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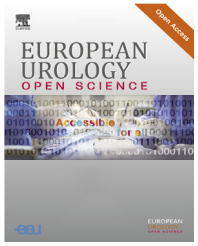

European Association of Urology

Prostate Cancer

High Detection Rates for Prostate-specific Membrane Antigen–avid Prostate Cancer Recurrence at Low Prostate-specific Antigen levels on Extended Axial Field-of-view Positron Emission Tomography/Computed Tomography

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Abstract

Background and objective: Although prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) has impacted the investigation and management of biochemical recurrence (BCR) of prostate cancer, negative scans are common at low rising prostate-specific antigen (PSA) levels. PET/CT devices with an extended axial field-of-view, such as the Siemens Biograph Vision Quadra (Quadra) scanner, have substantially higher sensitivity than conventional field-of-view scanners. Our aim was to assess whether the enhanced signal-to-noise ratios achieved on the Quadra scanner improve detection of low-volume disease and thereby increase detection of PC at low PSA levels.
Methods: We analysed data for the first 300 consecutive patients who underwent clinically indicated PSMA PET/CT for BCR using a Quadra scanner. We assessed scan positivity and the location of detected disease by PSA category.
Key findings and limitations: The positivity rate increased with the PSA level from 67% for PSA <0.2 ng/ml to >90% for PSA >1.0 ng/ml ($p < 0.05$). Disease location also differed by PSA category, with prostate bed recurrence alone identified in 63% of positive cases with PSA <0.2 ng/ml, but <25% of cases with PSA >1.0 ng/ml, and distant metastases present in only 6% of positive cases with PSA <0.2 ng/ml versus >40% of cases with PSA >1.0 ng/ml. In the group with PSA <0.2 ng/ml, pelvic nodal disease without local recurrence was identified in 31% of cases.
Conclusions and clinical implications: In comparison to literature data, the Quadra scanner has substantially higher positivity rates at very low PSA levels. At these levels, disease was largely confined to the pelvis and potentially amenable to

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salvage radiotherapy. However, more than one-third of these patients had disease exclusively outside the prostate bed, with implications for the efficacy and morbidity of current salvage radiotherapy approaches.

Patient summary: We investigated a new PET/CT scanner (positron emission tomography/computed tomography) for detection of prostate cancer recurrence. This more sensitive scanner had a higher detection rate, particularly for patients with low PSA (prostate-specific antigen) in their blood. Our results suggest that the new scanner can detect disease recurrence earlier and more accurately than standard PET/CT scanners, which can help in planning further treatment.

1. Introduction

Globally, prostate cancer (PC) is the second most frequently diagnosed cancer among men and a leading cause of death, with an estimated 1.4 million new cases and 375 000 deaths each year [1]. In Australia, PC was the most common cancer diagnosis among males in 2022, with an estimated 24 217 new cases, and the incidence rate is trending upwards [2].

In recent years, prostate-specific membrane antigen (PSMA) positron emission tomography (PET) has been established as a useful tool for staging and restaging of patients with PC, particularly when residual disease is suspected on the basis of prostate specific antigen (PSA) levels in blood after radical prostatectomy (RP) or radiotherapy (RT) with curative intent [3]. This clinical setting is termed biochemical recurrence (BCR) and is usually defined as PSA $\geq$0.2 ng/ml after RP or a >2 ng/ml rise above the PSA nadir after RT [4]. However, the introduction of high-sensitivity PSA testing has led to the diagnosis of residual disease at lower PSA levels after RP, particularly if levels are increasing on serial testing [5]. The rationale for monitoring for BCR is to identify patients whose recurrence is confined to the pelvis and therefore suitable for curative approaches. Unfortunately, patient selection for locoregional treatment approaches has been compromised by the limited sensitivity of conventional imaging—including abdominopelvic computed tomography (CT), magnetic resonance imaging, and whole-body bone scanning—at low PSA levels [6]. As a consequence of limited ability to accurately identify sites of recurrence in patients with BCR, treatments—including androgen deprivation therapy (ADT), RT, chemotherapy, and in some cases a combination of systemic therapies—have been selected on a largely empirical basis [7]. For individual patients, treatment choices have traditionally been guided by several variables, including the initial tumour grade, the degree of PSA elevation and the PSA doubling rate, patient age, and comorbidities [8].

