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Title:

Ga-68-prostate-specific membrane antigen (PSMA) PET/CT as a clinical decision-making tool in biochemically recurrent prostate cancer

Date:

2022-10-01

Citation:

Davies, A., Foo, M., Gan, C. L., Kourambas, J., Redgrave, N., Donnellan, S., Appu, S., Williams, S., Coleman, A., Segelov, E., Bradley, J., Soo, G., Ramdave, S., Kwan, E. M. & Azad, A. A. (2022). Ga-68-prostate-specific membrane antigen (PSMA) PET/CT as a clinical decision-making tool in biochemically recurrent prostate cancer. *ASIA-PACIFIC JOURNAL OF CLINICAL ONCOLOGY*, 18 (5), pp.E204-E210. <https://doi.org/10.1111/ajco.13595>.

Persistent Link:

<https://hdl.handle.net/11343/298670>

Article Type:

Original article

Title:

⁶⁸Ga-prostate specific membrane antigen (PSMA) PET/CT as a clinical decision-making tool in biochemically recurrent prostate cancer.

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ajco.13595](https://doi.org/10.1111/ajco.13595).

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Acknowledgements: AstraZeneca provided funding support for ^{68}Ga -PSMA-11 PET/CT image acquisition.

Word count:

Abstract: 244

Manuscript: 2,240

References: 38

Tables: 3

Figures: 2

Supplemental tables: 1

Data sharing statement:

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICTS OF INTEREST

Edmond Kwan receives honoraria from Janssen and Ipsen; travel & accommodation from Astellas Pharma, Pfizer and Ipsen; and institutional research funding from Astellas Pharma, AstraZeneca, Bristol Myers Squibb, Pfizer, and Merck Serono.

Arun Azad conflict of interest include: Consultant: Astellas, Janssen, Novartis. Speakers Bureau: Astellas, Janssen, Novartis, Amgen, Ipsen, Bristol Myers Squibb; Merck Serono. Honoraria: Astellas, Novartis, Sanofi, AstraZeneca, Tolmar, Pfizer, Telix; Merck Serono; Janssen, Bristol Myers Squibb, Ipsen, Bayer, Pfizer. Scientific Advisory Board: Astellas, Novartis, Sanofi, AstraZeneca, Tolmar, Pfizer, Telix; Merck Serono; Janssen, Bristol Myers Squibb, Ipsen, Bayer

Travel and accommodation: Astellas, Merck Serono, Amgen, Novartis, Janssen. Research Funding: Astellas (investigator), Merck Serono (investigator), Astra Zeneca (investigator), Bristol Myers Squibb (institutional), Astra Zeneca (institutional), Aptevo Therapeutics (institutional), Glaxo Smith Kline (institutional), Pfizer (institutional), MedImmune (institutional), Astellas (institutional), SYNthorx (institutional), Bionomics (institutional), Sanofi Aventis (institutional), Novartis (institutional).

No other co-authors declared any relevant Conflicts of Interest.

ABSTRACT

Objective: PSMA PET/CT has demonstrated superior sensitivity over conventional imaging in the detection of local and distant recurrence in biochemically relapsed (BCR) prostate cancer. We prospectively investigated the management impact of ^{68}Ga -PSMA PET/CT imaging in men with BCR, with the aim of identifying baseline clinicopathological predictors for management change.

Patients and Methods: Men with BCR who met eligibility criteria underwent ^{68}Ga -PSMA-11 PET/CT at Monash Health (Melbourne, Australia). Intended management plans were prospectively documented before and after ^{68}Ga -PSMA PET/CT imaging. Binary logistic regression analysis was performed to identify potential clinicopathological predictors of management change. Descriptive statistics were used to characterise the nature of these changes.

Results: Seventy men underwent ^{68}Ga -PSMA-11 PET/CT imaging. Median age was 67 years (IQR 63-72) and median PSA was 0.48ng/ml (IQR 0.21-1.9). PSMA-avid disease was observed in 56% (39/70) of patients. Pre-scan management plan was altered following scanning in 43% (30/70) of patients. Management changes were significantly more common in patients with higher baseline PSA levels (PSA \geq 2 ng/ml, $p=0.01$). 18/36 (50%) of the patients initially planned for watchful waiting had their management changed, including use of salvage pelvic

radiotherapy (n=7) and stereotactic ablative body radiotherapy to oligometastatic disease (n=6).

