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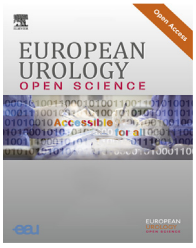

European Association of Urology

Prostate Cancer

Defining Prostatic Vascular Pedicle Recurrence and the Anatomy of Local Recurrence of Prostate Cancer on Prostate-specific Membrane Antigen Positron Emission Tomography/Computed Tomography

Philip Dundee[a,b,c,d,*], *Marc A. Furrer*[a,b,d,e], *Niall M. Corcoran*[a,c], *Justin Peters*[a,b,c,d], *Henry Pan*[e], *Zita Ballok*[f], *Andrew Ryan*[g], *Mario Guerrieri*[h], *Anthony J. Costello*[a,b,c,d]

[a] *Department of Urology, The University of Melbourne, Royal Melbourne Hospital, Grattan Street Parkville, Australia 3052;* [b] *The Australian Medical Robotics Academy, North Melbourne, Australia;* [c] *Australian Prostate Cancer Centre, North Melbourne, Australia;* [d] *Epworth Healthcare, Melbourne, Australia;* [e] *Department of Urology, University Hospital of Bern, University of Bern, Bern, Switzerland;* [f] *TissuPath, Mount Waverley, Australia;* [g] *Healthcare Imaging Services, Melbourne, Australia;* [h] *GenesisCare, Footscray, Australia*

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Abstract

Background: The term *local recurrence* in prostate cancer is considered to mean persistent local disease in the prostatic bed, most commonly at the site of the vesicourethral anastomosis (VUA). Since the introduction of prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging for assessment of early biochemical recurrence (BCR), we have found histologically confirmed prostate cancer in the prostatic vascular pedicle (PVP). If a significant proportion of local recurrences are distant to the VUA, it may be possible to alter adjuvant and salvage radiation fields in order to reduce the potential morbidity of radiation in selected patients.
Objective: To describe PVP local recurrence and to map the anatomic pattern of prostate bed recurrence on PSMA PET/CT.
Design, setting, and participants: This was a retrospective multicentre study of 185 patients imaged with PSMA PET/CT following radical prostatectomy (RP) between January 2016 and November 2018. All patient data and clinical outcomes were prospectively collected. Recurrences were documented according to anatomic location. For patients presenting with local recurrence, the precise location of the recurrence within the prostate bed was documented.
Intervention: PSMA PET/CT for BCR following RP.
Results and limitations: A total of 43 local recurrences in 41/185 patients (22%) were identified. Tumour recurrence at the PVP was found in 26 (63%), VUA in 15 (37%), and within a retained seminal vesicle and along the anterior rectal wall in the region of the neurovascular bundle in one (2.4%) each. Histological and surgical evidence of PVP recurrence was acquired in two patients. The study is limited by its retrospective nature with inherent selection bias. This is an observational study

* Corresponding author. Department of Urology, Royal Melbourne Hospital, The University of Melbourne, Parkville, Victoria, Australia. Tel. +61 3 9342 7294.
E-mail address: phildundee@gmail.com (P. Dundee).

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reporting on the anatomy of local recurrence and does not include follow-up for patient outcomes.

Conclusions: Our study showed that prostate cancer can recur in the PVP and is distant to the VUA more commonly than previously thought. This may have implications for RP technique and for the treatment of selected patients in the local recurrence setting.

Patient summary: We investigated more precise identification of the location of tumour recurrence after removal of the prostate for prostate cancer. We describe a new definition of local recurrence in an area called the prostatic vascular pedicle. This new concept may alter the treatment recommended for recurrent disease.