PSMA PET/CT has greater accuracy than conventional imaging and has significantly influenced evaluation of PC in both primary staging and BCR settings. An Australian multicentre prospective randomised controlled trial comparing PSMA PET/CT with conventional imaging demonstrated the superiority of PSMA PET for primary staging of intermediate- to high-risk PC, particularly by detecting nodal and distant metastatic disease [9]. In the trial, PSMA PET/CT findings resulted in a change of planned therapeutic management for approximately 50% of all patients. On the basis of these and other data, PSMA PET/CT is now reimbursed in Australia, but reimbursement is limited to one scan for primary staging and two lifetime studies for evaluation of BCR.

In the BCR setting, PSMA/CT PET has the greatest clinical utility for patients with PSA in the lower range, with management changes for 42.4% of patients with PSA 0.2–0.4 ng/ml; 27.7% of those with PSA 0.5–1 ng/ml; 21.2% of those with PSA 1.1–2 ng/ml; and 8.7% of patients with PSA >2 ng/ml [10]. At low PSA levels there is a higher likelihood of effective salvage local or locoregional RT because of the a priori likelihood that residual disease is sufficiently low in volume and/or confined in extent to justify locoregionally directed treatment, even when empirically directed [11]. In this treatment scenario, more accurate localisation of disease recurrence should increase the likelihood of treatment success and minimise unnecessary toxicity. Although the enhanced accuracy and treatment impact of PSMA PET/CT has impacted routine evaluation and reimbursement policies for patients with BCR worldwide, the likelihood of positive PSMA PET/CT findings is strongly impacted by the degree of PSA elevation when conventional field-of-view (CFOV) PET scanners are used. For example, a recent meta-analysis found that the positive rate for PSMA PET/CT averaged only 30%, 47%, and 65% at PSA levels of <0.2 ng/ml, 0.2–0.49 ng/ml, and 0.5–<1.0 ng/ml, respectively, with a relatively wide range among the studies evaluated [12].

With the reimbursement restrictions in Australia and the cost of imaging or lack of funding in other jurisdictions, such data have discouraged clinicians from referring patients for PSMA PET/CT at PSA levels <0.2 ng/ml because of the high risk of a false-negative study. When recurrence is detected at a low PSA level, empiric RT to the prostate bed with or without the pelvic nodes is an option despite the proven limitations of this approach [13], or when PSMA PET/CT evaluation is delayed, even though the chances of curative salvage treatment are diminished at higher PSA levels. More sensitive localisation of low-volume recurrence located outside RT template fields may identify patients who are unsuitable for empiric RT plans. More accurate localisation can also guide appropriate stereotactic RT in patients with oligometastatic disease without prostate bed

recurrence, sparing patients adverse effects from unnecessary prostate-bed RT and early use of ADT. Results from the TRANSFORM trial support this strategy [14], which has potential to significantly impact patient care pathways and quality of life.

Despite the incremental accuracy of PSMA PET/CT over conventional imaging, localisation of recurrent PC at low PSA levels is ultimately constrained by the technical ability of each PET scanner to detect small volumes of tumour. Using a CFOV PET/CT device, rigorous histopathological correlation of lymph node recurrences demonstrated that false-negative findings are strongly associated with both absolute nodal size and, perhaps more importantly, lesion size within nodes [15]. High signal-to-noise performance is particularly important for detection of small lesions. There have been substantial advances in recent years with the development of a new generation of digital PET scanners incorporating enhanced time-of-flight (TOF) information ($\leq$250 ps) with a significant improvement in performance [16]. These advances in PET detector performance have been incorporated in the Siemens Biograph Vision Quadra (Quadra) system, along with extended axial field-of-view (EFOV) PET (106 cm), resulting in greatly enhanced scanner sensitivity [17,18].

The aims of our study were to optimise PET acquisition protocols and to define appropriate use criteria for the high-sensitivity EFOV Quadra PET scanner for BCR evaluation. To this end, we analysed the positivity rate for our initial cohort of patients across PSA levels. We hypothesised that the superior sensitivity of this scanner, including practical application of dynamic imaging immediately after tracer injection, would improve the detection of residual disease at lower PSA levels in comparison to historical controls.