Conclusion: Management change after ^{68}Ga -PSMA PET/CT for BCR is common and typically resulted in treatment intensification strategies in those planned for a watchful waiting approach. This study adds to the growing pool of evidence supporting the clinical utility of PSMA PET/CT imaging in the care of patients with BCR after definitive therapy.

Keywords: biochemical relapse, decision-making, prostate cancer, PSMA PET/CT

INTRODUCTION

Localised prostate cancer has an excellent prognosis with 10-year survival rates exceeding 90% in high income countries.¹ While many patients will be cured with radical prostatectomy and/or external beam radiation therapy, approximately 27-53% will experience biochemical relapse² (BCR), manifested by a rise in serum prostate specific antigen (PSA), prompting the need for further imaging. Determining the site of recurrence holds important prognostic and management implications. Patients with localised recurrence may be suitable for curative-intent salvage therapies including pelvic irradiation or pelvic lymph node dissection. In contrast, management of distant recurrence is often

palliative, with strategies ranging from local treatments (e.g. stereotactic radiation therapy) or the commencement of potent systemic therapy (e.g. androgen deprivation therapy with addition of chemotherapy or novel androgen pathway inhibitors).³

In the BCR setting, conventional imaging modalities such as multiparametric pelvic MRI, CT and bone scintigraphy are commonly utilised.⁴ However, sensitivity and specificity of conventional imaging is frequently suboptimal for pelvic lymph nodes and skeletal metastases alike^{5,6}, particularly at low PSA levels. Recent phase III randomised trial data reports 27% greater accuracy with PSMA PET/CT in initial staging of men with high-risk disease.⁷ Major societal guidelines recommend that the use of conventional imaging in BCR be limited to patients with high baseline PSA (>10 ng/ml) prior to definitive treatment, unfavourable PSA kinetics (PSA doubling time [PSADT] < 6 months) or symptoms suggestive of metastatic disease.⁸ However, salvage therapies are often initiated well below these thresholds for detection.⁹ As such, alternative biomarkers beyond PSADT and absolute PSA level are urgently needed to better guide optimal implementation of salvage treatment strategies. PSMA PET/CT has rapidly emerged as a sensitive novel imaging modality to address this need.¹⁰

This study reports the impact of gallium-68 (⁶⁸Ga)-PSMA-11 PET/CT imaging on physician-directed intended management plans in a series of patients with biochemically recurrent prostate cancer and investigates the clinicopathological correlations associated with scan-

provoked management change. We found that PSMA PET/CT led to alterations in management in 43% of our cohort, most frequently resulting in treatment intensification strategies in those initially planned for watchful waiting approach. This study adds to the growing pool of evidence supporting the clinical utility of PSMA PET/CT imaging in the care of patients with BCR after definitive therapy.

PATIENTS AND METHODS

Patient population

This prospective study enrolled patients with BCR after definitive therapy for prostate cancer. BCR was defined as two consecutive rising PSA values ≥ 0.1 ng/ml. In patients treated with prior primary radiotherapy, BCR was defined using the Phoenix criteria: a rise in PSA of ≥ 2 ng/ml above the post-treatment nadir, independent of the use of concurrent hormonal therapy.¹¹ To facilitate study recruitment, patients were not required to undergo conventional imaging with CT or bone scintigraphy prior to study participation. Exclusion criteria included concurrent use of ADT in the last six months, prior use of cytotoxic chemotherapy, or concurrent malignancy. Clinicopathological data was collected, including demographics, definitive therapy, primary pathology, and most recent PSA level (within four weeks of study enrolment). The study was approved by the Monash Health Human Research Ethics Committee (HREC 17/MonH/403).