1. Introduction

Despite good oncological outcomes from radical prostatectomy (RP) in most patients, approximately 30% of patients will experience biochemical recurrence (BCR) after RP and many of these patients will be diagnosed with a "local recurrence" [1,2]. The term *local recurrence* is considered in most cases to mean persistent local disease in the prostatic bed, but there is evidence that, at least in some patients, local recurrence represents metastatic seeding back to the prostatic bed from distant sites [3]. The precise location of local recurrence has been described in a small number of studies on the basis of ultrasound and magnetic resonance imaging (MRI), including areas adjacent to the vesicourethral anastomosis (VUA), in the rectovesical space, or within retained seminal vesicles (SVs) or the SV bed. Perianastomotic recurrence is considered to be the most common site [4–7]. This belief has meant that adjuvant and salvage radiotherapy targeting and dosimetry strategies are universally inclusive of the anastomotic area in addition to the wider prostatic and SV bed, including the bladder base. This can sometimes lead to significant morbidity due to the development of anastomotic strictures, deterioration of continence, and the occurrence of radiation proctitis and cystitis. Patients suffering from these complications are often subjected to multiple surgical interventions and in extreme cases may require hyperbaric oxygen or even cystectomy.

The introduction of prostate cancer–specific molecular imaging for investigation of recurrence after primary treatment has improved the detection of metastatic disease in comparison to conventional imaging [8]. In many centres in Australia and other countries, prostate-specific membrane antigen (PSMA) positron emission tomography/computed tomography (PET/CT) is now used routinely for investigation of patients experiencing BCR following RP [9,10].

We hypothesise that local recurrence is distant to the VUA more commonly than previously thought and provide surgical and histological evidence of recurrence in the prostatic vascular pedicle (PVP). This has not previously been described. The pattern of local recurrence described may have implications for surgical techniques at RP as well as for salvage or adjuvant radiation treatment fields.

2. Patients and methods

2.1. Patient population

We retrospectively reviewed all patient discussion notes from multidisciplinary team (MDT) meetings on advanced prostate cancer between January 2016 and November 2018 to identify patients with local recurrence on PSMA PET/CT following RP. This period was chosen as it represents our initial experience with PSMA PET/CT, typically in patients with higher prostate-specific antigen (PSA) than in more recent patient populations resulting in a higher incidence of positive scans (supported by Perera et al [11], who reported positive scan rates of 42%, 58%, 76%, and 95% for the PSA categories 0–0.2, 0.2–1, 1–2, and >2 ng/ml, respectively). All patients referred for discussion in the MDT meeting who experienced biochemical failure following primary treatment were routinely offered imaging with PSMA PET/CT. All patient data were prospectively collected at the time of MDT discussion and clinical outcomes were prospectively followed up according to our institutional protocols. Patients were included for analysis if they experienced BCR after definitive management with RP and underwent subsequent PSMA PET/CT imaging.

Recurrences were documented according to anatomic location. For patients presenting with local recurrence, the precise location of the recurrence within the prostate bed or periprostatic area was documented. Images were viewed independently and blinded to the imaging report by an experienced urologist (P.D.) and a specialist nuclear medicine radiologist (Z.B.). Where there was discrepancy between location recurrences reported, the imaging was reviewed together so that agreement could be achieved. Any avidity directly adjacent to the VUA but separate from the bladder was considered to represent anastomotic recurrence. Avidity in the triangular space bounded by the obturator internus muscle laterally, the bladder anteromedially, and the mesorectal fat posteromedially was considered to represent a recurrence at the PVP. In many patients this was confirmed by the presence of vessel clips placed at the time of surgery to secure haemostasis in this large vascular pedicle, and in two patients recurrence in the PVP was confirmed both surgically and histologically. Recurrences separate to these two regions were described according to adjacent anatomic structures. We compared clinicopathological data with data for a similar cohort of patients presenting with pelvic recurrence without local recurrence over the same time frame in order to determine any predictors of prostate bed recurrence.

Demographic and clinical data were collected prospectively and included patient age, pathological grade, stage and margin status, PSA at PSMA PET/CT imaging, and time from RP to PSMA PET/CT imaging. Surgical and histological confirmation of PVP recurrence was obtained in two patients (Figs. 1 and 2). The study protocol was approved by the local ethics committee (QA2021004).