2. Methods

2.1. Study design

After receipt of ethics approval (Bellberry Human Resource Ethics Committee reference 2023-12-1561), a retrospective study was conducted at the Melbourne Theranostic Innovation Centre. Patients were included if they had a Quadra PSMA PET/CT scan for BCR as part of their routine clinical care and had a PSA blood test within 2 wk of the scan. The following imaging protocol was used:

- Initial dynamic series: 10-min acquisition commencing at bolus injection of 1 MBq/kg of [^{18}F]-DCFPyL from which images were reconstructed into ten 1-min frames encompassing the vertex of the skull to the proximal thighs.
- Delayed scan: 4-min static scan acquired approximately 60 min after tracer injection, with the same regions imaged.
- Additional delayed postdiuretic imaging if deemed necessary to resolve clinical uncertainty.

All PET images were acquired in list mode using a matrix of 440 and a slice thickness of 5 mm. All PET images were reconstructed using the iterative reconstruction ordered-subsets expectation maximization (OSEM) algorithm incorporating TrueX + TOF (ultra high-definition PET) with four iterations, five subsets, and 5-mm Gaussian filtering. Attenuation, decay, scatter, and random corrections were performed during reconstruction.

Low-dose CT was performed for attenuation correction and anatomic localisation purposes, using a tin filter, CARE kV, and ADMIRE reconstructions to reduce the effective CT dose. Patients were asked to hydrate on the day and were encouraged to void between the time of tracer injection and delayed imaging.

A total of 300 consecutive patients who underwent PSMA PET/CT were included in the analysis, stratified by PSA level into the following groups: 0–0.2 ng/ml; 0.2–0.5 ng/ml; 0.5–1.0 ng/ml; 1.0–2.0 ng/ml; and >2.0 ng/ml n g/ml.

Scans, including early dynamic phase images, were classified according to the clinical report by a nuclear medicine specialist with more than 30 yr of experience in PET, including almost 10 yr of reading PSMA PET studies. The positivity rate was calculated for each PSA subgroup, with scans graded as either positive, negative or equivocal, defined as follows:

- Positive: unequivocal evidence of PSMA-expressing disease.
- Equivocal: uptake only considered suspicious or possible evidence of PSMA-expressing disease, including either lack of a nodal correlate on CT in this initial phase of the evaluation or lesions in atypical locations considered to represent a potential alternative pathological process.
- Negative: no evidence of PSMA-expressing disease.

Scans were further classified by disease location into the following groups:

1. Local recurrence only: the vesicourethral anastomosis site and/or the prostatic vascular pedicles (PVPs; Figs. 1 and 2).
2. Pelvic nodal recurrence only: up to the lumbosacral junction.
3. Local and pelvic nodal recurrence.
4. Distant metastatic disease: retroperitoneal, mediastinal, or supraclavicular nodal, bone, or visceral lesions considered likely to represent metastasis.

3. Results

A total of 300 consecutive patient scans were collected for analysis. Figure 3 shows a summary of the results stratified for each PSA subgroup. Overall, 251 scans (83%) were reported as positive, five (2%) were reported as equivocal, and 44 (15%) were reported as negative. The rate of detection of PSMA-avid disease increased from 67% of cases at PSA <0.2 ng/ml to 75% at PSA 0.2–0.5 ng/ml, 84% at PSA 0.5–1.0 ng/ml, and 95% at PSA 1.0–2.0 ng/ml. There was a slight reduction in the rate of PSMA-avid disease in the highest PSA group (>2.0 ng/ml) to 92% of cases.