Imaging acquisition and interpretation

Patients underwent imaging with ^{68}Ga -PSMA-11 PET/CT using the same Siemens Biograph mCT Flow PET/CT scanner. A concurrent non-contrast CT scan was performed for attenuation correction and anatomic localisation. Images were acquired from vertex to upper thighs, 45-60 minutes after IV administration of 75-150 MBq of ^{68}Ga -PSMA-11. Images were interpreted independently by two experienced nuclear medicine physicians (G.S. and S.R.) with knowledge of the patient's clinical history and PSA results. PSMA-positivity was defined by any focal uptake of ^{68}Ga -PSMA-11 above background, acknowledging well-recognised causes of false-positive findings.¹² Descriptions of anatomical site of uptake on ^{68}Ga -PSMA-11 PET/CT were systematically reported, and included the prostatic bed, intrapelvic lymph nodes, extrapelvic lymph nodes, and distant visceral or bony metastatic disease.

Patient management questionnaire

Prior to ^{68}Ga -PSMA-11 PET/CT imaging, referring physicians prospectively completed a questionnaire detailing their proposed management plan. Following imaging, a separate questionnaire (**Supplemental Table 1**) was completed by the same physician.

Outcome measures and statistical analysis

The primary outcome was the frequency of change in management plans following ^{68}Ga -PSMA-11 PET/CT imaging. Chi-square statistics were used to compare management change rates between PSMA-positive and PSMA-negative patients. Binary logistic regression

analysis was performed to identify potential predictors of management change, including pre-imaging PSA categories (0-0.19, 0.20-0.99, 1.00-1.99, and ≥ 2 ng/ml), pathological variables (T-stage, extracapsular extension, surgical margin status, Gleason score), prior use of salvage radiotherapy, and time since definitive therapy. Statistics were produced using R Studio, version 1.1.463 (Integrated Development Environment for R, Boston, MA, USA), with statistical significance defined as $p < 0.05$.

RESULTS

Study population

From December 2017 to March 2020, 70 patients with biochemically recurrent prostate cancer underwent ^{68}Ga -PSMA-11 PET/CT imaging. No adverse events occurred as a result of ^{68}Ga -PSMA-11 PET/CT. Patient characteristics are shown in **Table 1**. The median time between definitive treatment and ^{68}Ga -PSMA-11 PET/CT imaging was 2.5 years (IQR 0.9-7.4). The median time between pre-imaging PSA level and ^{68}Ga -PSMA-11 PET/CT was 31 days (IQR 24 - 43).

^{68}Ga -PSMA PET/CT findings

Positive ^{68}Ga -PSMA-11 PET/CT scans were observed in 39 of 70 (56%) patients. Median PSA in patients with positive imaging findings was 1.45 ng/ml (IQR 0.48-5.2) and 0.24 ng/ml (IQR 0.17-0.38) in patients with negative ^{68}Ga -PSMA-11 PET/CT. The anatomical distribution of

disease recurrence is summarised in **Table 2**. No patients had visceral disease detected on PSMA PET/CT. For the PSA categories of 0-0.19 ng/ml, 0.20-0.99 ng/ml, 1.00-1.99 ng/ml and ≥ 2 ng/ml, the proportion of patients with PSMA PET/CT scans positive for local or distant lesions were 21% (3/14), 41% (13/32), 91% (10/11) and 92% (12/13) respectively.

Predictors of changes in patient management

In total, 30 of 70 (43%) patients underwent a change in their intended management following ^{68}Ga -PSMA-11 PET/CT imaging. Patients with positive scans were more likely to experience a change in their management plan (72% vs 6%, $p < 0.001$). **Table 3** shows the associations between baseline clinicopathologic variables and likelihood of management change following ^{68}Ga -PSMA-11 PET/CT imaging. Pre-imaging PSA categories of 1.00-1.99 ng/ml (OR 6.6, $p = 0.03$) and ≥ 2 ng/ml (OR 8.3, $p = 0.01$) significantly predicted for a greater likelihood of management change. No other baseline clinicopathological variables predicted for management change.

Impact on patient management

Pre-imaging management plan was watchful waiting and salvage radiation therapy in 51% (36 patients) and 41% (29 patients), respectively. **Figure 1** summarises the nature of management decisions following imaging. Eighteen (50%) patients planned for watchful waiting experienced a modification in their proposed management, most commonly to salvage radiation therapy (7/18, 39%). Six of the seven (86%) patients that switched from

watchful waiting to salvage radiotherapy had evidence of PSMA-avid disease in the prostate bed or pelvic nodal region. Comparatively, the proportion of patients initially planned for salvage radiation therapy that had their intended management altered was lower at 28% (8/29), most commonly to watchful waiting (4/8, 50%) in the presence of distant metastases to bone (n=3) or non-regional lymph nodes (n=1). **Figure 2** illustrates a patient that had their intended management modified based on findings on ⁶⁸Ga-PSMA-11 PET/CT.