2.2. Definition of BCR

BCR was defined as PSA ≥0.2 ng/ml on two consecutive measurements [12–14].

2.3. PSMA PET/CT acquisition

All patients but one underwent ^{68}Ga-PSMA-HBED-CC PSMA PET/CT imaging [15,16]. A single patient underwent ^{18}F-PSR PSMA PET/CT imaging. Scans were performed in different centres in Melbourne, Australia.

^{Ga}68-PSMA-HBED-CC was produced using an IRE Galli Eo ^{68}Ge/^{68}Ga generator with a Scintomics (FruFürstenfeldbruck, Germany) GRP module. Radiotracer purity was confirmed using instant thin-layer chromatography, high-performance liquid chromatography, and pH testing.

The patient dose was 1.3–2.0 MBq/kg and intravenous Lasix (20 mg) was administered 10 min after tracer injection unless significant urinary symptoms were reported. During the uptake phase of 60–90 min, patients were hydrated orally with water. Images were obtained using a Siemens (Munich, Germany) Biograph mCT 20 Excel scanner.

After voiding, imaging was started with low-dose CT scan acquisition (120 kV, 30–50 mAs, 16 × 1.2-mm collimation with 1.0 pitch, rotation time of 0.5 for a 780-mm field of view for attenuation correction) with a slice thickness of 3 mm in 2-mm increments using Siemens CARE Dose 4D.

PET acquisition was performed in the caudocranial direction from the mid-thigh to the vertex with a 3–4-min bed position; dose modulation was used for CT attenuation correction.

PET slices were reconstructed using iterative reconstruction and time of flight (two iteration/21 subsets) with transaxial spatial resolution of 7.0 mm (full width at half-maximum) in the reconstructed PET images. The lung field was also reconstructed separately using a lung kernel and a maximum intensity reconstruction.

Axial, sagittal, and coronal PET and CT images and fused PET/CT images were reviewed using Syngo (Siemens) software for image analysis and interpretation.

2.4. Tissue processing

Specimens were routinely fixed in their entirety in formalin and blocked in paraffin. Transverse sections at 3.5-mm intervals were cut perpendicular to the urethra from the apex to the base throughout the entire specimen. Sections of 5 mm were taken from each slice and stained with haematoxylin and eosin. All specimens were reviewed by the same specialist uropathologist. To define the cancer burden, tumour borders were outlined manually with a pen, the slides were digitised, and then the tumour and whole-gland volumes were calculated using image analysis software [17].

2.5. Statistical analysis

Qualitative data are presented as the frequency and percentage and were assessed using a χ^2 test or Fisher's exact test. Quantitative data are presented as the median and interquartile range (IQR) or mean and standard deviation and were assessed using the Kruskal-Wallis or Wilcoxon rank-sum test. Statistical significance was set at a two-sided p value <0.05 (SPSS v23.0; IBM, Armonk, NY, USA).

3. Results

Among 185 patients who were referred to our institution's advanced prostate cancer MDT after primary treatment