Scans positive for disease recurrence were subdivided into subgroups according to the recurrence location, as shown in Figure 3. The rate of distant metastasis increased

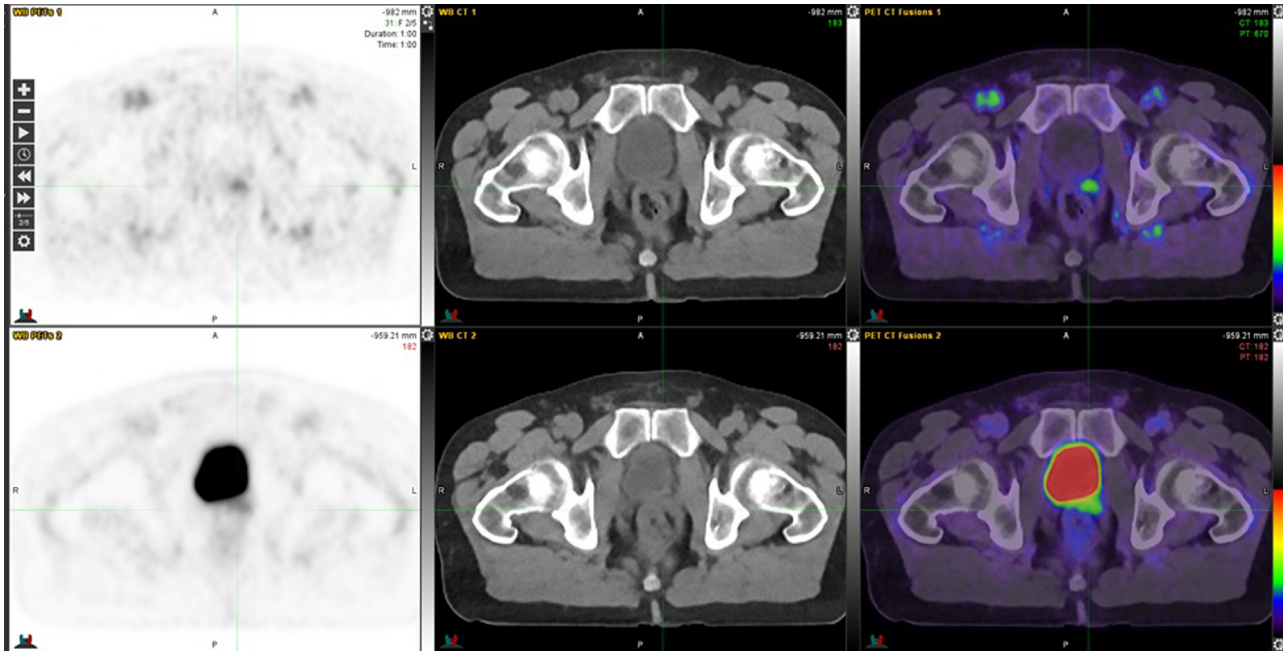

Fig. 1 – Example images for a 56-yr-old patient 3 yr after robot-assisted radical prostatectomy with prostate-specific antigen of 0.142 ng/ml and evidence of local recurrence only. Prostate-specific membrane antigen uptake is clearly evident in the prostatic vascular pedicles on the early blood pool image (top row) before bladder filling.