DISCUSSION

⁶⁸Ga-PSMA PET/CT has rapidly emerged as a potential alternative diagnostic tool in the BCR setting to inform clinical decision-making. A recently updated meta-analysis of 4790 patients continues to highlight the utility of ⁶⁸Ga-PSMA PET/CT even at low PSA levels, with scan positivity rates of 95% in patients with PSA \geq 2 ng/ml.¹³ Furthermore, ⁶⁸Ga-PSMA PET/CT accurately detects true disease with a positive predictive value of 76-84% accompanied by excellent interobserver reproducibility.¹⁴⁻¹⁶ Despite this, PSMA PET/CT imaging is not available in many countries and cost reimbursement remains a significant barrier to widespread patient access and adoption in routine clinical practice.^{17,18} Leveraging access to PSMA PET/CT, we undertook a prospective study investigating the impact of ⁶⁸Ga-PSMA-11 PET/CT on physician-directed management plans in men with BCR after definitive treatment for localised prostate cancer.

This prospective study reports that ^{68}Ga -PSMA-11 PET/CT altered intended management in 43% of all patients and in 72% of patients with a positive scan. Pre-imaging PSA levels were a strong predictor of subsequent change in intended management, likely due to a higher rate of positive scan findings. We found no other baseline variables that were associated with greater likelihood of post-imaging management change. Patients with initial conservative watchful waiting strategies were most likely to have their management plan altered, commonly resulting in treatment intensification to either salvage radiotherapy or stereotactic ablative body radiotherapy to oligometastatic disease sites. Comparatively, more than a quarter of patients planned for long-course pelvic radiotherapy had their treatment abandoned in favour of conservative approaches, sparing them the potential toxicities of futile salvage therapy.

These findings are consistent with prior studies measuring impact of ^{68}Ga -PSMA PET/CT on physician-directed decision-making, where treatment strategy is frequently altered in 54-76% of BCR patients.¹⁹⁻²² In a meta-analysis of 15 predominantly retrospective studies (11 in the BCR population), management change was more commonly observed in those with higher pre-imaging PSA levels, occurring in 69% at ≥ 2 ng/ml compared to 43% at ≤ 1.0 ng/ml.²² Interestingly, other prospective studies have not shown this association, particularly when PSA has been assessed as a continuous variable,^{21,23} suggesting that while PSA levels estimate scan positivity, post-scan variables including distribution of PSMA uptake is likely to have a far greater influence on treatment planning. Consistent with earlier studies,^{21,23} other baseline clinicopathological variables including tumour grade/stage,

margin positivity and time since definitive therapy were not associated with management change in this study, affirming these factors alone cannot be used to determine the utility of PSMA PET/CT imaging on a per-patient basis.

Interestingly, half of watchful waiting patients had their treatment escalated. While this study did not explore the rationale behind management decisions, watchful waiting is preferred in men considered poor candidates for salvage therapies based on adverse patient factors (advanced age, competing comorbidities) or disease factors (high absolute PSA levels or unfavourable PSA kinetics).²⁴ All but one patient that switched from watchful waiting to salvage radiotherapy had evidence of PSMA-avid prostate bed or pelvic nodal disease, suggesting that physicians, expecting distant disease may have been reassured that recurrence was confined to pelvic irradiation fields. Conversely, where distant metastatic disease was detected, less conventional approaches including stereotactic ablative body radiotherapy were favoured. This preference to delay systemic therapy in oligometastatic castration-naïve prostate cancer may be influenced by findings from the STOMP trial, which found that metastatic-direct therapy resulted in a delay in ADT administration compared to close surveillance.^{25,26} While other studies have supported this strategy,^{27,28} phase III trials with overall survival benefit are lacking, and concerns regarding long-term cognitive and cardiovascular consequences of prolonged ADT^{29,30} must be balanced against delaying highly effective systemic therapy shown to deliver a positive survival benefit.³¹ Furthermore, recent long-term data from the SABR-COMET study provide strong rationale for combining

metastasis-directed therapy with conventional systemic therapy, with an impressive 25% improvement in five-year overall survival rates compared to standard-of-care alone.