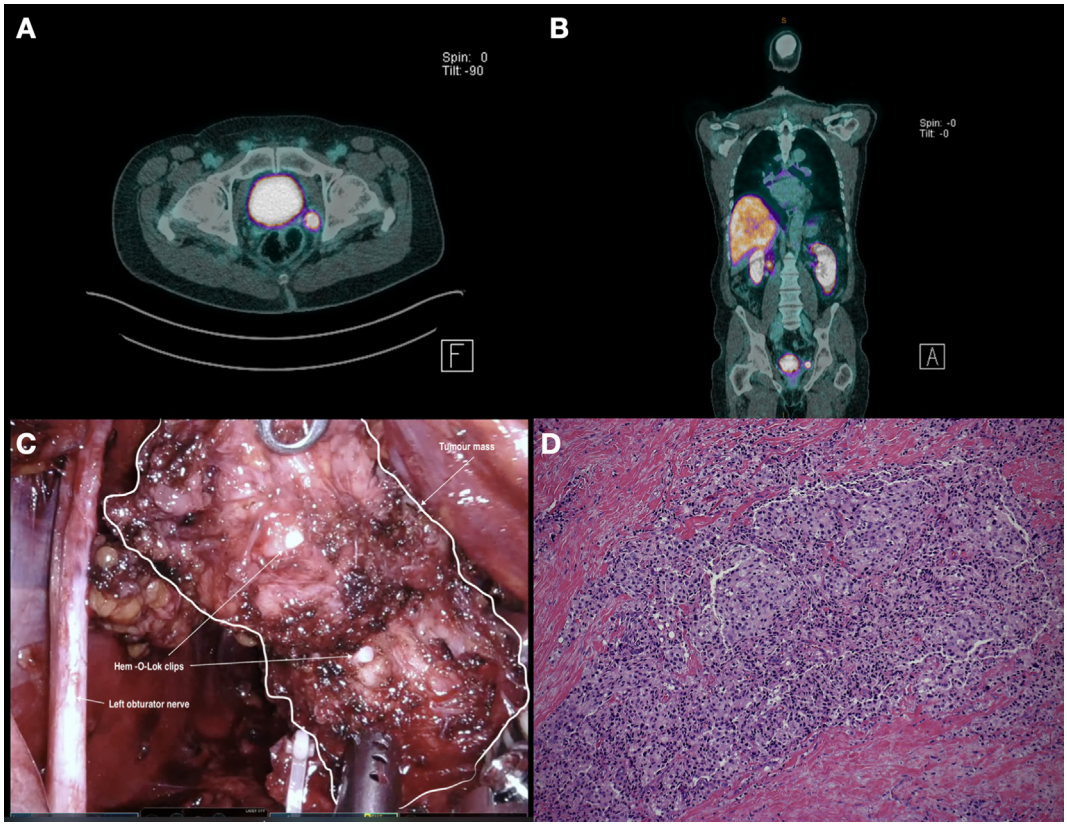

Fig. 1 – (A,B) Prostate-specific membrane antigen positron emission tomography imaging of an intensely avid recurrence in the region of the left prostatic vascular pedicle. (C) Intraoperative image of a tumour deposit centred on the prostatic pedicle with Hem-O-Lok clips clearly visible. (D) Histological confirmation of high-grade prostate adenocarcinoma within fibroadipose tissue with no visible lymphoid tissue.

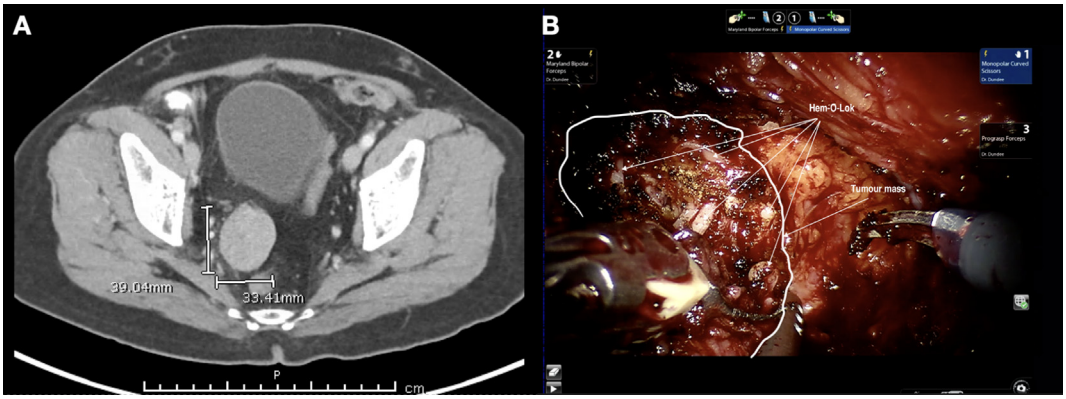

Fig. 2 – (A) Axial computed tomography imaging showing a large recurrence in the region of the right prostatic vascular pedicle. (B) Intraoperative imaging showing the base of the recurrence centred around multiple Hem-O-Lok clips.

with RP followed by PSMA PET/CT imaging for BCR, 43 local recurrences in 41 patients (22%) were identified (Table 1).