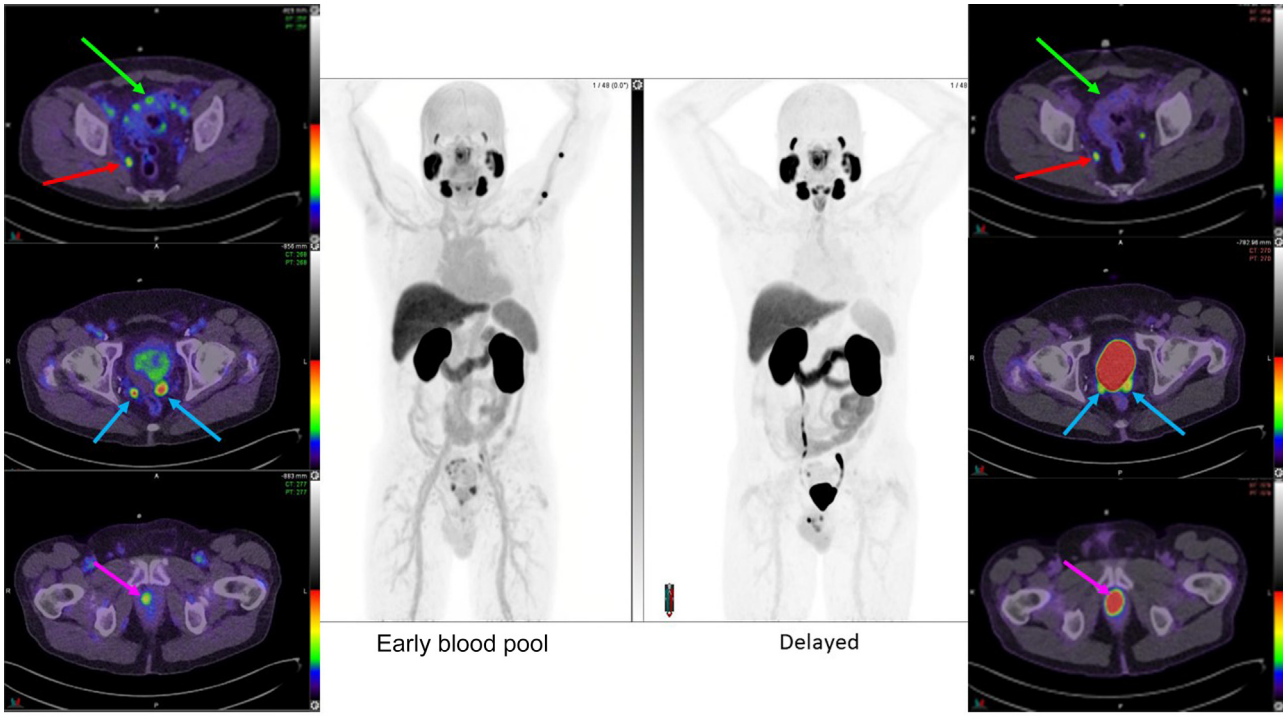

Fig. 2 – Example images for a 63-yr-old patient 6 yr after radical prostatectomy with positive margins and prostate-specific antigen of 18 ng/ml with local and pelvic nodal recurrence in bilateral prostatic vascular pedicles (blue arrows), the vesicourethral anastomosis site (pink arrow), and the right obturator node (red arrow). Bowel uptake on early blood pool imaging that washes out on the delayed scan indicates diverticulitis.

with the PSA level from 6% at PSA <0.2 ng/ml to >52% at PSA >2.0 ng/ml. Although a small proportion of patients in the lower PSA groups did have distant metastasis, as shown in Figure 4, these patients generally had only local (37%) or pelvic nodal (19%) recurrence. Importantly, when recurrence was detected, more than two-thirds of patients with PSA of 0.2–0.5 ng/ml had disease recurrence beyond the prostate bed. These are the patients who are most likely