Comparatively, patients planned for salvage radiation therapy had their management changed approximately half as often as watchful waiting patients. While this suggests that PSMA PET/CT may be of lesser value in patients destined to receive salvage radiation, its role in influencing radiotherapy planning is becoming increasingly apparent. ^{68}Ga -PSMA PET/CT has been shown to modify radiation planning in up to 56-59% of patients, most commonly by broadening the traditional pelvic lymph node target volume, or delivering a simultaneous boost to the prostate bed region.^{33,34} Conversely, a small but meaningful proportion of patients (~10%) may be suitable for pelvic nodal irradiation alone, sparing the toxicity associated with prostatic fossa treatment.²³ While this study did not prospectively collect data on changes to salvage radiotherapy fields, the role of PSMA-directed salvage radiation therapy is likely to become increasingly relevant as the value of salvage lymph node dissection is increasingly questioned.³⁵

Despite mounting evidence to support ^{68}Ga -PSMA PET/CT as the optimal imaging modality in biochemically relapsed prostate cancer, the clinical implications of imaging-driven changes in management remain poorly understood. Critically, current EAU and NCCN guidelines recommend PSMA PET/CT in instances where it is likely to result in a treatment change that confers improved outcomes.^{8,36} Prospective BCR trials exploring the effect of

PSMA PET/CT-directed management on oncological outcomes in BCR are now underway (ClinicalTrials.gov NCT03582774³⁷, NCT04222634). Importantly, these studies will be conducted alongside standard-of-care imaging. It is only through designing clinical trials that incorporate both conventional and novel imaging approaches can we seek to understand the ideal therapeutic applications of these new technologies.³⁸

The limitations of our study include small sample size, lack of mandated conventional imaging, and short follow-up time, with the latter restricting analysis to intended rather than implemented management change, which may differ in up to half of BCR patients.²¹

The pragmatic nature of the study questionnaire meant details regarding ⁶⁸Ga-PSMA PET/CT findings that influenced management change were not available, nor were specifics relating to radiation treatment fields. We acknowledge that bias may be present given referring physicians were aware of trial endpoints, including potential for management change.

Finally, long-term clinical outcomes were not collected, prohibiting any conclusions to be drawn about whether management changes were efficacious.

CONCLUSION

In this prospective study, findings from ⁶⁸Ga-PSMA PET/CT imaging in biochemically recurrent prostate cancer frequently resulted in patients undergoing a change in their intended management plan. Higher pre-imaging PSA levels significantly predicted for

management change. Patients initially planned for watchful waiting commonly had their treatment intensified following ^{68}Ga -PSMA-11 PET/CT, typically to salvage pelvic radiotherapy or stereotactic ablative body radiotherapy to oligometastatic disease. Further studies are needed to determine if PSMA PET/CT-guided management results in improved survival outcomes.

ACKNOWLEDGEMENTS

AstraZeneca provided funding support for ^{68}Ga -PSMA-11 PET/CT image acquisition.

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TABLES

Table 1: Patient demographics

| | Study cohort (n=70) |
|---|--------------------------------|
| AGE AT PET/CT | |
| Median, years (IQR) | 67 (63-72) |
| SERUM PSA LEVEL AT PET/CT, ng/ml | |
| Median (IQR) | 0.48 (0.21-1.93) |
| 0-0.19 | 14 (20) |
| 0.2-0.99 | 32 (46) |
| 1.0-1.99 | 11 (16) |
| ≥2.0 | 13 (19) |
| PRIMARY TREATMENT, N (%) | |
| Radical prostatectomy | 62 (89) |
| Radiation +/- ADT | 8 (11) |
| PRIMARY TUMOUR STAGE, N (%) | |
| T1-T2 | 28 (40) |
| T3-T4 | 42 (60) |
| PRIMARY NODAL STAGE, N (%) | |
| N0 | 38 (54) |
| N1 | 6 (8) |
| Unknown | 26(37) |

| GLEASON GRADE GROUP, N (%) | |
|--|---------------------|
| Grade Group 1-3 (Gleason ≤ 7) | 54 (77) |
| Grade Group 4-5 (Gleason ≥ 8) | 16 (23) |
| PRIOR SALVAGE RADIOTHERAPY, N (%) | |
| | (n=62) [#] |
| Yes | 12 (19) |
| No | 44 (71) |
| Unknown | 6 (10) |

ADT = androgen deprivation therapy; PSA = prostate specific antigen; RT = radiation therapy; PET/CT = positron emission tomography/computed tomography.