A further 72 patients (39%) with pelvic recurrence without local recurrence were identified. There were 67 patients without evidence of recurrence within the pelvis on PSMA PET/CT imaging. Among patients with local recurrence, the median PSA at PSMA PET/CT imaging was 1.34 ng/ml (IQR 0.65–2.84). The median time from RP to PSMA PET/CT imaging was 64 mo (IQR 22–112). Of the 41 patients with imaging and full pathology results available, 32 (78%) had International Society of Urological Pathology (ISUP) grade group ≥3 disease, 15 (37%) had stage pT3a cancer, 15 (37%) had SV invasion, and seven (17%) had positive lymph nodes (LNs). Surgical margins were involved by tumour in 21 patients (51%). Eleven patients (27%) had organ-confined and margin-negative disease.

There were 26 patients (63%) with recurrence in the PVP, 15 (37%) with recurrence at the VUA, one (2.4%) with recurrence within a retained SV, and one (2.4%) with recurrence along the anterior rectal wall in the region of the neurovascular bundle. Two patients had concurrent local recurrence at both the VUA and the PVP. The patient with disease within a retained SV had a soft tissue mass within a structure identical to a SV, which was confirmed on MRI. Of the 26 patients with recurrence within the PVP, only nine (35%) had a solitary recurrence. Among the remaining 17 patients with PVP recurrence, two had extrapelvic disease, 12 had recurrence in pelvic LNs, two had additional local recurrence at the VUA, and one had pelvic bone metastases. Among the patients with recurrence at the VUA, ten had a solitary VUA recurrence, two had concurrent local recurrence in the PVP, and three had concurrent nodal metastases. Some 62% (n = 16/26) of the patients with PVP recurrence and 27% (n = 4/15) of the patients with VUA recurrence had margin-positive disease (p = 0.06). Some 81% of the PVP recurrence group and 75% of the VUA recurrence group had unifocal margins (Table 2). Ten patients with local recurrence on PSMA PET/CT underwent pelvic MRI, which revealed local recurrence concordant with the PSMA PET/CT findings in only four cases. A single patient had a PVP local recurrence detected on MRI with negative PSMA PET/CT.

Table 1 – Comparison of clinicopathological data for patients with pelvic recurrence of prostate cancer on prostate-specific membrane antigen PET imaging with and without prostate bed recurrence

	Local recurrence (n = 41)	Pelvic recurrence, no local recurrence (n = 72)	p value
Age at RP, yr (standard deviation)	63.5 (7.74)	64.2 (7.7)	0.64
ISUP grade group ≥3, n (%)	32 (78)	59 (82)	0.63
Stage, n (%)			0.29
pT2	13 (32)	15 (21)	0.083
pT3a	15 (37)	26 (36)	
pT3b	15 (37)	26 (36)	
Positive margin, n (%)	21 (51)	23 (32)	0.15
pT2R0, n (%)	11 (27)	14 (19)	0.57
Time from RP to PET, mo (IQR)	64 (22–112)	46 (17–83)	0.07
Median PSA at PET, ng/ml (IQR)	1.34 (0.65–2.84)	1.44 (0.67–5.0)	0.3

IQR = interquartile range; ISUP = International Society of Urological Pathology; PET = positron emission tomography; PSA = prostate-specific antigen; RP = radical prostatectomy.