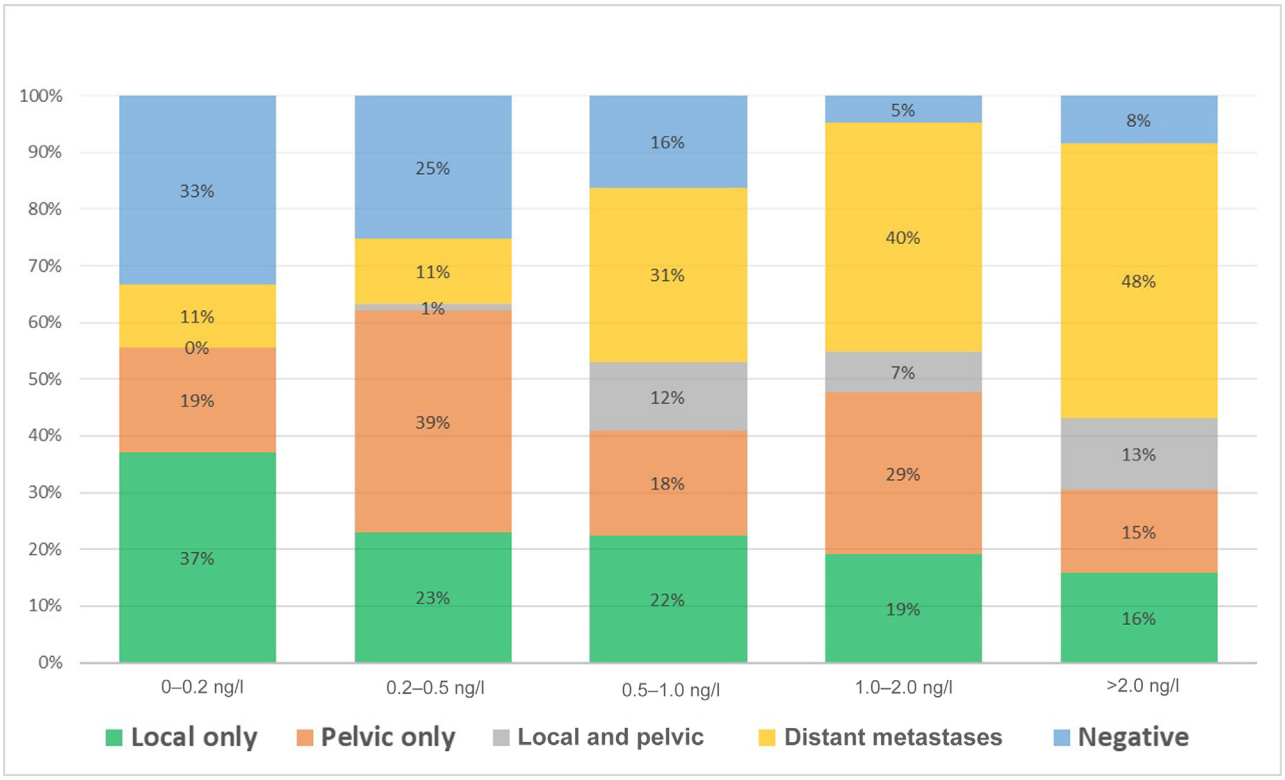

Fig. 3 – Detection rates via prostate-specific membrane antigen positron emission tomography by disease location for prostate-specific antigen levels of 0–0.2 ng/ml (*n* = 27), 0.2–0.5 ng/ml (*n* = 87), 0.5–1 ng/ml (*n* = 49), 1.0–2.0 ng/ml (*n* = 42), and >2.0 ng/ml (*n* = 95).