[#] Only 62 patients that underwent radical prostatectomy as primary treatment were included in salvage radiotherapy summary statistics.

Table 2: ⁶⁸Ga-PSMA-11 PET/CT imaging findings and distribution of lesions

| | Study cohort n=70 (%) | Total lesions n=86 (%) |
|--|----------------------------------|-----------------------------------|
| Positive ⁶⁸ Ga-PSMA-11 PET/CT imaging | 39 (56) | |
| Prostate / prostate bed | 11 (16) | 11 (13) |
| Intrapelvic lymph nodes (N1) | 22 (31) | 55 (64) |
| Extrapelvic lymph nodes (M1a) | 4 (6) | 4 (5) |
| Bone metastases (M1b) | 11(16) | 16 (19) |
| Visceral metastases (M1c) | 0 (0) | 0 (0) |

Table 3: Association of baseline clinicopathological variables and management change

| Variable | Management change following PSMA PET/CT | |
|---|---|----------------|
| | OR | <i>p value</i> |
| Pre-imaging PSA categories [#] | | |
| 0-0.19 ng/ml | REF | – |
| 0.20-0.99 ng/ml | 0.83 | 0.79 |
| 1.00-1.99 ng/ml | 6.6 | 0.03 |
| ≥2 ng/ml | 8.3 | 0.01 |
| T3-4 | 1.27 | 0.62 |
| Extracapsular extension | 1.11 | 0.83 |
| Positive surgical margin | 0.62 | 0.37 |
| Gleason score ≥ 8 | 1.05 | 0.93 |
| Prior salvage radiotherapy | 0.94 | 0.81 |
| Time since definitive therapy | 0.99 | 0.93 |

p values < 0.05 are highlighted in **bold**.