In the additional 72 patients with findings of pelvic recurrence without local recurrence, 66 had LN metastases, 13 had pelvic bone metastases, and 17 had extrapelvic metastases in addition to pelvic LN and/or pelvic bone metastases. Among these patients, the median PSA at PSMA PET/CT imaging was 1.44 ng/ml (IQR 0.67–5.0) and the median time from RP to PSMA PET/CT imaging was 46 mo (IQR 17–83). Fifty-nine patients (82%) had ISUP grade group ≥3 disease, 26 (36%) had stage pT3a cancer, 26 (36%) had SV invasion, and five (7%) had positive LNs. Full pathology was not available for four patients. Margins were positive in 23 patients (32%). Fourteen patients (20%) had organ-confined and margin-negative disease. We did not identify any clinical predictors of local recurrence as there were no significant differences between patients with local recurrence and those with pelvic recurrence without local recurrence (Table 1).

Table 2 – Detailed description of surgical margin status and margin location in 41 patients with local recurrence of prostate cancer

	PVP recurrence (n = 26)	VUA recurrence (n = 15)	p value
Positive surgical margin, n (%)	16 (62)	4 (27)	0.06
Margin location, n (%)			
Unifocal	13 (81)	3 (75)	
Apex	9 (56)	1 (25)	0.083
Base	2 (13)	1 (25)	
Bladder neck	2 (13)	1 (25)	
Multifocal			
Apex and base	1 (6)	1 (25)	0.57
Bilateral base	1 (6)	–	0.07
Apex and bladder neck	1 (6)	–	0.3

PVP = prostatic vascular pedicle; VUA = vesicourethral anastomosis.

4. Discussion

The anatomy of local recurrence in prostate cancer is ill defined. While recurrence is usually considered to represent incompletely resected disease, the relationship between margin status and local recurrence is complex. Positive margin status is known to increase the risk of BCR, and four randomised trials have shown that adjuvant radiation after RP improves BCR-free survival in comparison to a watchful waiting strategy, with the greatest benefit for those with positive margins [18–21]. While this evidence supports the hypothesis that local recurrence may represent incompletely resected disease, it is also true that approximately half of patients with a positive margin will not experience BCR [22]. Furthermore, imaging studies have been unable to show a correlation between positive margins and the development of macroscopically detectable disease [5,6].

Our data set shows that the distribution of local recurrence differs from previous descriptions that were based on ultrasound and MRI. We describe local recurrence in the PVP for the first time, having confirmed recurrence in this location histologically and pathologically in two patients. Although surgical resection is not the standard of care for local recurrence, in both patients the initial assessment was of recurrence in internal iliac LNs on PSMA PET/CT imaging. It was only at the time of salvage pelvic LN dissection that it became apparent the recurrences were in the PVP and not LNs, as evidenced by the absence of lymphoid tissue in the surgical specimens and the location of the recurrences, which were centred around the Hem-O-Lok clips placed on the pedicle at the time of RP.

Historically, local recurrence was a clinical diagnosis on the basis of palpable recurrence on rectal examination. Transrectal ultrasound, then MRI, and now molecular imaging have been utilised to diagnose early development of local recurrence at low PSA levels (>0.2 ng/ml) before it becomes palpable.

There are only a few publications documenting the exact anatomic location of local recurrence [4–6]. Transrectal ultrasound provides suboptimal image quality but can be used to guide core biopsy for pathological confirmation. Pelvic MRI has been the imaging modality of choice when local recurrence is suspected and can detect disease even at low PSA levels [6,23–27]. PSMA PET/CT imaging is able to detect disease at very low PSA levels, with up to 42% of scans positive when PSA is <0.2 ng/ml and, unlike pelvic MRI, distant disease can be documented in addition to local recurrence [11]. Resolution around the VUA on PSMA PET/CT may be compromised because of pooling of the tracer within the bladder and it is possible that some VUA recurrences may be missed on PSMA PET, but previous studies have shown no difference in the detection rate of local recurrence between PSMA PET/CT and pelvic MRI [28,29]. The combination of PSMA PET and MRI detects significantly more local recurrences than either modality alone [28,29]. Although there is a significant cost implication for combined PSMA PET scanning with MRI, this may be the optimal approach for defining the exact location of prostate bed and other recurrences.