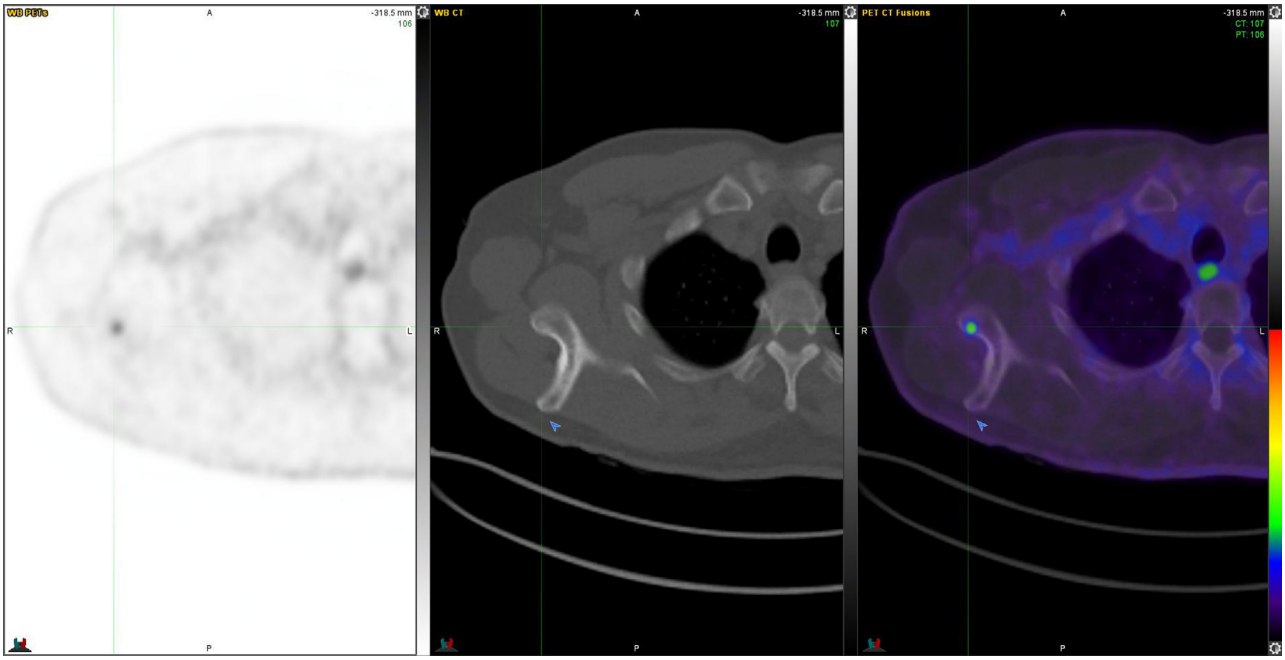

Fig. 4 – Prostate-specific membrane antigen positron emission tomography/computed tomography images for a 65-yr-old patient 11 yr after robot-assisted radical prostatectomy with positive margins and prior bone metastases and prostate-specific antigen of 0.03 ng/ml showing low-volume bone metastasis in the right scapula.

to receive salvage RT to the prostate bed under current management algorithms.

4. Discussion

These data suggest an improvement in detection rate for patients with BCR when scanned with an EFOV PET/CT scanner in comparison to historical controls imaged using CFOV PET/CT scanners [12,19]. In the very low PSA group (<0.2 ng/ml), the detection rate using the Quadra scanner was 67%, compared to a mean positivity rate of 30% reported in a recent meta-analysis [12]. The additional impact of early phase dynamic scanning was not analysed in the paper. However, there were examples in which recurrence in the prostate bed could only be visualised on the early dynamic sequence as it was subsequently obscured on the standard delayed time point because of urinary activity in the bladder (Fig. 1). A dynamic scan can, of course, be performed over the pelvis using a CFOV scanner and the benefits of dynamic imaging in identifying prostate bed recurrences has been demonstrated by others [20]. This does not preclude an incremental benefit from the use of an EFOV scanner, as dynamic series scans on CFOV PET/CT devices are potentially count-limited, which decreased the signal-to-noise ratio unless the list-mode data are processed as relatively long frames, which would compromise the temporal resolution of the scans. Our general reading regimen is to go to the last frame without bladder urinary activity and assess the vesicourethral anastomosis and PVP regions on this frame. Disease detected in the PVPs has been recognised as a site of local recurrence on PSMA PET/CT [21] and localisation is important, as the PVPs can be treated with stereotactic RT with a lower risk of continence issues than for treatment of the vesicourethral anastomosis. While detection of prostate bed recurrence might be considered of limited utility in patients with low PSA if their disease site would be covered by an empiric template for prostate bed RT, it is important to note that more than one-third of patients with PSA <0.2 ng/ml did not have evidence of local recurrence and only had pelvic nodal or distant disease. Such patients could potentially be spared the morbidity of prostate bed RT, including higher incidence of incontinence and bowel symptoms [22]. Furthermore, patients with PSA of 0.2–0.5 ng/ml had evidence of disease beyond the prostate bed and would be unlikely to benefit from RT regimens that only include the prostate bed. Although uncommon in this series, some cases of local recurrence required delayed postdiuretic imaging for confident identification. Higher confidence in dynamic phase abnormalities can be achieved by allowing a longer time for tracer accumulation at sites of disease and dilution of urinary activity. The benefits of delayed imaging have also been demonstrated by others [23]. On the basis of this experience and the workflow implications of three separate imaging series, we have changed our routine acquisition protocol to include only delayed postdiuretic imaging beyond 90 min in our patients with BCR. We are prospectively collecting data for patients imaged using this revised acquisition protocol. We feel that the amended protocol will have practical advantages for departmental workflows and will be less onerous for patients.

The higher effective sensitivity of the Quadra PET scanner appears to translate into a greater ability to detect recurrent or metastatic lesions in patients with very low PSA, which can facilitate early and accurate detection of disease, highlighting the need for a shift in the current practice of waiting until PSA exceeds 0.2 ng/ml. Of interest, the lowest PSA level with a positive finding in our data was 0.02 ng/ml. Our findings also confirm the utility of PSMA PET/CT at PSA >0.5 ng/ml in comparison to conventional imaging [24]. We suspect that the use of a longer uptake period and of diuretics to dilute urinary activity could potentially further enhance the positivity rate, particularly with respect to prostate bed recurrences and for small nodes close to vessels or the ureters, where blood pooling and urinary tracer clearance, respectively, will enhance the contrast between small lesions and adjacent tissues.