FIGURES

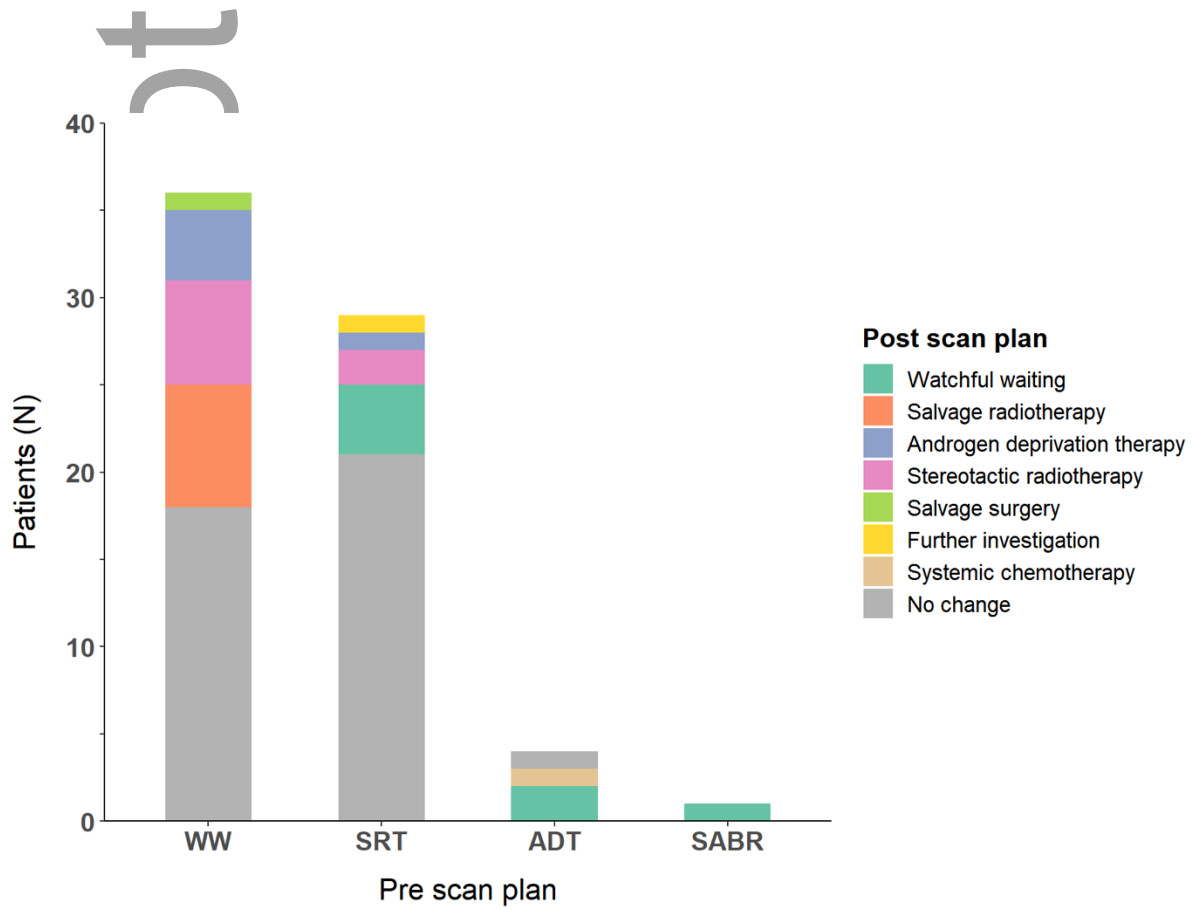


Figure 1: Summary of pre- and post- 68Ga-PSMA-11 PET/CT imaging management decisions

Abbreviations: WW: watchful waiting; SRT: salvage radiotherapy; ADT: androgen deprivation therapy; SABR: stereotactic ablative body radiotherapy.