Earlier imaging studies documenting local recurrence reported perianastomotic recurrence only, but later studies included recurrence that was thought to be within the retained SVs or in the SV bed, the retrovesicle space, and the anterior and lateral surgical margins [6]. The SVs have a characteristic appearance on imaging and recurrence within a retained SV should be easy to identify on either MRI or PSMA PET/CT. A previous MRI series of local recurrences described all recurrences as perianastomotic but included an image that appears to show a recurrence in the region of the PVP [4]. A further MRI study shows a soft tissue mass surrounding surgical clips at the site of the PVP and another image showing what is described as the "fibrotic remnants of the seminal vesicle", with a contralateral recurrence [6]. The imaging included appears to show PVP recurrences and it is probable that most recurrences previously described in the SV bed are probably PVP recurrences. In the current study, VUA recurrence was less common than PVP recurrence, but all regions of recurrence appear to be in relation to vascular structures around the prostate, such as the dorsal venous complex (DVC), or vascular structures at the bladder neck, PVP, and neurovascular bundles. Local recurrence, at least in some cases, may represent tumour in transit, associated with either lymphovascular or perineural invasion.

An understanding of the nature and precise anatomy of local recurrence is critical for determining the most effective treatment. The radiation fields for both adjuvant and salvage radiation have been determined via expert opinion, which in turn has been informed by older imaging studies of local recurrence [30–32]. As yet, there have been no trials to assess different adjuvant or salvage radiation fields to identify the field that optimises the treatment effect whilst minimising morbidity. Bladder neck contracture, radiation cystitis, and proctitis impose enduring morbidity with a profound reduction in quality of life that is very difficult to manage. If the nature and anatomy of local recurrence are better understood, it may be possible to alter the treatment fields (eg, radiation to the entire prostatic bed vs to the PVP recurrence alone) in order to reduce morbidity. Of note, the patients included in our series were at high risk of metatstatic disease according to the clinical features described following RP. This is reflected in the low rate of local recurrence in comparison to metastatic disease in this

series. It is unlikely that patients without local recurrence on molecular imaging but with metastatic disease would have benefited from salvage radiation, yet would have been exposed to potential complications.

A better understanding of the nature of local recurrence may also inform surgical technique for patients with high risk, such as those with ISUP grade group 4 and 5 disease or lymphovascular invasion on biopsy, as well as patients with clinical locally advanced disease. Wider resection of the pedicles, bundles, and DVC may be indicated for these patients. There is obviously a balance between eradicating pelvic disease and preserving functional outcomes, particularly continence, but surgical morbidity needs to be balanced against the potential additional morbidity of salvage pelvic irradiation.

This was a descriptive study only and does not report on long-term outcomes for patients with local recurrence. The study is limited by small numbers, its retrospective nature with inherent selection bias, and the lack of pelvic MRI for all patients. The median PSA was high in this series, but the anatomy of local recurrence is unlikely to differ for patients with lower PSA.

5. Conclusions

The concept of local recurrence of prostate cancer remains poorly understood. This study describes local recurrence within the PVP and the pattern of local recurrence on molecular imaging. This may better inform our understanding of local recurrence and should prompt discussion about surgical techniques and adjuvant or salvage radiation fields in selected patients.

Author contributions: Philip Dundee 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: Costello, Dundee.
Acquisition of data: Ballok, Pan, Ryan, Dundee.
Analysis and interpretation of data: Costello, Corcoran, Furrer, Peters, Dundee.
Drafting of the manuscript: Furrer, Costello, Dundee.
Critical revision of the manuscript for important intellectual content: All authors.
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