rate of equivocal imaging findings and radiation exposure are relevant patient outcomes that were assessed in this study.

We did not mandate the management of patients in this study. The decision, for example, to perform a pelvic lymph-node dissection was at the discretion of individual surgeons. Other series incorporating extended pelvic lymph-node dissection have reported lower sensitivity than we found for PSMA PET-CT for detecting nodal metastases.[23] Although the patient populations were different, our study might have overestimated the sensitivity of PSMA PET-CT given the absence of pelvic lymph-node dissection in all patients. Nevertheless, despite this limitation, our study provides robust comparative data, given the randomised design. Furthermore, the proPSMA cohort of men without distant metastases on PSMA PET-CT remain on protocol-defined follow-up to ascertain clinical treatment failure over time, which will be assessed after 54 months' follow-up.

PSMA PET-CT reveals disease beyond the classic pelvic lymph-node dissection or radiotherapy treatment field in 16–48% of cases.[15,24] Inadequate coverage is often seen with pararectal, inguinal, and presacral nodes, notwithstanding synchronous distant metastases never within treatment fields.[25] Identification and early treatment of oligometastases is another strategy that warrants further assessment.[26,27] Also, lymph-node dissection that is PSMA-targeted using radioguided surgery techniques might further enhance the value of pelvic lymph-node dissection.[28–30]

The cost of diagnostic imaging is increasingly recognised as a major component of health expenditure. Cost savings with PSMA PET-CT include not only the implications of a more accurate test but also the savings from a single rather than multiple imaging tests, from a patient and health-care perspective. The cost of PSMA PET-CT varies considerably by geographical region and further health-economic analyses are required.

In conclusion, in men with high-risk prostate cancer undergoing staging before curative-intent therapy, we found that a diagnostic pathway that used PSMA PET-CT as a first-line investigation as a replacement for conventional CT and bone scan was superior.

Contributors

MSH, RJF, AH, SW, and DGM designed the study. MSH, NL, RJF, CT, IV, PT, NR, JMM, MF, RS, L-MW, KT, STL, HS, PR, MN, IK, DH, PM, AM, SW, and DGM accrued patients and collected data. AI, RJH, and MSH did the imaging central review. EL and AH contributed to the statistical analysis. MSH was the coordinating principal investigator. All authors contributed to writing and approval of this report.

Declaration of interests

MSH reports grants from Prostate Cancer Foundation of Australia, Movember, and the Peter MacCallum Foundation, during the conduct of the study; other grants from Prostate Cancer Foundation, US Department of Defense, and Victorian Cancer Agency; personal fees and non-financial support from Ipsen, Sanofi Genzyme, and Jannsen, outside of the submitted work. PT reports grants from Prostate Cancer Foundation of Australia, during the conduct of the study. JMM reports grants from Mundipharma, and personal fees from Janssen and Ferring, outside of the submitted work. RJH reports stockholding from Telix Pharmaceuticals, outside of the submitted work. DGM reports personal fees from Astellas, Janssen, Bayer, Ferring, and Ipsen, outside of the submitted work. All other authors declare no competing interests.

Data sharing

Requests for specific analyses or data will be considered by the proPSMA trial management committee immediately following publication of the manuscript for researchers who provide a methodologically sound proposal. Data include (1) access to all of the individual participant data collected during the trial, after de-identification; and (2) the study protocol, statistical analysis plan, and analytic code. Proposal should be directed to michael.hofman@petermac.org. To gain access, data requestors will sign a data access agreement.

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