As expected, the rate of distant metastatic disease, often of low volume, increased with the PSA level. The implications of these findings for management strategies remain uncertain. However, of note are the cases of distant metastatic disease at very low PSA levels, which could have a significant impact on patient management. At the very least, these findings are likely to prevent futile and morbid local therapies. Whether the use of more highly targeted RT, including stereotactic treatment, for example to lower retroperitoneal nodal metastases will increase salvage rates or delay ADT use remains to be determined by clinical follow-up of patient outcomes. Results after salvage RT following negative CFOV PSMA PET/CT imaging are consistent with the importance of more sensitive detection of disease beyond the prostate bed at both low and higher PSA levels, with 4-yr BCR-free survival rates of 60.7% for PSA $\leq$0.5 ng/ml and only 43% for PSA >0.5 ng/ml [25]. In our series, only 63% of patients with a positive scan had disease confined to the prostate bed, which fell to 31% of patients with PSA between 0.2 and 0.5 ng/ml.

The slight reduction in the detection of PSMA-positive disease at PSA >2 ng/ml is also of interest. Many of the patients in our series with this level of PSA elevation had negative results from prior PSMA studies performed on a CFOV PET/CT scanner, so we suspect that pretest selection bias may have enriched this subgroup in patients whose tumours had no or very low PSMA expression.

Despite the encouraging results, our study has limitations inherent to its retrospective design and single-centre setting. Importantly, the analysis covered the first 300 patients evaluated on the scanner for BCR. Thus, although scans were read by a highly experienced PSMA PET/CT reader, there may have been a learning curve. Nevertheless, few equivocal cases were recorded. If there was selection bias, we suspect that it would have been towards patients with a lower rather than a higher likelihood of a false-negative result since many patients had previously been imaged using a CFOV scanner, with negative findings reported. Moreover, no pathological verification of positive findings was undertaken, but prior studies have confirmed the low false-positive rate of PSMA PET/CT imaging

[26–28]. Furthermore, in the context of elevated PSA, it can be assumed that most negative scans are false negatives. The possibility of other potential confounding variables cannot be excluded. Further prospective studies with larger and more diverse patient populations are needed to confirm these findings and assess the long-term impact of PSMA imaging using an EFOV PET/CT scanner on patient management and survival. In addition, cost-effectiveness analyses are crucial for determining the optimal role of this new technology in the clinical management of PC. A focus of future research will be the incremental value of initial dynamic imaging in comparison to delayed postdiuretic imaging, which we did not analyse in this study because of inconsistent use of the latter in this series. Longer-term follow-up will be needed to determine how the apparently more sensitive detection of disease and definition of disease extent impacts treatment choices and patient outcomes in terms of salvage or delayed use of ADT, or earlier introduction of more aggressive treatment regimens. Nevertheless, we feel that reporting of the results obtained so far is timely as groups consider investing in these substantially more expensive devices.

5. Conclusions

Our results demonstrate the potential of the Siemens Biograph Vision Quadra PET scanner, with its enhanced sensitivity, to improve the detection rate for PC recurrence in patients with BCR. In comparison to historical data captured using CFOV scanners, the Quadra PET/CT scanner identified a higher proportion of positive cases, especially at very low PSA levels. This finding suggests the potential for earlier and more accurate detection of recurrence and the possibility of better patient outcomes. The distribution of disease at different PSA levels also has important implications for salvage treatment approaches.

Author contributions: Jason Callahan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Hicks, Callahan, Thomas.
Acquisition of data: Hicks, Callahan, Ware, Thomas, Morgan, Ingbritsen, Munro.
Analysis and interpretation of data: Hicks, Ware, Callahan, Thomas, Conway, Dundee, Moon.
Drafting of the manuscript: Thomas, Callahan, Ware, Hicks.
Critical revision of the manuscript for important intellectual content: Hicks, Ware, Callahan, Thomas, Conway, Dundee, Moon.
Statistical analysis: Hicks, Callahan, Thomas.
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Administrative, technical, or material support: Hicks, Callahan, Ware, Thomas, Morgan, Ingbritsen, Munro.
Supervision: Hicks.
Other: None.

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