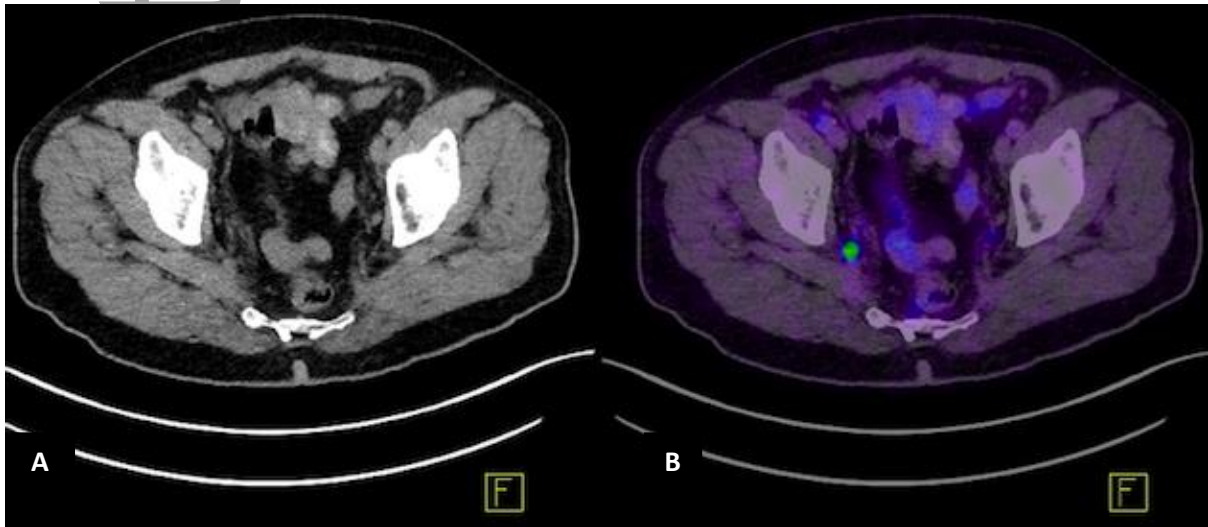
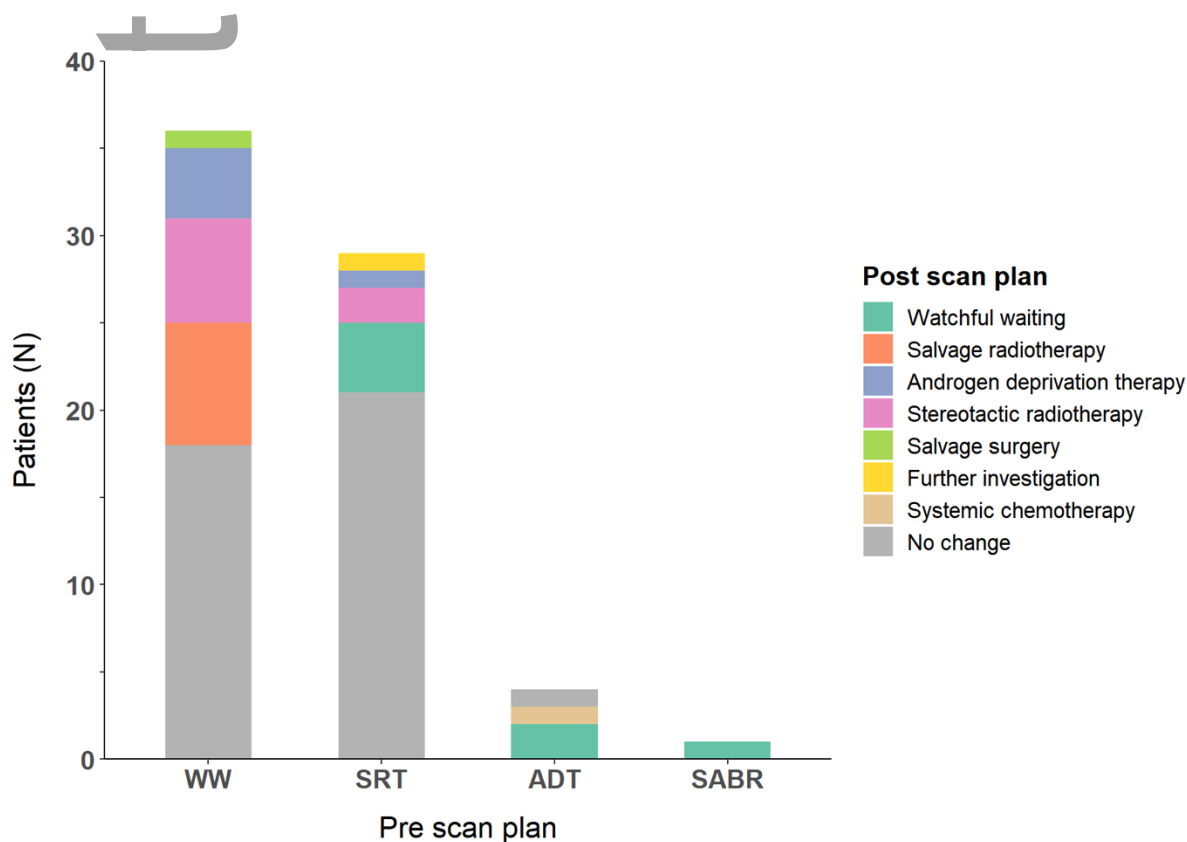


Figure 2. Comparison of low-resolution CT scan (A) and ^{68}Ga -PSMA-11 PET/CT (B) imaging in a 71-year-old male with BCR (PSA 0.48 ng/ml) nine years after radical prostatectomy for high-risk prostate cancer (Gleason 4+3=7, pT3a). Pre-imaging intended management plan was watchful waiting. PET/CT demonstrated bilateral, moderately intense ^{68}Ga -PSMA-11 uptake in two small pelvic lymph nodes (SUV_{max} 4.3 and 2.3). No corresponding lesion was seen on low-dose CT. Post-scan intended management plan was changed to salvage radiation therapy.

Graphical Abstract



Summary of pre- and post- ^{68}Ga -PSMA-11 PET/CT imaging management decisions

Abbreviations: WW: watchful waiting; SRT: salvage radiotherapy; ADT: androgen deprivation therapy; SABR: stereotactic ablative body radiotherapy.

MICROABSTRACT

PSMA PET/CT may assist in guiding optimal decision making in biochemically recurrent prostate cancer. We prospectively analysed management change following ^{68}Ga -PSMA PET/CT in 70 patients with biochemical relapse following definitive therapy for localised disease. Alterations in management occurred in 43%, most frequently in patients planned for a conservative, watchful waiting approach.